Editorial
Predictors and indicators

Review Article
Anesthetic management for non-cardiac surgery in patients with left ventricular assist devices

Clinical Research Articles
The impact of preoperative coronavirus disease 19 infection on early postoperative mortality during the vaccination era: a nationwide retrospective cohort study

Machine learning model of facial expression outperforms models using analgesia nociception index and vital signs to predict postoperative pain intensity: a pilot study

Frequency domain analysis of photoplethysmographic and arterial pressure waveforms for assessing hemodynamics in children with congenital heart surgery

Postoperative alterations in ventriculoarterial coupling are an indicator of cardiovascular outcomes in liver transplant recipients

Association of preoperative blood glucose level with delirium after non-cardiac surgery in diabetic patients

Effect of ultrafiltration on whole blood coagulation profile during cardiopulmonary bypass in cardiac surgery: a retrospective analysis

Experimental Research Article
Learning with our peers: peer-led versus instructor-led debriefing for simulated crises, a randomized controlled trial

Case Reports
Use of oxygen reserve index during bronchoscopic balloon dilation for subglottic stenosis in a patient with left ventricular assist device implantation

Venous air emboli during esophagoscopy confirmed by computed tomographic pulmonary angiography

Letters to the Editor
Corrigendum

Association between De Ritis ratio and intraoperative blood transfusion in patients undergoing surgical clipping of unruptured intracranial aneurysms: a single center, retrospective, propensity score-matched study

Comparison of the analgesic efficacy of the ultrasound-guided transversalis fascia plane block and erector spinae plane block in patients undergoing open inguinal hernia repair under spinal anesthesia

The KOREAN SOCIETY of ANESTHESIOLOGISTS

Online access in http://ekja.org
"Hana Pharm.,"
the manufacturer of
all kinds of anesthetic agents,
will be with you!
-Everlasting Partner-

Sevofran
Liquid for Inhalation

- The first and only sevoflurane agent manufactured in Korea
- Economic choice for minimizing the burden of medical expenses for patients
- Fast recovery and clinical safety have been proved.
AceScope
VIDEO LARYNGOSCOPE with Touch Screen

Smart easy to use.
Convenient touch screen.
Disposable channeled blade.

Wireless charger
A Quantitative Monitor for Neuromuscular Blockade

Radically innovative. Ridiculously simple.

TECHNICAL SPECIFICATIONS

Electrode Array:
- Single-Patient Use
- Monitors adductor pollicis or first dorsal interosseous muscle

Stimulation:
- Current Range: 10-80 mA
- Pulse Width: 100µs, 200µs, or 300µs
- Frequency: 1Hz - 50Hz ±5%
- Sequences: Train-of-Four, Post-Tetanic Count, Single Twitch, Tetanus

Electromyography:
- Accuracy: +/- 5%
- Dynamic noise canceling

Battery:
- Type: Lithium Ion, Rechargeable
- Battery Life: At least 6 hours when fully charged

Safety and Efficacy Compliance:
- IEC60601-1, IEC60601-1-2, IEC60601-2-40 (EMG)
Does PONV still remain unsolved?

Feel the difference with Ramosetron
Aims and Scope

The Korean Journal of Anesthesiology (Korean J Anesthesiol; KJA/ISSN: 2005-6419), an official journal of the Korean Society of Anesthesiologists, is an English-language, peer-reviewed journal that publishes articles in the fields of anesthesiology, critical care, and pain medicine. KJA aims to publish high-quality clinical and scientific materials on all aspects of anesthesiology, critical care, and pain medicine. Its regional focus is mainly Korea, but it also welcomes submissions from researchers all over the world.

In addition to publishing original articles, KJA features reviews, editorials, case reports, and letters to the editor. KJA also features statistical rounds to provide its readers with educational fundamentals and practical implications for clinical and experimental statistics. Additionally, KJA gladly publishes negative results, which will benefit clinical practice and promote further research activity.

The primary considerations for publication are clarity, uniqueness, and advancement in design, performance, and knowledge.

The journal has been partly supported by the Korean Federation of Science and Technology Societies. KJA is indexed/tracked/covered by SCIE (Science Citation Index Expanded), KCI (indexed by the National Research Foundation of Korea), PubMed, PubMed Central, EBSCOhost Databases, KoreaMed, KoMCI Web, KoreaMed Synapse, Science Central, SCOPUS, Embase, CAS (Chemical Abstracts Service), WPRIM (Western Pacific Regional Index Medicus), DOAJ (Directory of Open Access Journal) and Google Scholar. It has been indexed in MEDLINE by U.S. National Library of Medicine.
EDITORIAL BOARD

Publisher
Yon Jun Heum (Inje University, Korea)

Editor-in-Chief
Younsk Lee (Dongguk University, Korea)
Young Lan Kwak (Yonsei University, Korea)

Associate Editor-in-Chief

Seong-Hyop Kim (Konkuk University, Korea)
Sangseok Lee (Inje University, Korea)
Sung Yong Park (Ajou University, Korea)

Seunguk Bang (The Catholic University of Korea, Korea)
Paul Barach (Wayne State University, USA)
Marco Cascella (National Cancer Institute, Italy)
Geun Joo Choi (Chung-Ang University, Korea)
Yoon Ji Choi (Korea University, Korea)
Vladimir Cerny (Karolinska University, Sweden)
Traychit Chanthesiri (University of Health Sciences in Lao P.D.R, Laos)
Woosuk Chung (Chungnam National University, Korea)
Hari Har Das (Fortis Memorial Research Institute, India)
Paul Diprose (University Hospital Southampton, UK)
Lara Eriksson (Karolinska University, Sweden)
Carlos Galhardo (National Institute of Cardiology, Brazil)
Adrian W. Gelb (University of California, San Francisco, USA)
Axel Hofmann (University of Western Australia, Australia)
Sung Mi Hwang (Hallym University, Korea)
Erik Weber Jensen (Politechnic University of Catalonia, Spain)
Ji Seon Jeong (Sungkyunkwan University, Korea)
Ki Tae Jung (Chosun University, Gwangju, Korea)
Geraldine Raphaela B. Jose (Makati Medical Center, Philippines)
Masahiko Kawaguchi (Nara Medical University, Japan)
Edward Kim (Stanford University, USA)
Eunsoo Kim (Pusan National University, Korea)
Kh-mie Kim (Loyola University, USA)
Woongmo Kim (Chonnam National University, Korea)
Mikhail Kirov (Northern State Medical University, Russia)
Bon-Wook Koo (Seoul National University, Korea)
Hye-Mee Kwon (University of Ulsan, Korea)
Jae Hoon Lee (Yonsei University, Korea)
Ji-Hyun Lee (Seoul National University, Korea)

Statistical Editor
Hyonggin An (Korea University, Korea)
Yunhee Choi (Seoul National University, Korea)
Il-Hyun Lee (StatEdu Statistics Institute, Korea)

Eun-Jin Ahn (Chung-Ang University, Korea)
Boohwi Hong (Chungnam National University, Korea)
Junyong In (Dongguk University, Korea)
Hyun Kang (Chung-Ang University, Korea)
Hye Jin Kim (Yonsei University, Korea)
Jong Hae Kim (Daegu Catholic University, Korea)

Chi-Yeon Lim (Dongguk University, Korea)
Hyunsun Lim (National Health Insurance Service Ilsan Hospital, Korea)
Sung-Cheol Yun (University of Ulsan, Korea)

Tae Kyun Kim (Pusan National University, Korea)
Sang Gyu Kwak (Daegu Catholic University, Korea)
Dong Kyu Lee (Dongguk University, Korea)
Sangseok Lee (Inje University, Korea)
Francis Sahngun Nahm (Seoul National University, Korea)

Statistical Rounds Board

Jong-Yeon Park (University of Ulsan, Korea)
Jae Hang Shim (Hanyang University, Korea)

Nguyen, Duc Lam (Hanoi Medical University, Vietnam)
Kiwon Lee (Rutgers University, USA)
Suraphong Lormsrmadee (Chiang Mai University, Thailand)
Stephen Loney (Teleflex, UK)
Z. David Luo (University of California, Irvine, USA)
Carl Lynch III (University of Virginia, USA)
Daqing Ma (Imperial College London, UK)
Edward Mariano (Stanford University, USA)
Frederic Michard (MiCo Sàrl, Switzerland)
Cyrus Motamed (Institute Gustave Roussy, France)
Hasmizi Bin Muhammad (Sarawak Heart Center, Malaysia)
Masaji Nishimura (University of Tokushima, Japan)
Zurani Md Noor (Serang Hospital, Malaysia)
Raymond M. Planinsic (University of Pittsburgh, USA)
Junghee Ryu (Seoul National University, Korea)
Tetsuro Sakai (University of Pittsburgh, USA)
Won-Jung Shin (University of Ulsan, Korea)
Veronica I. Shubayev (University of California San Diego, USA)
Robert N. Sladen (Columbia University, USA)
Jong Wook Song (Yonsei University, Korea)
Kenichi Tanaka (University of Maryland, USA)
Serge Thal (Johannes Gutenberg University of Mainz, Germany)
Christopher A. Troianos (Cleveland Clinic, USA)
Mei Yung Tsou (Taipei Veterans General Hospital, Taiwan)
Laurence Weinberg (University of Melbourne, Australia)
Gordon Wong (Queen Mary Hospital, Hong Kong)
Hyub Huh (Kyung Hee University, Korea)

Manuscript Editor
Ji Youn Ha (The Korean Society of Anesthesiologists, Korea)
Editorial

173   Predictors and indicators
Jong Yeon Park

Review Article

175   Anesthetic management for non-cardiac surgery in patients with left ventricular assist devices
Jeong-Jin Min, Yang Hyun Cho, Sangmin M. Lee, Jong-Hwan Lee

Clinical Research Articles

185   The impact of preoperative coronavirus disease 19 infection on early postoperative mortality during the vaccination era: a nationwide retrospective cohort study
Jae-Woo Ju, Taeyup Kim, Soo-Hyuk Yoon, Won Ho Kim, Ha-Jin Lee

195   Machine learning model of facial expression outperforms models using analgesia nociception index and vital signs to predict postoperative pain intensity: a pilot study
Insin Park, Jae Hyon Park, Jongjin Yoon, Hya-Seok Na, Ah-Young Oh, Junghee Ryu, Bon-Wook Koo

205   Frequency domain analysis of photoplethysmographic and arterial pressure waveforms for assessing hemodynamics in children with congenital heart surgery
Hwa-Young Jang, In-Kyung Song, Sung-Hoon Kim, Won-Jung Shin

217   Postoperative alterations in ventriculoarterial coupling are an indicator of cardiovascular outcomes in liver transplant recipients
Ji Yeon Kim, Young-Jin Moon, Changjin Lee, Jin Ho Kim, Junghyun Park, Jung-Won Kim

226   Association of preoperative blood glucose level with delirium after non-cardiac surgery in diabetic patients
Soo Jung Park, Ah Ran Oh, Jong-Hwan Lee, Kwangmo Yang, Jungchan Park

236   Effect of ultrafiltration on whole blood coagulation profile during cardiopulmonary bypass in cardiac surgery: a retrospective analysis
Jaemoon Lee, Dong-Kyu Lee, Won-Kyoung Kwon, Sookyung Lee, Chung-Sik Oh, Klaus Görlinger, Tae-Yop Kim

246   Association between De Ritis ratio and intraoperative blood transfusion in patients undergoing surgical clipping of unruptured intracranial aneurysms: a single center, retrospective, propensity score-matched study
Ji-Hoon Sim, Chan-Sik Kim, Seungil Ha, Hyunkook Kim, Yong-Seok Park, Joung Uk Kim

255   Comparison of the analgesic efficacy of the ultrasound-guided transversalis fascia plane block and erector spinae plane block in patients undergoing open inguinal hernia repair under spinal anesthesia
Hale Kefeli Çelik, Serkan Tulgar, Ömer Faruk Buk, Kadom Koç, Murat Ünal, Caner Genç, Mustafa Süren

Experimental Research Article

265   Learning with our peers: peer-led versus instructor-led debriefing for simulated crises, a randomized controlled trial
Morgan Jaffrelot, Sylvain Boet, Yolande Floch, Nitan Garg, Daniel Dubois, Violaine Laparra, Lionel Touffet, M. Dylan Bould
Case Reports
273 Use of oxygen reserve index during bronchoscopic balloon dilation for subglottic stenosis in a patient with left ventricular assist device implantation
Jimin Lee, Minwoo Chung, Eui-Suk Sung, Jung-Pil Yoon, Yeong Min Yoo, Jaesang Bae, Hee Young Kim

278 Venous air emboli during esophagoscopy confirmed by computed tomographic pulmonary angiography
Thadakorn Tantisarasart, Thara Tantichamnanakul, Chanathee Kitsiripant, Panjai Choochuen

Letters to the Editor
283 Comment on “Usefulness of C-curved stylet for intubation with the C-MAC® Miller videolaryngoscope in neonates and infants: a prospective randomized controlled trial” Dong Ho Park, Jong Dal Chung, Chang Young Jeong, Hong-seul Yang
284 Response to “Comment on Usefulness of C-curved stylet for intubation with the C-MAC® Miller videolaryngoscope in neonates and infants: a prospective randomized controlled trial” Jung-Bin Park, Ji-Hyun Lee

Corrigendum
285 Association of the perfusion index with postoperative acute kidney injury: a retrospective study
Pyoyoong Kang, Jung-bin Park, Hyun-Kyu Yoon, Sang-Hwan Ji, Young-Eun Jang, Eun-Hee Kim, Ji-Hyun Lee, Hyung Chul Lee, Jin-Tae Kim, Hee-Soo Kim
Anesthetic management for non-cardiac surgery in patients with left ventricular assist devices

Jeong-Jin Min¹, Yang Hyun Cho², Sangmin M. Lee¹, Jong-Hwan Lee¹

Departments of ¹Anesthesiology and Pain Medicine, ²Thoracic & Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Written in English:

With the increasing number of patients receiving left ventricular assist device (LVAD) implants, their survival rates have improved, leading to an increase in the number of patients receiving LVAD heart surgery. As a result, anesthesiologists need to understand the unique circulatory physiology of patients with LVADs and prepare for intraoperative management. This review focuses on the current most used HeartMate 3™ device, including the basic circulatory physiology, interpretation of LVAD parameters, and considerations for safe intraoperative management, as well as the causes and management of possible hemodynamic changes during surgery.

Keywords: Anesthesia; General anesthesia; Heart-assist devices; Intraoperative monitoring; Surgical procedures; Ventricle-assist device.

Written in Korean:

좌심실 보조 장치 이식 환자의 비 심장 수술시 마취 관리

Jeong-Jin Min¹, Yang Hyun Cho², Sangmin M. Lee¹, Jong-Hwan Lee¹

Departments of ¹Anesthesiology and Pain Medicine, ²Thoracic & Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

좌심실 보조 장치(left ventricular assist device, LVAD) 이식을 받는 환자의 수가 증가하고 이들의 생존율이 개선됨에 따라, 더 많은 LVAD 이식 환자들이 다양한 형태의 비 심장수술을 받고 있다. 이에 따라, 안전하고 성공적인 수술을 위해서 마취과 의사들도 LVAD를 가진 환자에서의 독특한 순환생리를 이해하고 주술기 마취관리에 대비하는 것이 필요하다. 본 리뷰에서는 현재 가장 많이 사용되는 HeartMate 3™ 기기를 가진 환자에서의 기본적인 순환 생리, LVAD parameter의 해석과 안전한 주술기 관리를 위한 고려 사항, 수술 중 발생 가능한 혈역학적 이벤트의 원인 감별 및 적절한 환자 관리에 관한 내용을 정리하였다.

Keywords: Anesthesia; General anesthesia; Heart-assist devices; Intraoperative monitoring; Surgical procedures; Ventricle-assist device.


결과: 총 750,175명의 환자들 중, 28.2%가 수술 전에 2차 백신접종을 받았다. 수술 전 COVID-19 감염증이 없었던 환자와 비교하여, COVID-19 감염증 후 0–4주(보정 오즈비 [OR]: 4.28, 95% CI [1.81, 10.13], P = 0.001) 및 5–8주(보정 OR: 3.38, 95% CI [1.54, 7.44], P = 0.002)에 수술을 받았던 환자들에서는 수술 후 30일 내 사망률의 위험도가 유의하게 높게 나타났다. 수술 전 2차 백신접종은 90일 내 사망률(보정 OR: 0.93, 95% CI [0.89, 0.98], P = 0.007) 및 30일 내 호흡기 합병증(보정 OR: 0.85, 95% CI [0.82, 0.87], P < 0.001) 감소와 유의하게 연관되어 있었지만, 30일 내 사망률과는 유의한 연관성이 없었다(P = 0.916).

결론: 수술 전 8주 이내 COVID-19 감염증은 수술 후 30일 내 사망률 증가와 관련되어 있었다. 수술 전 2차 백신접종은 30일 내 사망률과 유의한 연관성이 없었지만 90일 내 사망률 및 30일 내 호흡기 합병증 위험도 감소와는 유의한 연관성이 있었다.

Keywords: Anesthesia; COVID-19; Mortality; Postoperative complications; Preoperative period; Surgery; Vaccination.
Machine learning model of facial expression outperforms models using analgesia nociception index and vital signs to predict postoperative pain intensity: a pilot study

Insun Park¹,*, Jae Hyon Park²,3,*, Jongjin Yoon², Hyo-Seok Na¹, Ah-Young Oh¹, Junghyee Ryu¹, Bon-Wook Koo¹

¹Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, ²Department of Radiology, Yonsei University College of Medicine, Seoul, ³Department of Radiology, Armed Forces Daejeon Hospital, Daejeon, Korea

Background: Accurate postoperative pain measurement is crucial. Recent automatic AI-based pain recognition technology has attracted attention. However, research on pain intensity prediction using AI has only reached the initial stage. This study aimed to develop and compare the performance of various machine learning models using facial expressions, analgesia nociception index (ANI), and vital signs to predict severe postoperative pain.

Methods: Facial expression data from 155 patients after upper abdominal surgery were collected postoperatively. Pain intensity was measured using a 11-point numerical rating scale (NRS). Two trained anesthesiologists assessed pain using the ANI score and vital signs. Various machine learning models were developed and compared using the area under the receiver operating characteristic (AUROC) curve.

Results: The facial expression-based model predicted NRS ≥ 7 with the highest AUROC of 0.93. Combining facial expression and vital signs improved prediction, with an AUROC of 0.84. The model combining ANI and vital signs performed better than a single indicator model but not as well as the facial expression model (P < 0.05). ANI scores were negatively correlated with NRS (r = -0.69) and AUROC (r = 0.68).

Conclusions: A machine learning model using facial expressions outperformed models using ANI and vital signs in predicting severe postoperative pain.

Keywords: Artificial intelligence; Facial expression; Machine learning; Pain measurement; Postoperative pain; Vital signs.
Frequency domain analysis of photoplethysmographic and arterial pressure waveforms for assessing hemodynamics in children with congenital heart surgery

Hwa-Young Jang, In-Kyung Song, Sung-Hoon Kim, Won-Jung Shin
Department of Anesthesiology and Pain Medicine, Laboratory for Cardiovascular Dynamics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: In children with congenital heart disease, hemodynamic monitoring in the operating room is often challenging due to altered cardiac and vascular compliance. This study aimed to evaluate the capability of photoplethysmographic (PPG) and arterial blood pressure (ABP) waveforms derived from frequency domain analysis to predict hemodynamic parameters in children undergoing congenital heart surgery.

Methods: Seventy-six children underwent congenital heart surgery. PPG and ABP waveforms were analyzed immediately after cardiopulmonary bypass. Fast Fourier Transform analysis was used to calculate the amplitude density at respiratory frequency from the baseline and amplitude modulation of PPG and ABP. The area under the receiver operating characteristic curve was used to determine the predictive value of these parameters for fluid requirements and vasopressor use.

Results: Children requiring more than 10 ml/kg of fluid (46%) had higher PPG-DC% than those not requiring fluid (median: 52.4%, 95% CI [24.8, 295.1] vs. 36.7% [10.7, 125.7], P = 0.017). Similarly, children requiring higher vasopressor scores (7.5) had higher PPG-ABP-CF/PPG-ABP-CF ratio than those not requiring vasopressor (3.6 [0.91, 10.8] vs. 1.2 [0.27, 5.5], P = 0.008).

Conclusion: Frequency domain analysis of PPG and ABP waveforms can provide useful information for predicting fluid and vasopressor requirements in children undergoing congenital heart surgery.

Keywords: Congenital heart disease; Hemodynamics; Photoplethysmography; Fluid therapy; Vasopressors.
Postoperative alterations in ventriculoarterial coupling are an indicator of cardiovascular outcomes in liver transplant recipients

Ji Yeon Kim¹, Young-Jin Moon², Changjin Lee³, Jin Ho Kim³, Junghyun Park³, Jung-Won Kim⁴

Department of Anesthesiology and Pain Medicine, ¹CHA Gangnam Medical Center, CHA University School of Medicine, ²Laboratory for Cardiovascular Dynamics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, ³CHA Bundang Medical Center, CHA University School of Medicine, ⁴Laboratory for Cardiovascular Dynamics, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

수술 후 심실-동맥 결합(VAC) 변화는 간 이식을 받은 환자에서 심혈관계 예후를 반영하는 지표이다

배경: 간 이식(liver transplant, LT)은 간장병성 심근병증 환자의 심장 및 혈관 작업 부하를 증가시킨다. 좌심실(LV)과 동맥계(심실-동맥 결합, VAC)와의 상호작용이 심혈관 기능의 핵심 결정인자임에도 불구하고, LT 후 VAC 변화에 대해서는 거의 알려져 있지 않다. 따라서 우리는 LT 후 VAC 변화와 심혈관 기능과의 관계를 평가하였다.

방법: 344명의 환자가 연속적으로 LT 전과 LT 후 30일 이내에 심장 초음파 검사를 받았다. 비침습적 동맥 탄성도(Ea), LV 수축기 말 탄성도(Ees), 및 LV 확장기 말 탄성도(Eed)를 계산하였다. 수술 후 평가변수는 주요 심혈관계 이상반응(major adverse cardiovascular events, MACE)의 발생과 중환자실(ICU) 및 병원 내 입원 기간이었다.

결과: 총 240명의 환자를 분석에 포함시켰다. LT 이후, Ea는 16% 증가하였고(Ea = 16% (P < 0.001), Ees와 수축기 속도의 수축 지수(S')는 각각 18% (P < 0.001)와 7% (P < 0.001) 증가하였다. Ees는 6% 증가하였으며(P < 0.001), VAC는 변화가 없었다(0.56에서 0.56으로, P = 0.912). 이 환자들 중, 29명에게서 MACE가 발생하였고, MACE 발생 환자들에게서는 수술 후 VAC가 유의하게 높게 나타났다. 추가로, 수술 후 높은 VAC는 수술 후 장기입원에 대한 독립적인 위험인자였다(P = 0.038).

결론: 이 데이터는 VA decoupling의 LT 후 불량한 결과와 연관이 있음을 시사한다.

Keywords: Cardiomyopathies; Echocardiography; Left ventricular dysfunction; Liver cirrhosis; Liver transplantation; Postoperative complications.
Association of preoperative blood glucose level with delirium after non-cardiac surgery in diabetic patients

Soo Jung Park1,2, Ah Ran Oh1,3, Jong-Hwan Lee1, Kwangmo Yang4, Jungchan Park1

Department of Anesthesiology and Pain Medicine, 1Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, 2Ajou University School of Medicine, Suwon, 3Kangwon National University Hospital, Chuncheon, 4Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Hyperglycemia is associated with cognitive dysfunction. We performed a retrospective analysis of postoperative delirium in patients with diabetes who underwent non-cardiac surgery to determine whether preoperative blood glucose levels and glycated hemoglobin (HbA1c) levels were associated with delirium.

Methods: We reviewed the medical records of 23,532 diabetic patients who underwent non-cardiac surgery at a tertiary hospital from January 2018 to December 2019. Patients were divided into two groups based on whether they met the criteria for acute (blood glucose >140 mg/dL or HbA1c >180 mg/dL) or chronic hyperglycemia (HbA1c >6.5% within the past 3 months). We compared the incidence of delirium between the two groups after adjusting for potential confounders using inverse probability weighting (IPW).

Results: Among the 23,532 patients, 21,585 (91.7%) had acute hyperglycemia and 18,452 (78.9%) had chronic hyperglycemia. After adjusting for potential confounders, patients with acute hyperglycemia had a higher risk of delirium compared to those without (adjusted relative risk: 1.33, 95% CI [1.10, 1.62], P = 0.004). However, chronic hyperglycemia was not associated with increased risk of delirium.

Conclusion: Preoperative hyperglycemia, especially acute hyperglycemia, may increase the risk of delirium after non-cardiac surgery in diabetic patients. However, chronic hyperglycemia does not seem to be associated with delirium.

Keywords: Blood glucose; Cognitive dysfunction; Emergence delirium; Glycated hemoglobin; Hyperglycemia; Mortality; Postoperative delirium.

Received: April 17, 2023
Revised: August 2, 2023 (1st); November 7, 2023 (2nd); December 15, 2023 (3rd)
Accepted: January 3, 2024

Corresponding author:
Jungchan Park, M.D.
Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-3214
Fax: +82-2-3410-2849
Email: jcp83.park@samsung.com
ORCID: https://orcid.org/0000-0002-7794-3547

@ The Korean Society of Anesthesiologists, 2024
This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
배경: 심장수술에서 심폐우회술 중 초여과(ultrafiltration) 적용은 응고인자들의 농도와 응고기능에 영향을 미칠 것이다.

방법: 한 대학병원에서 회전혈전탄성검사-기반 응고 관리하에 심장 수술을 받은 환자 75명의 전자의무기록을 후향적으로 검토하여서, 그 중 30명의 환자에서 심폐우회술 중 초과정을 적용하여 외인성 조직 응고인자 촉진 검사의 최대 혈전 강도(이하 최대혈전강도)를 변화시키는지 분석했다.

결과: 초여과로 제거된 수분량(중간값)은 1,350 ml이었고, 적혈구 용적률(중간값)은 81.8%이고 백혈구는 84.2%, 수신자 조작 특성곡선 아래 영역은 94.9%였다.

결론: 심폐우회술 중 초과정은 혈전 강도를 증가시키고, 초과정 시행 이전에 이미 최대혈전강도가 감소된 환자에서 증가 효과가 더 크게 나타난다.
Association between De Ritis ratio and intraoperative blood transfusion in patients undergoing surgical clipping of unruptured intracranial aneurysms: a single center, retrospective, propensity score-matched study

Ji-Hoon Sim*, Chan-Sik Kim*, Seungil Ha, Hyunkook Kim, Yong-Seok Park, Joung Uk Kim

Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

배경: 두개내 비파열성 동맥류(unruptured intracranial aneurysms, UIA) 수술이 증가하는 추세이지만, UIA 수술 중 수혈의 위험인자를 평가한 연구는 흔하지 않다. 본 연구에서는 UIA 결찰술을 시행받은 환자들에서 수술 전 De Ritis ratio와 수술 중 수혈 발생율 사이의 연관성을 평가하였다.

방법: UIA 결찰술을 시행받은 환자들은 수술 전 De Ritis ratio가 1.54 및 ≤ 1.54로 나누어 두 집단으로 분류하고, 성향점수 매칭 분석을 실시하여 수술 중 수혈 발생률을 비교하였다. 로지스틱 회귀모형을 사용하여 수술 중 수혈의 위험인자를 파악하였다. 순 재분류 개선(net reclassification improvement, NRI) 및 통합 판별 개선(integrated discrimination improvement, IDI) 분석을 수행하여 De Ritis ratio가 수술 중 수혈 예측 모델을 개선하는지 검증하였다.

결과: 수술 중 수혈 발생률은 15.4% (77/502)였다. De Ritis ratio ≥ 1.54는 수혈의 독립적 위험인자였으며, 수술 전 De Ritis ratio ≥ 1.54의 환자들 중 28.9% (10/34)가 수혈이 발생했다(OR: 3.04, 95% CI [1.53, 6.03], P = 0.002). 수술 전 혈액기판(HE) 수치는 수혈의 위험 인자였으며, 수술 전 혈액기판(HE) 수치는 수혈의 위험 인자였다(OR: 0.33, 95% CI [0.24, 0.47], P < 0.001). NRI 및 IDI 분석 결과, De Ritis ratio가 수술 중 수혈 예측 모델을 개선하는 것으로 나타났다(각각 P = 0.031 및 P = 0.049).

결론: De Ritis ratio는 UIA 수술에서 수술 중 수혈의 유의한 위험인자일 수 있다.

Keywords: Alanine transaminase; Aspartate aminotransferases; Blood coagulation; Blood transfusion; Intracranial aneurysm; Propensity score.
Comparison of the analgesic efficacy of the ultrasound-guided transversalis fascia plane block and erector spinae plane block in patients undergoing open inguinal hernia repair under spinal anesthesia

Hale Kefeli Çelik¹, Serkan Tulgar¹, Ömer Faruk Bülk², Kadem Koç¹, Murat Ünal¹, Caner Genç¹, Mustafa Süren¹

Departments of ¹Anesthesiology and Reanimation, ²General Surgery, Samsun University Faculty of Medicine, Samsun Training and Research Hospital, Samsun, Turkey

Keywords: Analgesia; Chronic pain; Herniorrhaphy; Inguinal hernia; Nerve block; Regional anesthesia; Ultrasonography.

Received: May 22, 2023
Revised: July 11, 2023 (1st); August 25, 2023 (2nd); September 3, 2023 (3rd); October 12, 2023 (4th); November 30, 2023 (5th)
Accepted: January 7, 2024

Corresponding author:
Hale Kefeli Çelik, M.D.
Department of Anesthesiology and Reanimation, Samsun University Faculty of Medicine, Samsun Training and Research Hospital, Banş Bulvarı, İlikadım, Samsun 55090, Turkey
Tel: +90-3623111500
Fax: +90-3622778865
Email: Hale.KefeliCelik@saglik.gov.tr
ORCID: https://orcid.org/0000-0002-0850-4524

The Korean Society of Anesthesiologists, 2024
This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Online access in http://ekja.org
Learning with our peers: peer-led versus instructor-led debriefing for simulated crises, a randomized controlled trial

Morgan Jaffrelot¹,²,³, Sylvain Boet⁴,⁵,⁶,⁷, Yolande Floch², Nitan Garg⁴, Daniel Dubois⁵, Violaine Laparra², Lionel Touffet⁷, M. Dylan Bould⁵,⁶,⁸

¹University of Ottawa Skills and Simulation Center and Academy for Innovation in Medical Education, University of Ottawa, Ottawa, ON, Canada, ²Simulation Center, University of Western Brittany and University Hospital of Brest, ³Education and Health Promotion Laboratory EA 3412, Paris 13-Sorbonne Paris Cité University, France, ⁴Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, ⁵The Ottawa Hospital Research Institute, ⁶Department of Innovation in Medical Education, Faculty of Medicine, University of Ottawa, ⁷Institut du Savoir Montfort, ⁸Department of Pediatric Anesthesia, Children’s Hospital of Eastern Ontario, Ottawa, ON, Canada

배경: 동료지원 학습은 의학교육 시 상호 학습에 효과적인 것으로 알려져 있지만 시뮬레이션 교육에 대해서는 연구된 바 없다. 우리는 위기상황 시뮬레이션에서 비기술적 능력을 학습하는 데 있어 디브리핑(debriefing)에 의한 동료지원 학습의 효과를 강사주도 디브리핑의 효과와 비교 연구하였다.

방법: 61명의 의과대학생을 대조군(강사주도 디브리핑) 또는 중재군(동료주도 디브리핑 시행자 또는 동료주도 디브리핑 대상자 중 하나로 배정됨)에 무작위로 배정하였다. 사전검사 시뮬레이션 후, 참가자들은 2차례의 시뮬레이션 시나리오에 참가하였고 각각의 시뮬레이션 후에는 디브리핑 세션을 가졌다. 두 번째 디브리핑 세션 이후, 참가자들은 같은 날에 즉시 사후검사 시뮬레이션을 시행했다. 두 명의 평점 평가자가 사전검사, 즉시 사후검사, 지연 사후검사 시뮬레이션에서 비기술적 능력을 오타와 글로벌 등급 척도(Ottawa Global Rating Scale, OGRS)를 이용하여 평가하였다.

결과: 모든 군에서는 사전검사보다 2차례의 사후검사 시 비기술적 능력 성적이 유의하게 개선된 것으로 나타났다. OGRS 점수의 변화는 강사 주도군에서 15.0점(95% CI [11.4, 18.7]), 디브리핑 시행자군에서는 15.3점(11.5, 19.0), 디브리핑 대상자군에서는 17.6점(13.9, 21.4)이었다. 의내과학 영역으로 인한 영향을 보정한 후 집단 간의 성격에는 유의한 차이가 없었고(\(P = 0.147\)), 사후검사와 사후검사 사이에도 유의한 차이가 없었다(\(P = 0.358\)).

결론: 동료 디브리핑은 위기상황 시뮬레이션 교육에서 의과대학생들의 비기술적 능력을 개선하는 데 있어 강사주도 디브리핑만큼 효과적이었다. 동료 디브리핑 시행자들도 시뮬레이션 앞에서의 능력이 개선되었다. 동료 디브리핑 모델은, 더 높은 비용이 요구되는 전통적인 강사주도 디브리핑의 대안으로 활용될 수 있을 것으로 기대된다.

Keywords: Critical care; Education; Feedback; Peer group; Professional competence; Simulation training.
In the current issue of the *Korean Journal of Anesthesiology* (KJA), prediction-related words such as impact, predict, assessing, indicator, association, and effect are included in the titles of clinical research papers. Ju et al. [1] reported that COVID-19 infections eight weeks preoperatively were associated with an increase in the 30-day postoperative mortality. In the study conducted by Park et al. [2], a machine learning model constructed using facial expressions was a superior predictor of severe postoperative pain (numeric rating scale [NRS] ≥ 7), outperforming models constructed from physiological signals. Jang et al. [3] reported that a frequency-domain analysis of photoplethysmography and arterial blood pressure may assess hemodynamic status requiring fluid or vasoactive inotropic therapy after congenital heart surgery. Kim et al. [4] reported that the development of ventricular-arterial decoupling is associated with poor postoperative outcomes after liver transplantation. Preoperative acute hyperglycemia was found to be associated with postoperative delirium in the study by Park et al. [5]. Finally, Lee et al. [6] reported that applying ultrafiltration improved clot firmness, with more pronounced improvement when pre-ultrafiltration maximum clot firmness-extrinsically activated test with tissue factor was reduced using cardiopulmonary bypass.

If anesthesiologists could make accurate predictions, patients could be diagnosed and treated earlier, thus improving postoperative outcomes. A predictor is defined as something such as an event or fact that enables one to anticipate a future occurrence. An indicator is a specific, measurable or observable characteristic, or trait, that is used to show progress or something that has happened. Research studies aimed at discovering appropriate predictors or indicators to improve postoperative outcomes are continuously being conducted.

In the current issue of the KJA, Park et al. [5] investigate the relationship between hyperglycemia and postoperative delirium. In that study, acute hyperglycemia was defined as at least one fasting blood glucose level > 140 mg/dl or a random blood glucose level > 180 mg/dl within 24 h before surgical incision. Chronic hyperglycemia was defined as an HbA1c level > 6.5% within three months before surgery. Postoperative delirium is diagnosed by a psychiatrist using the Confusion Assessment Method. Among the patients in the acute hyperglycemia group, the ratio of chronic kidney disease to intraoperative transfusion was considerably higher than that in the no acute hyperglycemia group. Park et al. [2] investigated a machine learning model of facial expressions and outperformed models using the analgesia nociception index and vital signs to predict postoperative pain intensity. In that study, 155 facial expressions, analgesia nociception index scores, vital signs, and self-assessed pain intensity based on the NRS were recorded postoperatively in patients who underwent gastrectomy.

Anesthesiologists should consider the importance of preoperative evaluations, predictors, and indicators for improving postoperative outcomes.
Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

Introduction

Since the Korean national insurance began to cover durable left ventricular assist device (LVAD) implantations in September 2018, the number of LVAD implantations performed in South Korea has been increasing [1]. The annual volume of LVAD implantations in South Korea has increased from 30 cases in 2018 to 61 in 2019, 58 in 2020, 82 in 2021, and 123 in 2022 per the Korean Society of Heart Failure Surgery. Considering the increasing volume of patients undergoing LVAD implantations and their improved longevity [2–4], the possibility of these patients requiring non-cardiac surgery has increased. Therefore, anesthesiologists need to understand the physiology of this unique patient population and adequately prepare for the perioperative management of this unique patient population. This review addresses perioperative considerations and intraoperative management for the safe and successful management of patients with an LVAD undergoing non-cardiac surgery. Understanding the basic physiology of preload dependency and afterload sensitivity in these patients is essential. The main considerations include a collaborative preoperative multidisciplinary approach, perioperative care aimed at optimizing the intravascular volume and right ventricular function, and maintaining the afterload within recommended ranges for optimal LVAD function.

Keywords: Anesthesia; General anesthesia; Heart-assist devices; Intraoperative monitoring; Surgical procedures; Ventricle-assist device.

Types of left ventricular assist device (LVAD)

From the first implantation of an LVAD (the HeartMate II) in August 2012 until September 2020, the HeartMate II and HeartWare VAD (HVAD), were the most commonly implanted devices in Korean patients. After the HeartMate 3 was introduced in Septem-
ber 2020, the HVAD and HeartMate 3 became the most commonly implanted devices. However, in June 2021, the HVAD system was recalled as a result of safety concerns associated with potentially fatal pump malfunctions from electrical faults causing battery failure [6]. Therefore, the HeartMate 3 is currently the most commonly implanted LVAD in South Korea. Although patients scheduled for non-cardiac surgery are more likely to have third-generation devices (the HVAD or HeartMate 3) implanted, surviving patients who received their LVADs earlier may have any of these devices.

For an optimal hemodynamic profile or according to concerns regarding hemorrhagic or thrombotic complications, the recommended ranges for the device parameters differ according to the type of LVAD (Table 1, Fig. 1) [7,8]. Therefore, prior to surgery, physicians need to identify the type of device implanted in each patient scheduled for non-cardiac surgery. Details regarding the different types of LVADs have been described in previous articles [9–11].

**Pump flow principle and basic physiology**

The components of the HeartMate 3 LVAD are shown in Fig. 1. The volume flow rate generated by the LVAD is mainly determined by the pump speed and the pressure gradient across the pump. With the same afterload, the pump flow increases proportionally with a higher rotor speed, and at the same rotor speed, the pump flow is inversely related to the pressure gradient across the pump [11,12]. The pump speed can be adjusted; however, the surgeon usually sets a fixed value that is optimized to the patient. The recommended ranges for the pump speed (in revolutions per minute [RPM]) for each device type are listed in Table 1. Each parameter is described in the following sections.

**Speed**

As briefly described above, the LVAD operates at a fixed speed (reported in RPM), and the recommended ranges differ according to the device type (Table 1). This fixed speed is determined or set by the physician, but it is not the same as a constant-speed mode. The HeartMate 3 in particular produces periodic variations in speed, generating an artificial pulse every two seconds (Fig. 2B).

![Fig. 1. Components of the HeartMate 3™ left ventricular assist system (reproduced with permission from Abbott). The HeartMate 3 pump is connected to a system controller via a driveline.](https://doi.org/10.4097/kja.23169)

<table>
<thead>
<tr>
<th>Table 1. Operating Parameters for Continuous Flow Left Ventricular Assist Devices</th>
<th>HeartMate II</th>
<th>HVAD</th>
<th>HeartMate 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed (RPM)</td>
<td>8,000–10,000</td>
<td>2,400–3,200</td>
<td>5,000–6,000</td>
</tr>
<tr>
<td>Power (W)</td>
<td>5–8</td>
<td>3–7</td>
<td>4.5–6.5</td>
</tr>
<tr>
<td>Flow (L/min)</td>
<td>4–7</td>
<td>4–6</td>
<td>4–6</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>5–8</td>
<td>Not provided*</td>
<td>3.5–5.5</td>
</tr>
</tbody>
</table>

HVAD: HeartWare VAD. *Flow/time waveform pulsatility of 2–4 L/min from peak to trough.
Power and flow

While power (in watts [W]) is a direct measurement of pump motor voltage and current by the system controller, displayed flow (in liters per minute [L/min]) is an estimation based on power. The device power and flow generally exhibit a linear relationship at a given speed. Changes in pump speed, flow, or physiological demand can affect the pump power. Gradual increases in power (over hours or days) may indicate aortic insufficiency or thrombus deposits inside the pump. Gradual decreases in power may indicate an obstruction of flow and require evaluation. Occlusion of the flow path may decrease the flow through the pump and cause a decrease in power.

Pulsatility index (PI)

When the native left ventricle contracts during cardiac systole, the increase in ventricular pressure causes an increase in pump flow, and the magnitude of flow pulses through the pump is measured and averaged over 15 s intervals to produce the PI. The PI represents the degree of pump power variability (usually the same as the flow variability) and, ultimately, native heart contractility. Typical ranges of the PI values are shown in Table 1. In general, the magnitude of the PI is related to the amount of assistance provided by the LVAD pump. Higher values indicate greater ventricular filling and higher pulsatility (i.e., the LVAD provides less support to native heart contractility). Lower values indicate less ventricular filling and lower pulsatility (i.e., the LVAD provides greater support to unload the ventricle). The PI is useful in the management of patients with a HeartMate 3 implanted, particularly when combined with the pump flow (Fig. 3).

Preanesthesia assessment

Anesthetic considerations and preparations may vary depending on the type of non-cardiac surgery scheduled for the patient with an LVAD. Because LVADs only function effectively when the left ventricle is adequately filled by the right ventricle, preoperative assessment of right ventricular function, the presence of ventricular tachyarrhythmia, and the degree of pulmonary hypertension are crucial for identifying patients who need invasive monitoring (e.g., central venous catheters, pulmonary artery catheters, or transesophageal echocardiography [TEE]), early initiation of inotropic therapy, or other right ventricular optimization strategies (e.g., judicious volume therapy or ventilator setting adjustments) [12–14]. To facilitate awareness of any patient-specific or device-specific problems, preoperative discussions with knowledgeable clinicians (e.g., a specialized VAD team, if available) is important [12,15].

Device-related history

The LVAD-specific medical history must be reviewed, including the type of device, date of implantation, current device parameter values on the VAD monitor (pump speed, pump flow, pump power, and PI), and any previous LVAD-related alarms or events, such that the patient’s ideal flow parameters can be estimated. If the patient underwent aortic valve closure at the time of LVAD surgery because of aortic insufficiency, the patient’s native heart will not be able to generate any forward blood flow and will be completely dependent on the flow from the LVAD [10]. Additionally, the driveline and externalized abdominal site must be inspected for any signs of infection or perioperative changes.
Assessment of the overall condition

In addition to the severity and urgency of the current surgical problem, the degree of impairment in the function of any major organ; current medications; post-implantation complications; and most recent blood test results, including blood cell counts, electrolytes, coagulation, and renal and hepatic function tests, should be reviewed. The most recent echocardiography also provides vital information on cannula position and valvular and right ventricular function [3,9,11,12,16,17].

Management of cardiovascular implantable electronic devices

The main concern regarding the presence of cardiovascular implantable electronic devices (CIEDs) is the potential for interactions between the CIED and electromagnetic interference due to the intraoperative use of electrocautery [18]. Because up to 40% of patients with LVADs have a pacemaker or implantable cardioverter defibrillator, collectively known as CIEDs [4], deactivation should be planned before surgery to avoid inappropriate shocks in the operating room [19,20]. Deactivation may involve reprogramming the CIED to asynchronous pacing mode (VOO or DOO) or placing a magnet over the CIED. These patients require continuous 5-lead electrocardiography monitoring, and external adhesive defibrillation pads should be applied during the inactivation period [19].

Management of anticoagulation

Discontinuing anticoagulation therapy must be decided on a case-by-case basis, with the risk of bleeding weighed against the risk of a pump thrombus. Currently, anticoagulation with a vitamin K antagonist (warfarin) is recommended for patients with an LVAD, with a target international normalized ratio (INR) between 2.0 and 3.0 [21,22]. Aspirin can be added as antiplatelet therapy [21]. However, as an adverse effect of antithrombotic therapy, bleeding episodes, such as bleeding from the gastrointestinal tract, can occur in over 50% of patients with LVADs. As such events are most commonly associated with an INR > 2.5 [23], some centers have lowered the target INR to 2.0–2.5 for centrifugal pumps [24,25]. In addition, the development of acquired von Willebrand disease (vWD) also contributes to bleeding predisposition in patients with an LVAD. Acquired vWD is an acquired loss of large von Willebrand factor (vWF) monomers by increased proteolysis of vWFs, mediated by shear stress-induced amplification of vWF-cleaving protease (ADAMTS 13) [26,27]. This acquired vWD can prevent the binding of collagen and platelets at the sites of vascular injury [28].

If the risk of bleeding is low, aspirin and warfarin may be continued perioperatively or the goal may be decreased to the lower limit of therapeutic levels for most elective non-cardiac surgeries [21,29]. However, if the risk of bleeding is high, warfarin may be discontinued and bridged with heparin or heparin alternatives to be discontinued on the morning of the procedure [21,30]. For
emergency, neurosurgical, or ophthalmologic surgeries, the anticoagulation effect may be rapidly reversed with fresh frozen plasma or prothrombin complex concentrate [16,29]. After the procedure, the early initiation of warfarin and antiplatelet therapy is recommended when the risk of surgical bleeding is acceptable [31].

Selection of anesthetic technique

Patients with an LVAD receive general anesthesia during most surgical procedures. However, if the surgical procedure can be performed under local anesthesia or an ultrasound-guided peripheral nerve block, sedation with monitored anesthetic care may be a safe option for upper- or lower-extremity surgeries. Although regional anesthesia is not inherently contraindicated in the presence of an LVAD, literature supporting the use of spinal anesthesia in patients with LVADs is extremely limited, and the use of neuraxial anesthesia is particularly infrequent (< 1%) [3,32,33]. The American Society of Regional Anesthesia recommends that the coagulation status be normalized before placing a neuraxial block [34]. When regional anesthesia is planned, interruption of warfarin therapy for five days before the elective procedure and normalization of the clotting status are recommended [32]. Another worrisome potential complication following neuraxial anesthesia is acute sympathectomy, which may provoke hemodynamic instability in patients with LVADs. Because these patients are dependent on adequate venous return, acute peripheral vasodilation and subsequent decrease in preload can increase the risk for “suction” events with inflow cannula obstruction [3,33].

Multidisciplinary care

When possible, surgical procedures should be performed in an LVAD-specialized center with a cardiac anesthesiologist or with access to an LVAD specialist, especially for major procedures or for patients with significant comorbidities [16,20]. However, as the number of patients with an LVAD increases, the proportion of care that must be provided by non-cardiac anesthesiologists also increases. [3]. Moreover, for several patient outcome indicators, no significant differences according to anesthesiology provider type have been reported, at least for low-risk procedures [35]. However, up to 72% of patients with an LVAD may require some intraoperative cardiovascular pharmacological support; thus, anesthesiologists caring for these patients must be familiar with the administration of vasopressors and inotropic medications [3].

Patient transfer and management of the VAD power source

When the patient is ready to be transferred after the LVAD’s main power is transitioned to battery power, the console is moved together, accompanied by a VAD specialist nurse to maintain intraoperative VAD monitoring. During both patient transfer and surgery, care must be taken to avoid dropping the system controller or monitor or pulling the driveline, because this may induce unexpected interruption of the pump or soft tissue injury, leading to a driveline tunnel infection [36]. Because the driveline carries power to the pump and communicates information with the system controller, any damage to or mishandling of the driveline (e.g., bending, twisting, or allowing to get wet) should be prevented.

In the operating room, the power supply for the LVAD should be transferred to a portable power unit and connected to the wall power supply [12,29].

Intraoperative monitoring

Both reduced native cardiac contractility and LVAD-induced unloading of the left ventricle result in low pulse pressure in patients with an LVAD. If a palpable pulse is present, an automated cuff system can provide reliable measurements. However, a pulse pressure < 15 mmHg is not palpable and will not be detected by an automated blood pressure cuff. Thus, patients with an LVAD may not have a pulse, especially during anesthesia, making pulse oximetry and noninvasive blood pressure monitoring difficult. The mean arterial pressure (MAP) should therefore be measured and reported in these patients [37], and intra arterial MAP monitoring is advisable for surgeries requiring general anesthesia [21]. The ultrasound-guided technique can facilitate arterial catheter placement in patients with diminished palpable pulses [38]. The HeartMate 3 generates an artificial pulse every 2 s by an algorithm that produces periodic variations in the impeller speed (Fig. 2B). Pulsatility reduces blood stasis and the potential for thrombus formation. Tissue oxygenation can be monitored using arterial blood gases, and cerebral oximetry can be used to ensure brain oxygenation. A central venous catheter may be indicated for central venous pressure (CVP) monitoring and vasoactive drug administration during major surgical procedures or in patients that are unstable [21,38]. When TEE is used, the position of the interventricular septum can be monitored to provide information on volume status and the proper speed of the LVAD.
Intraoperative hemodynamic management

The LVAD is preload-dependent and afterload-sensitive. Adequate filling of the left ventricle is essential for the optimal function of an LVAD, and afterload sensitivity indicates that hypertension can decrease pump flow.

Afterload to the LVAD

Maintaining an adequate depth of anesthesia and analgesia is important to avoid excessive sympathetic stimulation during laryngoscopy for tracheal intubation and surgical procedures. Light anesthesia may acutely increase the systemic vascular tone (afterload) and decrease the forward pump flow, which can be associated with myocardial or cerebral ischemia, ventricular arrhythmia, and end-organ injury [39,40]. The recommended range of the MAP for patients with an LVAD is 70–85 mmHg [21,31]. High blood pressure can be controlled by antihypertensive medications, but beta-blockers should be used cautiously in patients with right ventricular dysfunction.

A decrease in afterload due to anesthetic agents, especially during anesthesia induction, can induce intraoperative hypotension. On the lower side, a MAP < 60 mmHg is associated with hypoperfusion and therefore must be avoided. If necessary, vasopressors should be used judiciously in small bolus doses to avoid excessive right ventricular afterload. Low-dose vasopressin can be used given its minimal effect on the pulmonary vasculature [41].

Preload to the LVAD

Factors critical to preload include intravascular volume status, patient positioning, surgical approach (laparoscopic vs. open), arrhythmias, and right ventricular function or afterload. In the event of decreased venous return, strategies for placing the patient in a slight Trendelenburg position, initiating judicious fluid loading, and adjusting ventilatory settings are advisable until recovery of the pump preload or vascular tone [14]. Possible hemodynamic effects of intraoperative patient positioning should also be considered. Preload can be reduced if the surgical approach requires a position other than the supine position, such as reverse Trendelenburg, beach chair, lateral decubitus with one-lung ventilation, or prone positions. Therefore, positioning changes should be made slowly with calibrated fluid therapy according to the situation, and limiting the duration or degree of the position to minimize venous pooling in the limbs may be considered [42–44]. In addition, high positive end-expiratory pressure applied with a pneumoperitoneum can significantly reduce venous return [45,46]. During laparoscopic procedures, stepwise peritoneal gas insufflation with judicious fluid therapy could be beneficial, and an intra-abdominal pressure > 15 mmHg should be avoided when the reverse Trendelenburg position is incorporated [45]. The overall effect of pneumoperitoneum on venous return can vary depending on the position, and preload may increase as a result of blood shifting from the abdomen to the thorax in the steep Trendelenburg, lithotomy, or lateral positions [47].

Adequate right ventricular function must be maintained, and an increase in the pulmonary vascular resistance (often resulting from hypoxia, hypercarbia, or acidosis) should be avoided [48].

Monitoring and management of PI

PI values should be monitored and significant variation should not be present. If sudden and substantial changes in the PI (i.e., PI events) occur, the causes must be identified. Most PI events are not suction events, and often result from other causes. Under otherwise stable conditions, a significant drop in the PI value in the operating room indicates a sudden change in the intravascular volume status due to surgical bleeding, and adequate fluid therapy or a blood transfusion is required. Other possible causes include arrhythmias, sudden changes in the power or pump speed, and ventricular suction (Fig. 3). Suction events, which can be easily confirmed using TEE imaging, are more common when the left ventricle is relatively underfilled. Immediate management involves momentarily decreasing the LVAD speed while administering intravenous volume therapy.

When excessive unloading of the left ventricle is encountered, momentarily decreasing the LVAD speed may improve left ventricular filling, although this requires close coordination with the VAD specialist [15]. In the HeartMate 3, when the calculated PI (per second) differs by more than 45% from the PI value averaged for 15 s, the system detects a PI event and the pump speed automatically drops to the low-speed limit and slowly ramps back up to the fixed set-point value. This drop in speed is accompanied by a reduction in the pump flow; therefore, it is important to differentiate between clinically important PI events and effectively address the causes.

Common causes of decreased pump flow in the operating room include right ventricular dysfunction and hypovolemia. Since these two conditions require different management strategies, it is important to diagnose right ventricular dysfunction early based on the clinical situation, TEE imaging, and monitoring parameters for high CVP (> 15 mmHg, as an estimate of right ventricular filling pressure) or low pulmonary arterial pressure, if available [11]. Examples of TEE images indicating severe right ventricular...
dysfunction resulting in LVAD suction events are shown in Supplementary Videos 1A and B. When severe right ventricular dysfunction is observed, a careful combination of therapies is required, including inotropic medication; optimization of right ventricular preload (judicious volume management) and afterload; optimal ventilation strategies to avoid hypoxemia, hypercapnia, or excessive mean airway pressure; and maintaining normal cardiac rhythm with atrioventricular synchrony [49].

Management of intraoperative ventricular arrhythmias

Because ventricular arrhythmias may impair right ventricular function and decrease inflow to the LVAD, patients should be kept in normal sinus rhythm when possible [50]. Causes of arrhythmia include a previous history of arrhythmia, electrolyte abnormality, metabolic imbalance, the effect of inotropic drugs, or mechanical irritation of the ventricular wall from the inflow cannula (e.g., suction events). If a patient is hemodynamically stable, reversible causes should be identified and corrected. Cardioversion is recommended when ventricular tachycardia or atrial fibrillation with rapid ventricular rates compromise the LVAD flow and/or hemodynamic status [21]. Amiodarone infusion is considered acceptable, and beta blockers should be used carefully. With recurrent ventricular arrhythmias that are difficult to treat, the MAP must be maintained at approximately 80 mmHg to ensure coronary perfusion. Slower arrhythmia is well-tolerated and may not always require therapy.

Advanced cardiovascular life support (ACLS) in patients with an LVAD

There are several unique considerations for cardiopulmonary resuscitation in patients with LVADs [10]. Because the assessment of pulse or noninvasive blood pressure is limited by continuous flow physiology, replacing the pulse concept with perfusion is necessary. The two most common causes of pump failure are disconnection of the power and failure of the driveline; therefore, all connections must be assessed and an adequate power source confirmed, along with frequent checks for device parameters/alarms and auscultation for the LVAD hum when these patients are unresponsive perioperatively [10,51]. When the MAP is monitored, the protocol should be the same as any other peri-arrest situation. If blood pressure is not detectable in an intubated patient, the partial pressure of end-tidal carbon dioxide (EtCO₂) can be measured. If volume refractory hypotension is present with the MAP < 30 or 40 mmHg and/or EtCO₂ < 20 mmHg in an intubated patient, advanced cardiovascular life support (ACLS) should be initiated, as with any other patient, including chest compressions. Although performing external chest compressions on patients with LVADs has been controversial, a recent consensus states that in cardiac arrest, withholding chest compressions may cause more harm than that associated with the potential dislodgment of the inflow cannula [10]. During resuscitation, a backup plan, such as a venoarterial extracorporeal membrane oxygenator, can be prepared. If inevitable, bolus doses of epinephrine or other vasopressors should be used with caution to avoid an extremely high increase in afterload, which can lead to decreased pump flow, a rapid increase in left atrial pressure, and resultant pulmonary edema.

Postoperative management

care should be taken to minimize hemodynamic changes, such as hypertension and tachycardia, during extubation or the postoperative recovery period for optimal LVAD function. Deactivated CIEDs must be reprogrammed for active therapy. The patient can recover in the standard post-anesthesia care unit after minor procedures; however, it would be safer for the patient to be transferred to an intensive care unit after major surgeries [28]. As anesthetic effects and subsequent hypoventilation have resulted in unexpected adverse outcomes [52], common causes of an increase in right ventricular afterload, such as hypoxia, hypercarbia, and acidosis, should be avoided.

Conclusion

To safely and successfully manage patients with an LVAD undergoing non-cardiac surgery, anesthesiologists must know the type of LVAD and understand the preload-dependent and afterload-sensitive physiology of this population. Additionally, collaborative preoperative multidisciplinary discussions, perioperative management aimed at optimizing intravascular volume and right ventricular function, and management of systemic vascular resistance within adequate ranges for optimal LVAD function are essential.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.
Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

Jeong-Jin Min (Conceptualization; Data curation; Writing – original draft; Writing – review & editing)
Yang Hyun Cho (Conceptualization; Supervision; Validation; Writing – review & editing)
Sangmin M. Lee (Conceptualization; Supervision; Writing – review & editing)
Jong-Hwan Lee (Conceptualization; Data curation; Investigation; Supervision; Validation; Writing – review & editing)

ORCID

Jeong-Jin Min, https://orcid.org/0000-0002-7584-2670
Yang Hyun Cho, https://orcid.org/0000-0003-1685-3641
Sangmin M. Lee, https://orcid.org/0000-0001-8460-2233
Jong-Hwan Lee, https://orcid.org/0000-0001-8249-5550

Supplementary Materials

Supplementary Video 1. Examples of a transesophageal echocardiography of severe right ventricular dysfunction in patients with an LVAD. (A) A leftward shift of the interventricular septum, (B) Severe tricuspid regurgitation. Right ventricular failure can be a cause or consequence of a suction event.

References


https://doi.org/10.4097/kja.23169
ment of LVAD-supported patients for the non-LVAD specialist healthcare provider Part 3: at the hospital and discharge. ESC Heart Fail 2021; 8: 4425-43.

17. DeVore AD, Patel PA, Patel CB. Medical management of patients with a left ventricular assist device for the non-left ventricular assist device specialist. JACC Heart Fail 2017; 5: 621-31.


38. Hessel EA. Management of patients with implanted ventricular assist devices for noncardiac surgery: a clinical review. Se-


Background: We aimed to investigate the optimal surgical timing in patients with preoperative coronavirus disease 2019 (COVID-19) infection to minimize postoperative morbidity and mortality during the COVID-19 vaccination era.

Methods: The Korean nationwide data on patients who underwent standard surgery under general anesthesia in 2021 were analyzed. Patients were categorized based on the time from COVID-19 diagnosis to surgery: 0–4, 5–8, > 8 weeks, and those without preoperative COVID-19 infection. Multivariable logistic regression analysis, considering preoperative COVID-19 vaccination status (fully vaccinated vs. unvaccinated or partially vaccinated), was performed to associate the preoperative COVID-19 infection timing with 30- and 90-day postoperative mortality and 30-day respiratory complications.

Results: Among the 750,175 included patients, 28.2% were preoperatively fully vaccinated. Compared with patients without prior COVID-19 infection, those who had surgery 0–4 weeks (adjusted odds ratio [OR]: 4.28, 95% CI [1.81, 10.13], P = 0.001) and 5–8 weeks (adjusted OR: 3.38, 95% CI [1.54, 7.44], P = 0.002) after COVID-19 infection had a significantly increased risk of 30-day mortality. Preoperative full vaccination was significantly associated with a decrease in 90-day mortality (adjusted OR: 0.93, 95% CI [0.89, 0.98], P = 0.007) and 30-day respiratory complications (adjusted OR: 0.85, 95% CI [0.82, 0.87], P < 0.001), but not with 30-day mortality (P = 0.916).

Conclusions: COVID-19 infection eight weeks preoperatively was associated with an increased 30-day postoperative mortality. Preoperative full vaccination was not associated with 30-day mortality but was related to lower risk of 90-day mortality and 30-day respiratory complications.

Keywords: Anesthesia; COVID-19; Mortality; Postoperative complications; Preoperative period; Surgery; Vaccination.

Introduction

It is crucial to determine the appropriate timing of surgery in patients with preoperative coronavirus disease 2019 (COVID-19) infection. COVID-19 infection is associated with multiple organ injuries [1,2] that may have unexpectedly extended aftereffects [3]. Preoperative COVID-19 infection is associated with increased postoperative morbidity and mortality [4]; however, postponing the surgery can also worsen postoperative out-
comes and increase medical costs [5,6], especially in cancer surgeries [7]. This further demonstrates why it is vital for anesthesiologists to determine the appropriate surgery timing for patients with a history of COVID-19 infection before surgery.

An international prospective cohort study published in 2021 reported that preoperative COVID-19 infection within seven weeks before surgery was associated with an increase in postoperative 30-day mortality [8]. Consequently, recommendations from the expert consensus for managing surgical patients with a history of COVID-19 infection have been established in several countries based on this result [9–12], with other studies reporting consistent findings [13,14]. However, the patients in this international prospective cohort study were recruited in October 2020 [8] before the introduction of COVID-19 vaccines, and the severity of COVID-19 infection was worse than it is now [15]. COVID-19 vaccination in South Korea started in February 2021. There is a need for a more comprehensive investigation of the influence of preoperative COVID-19 infection on surgical prognosis due to the increased availability of vaccines and medical resources since the initial outbreaks [16–18].

Therefore, in this retrospective study, we aimed to examine the association between preoperative COVID-19 infection and 30-day postoperative mortality in patients who underwent surgery in 2021 using the Korea Disease Control and Prevention Agency–COVID-19 National Health Insurance Service (K-COV-N) cohort data. Our results could help determine the appropriate timing of surgery during the vaccination era in patients with a history of COVID-19 infection.

Materials and Methods

Study design and population

This nationwide retrospective cohort study’s protocol was exempted from review by our institution’s Institutional Review Board due to the study’s retrospective nature and the use of de-identified data. This study was also approved by the Korea Disease Control and Prevention Agency (KDCA) and National Health Insurance Service (NHIS) (approval number: KDCA-NHIS-2022-1-620). The present study was also conducted following the principles outlined in the Declaration of Helsinki, 2013 and has been reported following the STrengthening the Reporting of Observational studies in Epidemiology guidelines [19].

Notably, all data were obtained from the K-COV-N cohort database combined with the KDCA and NHIS data. Korea has a universal compulsory national health insurance system that covers virtually all Korean residents [20]. The NHIS database contains information regarding all inpatient and outpatient medical services, including diagnoses based on the International Classification of Diseases 10th Revision (ICD-10) codes, prescription, and prescription codes. In addition, the KDCA database contains detailed information regarding COVID-19 confirmation and vaccination. Therefore, the K-COV-N cohort database includes data regarding the confirmation date of COVID-19 infection and the data on the date and type of the COVID-19 vaccination.

We included patients who underwent surgery under general anesthesia (procedure codes: L0101, L1211, and L1212) in South Korea between January 2021 and December 2021. The K-COV-N cohort database provided information regarding the COVID-19 confirmation date between October 8, 2020, and December 31, 2021. Notably, only the confirmation year was obtained for patients before this period. We excluded patients who did not undergo predefined standard surgery during the study period. Standard surgery was defined based on a list of procedure codes used to establish surgical healthcare statistics that inform national health policies in Korea. The procedure codes were listed in the NHIS’s Main Surgery Statistical Yearbook for 2020 and the Standard Guide to Statistics of Disease and Procedure published by the Health Insurance Review and Assessment Service in Korea (Supplementary Table 1) [21,22]. Moreover, we excluded patients diagnosed with COVID-19 within 30 days after the index surgery. Only the first surgery was analyzed if a patient underwent multiple standard surgeries.

Data collection

We collected data regarding demographics (age and sex), preoperative comorbidity (congestive heart failure, dementia, chronic pulmonary disease, rheumatologic disease, mild liver disease, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, including leukemia and lymphoma, moderate or severe liver disease, metastatic solid tumor, acquired immune deficiency syndrome, or human immunodeficiency virus infection), confirmation date of COVID-19 infection, COVID-19 vaccination-related variables (vaccination date, vaccination series, and vaccine type), surgery-related variables (department of surgery, surgical type, relative work unit, and urgency), income level (as quartiles), residence level (capital city, metropolitan city, or other areas), postoperative complications within 30 days after surgery, and date of all-cause death. Preoperative comorbidities were indicated by at least two corresponding ICD-10 codes recorded within one year before surgery (Supplementary Table 2). The updated Charlson comorbidity index (CCI) score was also calculated [23]. The status of COVID-19 vaccination was consid-
ered ‘fully vaccinated’ if patients received at least one dose of Ad.26.COV2.S or at least two doses of BNT162b2 or mRNA-173 vaccines 14 days before the index surgery [24]. ‘Not fully vaccinated’ was defined as receiving only one BNT162b2 or mRNA-173 vaccine 14 days before the surgery; otherwise, patients were regarded as ‘not vaccinated.’ We did not consider the period between vaccination and COVID-19 confirmation due to a previous report on the beneficial effect of COVID-19 vaccination in patients without COVID-19 infection [16]. The guidelines for COVID-19 vaccination in South Korea recommend vaccination at least four weeks after COVID-19 confirmation [25]. The relative work unit is a calculated score that considers the relative risk of medical practice in South Korea, and it was used to classify the risk of surgery into quartiles (first quartile, very low-risk surgery; second quartile, low-risk surgery; third quartile, intermediate-risk surgery; fourth quartile, high-risk surgery). Postoperative complications within 30 days after surgery were derived from the NHIS database using the corresponding ICD-10 diagnostic codes. Supplementary Table 3 summarizes the ICD-10 codes for postoperative complications [26].

**Study group and outcomes**

Patients were categorized into four groups based on the duration from the confirmation date of COVID-19 infection to the date of index surgery [24,27]: 0–4 weeks, 5–8 weeks, > 8 weeks, and those without a preoperative history of COVID-19 (Fig. 1). During the study period, a COVID-19 real-time reverse transcription polymerase chain reaction test confirmed COVID-19 infection following the nationwide Korean policy [28]. This study’s primary outcome was the 30-day postoperative mortality. The secondary outcomes were 90-day postoperative mortality and 30-day respiratory complications.

**Statistical analyses**

All statistical analyses were performed using SAS® version 9.4 (SAS Institute). Statistical significance was set at a two-sided P value < 0.05. Continuous variables are appropriately reported as the mean (standard deviation) or median (interquartile range), whereas categorical variables are reported as numbers (percentage).

We performed among-group comparisons of the 30-day postoperative mortality using logistic regression analyses. Firth correction was used to mitigate bias associated with rare events [29]. Univariate logistic regression analyses for the primary outcome were performed for the study group with the following potential confounders: age, female sex, CCI score, COVID-19 vaccination status, emergency surgery (vs. elective surgery), risk of surgery (as quartiles), income level (as quartiles), and residence level. Age (0–49 years, 50–69 years, and ≥ 70 years) and CCI score (0–3, 4–5, and ≥ 6) were considered categorical variables. The COVID-19 vaccination status was dichotomized into a binary variable (fully vaccinated vs. not or not fully vaccinated). After the univariate analyses, the study group and other confounders were entered into multivariable analysis without the variable selection method. The absence of multicollinearity among variables was confirmed by examining the variance inflation factor (< 2) before incorporating the variables into the multivariable model. The results are reported as odds ratios (ORs) with 95% CIs. In addition, we calculated the C-statistic of the multivariable model. Logistic regression analyses were repeated for the secondary outcomes using
methods similar to that for the primary outcome. Subgroup analyses of the primary outcome were performed to investigate whether the effect of preoperative COVID-19 infection differed according to subgroups. Multivariable logistic regression analyses with adjustment for all these confounders were performed in each subgroup: age (0–49 years, 50–69 years, and ≥ 70 years), sex, CCI score (0–3, 4–5, and ≥ 6), COVID-19 vaccination status, risk of surgery, income level, and residence level. The P-value for interaction was estimated using a likelihood ratio test, wherein multivariable models with and without the interaction term were compared.

**Results**

In total, 1,425,360 patients received general anesthesia in South Korea in 2021. After excluding patients who did not undergo pre-defined standard surgery (n = 674,586) and those who were diagnosed with COVID-19 within 30 days after surgery (n = 599), the remaining 750,175 patients were included in the final analysis (Fig. 2). Among them, 2,669 (0.36%) patients were diagnosed with COVID-19 infection before the surgery. Regarding the duration from the confirmation date of COVID-19 infection to the index surgery date, 352 (0.05%), 474 (0.06%), and 1,843 (0.25%) patients underwent surgery at 0–4 weeks, 5–8 weeks, and > 8 weeks after COVID-19 infection, respectively. The baseline characteristics and surgical variables are summarized in Supplementary Table 4. Among the analyzed patients, 28.2% were identified as fully vaccinated before surgery.

The postoperative outcomes are summarized in Table 1. The incidence rates of 30-day postoperative mortality were 0.4% (3,331/747,506) in patients without prior COVID-19 infection and 1.4% (5/352), 1.3% (6/474), and 0.5% (10/1,843) in patients who underwent surgery at 0–4 weeks, 5–8 weeks, and > 8 weeks after COVID-19 infection, respectively.

The univariate and multivariable logistic regression analysis results for 30-day postoperative mortality are presented in Table 2 and Supplementary Table 5. Compared with patients without prior COVID-19 infection, those who underwent surgery at 0–4 weeks (adjusted OR: 4.28, 95% CI [1.81, 10.13], P = 0.001) and 5–8 weeks (adjusted OR: 3.38, 95% CI [1.54, 7.44], P = 0.002) after COVID-19 infection were significantly associated with a higher risk of 30-day postoperative mortality, respectively. However, there was no significant association between patients who underwent surgery more than eight weeks after COVID-19 infection and risk of 30-day mortality compared with those without prior COVID-19 infection (adjusted OR: 1.58, 95% CI [0.85, 2.92], P = 0.146). In addition, higher age, male sex, higher CCI score, emergent surgery, higher risk of surgery, lower income level, and residence, except for the capital city, were associated with a higher risk of 30-day postoperative mortality. However, a fully vaccinated status (OR: 1.00, 95% CI [0.93, 1.07], P = 0.916) was not associated with a significantly lower risk of 30-day postoperative mortali-

---

**Fig. 2.** Flowchart of the study. NHIS: National Health Insurance Service, COVID-19: coronavirus disease 19.
The C-statistic of the multivariable model for predicting 30-day postoperative mortality was 0.823.

Multivariable logistic regression analysis of 90-day mortality is presented in Table 2 and Supplementary Table 6. Patients who underwent surgery at 0–4 weeks (adjusted OR: 3.13, 95% CI [1.61, 6.10], P = 0.001) and 5–8 weeks (adjusted OR: 2.34, 95% CI [1.25, 4.38], P = 0.008) after COVID-19 infection were significantly associated with a higher risk for 90-day postoperative mortality than those without prior COVID-19 infection. Patients who underwent surgery more than eight weeks after COVID-19 infection were not significantly associated with 90-day postoperative mortality (P = 0.856). Fully vaccinated status was associated with a substantially lower risk of 90-day postoperative mortality (OR: 0.93, 95% CI [0.89, 0.98], P = 0.007). The C-statistic of the multivariable model for predicting 90-day postoperative mortality was 0.819.

In the multivariable logistic regression analysis, patients who underwent surgery 0–4 weeks after COVID-19 infection were significantly associated with an increased risk of 30-day respiratory complication (adjusted OR: 3.79, 95% CI [2.66, 5.40], P < 0.001) (Supplementary Table 7). However, patients who underwent surgery at 5–8 or > 8 weeks after COVID-19 infection were not significantly associated with 30-day respiratory complications (P = 0.096 and 0.134, respectively). A fully vaccinated status was associated with a substantially lower risk of 30-day respiratory complications (OR: 0.85, 95% CI [0.82, 0.87], P < 0.001). The C-statistic of the multivariable model for predicting 30-day respiratory complications was 0.658.

The subgroup analyses showed no significant interaction effects between preoperative COVID-19 infection and covariates on 30-day postoperative mortality (Supplementary Tables 8 and 9).

**Discussion**

Our study showed a significant association between COVID-19 infection within eight weeks before surgery and 30-day postoperative mortality, consistent with previous reports [8,13,14,27]. Preoperative COVID-19 vaccination was not significantly associated with a decrease in 30-day postoperative mortality. However, it significantly correlated with reduced 90-day postoperative mortality and 30-day respiratory complications. The subgroup analyses showed no significant interaction effects between preoperative COVID-19 infection and the predefined covariates on 30-day postoperative mortality. This suggests that the association between COVID-19 infection occurring within eight weeks preoperatively and the risk of 30-day postoperative mortality might remain uniform across all the subgroups. Our findings may provide additional meaningful information on this critical issue given that our patient cohort comprised more vaccinated patients and thus reflected a more contemporary community vaccination status compared with previous studies [8,13,30].

We observed a significant association between preoperative COVID-19 infection and 30-day postoperative mortality, inconsistent with a recent report of a nonsignificant association between them [30]. Specifically, this previous study found that preoperative COVID-19 infection, even less than four weeks prior,

### Table 1. Postoperative Outcomes after Standard Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>No preoperative COVID-19 (n = 747,506)</th>
<th>Preoperative COVID-19 infection (by timing of diagnosis prior to surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–4 weeks (n = 352)</td>
</tr>
<tr>
<td>Thirty-day postoperative mortality</td>
<td>3,331 (0.4)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Ninety-day postoperative mortality</td>
<td>7,645 (1.0)</td>
<td>9 (2.6)</td>
</tr>
<tr>
<td>Thirty-day postoperative complications</td>
<td>113,584 (15.2)</td>
<td>76 (21.6)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>22,603 (3.0)</td>
<td>35 (9.9)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>27,152 (3.6)</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>Infections</td>
<td>33,828 (4.5)</td>
<td>22 (6.3)</td>
</tr>
<tr>
<td>Surgical wound rupture</td>
<td>2,435 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>9,116 (1.2)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3,533 (0.5)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Embolism</td>
<td>2,440 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Nutrition</td>
<td>3,472 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>423 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mechanical implantation</td>
<td>3,245 (0.4)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Other complications</td>
<td>18,590 (2.5)</td>
<td>12 (3.4)</td>
</tr>
</tbody>
</table>

Table 2. Multivariable Logistic Regression Analyses for 30- and 90-day Postoperative Mortality after Standard Surgery

<table>
<thead>
<tr>
<th>Timing of diagnosis of COVID-19 prior to surgery</th>
<th>Univariate</th>
<th></th>
<th>Multivariable</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thirty-day postoperative mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No preoperative COVID-19</td>
<td>Reference</td>
<td>0.003*</td>
<td>Reference</td>
<td>0.001*</td>
</tr>
<tr>
<td>0–4 weeks</td>
<td>3.55 (1.53, 8.25)</td>
<td></td>
<td>4.28 (1.81, 10.13)</td>
<td></td>
</tr>
<tr>
<td>5–8 weeks</td>
<td>3.10 (1.43, 6.74)</td>
<td>0.004*</td>
<td>3.38 (1.54, 7.44)</td>
<td>0.002*</td>
</tr>
<tr>
<td>&gt; 8 weeks</td>
<td>1.28 (0.70, 2.35)</td>
<td>0.427</td>
<td>1.58 (0.85, 2.92)</td>
<td>0.146</td>
</tr>
<tr>
<td>Ninety-day postoperative mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No preoperative COVID-19</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>0–4 weeks</td>
<td>2.68 (1.40, 5.11)</td>
<td>0.003*</td>
<td>3.13 (1.61, 6.10)</td>
<td>0.008*</td>
</tr>
<tr>
<td>5–8 weeks</td>
<td>2.19 (1.19, 4.04)</td>
<td>0.012*</td>
<td>2.34 (1.25, 4.38)</td>
<td>0.008</td>
</tr>
<tr>
<td>&gt; 8 weeks</td>
<td>0.87 (0.54, 1.42)</td>
<td>0.586</td>
<td>1.05 (0.64, 1.72)</td>
<td>0.856</td>
</tr>
</tbody>
</table>

COVID-19: coronavirus disease 19, OR: odds ratio. *Statistically significant (P < 0.05).

was not associated with worsened postoperative outcomes following elective major noncardiac surgery [30]. In addition, they observed a nonsignificant association between preoperative COVID-19 vaccination and postoperative outcomes. Notably, the study included a relatively contemporary patient population between April 2020 and October 2021; these nonsignificant results were attributed to the fact that their medical resource was less affected by the COVID-19 pandemic than earlier studies. Moreover, relatively small number of patients with preoperative COVID-19 infection (960 patients), and significantly low rates of death and major adverse cardiovascular events suggest that the study were inadequately powered to find a significant association between preoperative COVID-19 infection and postoperative outcomes.

Our study could not find a significant association between preoperative COVID-19 vaccination and 30-day postoperative mortality; however, it did show a significant association with reduced 90-day postoperative mortality and decreased 30-day respiratory complications. COVID-19 vaccination status can have a significant effect on postoperative outcomes. The availability of the COVID-19 vaccine that was available in the United States and the United Kingdom from December 2020 was a crucial turning point in the COVID-19 pandemic [31,32]. COVID-19 vaccination weakens the severity of COVID-19 infection, reducing COVID-19 infection-related hospitalizations and deaths [33,34]. These positive effects of COVID-19 vaccination have also been reported in surgical patients. A recent nationwide retrospective study reported that preoperative COVID-19 vaccination significantly reduced postoperative pulmonary complications and the length of hospital stay at Veterans Affairs facilities [16]. However, there was no significant association between preoperative COVID-19 vaccination and postoperative mortality due to the minimal number of events [16]. Conversely, their subsequent larger-scale study observed a significant association of preoperative COVID-19 vaccination with a decrease in postoperative mortality, regardless of the degree of preoperative vaccination [35]. In contrast, our study failed to demonstrate a significant association between preoperative COVID-19 vaccination and 30-day postoperative mortality. The postoperative 30-day period may not have sufficiently observed the benefits of preoperative COVID-19 vaccination. Although 30-day postoperative mortality is one of the widely used indicators of postoperative outcomes, there have been arguments that it is less effective in reflecting perioperative outcomes compared to 90-day postoperative mortality [36,37]. Moreover, although our study included a large sample size of 750,175 individuals, the 30-day postoperative mortality rate was only 0.4%. In addition, the initial phase of vaccination in South Korea that primarily targeted individuals with underlying health conditions or those in older age groups following the government's priority policy may also have influenced these results [38]. Nevertheless, since preoperative COVID-19 vaccination showed a significant association with a decrease in 90-day postoperative mortality and 30-day respiratory complications, further research is required to determine the effect of preoperative COVID-19 vaccination on postoperative outcomes.

Notably, we could not confirm whether full vaccination can completely offset the impact of preoperative COVID-19 infection on postoperative mortality [24]. A previous large-scale retrospective study reported that preoperative COVID-19 infection was not significantly associated with postoperative complications at any time interval in fully vaccinated patients; however, preoperative COVID-19 infection within four weeks was significantly associated with increased postoperative complications in patients who were not fully vaccinated [24]. Another retrospective study reported that the time interval from preoperative COVID-19 infec-
tion to surgery was negatively associated with the rate of major cardiovascular postoperative complications, even in patients who had received at least one dose of the COVID-19 vaccine preoperatively [39]. Furthermore, since the COVID-19 vaccine against the Omicron variant is less effective than that against the Delta variant and the effectiveness wanes over time [33,40,41], it is difficult to disregard the effect of preoperative COVID-19 infection, even in fully vaccinated patients. Therefore, further studies are required to explore the association between the status of COVID-19 vaccination and postoperative outcomes in more contemporary patient populations.

This study has some limitations. First, despite the robust adjustments undertaken in the analysis, there may be residual confounding factors due to the inherent limitations of a retrospective study design. Precisely, we could not determine whether patients with preoperative COVID-19 infection had COVID-19-related symptoms at the time of the index surgery. Current guidelines recommend that patients with a history of COVID-19 infection are scheduled for elective surgery seven weeks after the infection. In addition, the decision to proceed or delay the surgery should be made based on the presence or severity of persistent COVID-19 symptoms [9]. Second, our study involved patients who underwent index surgery before the emergence and predominance of the Omicron variant of COVID-19. Since the Omicron variant is less likely to cause severe infections compared with the Delta variant [33,42], our results may not be directly generalizable to patients infected with the Omicron variant. Third, we could not analyze the effect of administering booster vaccine doses. In Korea, booster doses became available nationwide in October 2021, and the proportion of patients who received the booster dose before the index surgery was significantly small. Further studies are necessary to clarify this issue. Fourth, given our cohort’s remarkably low mortality rate, we set the between-group interval as four weeks rather than two weeks to ensure an adequate mortality incidence for statistical analysis in each group. Finally, the 30-day mortality rate was 0.4%, significantly lower than previously reported values [8]. Since there is a considerable disparity in postoperative mortality rates among different countries [43], it may be inappropriate to directly extrapolate our findings to patients in other countries.

In conclusion, our study found a significant association between COVID-19 infection within eight weeks preoperatively and an increased risk of 30-day postoperative mortality, regardless of the preoperative vaccination status. Our study suggests that anesthesiologists should carefully determine the timing of surgery for patients who have a recent history of COVID-19 infection but are yet to receive COVID-19 vaccination. Further studies will also be required to reflect the current status of COVID-19 infection on this issue.

Acknowledgements

This study used the database of the Korea Disease Control and Prevention Agency (KDCA, Republic of Korea) and National Health Insurance Service (NHIS, Republic of Korea) for policy and academic research. The research number of this study is KDCA-NHIS-2022-1-620. We would like to thank the Division of Statistics in the Medical Research Collaborating Centre at Seoul National University Hospital for helping with statistical analyses.

Funding

This study was supported by an institutional research grant from Seoul National University Hospital (Grant No. 0420222160).

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The data that support the findings of this study are available from the Korea National Health Insurance Service but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with permission of the Korea National Health Insurance Service.

Author Contributions

Jae-Woo Ju (Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft)
Taeyup Kim (Data curation; Formal analysis)
Soo-Hyuk Yoon (Data curation; Formal analysis)
Won Ho Kim (Formal analysis; Writing – review & editing)
Ho-Jin Lee (Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Supervision; Writing – review & editing)

ORCID

Jae-Woo Ju, https://orcid.org/0000-0001-7971-0993

https://doi.org/10.4097/kja.23761
Supplementary Materials

Supplementary Table 1. Procedure codes of the National Health Insurance Service database for the standard surgery.

Supplementary Table 2. The ICD-10 codes for the covariates.

Supplementary Table 3. The ICD-10 codes for the outcomes.

Supplementary Table 4. Baseline characteristics and surgical variables.

Supplementary Table 5. Univariate and multivariable logistic regression analyses for 30-day postoperative mortality after standard surgery.

Supplementary Table 6. Univariate and multivariable logistic regression analyses for 90-day postoperative mortality after standard surgery.

Supplementary Table 7. Univariate and multivariable logistic regression analyses for 30-day respiratory complications after standard surgery.

Supplementary Table 8. Subgroup analyses of 30-day postoperative mortality after standard surgery.

Supplementary Table 9. Incidence of 30-day postoperative mortality after standard surgery.

References


13.e1.


Machine learning model of facial expression outperforms models using analgesia nociception index and vital signs to predict postoperative pain intensity: a pilot study

Insun Park¹,*, Jae Hyon Park²,³,*, Jongjin Yoon², Hyo-Seok Na¹, Ah-Young Oh¹, Junhee Ryul¹, Bon-Wook Koo¹

¹Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, ²Department of Radiology, Yonsei University College of Medicine, Seoul, ³Department of Radiology, Armed Forces Daejeon Hospital, Daejeon, Korea

Background: Few studies have evaluated the use of automated artificial intelligence (AI)-based pain recognition in postoperative settings or the correlation with pain intensity. In this study, various machine learning (ML)-based models using facial expressions, the analgesia nociception index (ANI), and vital signs were developed to predict postoperative pain intensity, and their performances for predicting severe postoperative pain were compared.

Methods: In total, 155 facial expressions from patients who underwent gastrectomy were recorded postoperatively; one blinded anesthesiologist simultaneously recorded the ANI score, vital signs, and patient self-assessed pain intensity based on the 11-point numerical ranking scale (NRS). The ML models' area under the receiver operating characteristic curves (AUROCs) were calculated and compared using DeLong's test.

Results: ML models were constructed using facial expressions, ANI, vital signs, and different combinations of the three datasets. The ML model constructed using facial expressions best predicted an NRS ≥ 7 (AUROC 0.93) followed by the ML model combining facial expressions and vital signs (AUROC 0.84) in the test-set. ML models constructed using combined physiological signals (vital signs, ANI) performed better than models based on individual parameters for predicting NRS ≥ 7, although the AUROCs were inferior to those of the ML model based on facial expressions (all P < 0.05). Among these parameters, absolute and relative ANI had the worst AUROCs (0.69 and 0.68, respectively) for predicting NRS ≥ 7.

Conclusions: The ML model constructed using facial expressions best predicted severe postoperative pain (NRS ≥ 7) and outperformed models constructed from physiological signals.

Keywords: Artificial intelligence; Facial expression; Machine learning; Pain measurement; Postoperative pain; Vital signs.

Introduction

Postoperative pain remains a prevalent but underestimated issue, with a reported occurrence of 30%–71% depending on the surgery type [1,2]. An 11-point numerical rating scale (NRS) is a widely used self-reported measure of pain intensity, with validated significant correlations to other pain rating measures [3,4]. It is preferred over other measures.
such as the visual analog scale (VAS) across different patient populations and cultures [5,6]. Although the NRS is simple and easy to use, pain intensity can only be evaluated at the assessment time. Since the recent guidelines by the American Pain Society, American Society of Regional Anesthesia and Pain Medicine, and American Society of Anesthesiologists (ASA) [7] recommend postoperative pain assessment every 15 min initially and every 1–2 h as the intensity decreases, assessments must be physically performed multiple times by a health practitioner. Furthermore, accurate NRS assessment may be difficult if patients are heavily sedated or cannot communicate during the immediate postoperative period [8]. As an alternative, alterations in visual cues such as facial expressions [9], and physiological indicators such as vital signs and the analgesia nociception index (ANI) [10], have been suggested as more objective measures of pain intensity, wherein facial expressions, ANI, and vital signs may be used for automated continuous pain assessment without a health practitioner.

Machine learning (ML) is an advanced technology that enables computers to learn from data, create algorithms and models, and make predictions without explicit instructions. ML can model complex, multicollinear relationships between variables and outcomes, surpassing traditional statistical methods [11,12].

Recent technical advances have facilitated automated artificial intelligence (AI)-based pain recognition [13–17]; however, few studies attempted to correlate it with pain intensity assessment [14,15] and rarely in postoperative settings [16,17]. In two studies [16,17], facial expressions were decomposed into action units that are constituent movements defined by the Facial Action Coding System [18] to construct AI models to predict NRS scores. In these earlier studies, other essential facial features such as geometry and landmarks were not incorporated into the models, and consequently, the models showed lower specificity, despite higher sensitivity, than the nurses’ pain assessments [17].

Additionally, while studies have reported the usefulness of physiological signals such as the ANI [19,20], and vital signs [21] for predicting self-reported postoperative pain intensity, the usefulness of fused modalities, especially those using AI, has not been explored, although implementing combinations of physiological signals have been suggested to improve pain monitoring [22].

Thus, in this pilot study, we constructed ML models using various combinations of facial expressions, the ANI, and vital signs, and compared their performances for predicting severe postoperative pain, defined as NRS ≥ 7. For the facial expression ML model, we incorporated all possible facial features including those relevant to appearance, geometry, and landmarks in addition to action units. To the best of our knowledge, this study was the first to develop an AI model using the ANI and vital signs to predict patient postoperative pain. The purpose of this pilot study was to evaluate whether various combinations of objective measures such as facial expression and physiological signals can be used to predict patient postoperative pain intensity when assisted by AI.

Materials and Methods

Study patients

This prospective randomized controlled trial was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-2205-757-304) and registered at ClinicalTrials.gov (NCT05477303). It was conducted in accordance with the principles of the Declaration of Helsinki, 2013. Patients with gastric cancer who underwent surgery from June 2022 to October 2022 were assessed for eligibility, and informed written consent was obtained from all participants.

The inclusion criteria were: age ≥ 18 years, scheduled to be admitted to the postanesthesia care unit (PACU) after surgery, and ASA physical status I–II. Patients with inability to communicate to report subjective pain, body mass index (BMI) > 35 kg/m² or < 18.5 kg/m², alcohol or drug dependency, severe or acute respiratory depression, and/or admission to the intensive care unit after surgery were excluded. Data on baseline characteristics of patients were extracted from electronic medical records. Before surgery, all patients were educated about the NRS pain assessment method. Fig. 1 presents the study flowchart.

General anesthesia

Noninvasive blood pressure, electrocardiography, pulse oximetry, and instantaneous ANI were measured upon arrival in the operating room. Anesthesia was induced with 1 mg/kg propofol and target-controlled remifentanil infusion at 3.0 ng/ml of effect site concentration and maintained with desflurane and remifentanil. Following recovery of consciousness and spontaneous breathing, extubation was performed, and patients were transferred to the PACU.

Data acquisition

One board-certified anesthesiologist captured the facial expressions of patients before surgery, immediately after entering the PACU, and before and after administering rescue analgesics (fentanyl) in the PACU using the camera of an iPhone XS™ (Apple Inc.) dedicated for this study, and saved the images as JPEG files. All facial expressions were captured from a front view at a consis-
tent distance of approximately 45–50 cm from the camera, with uniform camera settings (such as camera mode, exposure/focus, lens correction) to mitigate potential bias arising from variations in camera settings and facial expression capture methods. No cues or signals were given when taking the facial expression. The facial expression captured immediately after operating room entry before surgery was considered a zero-NRS score by default. The number of facial expressions captured per patient varied depending on the number of rescue analgesics required for each patient. Facial expressions were recorded both before and 10 min after administering rescue analgesics. Simultaneously, the patient was asked to state pain intensity using an 11-point NRS while the facial expression was noted.

At each assessment, vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were also recorded. Differences from the initial SBP, DBP, and HR before surgery were calculated and annotated as ΔSBP, ΔDBP, and ΔHR, respectively. In addition, using the ANI electrodes in V1 and V5 ECG positions, instantaneous ANI values were displayed on a stand-alone ANI monitor (MDoloris Medical System); the values were recorded at the time of assessment. Absolute ANI values and differences between the ANI values and the initial ANI value before anesthesia and operation (hereafter, ‘relative ANI value’) were used in the analysis.

**Feature extraction from facial expressions**

To construct ML models, various quantitative features such as appearance features, geometry features, and facial landmarks were extracted from each facial expression in addition to the action units using the OpenFace 2.0 toolkit, a popular open-source facial detection and analysis tool known for its robustness and performance. A total of 709 features (hereafter, ‘facial features’) were extracted from each facial expression, with a mean confidence level of 0.942 (0.118).

**ML model construction**

The NRS scores were first divided into two groups: NRS ≥ 7 and NRS < 7. The cut-off score for severe postoperative pain was defined as NRS ≥ 7 in accordance to previous guidelines for pain managements [23,24], and because patients with NRS ≥ 7 are administered fentanyl 50 μg in contrast to patients with 3 < NRS < 7 who are administered fentanyl 25 μg, according to the institu-
tional protocol. Additionally, as a pilot study, facial expressions, ANI, and vital signs in patients with severe pain were speculated to show greater differences than those obtained in patients with mild-to-moderate pain that would allow for a better evaluation of which AI-model would perform best at predicting the self-report ed pain intensity.

Out of the total 155 facial expressions, 95 and 60 were in the NRS ≥ 7 and NRS < 7 groups, respectively. Since imbalanced data-sets can introduce bias and impede the binary classifier model from learning the decision boundary, the synthetic minority over-sampling technique (SMOTE) algorithm [25] that generates synthetic data from the existing five neighboring data was used to generate synthetic facial features in the NRS < 7 group to match the number of facial features in the NRS ≥ 7 group (Fig. 2). The training and test sets were randomly split in a 7:3 ratio. Using forward feature selection (FFS) (hyperparameters: estimator = LinearRegression(); k features = 32 or 4 [32 for facial features and four for vital signs]; forward = true; floating = false; and scoring = r²) [25], 32 facial features were selected from 709 initial facial features, and four features were selected from six vital signs (SBP, DBP, HR, ΔSBP, ΔDBP, and ΔHR). A support vector machine (SVM) with a linear kernel was used to construct the ‘facial features model’ from 32 facial features and the ‘vital signs model’ from four vital signs features (hyperparameters: kernel = linear; probability = true). Similarly, FFS was used to select 32 features from 709 facial and six vital sign features to construct a ‘facial features + vital signs’ model. In addition, FFS was used to select four out of the six vital signs features and absolute ANI or relative ANI to construct ‘vital signs + absolute ANI’ and ‘vital signs + relative ANI’ models. Hyperparameter tuning for the SVM model was conducted using Scikit-learn’s GridSearchCV module, exploring variations in hyperparameters such as C, kernel, degree, gamma, shrinking, probability, tol, class_weight, verbose, decision_function_shape, and break_ties.

After constructing the five ML models, the best one was selected based on performance and compared to the absolute ANI and relative ANI models. For the absolute and relative ANI models, the threshold value was calculated based on the maximum Youden index. The performance of these three models was compared by applying them to all 155 datasets.

**Study outcomes**

The primary outcome was the performances of various ML models constructed using one or combinations of facial expression, vital signs, and ANI for predicting NRS ≥ 7. The secondary outcomes were correlation between absolute or relative ANI and NRS, as well as performances of absolute and relative ANI for predicting NRS ≥ 7.

**Implementation**

All codes were written and run in Google Colab (https://colab.research.google.com) that had 12 GB RAM and an NVIDIA Tesla

---

**Fig. 2.** Construction of ML model using facial expressions. NRS: numerical rating scale, ML: machine learning.
K80 GPU. Python 3.10.4 was used along with the following Python libraries: NumPy and Pandas that were used for data processing; Pillow was used for image processing; Imblearn was used to conduct SMOTE via minority sampling strategy; Scikit-learn was used to perform FFS and construct the SVM model; and Matplotlib and Seaborn were used for data visualization.

Sample size calculation

The required sample size for comparison under the area under the receiver operating characteristic curve (AUROC) was calculated as this metric was primarily used to compare the ML models. For the sample size calculation, a type I error (α) of 0.05 and type II error (β) of 0.20 (power of 80%) were used. The anticipated AUROC of our ML model was 0.65 and the AUROC of the null hypothesis was set to 0.50 because at this AUROC, there is no discriminative power to predict postoperative NRS, and a previous study reported AUROC of 0.53 at best for ML model based on facial expression action units [17]. We assumed an equal number of negative (NRS < 7) and positive (NRS ≥ 7) cases. Based on these parameters, the number of samples (facial expressions, the ANI, and vital signs) needed for the NRS < 7 and NRS ≥ 7 groups were 57 in each group, totaling 114 samples that is less than the number included in this study.

Statistical analyses

The Shapiro–Wilk test was used to evaluate normality. Non-normally distributed continuous variables are presented as median (Q1, Q3), and normally distributed continuous variables are presented as mean (standard deviation). Correlations between absolute or relative ANI and NRS was evaluated via the Spearman’s rank correlation analysis. Spearman’s ρ of 0–0.19, 0.20–0.39, 0.40–0.59, 0.60–0.79, and 0.80–1.0 represented very weak, weak, moderate, strong, and very strong correlations, respectively.

The performance and evaluation metrics of the proposed ML models were evaluated by calculating sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. AUROC was calculated and compared using DeLong’s test. Additionally, models’ sensitivities and specificities were compared via McNemar’s test. All statistical analyses were performed using Google Colab or SAS software (version 9.4; SAS Institute, Inc.). Two-sided P values < 0.05 were considered statistically significant.

### Results

Study participant characteristics

A total of 155 captured facial expressions, along with measurements of vital signs and ANI, were used for the final analysis. Among these, 95 were categorized to reflect postoperative pain intensities of NRS ≥ 7, while 60 were categorized as NRS < 7. Baseline characteristics of the study patients are listed in Table 1.

The median age of the patients who participated in this study was 64.5 (60.0, 69.0) years with twice as many men than women. Most patients (87%) underwent subtotal gastrectomy; the rest received total gastrectomy. The median length of stay in the PACU for patients was 36.5 (28.5, 45.5) min.

Performances of ML models

Five ML models were constructed, wherein two models were constructed using either facial features or vital signs only and three models were constructed using different combinations of ‘facial features + vital signs,’ ‘vital signs + absolute ANI,’ and ‘vital signs + relative ANI.’ The performances of these models are pre-

### Table 1. Patients’ Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>(n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.5 (60.0, 69.0)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>20 (67)/10 (33)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.1 (157.4, 167.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.6 (61.4, 71.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 (22.5, 27.0)</td>
</tr>
<tr>
<td>ASA PS (1/II)</td>
<td>6 (20)/24 (80)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Asthma</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Early gastric cancer</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Advanced gastric cancer</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>215.0 (180.0, 240.0)</td>
</tr>
<tr>
<td>Anesthesia time (min)</td>
<td>247.5 (210.0, 270.0)</td>
</tr>
<tr>
<td>Total remifentanil (µg)</td>
<td>493.0 (350.0, 649.0)</td>
</tr>
<tr>
<td>PACU time (min)</td>
<td>36.5 (28.5, 45.5)</td>
</tr>
<tr>
<td>PACU fentanyl (µg)</td>
<td>100 (50, 100)</td>
</tr>
<tr>
<td>Anti-emetics use</td>
<td>1 (3.3)</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or number (%). BMI: body mass index, ASA PS: American Society of Anesthesiologists physical status, PACU: postanesthesia care unit.

https://doi.org/10.4097/kja.23583
sented in Table 2. In the training set, the ‘facial features + vital signs’ model showed the highest AUROC (0.97), followed by the ‘facial features’ model (0.96) for predicting NRS ≥ 7, and the accuracies of both models were ≥ 0.90. Models built without facial features, including ‘vital signs,’ ‘absolute ANI + vital signs,’ and ‘relative ANI + vital signs’ showed AUROCs < 0.8, and were inferior to the above-mentioned models (P < 0.001, all). In the test set, the ‘facial features + vital signs’ and ‘facial features’ models again showed better accuracies and AUROCs than the other models for predicting NRS ≥ 7; but between the two models, the ‘facial features’ model showed non-significantly higher AUROC than the ‘facial features + vital signs’ model (0.93 vs. 0.84, P = 0.054). The receiver operating curves (ROCs) of the training and test sets are presented in Fig. 3, and the precision-recall curves of the training and test sets are shown in Supplementary Fig. 1. The Shapley Additive exPlanations summary plots showing the importance of features of the ML models are shown in Supplementary Fig. 2.

Performances of the best ML model vs. the ANI

Among the various ML models, the ‘facial features’ model was considered the best based on the highest accuracy and AUROC for predicting NRS ≥ 7 in the test set. Since the absolute and relative ANI alone may possibly be a better predictor of NRS ≥ 7 without combination to vital signs or facial features by ML, their performance in predicting NRS ≥ 7 was additionally explored.

The Spearman’s rank correlation analysis revealed significant but weak inverse correlations between the absolute ANI and NRS (p = –0.34, P < 0.001), and also between the relative ANI and NRS (p = –0.33, P < 0.001). The absolute and relative ANI showed a maximum AUROC of 0.69 and 0.68 at cutoff values of 42 and –14, respectively (Table 3). The calculated AUROCs of absolute and relative ANI were both significantly inferior to that of the ‘facial features’ ML model (P < 0.001). Their inferior AUROCs were due to significantly lower sensitivities: the sensitivities of absolute and relative ANI were 0.35 and 0.60, respectively, and less than the 0.91 of the ‘facial features’ ML model. Between the absolute and relative ANI, there was no difference in AUROCs for predicting NRS ≥ 7 (P = 0.824).

Discussion

Herein, we developed a number of ML models with various combinations of ‘facial features’ from facial expressions, vital signs, and either the absolute or relative ANI. In contrast to previous studies [16,17], all possible facial features including features relevant to appearance, geometry, and landmarks, in addition to

### Table 2. Comparison of Sensitivity, Specificity, PPV, NPV, and Accuracy of Various ML Models for Predicting NRS ≥ 7 Using the Training-and Test-Sets

<table>
<thead>
<tr>
<th>Data-set</th>
<th>Models</th>
<th>Sensitivity, 95% CI</th>
<th>Specificity, 95% CI</th>
<th>PPV, 95% CI</th>
<th>NPV, 95% CI</th>
<th>Accuracy, 95% CI</th>
<th>AUPRC, 95% CI</th>
<th>AUROC, 95% CI</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training set</td>
<td>‘Facial features’ model</td>
<td>0.986 (0.925, 0.998)</td>
<td>0.869 (0.762, 0.932)</td>
<td>0.899 (0.813, 0.948)</td>
<td>0.981 (0.902, 0.997)</td>
<td>0.932 (0.876, 0.964)</td>
<td>0.947 (0.893, 0.994)</td>
<td>0.961 (0.912, 0.987)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>‘Vital signs’ model</td>
<td>0.833 (0.731, 0.902)</td>
<td>0.590 (0.465, 0.705)</td>
<td>0.706 (0.602, 0.792)</td>
<td>0.750 (0.612, 0.851)</td>
<td>0.722 (0.640, 0.791)</td>
<td>0.727 (0.615, 0.833)</td>
<td>0.726 (0.642, 0.800)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>‘Facial features + vital signs’ model</td>
<td>0.944 (0.866, 0.978)</td>
<td>0.902 (0.802, 0.954)</td>
<td>0.919 (0.934, 0.962)</td>
<td>0.932 (0.838, 0.973)</td>
<td>0.925 (0.867, 0.959)</td>
<td>0.965 (0.912, 0.998)</td>
<td>0.974 (0.931, 0.994)</td>
<td>0.362</td>
</tr>
<tr>
<td></td>
<td>‘Absolute ANI + vital signs’ model</td>
<td>0.639 (0.524, 0.740)</td>
<td>0.622 (0.497, 0.734)</td>
<td>0.667 (0.549, 0.766)</td>
<td>0.594 (0.471, 0.705)</td>
<td>0.632 (0.547, 0.709)</td>
<td>0.825 (0.749, 0.888)</td>
<td>0.758 (0.676, 0.828)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>‘Relative ANI + vital signs’ model</td>
<td>0.694 (0.580, 0.789)</td>
<td>0.656 (0.530, 0.763)</td>
<td>0.704 (0.590, 0.800)</td>
<td>0.645 (0.521, 0.753)</td>
<td>0.677 (0.593, 0.730)</td>
<td>0.718 (0.544, 0.858)</td>
<td>0.743 (0.660, 0.815)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Test set</td>
<td>‘Facial features’ model</td>
<td>0.913 (0.732, 0.976)</td>
<td>0.824 (0.665, 0.917)</td>
<td>0.778 (0.592, 0.894)</td>
<td>0.933 (0.787, 0.982)</td>
<td>0.860 (0.747, 0.927)</td>
<td>0.899 (0.789, 0.975)</td>
<td>0.892 (0.828, 0.980)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>‘Vital signs’ model</td>
<td>0.696 (0.491, 0.844)</td>
<td>0.647 (0.479, 0.785)</td>
<td>0.571 (0.391, 0.735)</td>
<td>0.759 (0.579, 0.878)</td>
<td>0.667 (0.537, 0.775)</td>
<td>0.683 (0.487, 0.845)</td>
<td>0.723 (0.588, 0.833)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>‘Facial features + vital signs’ model</td>
<td>0.826 (0.629, 0.930)</td>
<td>0.853 (0.699, 0.936)</td>
<td>0.792 (0.595, 0.908)</td>
<td>0.879 (0.727, 0.952)</td>
<td>0.842 (0.727, 0.915)</td>
<td>0.764 (0.574, 0.929)</td>
<td>0.844 (0.724, 0.927)</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>‘Absolute ANI + vital signs’ model</td>
<td>0.696 (0.491, 0.844)</td>
<td>0.794 (0.632, 0.897)</td>
<td>0.696 (0.491, 0.844)</td>
<td>0.794 (0.632, 0.897)</td>
<td>0.754 (0.629, 0.848)</td>
<td>0.802 (0.635, 0.920)</td>
<td>0.816 (0.691, 0.906)</td>
<td>0.081</td>
</tr>
<tr>
<td></td>
<td>‘Relative ANI + vital signs’ model</td>
<td>0.565 (0.368, 0.744)</td>
<td>0.765 (0.600, 0.876)</td>
<td>0.619 (0.409, 0.792)</td>
<td>0.722 (0.560, 0.842)</td>
<td>0.684 (0.555, 0.790)</td>
<td>0.765 (0.656, 0.849)</td>
<td>0.730 (0.596, 0.839)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

PPV: positive predictive value, NPV: negative predictive value, ML: machine learning, NRS: numerical rating scale, AUPRC: area under the precision-recall curve, AUROC: area under the receiver operating characteristic curve, ANI: analgesia nociception index. *P value was computed by comparing the AUROC of the model to the AUROC of the ‘facial features’ model via DeLong’s test.
the action units, were used to construct the ML model; consequently, the ‘facial features’ model had higher accuracy in predicting postoperative pain than those reported by previous studies [16,17]. In addition, among the several ML models developed in this study, the ‘facial features’ model was best at predicting NRS ≥ 7. Herein, we even developed ML models that combined vital signs and the absolute/relative ANI, but their performances were inferior to that of the ‘facial features’ model. Furthermore, while absolute and relative ANI were significantly inversely correlated to the NRS, their individual ability to predict NRS ≥ 7 was inferior to the ‘facial features’ ML models.

To the best of our knowledge, this is the first study to use ML on the ANI to construct AI models for predicting postoperative pain. ANI is a 0–100 index derived from HR variability, and it measures parasympathetic tone as a surrogate for analgesia/nociception balance [26]. Studies have suggested that ANI is an objective and reliable indicator for predicting intraoperative pain [10,20,27]. Although its correlation has been weak when applied to conscious patients, a previous meta-analysis has reported the ANI to be more helpful when applied immediately after sedation or surgery [28]. To date, there is insufficient evidence to assess nociception or pain solely using ANI, especially in the awake state. However, the use of ANI as a non-invasive indirect measure of pain has received more attention in recent years [29]. Similar to our study, Boselli et al. [20] also evaluated ANI performance in predicting immediate postoperative pain in patients who were

Table 3. Comparison of Sensitivity, Specificity, PPV, NPV, and Accuracy between the Best ML Model (‘Facial Features’ Model) and Absolute ANI and Relative ANI

<table>
<thead>
<tr>
<th>Model</th>
<th>Sensitivity, 95% CI</th>
<th>Specificity, 95% CI</th>
<th>PPV, 95% CI</th>
<th>NPV, 95% CI</th>
<th>Accuracy, 95% CI</th>
<th>AUPRC, 95% CI</th>
<th>AUROC, 95% CI</th>
<th>P value*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Facial features' model</td>
<td>0.913 (0.732, 0.976)</td>
<td>0.824 (0.665, 0.917)</td>
<td>0.933 (0.592, 0.894)</td>
<td>0.860 (0.787, 0.982)</td>
<td>0.900 (0.747, 0.927)</td>
<td>0.949 (0.820, 0.969)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute ANI (≤ 42)</td>
<td>0.350 (0.231, 0.484)</td>
<td>0.979 (0.926, 0.997)</td>
<td>0.913 (0.719, 0.977)</td>
<td>0.705 (0.664, 0.742)</td>
<td>0.669 (0.659, 0.803)</td>
<td>0.687 (0.557, 0.765)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative ANI (≤ −14)</td>
<td>0.600 (0.465, 0.724)</td>
<td>0.768 (0.671, 0.849)</td>
<td>0.621 (0.518, 0.714)</td>
<td>0.753 (0.686, 0.809)</td>
<td>0.703 (0.625, 0.774)</td>
<td>0.677 (0.504, 0.748)</td>
<td>&lt; 0.001</td>
<td>0.824</td>
<td></td>
</tr>
</tbody>
</table>

PPV: positive predictive value, NPV: negative predictive value, ML: machine learning, ANI: analgesia nociception index, AUPRC: area under the precision-recall curve, AUROC: area under the receiver operating characteristic curve. *P value is computed by comparing two models (Absolute ANI [≤ 42], and Relative ANI [≤ −14]) to the ‘facial features’ model by DeLong’s test. †P value is computed by comparing Relative ANI (≤ −14) model to Absolute ANI (≤ 42) model by DeLong’s test.
initially induced using propofol. However, in our study, ANI performance was suboptimal compared to that of Boselli et al’s study [20]. Specifically, ANI specificity was better (absolute ANI, 0.98 in our study vs. Boselli et al. [20], 0.87), but the sensitivity was lower (absolute ANI, 0.35 vs. Boselli et al. [20], 0.89). Although this discrepancy may be attributed to the use of different pain thresholds (NRS ≥ 7 in our study vs. NRS ≥ 3 in the other study [20]), our results indicated that ANI may not effectively discriminate severe pain when applied to patients during the immediate postoperative period.

To overcome ANI shortcomings, the ML models that combined vital signs and absolute or relative ANI were constructed and explored. The performance of combined models was better than that of absolute or relative ANI alone, proving that combinations of physiological signals were more accurate than individual parameters for pain assessment. Still, our results indicated that the ML model based on facial expressions was more accurate than the ML model based on physiological signals for predicting severe postoperative pain.

Our ML model that utilized a diverse set of facial expression features had higher performance for predicting severe pain compared to models that primarily relied on action units [16,17]. Fontaine et al. [17] also used the OpenFace toolkit to extract action units, similar to our study. However, OpenFace extracts a maximum of 18 distinct action units, implying that models exclusively based only on it are inherently limited to employing a maximum of 18 variables. In addition, in another study by Sikka et al. [16], the model was constructed using 10 different action units and four additional facial features, including smile, yaw, pitch, and roll. In contrast, our approach involved the extraction of 709 distinct facial features, covering various aspects related to facial appearance, geometry, landmarks, and action units. From this extensive feature set, FFS was used to identify the 32 most relevant features for modeling. Upon closer examination, the majority of the 32 selected features were associated with facial appearance, geometry, and landmarks, while only a minority were related to action units. This finding demonstrated that while action units represent objective, anatomically based movements as defined by the Facial Action Coding System [18], they may not have captured the full spectrum of subtle changes in facial expression attributable to pain [17].

Interestingly, the ML model based on facial expressions performed better than the ML models that combined facial expressions and physiological signals (either vital signs or ANI). A possible explanation may be that acute postoperative pain is quickly manifested as drastic changes in the facial expression before being manifested as perturbations in the physiological signals. In addition, changes in the features of a facial expression had sufficient information for the ML model to identify patients with severe postoperative pain without the need for physiological signals. Based on these results, there is potential for an automated AI system to continuously monitor postoperative pain intensity through the facial expressions in the PACU. Whether the actual clinical application of AI can lead to an improved patient quality of recovery, and decrease the mundane task of repetitive pain assessments for anesthesiologists and nurses needs to be confirmed in future studies.

This study had several limitations. First, it was a single institutional prospective pilot study, and there may have been a selection bias. Second, facial features were extracted using OpenFace, one of several available facial detection and analysis tools, and the performance of the AI model may vary depending on the tool used for feature extraction. Third, the most commonly used self-reporting pain assessment tool, NRS, was used over other assessment tools, including the verbal rating scale and VAS; however, there is insufficient evidence to recommend a specific assessment over another in the postoperative period [7]. Finally, although we utilized a sufficient number of facial expressions, ANI, and vital signs to construct the ML model for comparing performances in predicting severe pain, a limited data-set was still used for training and test purposes in this pilot study.

In conclusion, the ML model based on facial expressions successfully predicted significant postoperative pain intensity (NRS ≥ 7) with high accuracy and outperformed the ML models based on physiological signals including the vital signs and ANI. The results of this study open up potential for future studies to investigate whether patient quality of recovery can be improved with the use of an AI model for faster pain recognition and management in the PACU.

Acknowledgements

We would like to thank Ingyeong Park for contributing to the development of the ML models.

Funding

None.

Conflicts of Interest

Jung-Hee Ryu has been an editor for the Korean Journal of Anesthesiology (KJA) since 2018 and Bon-Wook Koo has also been an editor for the KJA since 2023. However, they were not involved...
in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

**Data Availability**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Author Contributions**

Insun Park (Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing)
Jae Hyon Park (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing)
Jongjin Yoon (Formal analysis; Methodology; Visualization; Writing – review & editing)
Hyo-Seok Na (Writing – review & editing)
Ah-Young Oh (Writing – review & editing)
Junghee Ryu (Writing – review & editing)
Bon-Wook Koo (Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing)

**ORCID**

Insun Park, https://orcid.org/0000-0002-6413-752X
Jae Hyon Park, https://orcid.org/0000-0002-7626-194X
Jongjin Yoon, https://orcid.org/0000-0003-4733-7658
Hyo-Seok Na, https://orcid.org/0000-0003-0986-3243
Ah-Young Oh, https://orcid.org/0000-0002-3659-6171
Junghee Ryu, https://orcid.org/0000-0001-9331-5658
Bon-Wook Koo, https://orcid.org/0000-0002-3590-5542

**Supplementary Materials**

Supplementary Fig. 1. Precision-recall curves of various ML models for the (A) training set and (B) validation set as well as (C) precision-recall curves comparing the “facial features” ML model, Absolute ANI (≤ 42), and Relative ANI (≤ –14). ANI: analgesia nociception index, ML: machine learning.

Supplementary Fig. 2. SHAP summary plots showing importance of features for various ML models: (A) “Facial features” model, (B) “Vital signs” model, (C) “Facial features + vital signs” model, (D) “Absolute ANI + vital signs” model, and (E) “Relative ANI + vital signs” model. ML: machine learning, SHAP: Shapley Additive ex-Planations.

**References**

12. Ngiam KY, Khor IW. Big data and machine learning algorithms


Frequency domain analysis of photoplethysmographic and arterial pressure waveforms for assessing hemodynamics in children with congenital heart surgery

Hwa-Young Jang, In-Kyung Song, Sung-Hoon Kim, Won-Jung Shin

Department of Anesthesiology and Pain Medicine, Laboratory for Cardiovascular Dynamics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Time-domain parameters are less reliable in children due to increased arterial and chest wall compliance. We assessed the ability of indices derived from frequency analysis of photoplethysmography (PPG) and arterial blood pressure (ABP) waveforms to predict the hemodynamic state in children undergoing congenital heart surgery.

Methods: We analyzed waveforms after cardiopulmonary bypass period in 76 children who underwent total repair of congenital heart disease. Amplitude density of baseline and amplitude modulation in PPG and ABP by respiratory frequency were obtained using fast Fourier transform analysis and normalized by cardiac pulse height (representing respiratory modulations in venous blood [PPG-DC%] and in amplitude [PPG-AC%] at respiratory frequency). The ratio of amplitude density of PPG at the cardiac frequency (CF) to ABP-CF was used to assess vascular compliance. We assessed volume replacement (ml/kg) and vasoactive inotropic score (VIS).

Results: Children requiring volume replacement > 10 ml/kg (15.8%) showed higher PPG-DC% than those not requiring it (median: 52.4%, 95% CI [24.8, 295.1] vs. 36.7% [10.7, 125.7], P = 0.017). In addition, children with a VIS > 7 (22.4%) showed higher PPG-CF/ABP-CF (3.6 [0.91, 10.8] vs. 1.2 [0.27, 5.5], P = 0.008). On receiver operating characteristic curve analysis, PPG-DC% predicted a higher fluid requirement (area under the curve: 0.71, 95% CI [0.604, 0.816], P = 0.009), while PPG-CF/ABP-CF predicted a higher VIS (0.714, [0.599, 0.812], P = 0.004).

Conclusions: Frequency domain analysis of PPG and ABP may assess hemodynamic status requiring fluid or vasoactive inotropic therapy after congenital heart surgery.

Keywords: Cardiac surgical procedures; Cardiovascular agents; Child; Congenital; Fluid therapy; Hemodynamic monitoring; Photoplethysmography.
cause hyperdynamic outflow obstruction or afterload overloading [1,5]. Unfortunately, hemodynamic monitoring following congenital heart surgery in pediatric patients has been challenging.

Dynamic indices based on ventilation-induced fluctuations in arterial pressure or stroke volume have been established as predictors of fluid responsiveness in various clinical situations over the past two decades. Unlike adults, the increased compliance of arterial and chest walls in young infants contributes to inconclusive results in numerous studies investigating the reliability of dynamic indices [6,7]. The photoplethysmographic (PPG) waveform appears to be dependent on alterations in blood volume within peripheral blood vessels [8]. Considering that PPG is relatively unaffected by arterial and thoracic compliance, PPG indices, such as respiratory changes in PPG amplitude (ΔPOP) or pleth variability index (PVI), have been suggested. However, parameters derived from time-domain analysis, such as ΔPOP and PVI, are also limited in children [9].

Frequency-domain analysis of PPG has been introduced for the early detection of hypovolemia in children undergoing surgery [10,11]. The parameter of baseline modulation of PPG at respiratory frequency (PPG-amplitude density of baseline [DC]) reflects fluctuations in nonpulsatile venous blood volume and can be sensitive to intravascular reserve volume [10]. Additionally, it has been suggested that peripheral arterial compliance can be estimated by calculating the ratio of amplitude fluctuations in volume (PPG) at cardiac frequency (CF) (PPG-CF) to amplitude fluctuations in arterial blood pressure (ABP) at CF (ABP-CF) [12]. Frequency analysis of PPG variability can address the limitations of time-domain analysis by performing the analysis within a sufficiently large window to overcome artifacts and ragged variations.

Therefore, we aimed to investigate the feasibility of frequency-analyzed variables of PPG and ABP for predicting the requirement of fluid and vasoactive inotropic agents during the immediate postoperative period of congenital heart surgery in children.

Materials and Methods

Study design and subjects

This retrospective study utilized electronic medical records and a database of children under six years of age who underwent total repair of congenital heart defects with median sternotomy at a single tertiary institution between April 2019 and May 2020. Patients with incomplete data and those whose operations concluded with an open sternum were excluded. The study design was approved, and informed consent was waived by the local Institutional Review Board (Asan Medical Center, protocol number 2023-0489). The study was conducted in accordance with the Declaration of Helsinki, 2013 and its subsequent amendments.

General anesthesia and hemodynamic monitoring

As per the standardized protocol of our institution [13], all patients received an intravenous premedication with 0.5–1.0 mg/kg of midazolam upon entering the operating room. Anesthesia was induced using thiopental sodium (1.5–2.0 mg/kg) or ketamine (1–2 mg/kg), subsequent to midazolam (0.1–0.2 mg/kg), depending on the anesthesiologist’s judgment with clinical endpoints, such as loss of eyelash reflex. In patients where maintaining systemic vascular resistance is crucial, such as in cases of tetralogy of Fallot, anesthesia was induced with ketamine instead of thiopental. After endotracheal intubation facilitated by rocuronium, anesthesia was maintained through a continuous infusion of midazolam, remifentanil, and rocuronium.

Intraoperative routine monitoring included five-lead electrocardiography, pulse oximetry, ABP, central venous pressure, capnography, and regional oxygen saturation of the brain, kidneys, and intestines. All measurements collected from monitoring devices were recorded in the database using Vital Recorder that automatically records the physiological data of surgical patients in real-time (https://vitaldb.net) [14].

Management during the post-cardiopulmonary bypass period

The patient was successfully weaned from cardiopulmonary bypass after total corrective surgery, as confirmed by transesophageal echocardiographic evaluation performed by a pediatric cardiologist. Dopamine, epinephrine, and/or milrinone were administered if ventricular function was impaired based on transesophageal echocardiographic findings. Fluid replacement was also carried out when preload was insufficient. The hematocrit was maintained at 27%–30% through transfusion of leukocyte-filtered red blood cells. Mechanical ventilation was set at 8–10 ml/kg of expiratory tidal volume, and the respiratory rate was adjusted based on PaCO₂ and acid-base balance.

Frequency domain analysis of PPG and ABP

Waveforms of PPG and ABP were extracted during the post-cardiopulmonary bypass stage for a duration of 3 min, specifically between sternum closure and the end of surgery. We excluded data with poor signal quality, determined visually, and based on the PPG reliability index of 0.1 provided by the patient.
monitor (Intellivue™ Patient Monitor MP70, Philips Medizin Systeme Boeblingen GmbH). These waveforms were then analyzed using LabChart 7.37 (ADInstruments). Fast Fourier transform was applied for frequency-domain analysis of the waveforms, with the spectrum view set using the following parameters: spectrum, 4K (40 s at 100 Hz) Hamming window, amplitude density, and 93.75% overlap over a three-minute window [12]. Parameters of PPG and ABP were calculated following the method described by Alian et al. [10,12], and are presented as follows and shown in Fig. 1;

PPG-DC: This represents the amplitude density of the peak at the respiratory frequency on the spectrum derived from the analysis of baseline changes in raw PPG. It indicates the modulation of non-pulsatile venous blood volume (Figs. 1A, C and E).

ABP-DC: This indicates the amplitude density of the peak at the respiratory frequency on the spectrum derived from ABP analysis, known as mean arterial pressure modulation (Figs. 1B, D and F).

PPG-AC: This signifies the amplitude density of the peak at the respiratory frequency on the spectral analysis of PPG pulse height, demonstrating the modulation of PPG amplitude corresponding to ΔPOP by time-domain analysis (Figs. 1G, I and K).

ABP-AC: This denotes the amplitude density of the peak at the respiratory frequency on the spectrum of pulse pressure analysis, corresponding to pulse pressure variation by time-domain analysis (Figs. 1H, J and L).

For intraindividual normalization of DC and AC parameters, all variables were divided by the amplitude density of the peak at the CF (cardiac pulse height) on the spectrum of each waveform analysis. Each normalized parameter was expressed as a percentage (DC% and AC%) (Fig. 1).

Peripheral vascular compliance was estimated by calculating the ratio of the PPG-CF to the ABP-CF; Peripheral vascular compliance = PPG-CF/ABP-CF).

**Postoperative outcomes**

All patients were managed according to the protocol under the supervision of the intensive care specialist from the Department of Pediatric Cardiac Surgery. The total volume of albumin, red blood cells, and fresh frozen plasma administered within 2 h after arrival in the intensive care unit (ICU) was measured, excluding the total volume of crystalloids. The volume replaced in the ICU was divided by the patient's weight (ml/kg). The maximal dosages of vasoactive inotropic agents during the first two hours in the ICU were recorded, and the vasoactive inotropic score (VIS) was calculated using the formula: VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (units/kg/min) + 100 × norepinephrine dose (μg/kg/min) [15]. Additionally, the durations of mechanical ventilation and ICU stay were obtained.

**Statistical analyses**

The data were presented as the median with interquartile range (IQR) or median with 95% CI. Fisher’s exact test was used for categorical variables, while the Mann–Whitney U test was applied for continuous variables to compare between the two groups. Associations among frequency domain variables were determined using Pearson correlation after log-transforming non-normally distributed variables before analysis.

Higher requirements of fluid and vasoactive inotropic agents were defined as a volume of fluid > 10 ml/kg and VIS > 7, respectively. These outcomes were dichotomized using cutoff values based on the third quartile of each variable. Patients meeting the cutoff value (fluid = 10 ml/kg and VIS = 7) were classified into the group with lower requirements. The predictive abilities of frequency domain-derived parameters for a higher requirement of fluid and vasoactive inotropic agents were assessed using receiver operating characteristic (ROC) analysis. The areas under the curves (AUCs) were compared across different variables, and optimal thresholds were determined.

All statistical analyses were performed using the R statistical package system version 4.2.0 (GNU General Public License, Copyright Free Software Foundation, Inc. https://www.r-project.org/), employing the ggplot2 (github.com/tidyverse/ggplot2) and plotROC (https://sachsmc.github.io/plotROC/) packages. A P value < 0.05 was considered statistically significant.

**Results**

The final analysis included data from 76 patients. The demographic characteristics and data derived from the frequency domain analysis are summarized in Table 1. Ventricular septal defect was the most frequently diagnosed condition, followed by tetralogy of Fallot (Supplementary Table 1). The median fluid amount administered during the 2 h after ICU admission was 8 ml/kg (0, 10), and the median VIS was 5 (1.5, 7). Pulmonary hypertension was observed in 19.7% of cases, predominantly attributed to ventricular septal defects with right-to-left shunts (Supplementary Table 1). Patients with pulmonary hypertension exhibited longer mechanical ventilation periods and ICU stays compared to those without it; however, no significant differences were observed in
Fig. 1. Waveforms of PPG and ABP extracted during the post-cardiopulmonary bypass period and frequency analysis of each parameter. Low-pass filter (< 0.8 Hz) is applied to the raw PPG and ABP waveforms (A and B) for extracting respiratory-induced baseline modulation (C and D). Using fast Fourier transformation of these waveforms, the DC component at respiratory frequency and pulse height peak at CF can be obtained (E and F). Corresponding to the changes in the PPG amplitude and pulse pressure (G and H), respiratory-induced height modulation is obtained using high-pass filter (≥ 0.8 Hz) (I and J) on the raw PPG and ABP waveforms. The AC peak at the respiratory frequency (K and L) is obtained using the same method as described above. ABP: arterial blood pressure, AC: amplitude modulation at respiratory frequency, Au: arbitrary unit, CF: cardiac frequency, DC: baseline modulation at respiratory frequency, PPG: photoplethysmography. All variables are normalized by dividing the DC and AC parameters by the amplitude density of pulse height at CF of raw PPG and ABP waveforms (DC% and AC%). The meanings of each are as follows. PPG-DC%: modulation of non-pulsatile venous blood volume, ABP-DC%: mean arterial pressure modulation, PPG-AC%: corresponding respiratory changes in PPG amplitude by time-domain analysis, ABP-AC%: corresponding to pulse pressure variation by time-domain analysis.

other variables (Supplementary Table 2). Among patients with concomitant pulmonary hypertension, two cases (2/15) demonstrated a higher requirement for fluid, and their PPG-DC% values were 93.8% and 99.1%, respectively, higher than patients with lower fluid requirements. Additionally, peripheral vascular compliance was higher in patients with high VIS in the presence of pulmonary artery hypertension, with a median value of 5.0, compared to that in patients with low VIS (Supplementary Table 3).

Patients who received fluid > 10 ml/kg (n = 12, 15.8%) did not show significant differences in demographics and postoperative
### Table 1. Patient Characteristics and PPG and ABP Derived Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 76)</th>
<th>Fluid replacement in ICU</th>
<th>VIS in ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤ 10 ml/kg (n = 64)</td>
<td>&gt; 10 ml/kg (n = 12)</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>4.0 (3.0, 12.5)</td>
<td>4.0 (2.9, 13.0)</td>
<td>4.0 (3.0, 4.5)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>42 (55.3)</td>
<td>33 (51.6)</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>6.5 (5.0, 9.0)</td>
<td>6.6 (4.9, 9.0)</td>
<td>6.4 (5.1, 7.1)</td>
</tr>
<tr>
<td>Intraoperative variables before leaving the operating room</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>152 (138, 170)</td>
<td>152 (140, 167)</td>
<td>160 (134, 175)</td>
</tr>
<tr>
<td>Systolic ABP (mmHg)</td>
<td>93 (82, 100)</td>
<td>93 (82, 102)</td>
<td>88 (83, 98)</td>
</tr>
<tr>
<td>Diastolic ABP (mmHg)</td>
<td>51 (45, 56)</td>
<td>51 (45, 56)</td>
<td>52 (48, 56)</td>
</tr>
<tr>
<td>Tidal volume (ml/kg)</td>
<td>9.3 (8.7, 9.8)</td>
<td>9.3 (8.7, 9.8)</td>
<td>9.3 (9.0, 9.8)</td>
</tr>
<tr>
<td>Peak inspiratory pressure (cmH₂O)</td>
<td>18 (17, 20)</td>
<td>18 (17, 20)</td>
<td>18 (18, 20)</td>
</tr>
<tr>
<td>Respiratory rate (/min)</td>
<td>25 (22, 27)</td>
<td>25 (22, 28)</td>
<td>24 (21, 26)</td>
</tr>
<tr>
<td>ABP-AC%</td>
<td>13.8 (9.0, 20.4)</td>
<td>13.6 (9.0, 19.7)</td>
<td>20.3 (9.2, 27.0)</td>
</tr>
<tr>
<td>ABP-DC%</td>
<td>18.0 (13.9, 25.0)</td>
<td>17.6 (13.1, 24.7)</td>
<td>23.1 (15.0, 29.4)</td>
</tr>
<tr>
<td>PPG-AC%</td>
<td>20.4 (12.1, 34.7)</td>
<td>18.4 (11.7, 30.5)</td>
<td>37.6 (21.9, 90.1)*</td>
</tr>
<tr>
<td>PPG-DC%</td>
<td>39.5 (24.3, 35.0)</td>
<td>36.7 (23.5, 50.7)</td>
<td>52.4 (40.9, 96.5)*</td>
</tr>
<tr>
<td>Compliance (PPG-CF/ABP-CF)</td>
<td>1.3 (0.9, 2.1)</td>
<td>1.3 (0.9, 2.1)</td>
<td>1.6 (1.1, 6.2)</td>
</tr>
<tr>
<td>Variables within the first 2 h after ICU admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>157 (146, 172)</td>
<td>157 (148, 170)</td>
<td>163 (138, 177)</td>
</tr>
<tr>
<td>Systolic ABP (mmHg)</td>
<td>114 (92, 126)</td>
<td>116 (98, 128)</td>
<td>98 (90, 124)</td>
</tr>
<tr>
<td>Diastolic ABP (mmHg)</td>
<td>64 (52, 72)</td>
<td>65 (52, 74)</td>
<td>57 (50, 68)</td>
</tr>
<tr>
<td>Fluid replacement (ml/kg)</td>
<td>8.1 (0.0, 10.0)</td>
<td>5.6 (0.0, 9.7)</td>
<td>14.8 (13.2, 16.0)*</td>
</tr>
<tr>
<td>VIS</td>
<td>5.0 (1.5, 7.0)</td>
<td>5.0 (1.5, 7.0)</td>
<td>5.0 (1.5, 7.1)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV duration (h)</td>
<td>16 (12, 43)</td>
<td>18 (12, 44)</td>
<td>16 (14, 20)</td>
</tr>
<tr>
<td>ICU stays (d)</td>
<td>2 (1, 3)</td>
<td>2 (1, 3)</td>
<td>1 (1, 2)</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or number (%). PPG: photoplethysmography, ABP: arterial blood pressure, ICU: intensive care unit, VIS: vasoactive inotropic score, AC: amplitude modulation at respiratory frequency, DC: baseline modulation at respiratory frequency, CF: cardiac frequency, MV: mechanical ventilation. For intraindividual normalization of DC and AC parameters, all frequency domain parameters are divided by the amplitude density of the peak at the CF on the spectrum of each waveform analysis. Each normalized parameter was expressed as a percentage (DC% and AC%). *P < 0.05.

Outcomes were compared to those who received fluid ≤ 10 ml/kg. However, PPG-AC% and PPG-DC% in patients with a higher requirement of fluid were significantly higher compared to that in patients who did not have a higher requirement (PPG-AC%: median 37.6%, 95% CI [5.6, 202.6] vs. 18.4 [3.5, 95.3], P = 0.022; PPG-DC%: 52.4 [24.8, 295.1] vs. 36.7 [10.7, 125.7], P = 0.017), while there was no difference in ABP-AC% and ABP-DC% (Table 1). Among patients with a higher VIS (> 7) (n = 17, 22.3%), significant differences were observed—they were notably younger and had longer durations of mechanical ventilation and ICU stay. During the first 2 h after ICU admission, lower systolic and diastolic ABP were observed. Peripheral vascular compliance was significantly higher in patients with VIS > 7 compared to that in patients with VIS ≤ 7 (median: 3.6, 95% CI [0.91, 10.8] vs. 1.2 [0.27, 5.5], P = 0.008) (Table 1).

The DC% of PPG and ABP showed a high correlation with the AC% of PPG and ABP, respectively (r = 0.645, P < 0.001 and r = 0.893, P < 0.001). Although the correlation between PPG and ABP was statistically significant for DC% and AC%, the correlation coefficient was relatively low. Linear correlation between frequency domain variables and fluid requirements or VIS was not statistically significant (Fig. 2). ROC curve analysis revealed that the AUC of PPG-DC% was the greatest for predicting a higher requirement of fluid (AUC: 0.719, 95% CI [0.604, 0.816], P = 0.005).
0.009), with a cutoff value > 39.7%. PPG-AC% also had a significant AUC (0.710, 95% CI [0.594, 0.808], P = 0.036), with a cutoff value > 29.7% (Figs. 3A and B). However, ABP-AC% and ABP-DC% did not show significance in predicting fluid requirements (Figs. 3C and D). Peripheral vascular compliance > 2.9 predicted a VIS > 7 with an AUC of 0.714 (95% CI [0.599, 0.812], P = 0.004) (Fig. 4).

A representative example is shown in Fig. 5. There was a significant difference in PPG-DC% and PPG-AC% between patients who received a larger volume of fluid and those who did not. On the other hand, the difference in ABP-DC% and ABP-AC% was not significant (Fig. 5).

**Discussion**

The present study showed that the frequency domain analysis of PPG and ABP waveforms can predict the requirement of fluid by providing information on the fluctuation in intravascular volume according to ventilation. Specifically, we found that the baseline modulation of PPG (PPG-DC%) was a more reliable predictor of fluid requirement compared to that in ABP-derived indices. Waveforms of PPG can be distinguished from waveforms of ABP in that a pulse of PPG reflects a change in blood volume within the peripheral blood vessels beneath the pulse oximetry sensor [8]. Based on the principles of pulse oximetry, baseline modulation refers to

---

**Fig. 2.** Scatter plots of correlations of each pair of AC% and DC% of PPG and ABP. The DC% of PPG and ABP showed a high correlation with the AC% of PPG and ABP, respectively. All variables are logarithmic transformed for diagonal distribution with Pearson correlation. ABP: arterial blood pressure, AC: amplitude modulation at respiratory frequency, Corr: correlation coefficient, DC: baseline modulation at respiratory frequency, PPG: photoplethysmography. *P < 0.001. For intraindividual normalization of DC and AC parameters, all frequency domain parameters are divided by the amplitude density of the peak at the cardiac frequency on the spectrum of each waveform analysis (DC% and AC%).

---

https://doi.org/10.4097/kja.23433
changes in non-pulsatile venous blood volume, while modulation of the cardiac pulse reflects changes in arterial blood volume, represented by PPG-DC% and PPG-AC%, respectively [10,12]. In this study, the correlation between PPG and ABP was statistically significant for DC% and AC%; however, the correlation coefficient was relatively low. This can be attributed to the difference in what PPG and ABP represent. PPG reflects changes in blood volume, whereas ABP reflects changes in pressure as represented by each
creased vascular compliance. ABP-derived dynamic indices can be mainly explained by intravascular volume status. In children, the unreliability of arterial pulsation, and PPG-DC%, indicating venous reserve, may serve volume will decrease first to maintain effective circulating volume in the arterial system. Additionally, it is known that the AC component of PPG varies depending on the vascular compliance affected by the sympathetic tone. Therefore, fluctuations in peripheral venous volume occur earlier than those in arterial pulsation, and PPG-DC%, indicating venous reserve, may be more predictable for the early detection of hypovolemia compared to PPG-AC%.

In contrast, ABP waveforms are formed by changes in pressure. As pressure is influenced by heart rate and vascular resistance/compliance, as well as volume, oscillation in ABP solely reflects intravascular volume status. In children, the unreliability of ABP-derived dynamic indices can be mainly explained by increased vascular compliance [17,18]. Theoretically, the non-pulsatile venous blood volume of baseline modulation of PPG is nearly impervious to local vascular compliance [16,19]. Therefore, ABP-DC% and ABP-AC% may be insufficient as indices for predicting fluid responsiveness (Fig. 5).

Frequency domain analysis using the fast Fourier transform allows us to isolate oscillations in waveforms at specific frequencies. This method enables the quantification of oscillatory magnitude at cardiac or respiratory frequencies, as needed. Particularly for young infants with rapid respiratory rates, low tidal volume, and subtle changes in low amplitude, spectral analysis may be a preferable method for integrating changes across a time window sufficient to reflect heart-lung interaction.

Arterial compliance can be calculated from the pressure-volume relation that is defined as volume divided by pressure. Similarly, peripheral vascular compliance, as determined by the frequency domain analysis, is regarded as the ratio of the amplitude density of PPG at the CF (PPG-CF, corresponding to Δ volume) to the amplitude density of ABP at the CF (ABP-CF, corresponding to Δ pressure) [12,20]. Previous reports have demonstrated substantial changes in peripheral vascular compliance derived from PPG in patients with pheochromocytoma under the influence of vasodilators (e.g., nitroprusside) or surgical stimulation [12].

In the current study, we established the cutoff values for higher requirements of fluid and vasoactive inotropic agents using the third quartile of each variable. While there are limited studies on higher fluid requirement in children immediately after cardiac surgery, one study showed that the median fluid bolus dose in a cardiac ICU for children with hypotension was 5 ml/kg [21]. Although the cutoff values were derived from our study’s dataset, they may be broadly applicable, as most studies investigating fluid responsiveness have selected a fluid bolus dose of 10 ml/kg [6]. Regarding higher VIS, it has been reported that VIS > 5–10 is associated with postoperative outcomes [22,23].

Patients with higher VIS experienced a more prolonged duration of mechanical ventilation and ICU stay compared to those with lower VIS. This finding can be explained by the observation that younger patients, including neonates, are more susceptible to cardiovascular dysfunction immediately after cardiopulmonary bypass [24]. Consequently, they require a higher dose of vasoactive inotropic agents to maintain hemodynamic stability. Intraoperative ABP just before leaving the operating room did not differ between patients with higher VIS and lower VIS, whereas peripheral vascular compliance was significantly different between the two groups. This result supports the hypothesis that PPG-CF/ABP-CF, as an index reflecting early changes in vascular compliance, could help determine whether the addition of vasoactive inotropic agents is needed to maintain adequate ABP.
In our study, approximately 20% of patients had pulmonary hypertension. Among infants undergoing congenital heart surgery, ventricular septal defects with unrestricted left-to-right shunts were the most common. These patients often experience impaired cardiac function immediately after surgery, requiring caution in fluid administration. However, conventional indicators are known to be less reliable in cases of right ventricular dysfunction or pulmonary hypertension due to the influence of the heart-lung interaction [25,26]. Considering the possible impact of the cardiac-pulmonary interaction on the waveform changes of PPG and ABP in our study, careful interpretation is necessary. In this study, statistical significance in the sub-group analysis of pulmonary hypertension couldn’t be reasonably assured due to the small sample size. Nevertheless, among patients with pulmonary hypertension, those requiring higher fluid showed elevated PPG-DC% and the high VIS group exhibited increased peripheral vascular compliance. These findings support the fact that PPG-DC% may be less affected by right ventricular dysfunction or pulmonary hypertension compared to other indicators, as it reflects the reserve of basal venous blood flow. However, a fluid challenge may not induce an increase in the LV preload and stroke volume since the venous return into the right heart with pulmonary hypertension may not produce adequate ejection to the left heart [26]. Further research is needed to investigate the predictability of fluid responsiveness using frequency domain analysis of PPG in patients with right ventricular dysfunction, including pulmonary hypertension.

This study has some limitations. Firstly, we investigated the abilities of the frequency domain variables from PPG and ABP waveform analysis to predict hypovolemia or increased vascular tone in advance. Additionally, this study was performed retrospectively that inherently limited our control over intraoperative and postoperative management, despite having a predefined and standardized protocol. Therefore, prospective studies are needed to elucidate the reliability of frequency domain variables as functional hemodynamic monitoring tools, by directly measuring changes in cardiac output or vascular compliance in response to fluid/drug challenges. Secondly, there is currently no known method to calibrate one's PPG waveform for inter-personal com-

![Fig. 5. Representative waveforms of PPG and ABP. One patient who postoperatively received 26.5 ml/kg of fluid shows markedly higher values of PPG-DC% and PPG-AC% than a patient with the fluid requirement of 1.7 ml/kg. In comparison with PPG variables, ABP-DC% and ABP-AC% are not significantly different between the two patients. PPG: photoplethysmography, DC: baseline modulation at respiratory frequency, AC: amplitude modulation at respiratory frequency, ABP: arterial blood pressure. For intraindividual normalization of DC and AC parameters, all frequency domain parameters are divided by the amplitude density of the peak at the cardiac frequency on the spectrum of each waveform analysis (DC% and AC%).](https://doi.org/10.4097/kja.23433)
parison using absolute values. Moreover, commercial pulse oximetry devices have functions such as auto-gain and filtration to optimize PPG display [27]. Therefore, we applied normalization of parameters derived from PPG fluctuations by dividing the amplitude of the cardiac pulse [10]. This method has been previously employed in known time-domain variables such as ΔPOP and pulse pressure variation by dividing the differences in the maximum and minimum amplitude by the average value of the maximum and minimum amplitude [28]. In addition, rapid changes in the body temperature related to cardiopulmonary bypass can lead to differences between the central and peripheral blood pressure. Even though the difference between the central and peripheral pressures is less significant in infants compared to adults, it may not be eliminated [29]. Therefore, ABP-derived dynamic indices that are primarily influenced by vascular compliance may be less reliable immediately after cardiopulmonary bypass. The vasomotor changes that occur immediately after cardiopulmonary bypass also affect the PPG waveform [8,30]. To minimize this effect, we used PPG waveforms obtained stably at normal body temperature during skin closure. Additionally, we excluded the data considering poor signal quality based on the PPG reliability index.

In children immediately after cardiopulmonary bypass for congenital heart surgery, determining whether the patient requires fluid or vasoactive inotropic agents when hemodynamic instability occurs is crucial. Our study demonstrated that increased respiratory baseline modulation in PPG waveforms (PPG-DC%) is a more reliable predictor of fluid requirements compared to ABP-derived parameters. In addition, vascular compliance, assessed using frequency domain analysis of PPG and ABP (PPG-CF/ABP-CF), can predict the immediate postoperative need for vasoactive inotropic drugs. Current PPG waveform monitoring provides information such as arterial oxygen saturation and PVI. However, by incorporating spectrogram analysis through software or algorithms into existing monitoring systems, real-time changes in the PPG waveform according to respiration can be easily visualized, making it applicable in clinical settings. Further studies are needed to validate whether frequency domain variables of PPG and ABP could be considered as indices reflecting the response of stroke volume to the fluid challenge using echocardiography, and to establish applicable methods for timely resuscitation in clinical practice.

Funding

This study was partly supported by the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare of the Republic of Korea (HR20C0026). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Conflicts of Interest

Won-Jung Shin has been an editor for the Korean Journal of Anesthesiology since 2018. However, she was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Hwa-Young Jang (Data curation; Writing – original draft)
In-Kyung Song (Data curation; Interpretation of data)
Sung-Hoon Kim (Data curation)
Won-Jung Shin (Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing)

ORCID

Hwa-Young Jang, https://orcid.org/0000-0002-0864-9571
In-Kyung Song, https://orcid.org/0000-0002-7699-2005
Sung-Hoon Kim, https://orcid.org/0000-0001-5215-7585
Won-Jung Shin, https://orcid.org/0000-0002-6790-3859

Supplementary Materials

Supplementary Table 1. Diagnosis of congenital heart disease according to the presence of pulmonary hypertension.
Supplementary Table 2. Patient characteristics and hemodynamic parameters based on the presence of pulmonary hypertension.
Supplementary Table 3. Comparison of hemodynamic parameters derived from frequency analysis in relation to fluid requirement and VIS, based on the presence of pulmonary hypertension.

References


Postoperative alterations in ventriculoarterial coupling are an indicator of cardiovascular outcomes in liver transplant recipients

Ji Yeon Kim¹, Young-Jin Moon², Changjin Lee³, Jin Ho Kim³, Junghyun Park³, Jung-Won Kim⁴

Department of Anesthesiology and Pain Medicine, ¹CHA Gangnam Medical Center, CHA University School of Medicine, ²Laboratory for Cardiovascular Dynamics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, ³CHA Bundang Medical Center, CHA University School of Medicine, ⁴Laboratory for Cardiovascular Dynamics, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

Background: Liver transplantation (LT) increases the heart and vessel workload in patients with cirrhotic cardiomyopathy. While the interaction of the left ventricle (LV) with the arterial system (ventriculoarterial coupling, VAC) is a key determinant of cardiovascular performance, little is known about changes in VAC after LT. Therefore, we evaluated the relationship between VAC after LT and cardiovascular outcomes.

Methods: 344 consecutive patients underwent echocardiographic assessments before and within 30 days after LT. Non-invasive arterial elastance (Eₐ), LV end-systolic elastance (Eₚₑₛₑ), and LV end-diastolic elastance (Eₚₑ₅₀) were calculated. The postoperative outcomes included the development of major adverse cardiovascular events (MACE) and the length of stay in the intensive care unit and hospital.

Results: A total of 240 patients were included in the analyses. After LT, Eₐ increased by 16% (P < 0.001), and Eₚₑₛₑ and contractility index of systolic velocity (S') increased by 18% (P < 0.001) and 7% (P < 0.001), respectively. The Eₚₑ₅₀ increased by 6% (P < 0.001). The VAC remained unchanged (0.56 to 0.56, P = 0.912). Of these patients, 29 had MACE, and those with MACE had significantly higher postoperative VAC. Additionally, a higher postoperative VAC was an independent risk factor for a longer postoperative hospital stay (P = 0.038).

Conclusions: These data suggest that ventriculoarterial decoupling is associated with poor postoperative outcomes after LT.

Keywords: Cardiomyopathies; Echocardiography; Left ventricular dysfunction; Liver cirrhosis; Liver transplantation; Postoperative complications.

Introduction

Patients with end-stage liver disease frequently have cardiovascular dysfunction, termed cirrhotic cardiomyopathy [1] that is characterized by an impaired contractile response to stress. The cause of cirrhotic cardiomyopathy is unclear; however, this syndrome is considered to be related to both portal hypertension and cirrhosis [2]. Advanced liver disease is associated with a hyperdynamic circulatory state characterized by high cardiac output and low systemic vascular resistance [3]. Furthermore, arterial compliance is directly related to cirrhosis severity and hyperdynamic circulatory derangement. Although liver transplantation (LT) is known to reverse cardiovascular dysfunction within
6–12 months [4], progression of pre-existing or new-onset cardiac events has been reported[5], possibly due to acute changes in loading conditions in the immediate postoperative period.

The left ventricular (LV) pressure–volume relationship, estimated from echocardiographic measurements, has been proposed to assess the interaction between the arterial and ventricular systems [6]. Ventriculoarterial coupling (VAC) is defined as the ratio of arterial elastance (Ea) to LV end-systolic elastance (Ees). Suga [6] first proposed the use of VAC to evaluate interactions between cardiac performance and vascular function. Although the interaction of the left ventricle (LV) with the arterial system, or VAC, is a key determinant of cardiovascular performance [7], little is known about the changes in Ee, Ea (stiffness), and VAC (Ea/Ees) after LT. Therefore, we evaluated the Ee, Ea, and Ea/Ees ratios in patients undergoing LT, as well as alterations in these parameters immediately after LT. Furthermore, we examined whether decoupling the ventriculoarterial relationship was associated with postoperative complications and length of hospital stay.

Materials and Methods

Patients

This study was a retrospective analysis of prospectively collected data and was approved by Asan Medical Center Institutional Review Board (2015-0060). The electronic medical records of 344 patients who underwent living- or deceased-donor LT between January and December 2012 were reviewed. Data from 104 patients were excluded because two patients had valvular heart disease, four patients had chronic renal disease, 80 patients did not undergo preoperative or postoperative transthoracic echocardiography (TTE), and 18 patients underwent postoperative echocardiography for more than 30 days after LT. Finally, 240 patients were enrolled in the analyses. The use of diuretics or beta-blockers was continued if they were used at the time of admission.

Pre- and post-transplant echocardiographic measurements

TTE was routinely performed twice, preoperatively and postoperatively within 30 days before discharge, in LT recipients. Patients who had undergone TTE at the time of deterioration were excluded. We only included results from routine TTE performed in the echocardiography laboratory. The ventricular dimensions, wall thickness, and chamber volume were determined using two-dimensional echocardiography. Blood pressure (BP) was measured using sphygmomanometry simultaneously during TTE or as the average of the same day. End-systolic pressure (ESP) was estimated from the product of 0.9 × systolic blood pressure (SBP) [7]. The apical four-chamber LV end-diastolic volume (EDV), end-systolic volume (ESV), and stroke volume (SV) were determined using the Teichholz method or modified Simpson’s method. The E/A ratio was measured using pulsed-wave Doppler examination of the mitral inflow. E’ is the mitral septal annulus early diastolic velocity, and systolic velocity (S) is the index of contractility obtained by tissue Doppler imaging. The ratio of early mitral peak velocity to tissue Doppler early mitral annular velocity (E/E’ was used to estimate LV end-diastolic pressure (LVEDP), as previously validated ( = 11.96 + 0.596 × E/E’) [8].

LV pressure–volume relationships

To evaluate the ESP–volume relationships non-invasively, we used a modified single-beat method [6]. LV end-diastolic chamber stiffness (end-diastolic elastance, Ees) was estimated from the ratio of the LVEDP to the EDV [9]. The effective Ees that is a measure of the total arterial load was estimated using the ESP/SV ratio [7]. Although Ees is a useful load-independent index of LV contractility, it may be influenced by cardiac chamber remodeling and geometry [7]. Ea can be calculated by ESP/(ESV - Vao), assuming that Vao is negligible compared to ESV. The Ea/Ees ratio is an interaction between the LV and the arterial system and is used to assess VAC. The SV/pulse pressure (PP) ratio was measured and used to estimate the total arterial compliance (TAC) [10].

Postoperative outcomes

Postoperative outcomes included the development of major adverse cardiovascular events (MACE) and length of stay in the intensive care unit (ICU) and hospital. MACE included cardiovascular complications, such as non-fatal myocardial infarction (indicated in the medical records, by electrocardiographic findings, and elevated troponin I levels > 0.2 ng/ml), serious arrhythmia (atrial fibrillation with rapid ventricular response, ventricular tachycardia, or ventricular fibrillation), new-onset or aggravated heart failure, or cardiac death during the postoperative period [11]. New-onset or aggravated heart failure was clinically defined as the presence of at least two symptoms of heart failure (paroxysmal nocturnal dyspnea, orthopnea, lower extremity edema, and shortness of breath) in addition to one clinical feature (jugular venous distension and pulmonary rales) and either an elevated brain natriuretic peptide level > 100 pg/ml or chest X-ray findings of pulmonary edema [5].
Statistical analyses

Data are expressed as means and standard deviations or medians and ranges, as appropriate. Categorical data are expressed as counts and percentages. Differences between the preoperative and postoperative TTE examinations were assessed using paired t-tests. Pearson’s correlation analysis was performed between E\textsubscript{a} and other vascular parameters, E\textsubscript{es} and other parameters of LV contractility.

Univariate linear regression analysis was performed to determine the factors associated with the development of MACE and prolonged postoperative hospital stay. The development of MACE was divided into two groups, and the length of postoperative hospital stay was categorized into two groups according to their 90th percentile value. The two groups were then compared using paired t-tests. Covariates with a value of P < 0.1 by univariate analysis, were included in multivariate linear regression analyses (forward step). Statistical significance set at P < 0.05 was considered significant. Analyses were performed using SPSS version 21.0 (IBM Corp.) and SigmaPlot (version 12.0; Systat).

Results

None of the patients received inotropic agents or vasopressors preoperatively. The baseline characteristics of the 240 patients are summarized in Table 1.

All patients underwent echocardiography within 30 postoperative days (16 [14, 19]) before discharge from the hospital. After LT, the ESP was elevated from 98 ± 12 to 107 ± 14 (P < 0.001) and was associated with an increase in LV mass index. Cardiac volume decreased, as evidenced by left atrial volume (P < 0.001), LV ESV (P = 0.010), LV EDV (P = 0.001), and SV (P = 0.001) (Table 2).

E\textsubscript{a} was highly correlated with the SV/PP ratio (preoperative and postoperative, r = −0.799 and −0.738, respectively). Thirty days following LT, E\textsubscript{a} increased by 16% (P < 0.001) and TAC decreased by 14% (P < 0.001). Additionally, E\textsubscript{es} was correlated with the LV ejection fraction (EF) and S’ preoperatively (P = 0.032 and P < 0.001, respectively) and postoperatively (P = 0.048 and P < 0.001, respectively). E\textsubscript{a} and the contractility index of S’ increased by 18% (P < 0.001) and 7% (P < 0.001), respectively; however, LV EF was unaltered (P = 0.427). The increase in E\textsubscript{a} and E\textsubscript{es} increased the E\textsubscript{es}/E\textsubscript{a} ratio remained unchanged (0.56 to 0.56, P = 0.912) (Fig. 1).

LV diastolic function changed immediately after LT within one month and the E/A ratio decreased by 16% (P < 0.001), whereas E/E’ and E\textsubscript{es} increased by 5% (P = 0.017) and 6% (P < 0.001), respectively, in association with an increase in LVEDP (P = 0.017).

The median lengths of postoperative ICU and hospital stays were 2 days (1, 3) and 22 days (20, 29), respectively (Table 3). In the univariate linear regression analysis, the postoperative hospital stay length was significantly associated with the Model for End-Stage Liver Disease (MELD) score (r = 0.283, P < 0.001), postoperative E\textsubscript{a} (r = 0.157, P = 0.016), E\textsubscript{es} (r = −0.157, P = 0.019), and E\textsubscript{es}/E\textsubscript{a} ratio (r = 0.695, P < 0.001). However, the postoperative E/A ratio (P = 0.967), E/E’ (P = 0.939), and S’ (P = 0.536) were not significantly correlated with the postoperative length of stay (Table 4).

Patients with prolonged postoperative hospital stays (≥ 42 days; 90th percentile) had a higher postoperative E\textsubscript{es}/E\textsubscript{a} ratio (0.54 ± 0.10 vs. 0.71 ± 0.47, P = 0.005), E/E’ (9.7 ± 2.6 vs. 11.5 ± 4.4, P = 0.006), and LVEDP (17.7 ± 15 vs. 18.8 ± 2.6, P = 0.006), and...
Table 2. Clinical and Echocardiographic Parameters of End-Stage Liver Disease before and after LT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Changes (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>108 ± 14</td>
<td>119 ± 15</td>
<td>10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>69 ± 10</td>
<td>75 ± 10</td>
<td>9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ESP (mmHg)</td>
<td>98 ± 12</td>
<td>107 ± 14</td>
<td>9</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Echocardiographic measurements

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Changes (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESV (ml)</td>
<td>39 ± 12</td>
<td>37 ± 13</td>
<td>−5</td>
<td>0.010</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>110 ± 28</td>
<td>103 ± 26</td>
<td>−6</td>
<td>0.001</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>70 ± 18</td>
<td>66 ± 16</td>
<td>−6</td>
<td>0.001</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>64.3 ± 12</td>
<td>64.7 ± 5.2</td>
<td>0.6</td>
<td>0.427</td>
</tr>
<tr>
<td>Peak E velocity (cm/s)</td>
<td>72 ± 19</td>
<td>67 ± 18</td>
<td>−7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peak A velocity (cm/s)</td>
<td>63 ± 17</td>
<td>69 ± 17</td>
<td>10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>213 ± 45</td>
<td>208 ± 46</td>
<td>−2</td>
<td>0.248</td>
</tr>
<tr>
<td>DTI E’ (cm/s)</td>
<td>8.2 ± 4.2</td>
<td>7.0 ± 1.7</td>
<td>−15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DTI A’ (cm/s)</td>
<td>9.3 ± 2.1</td>
<td>10.0 ± 2.1</td>
<td>8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DTI S’ (cm/s)</td>
<td>8.5 ± 1.7</td>
<td>9.1 ± 1.7</td>
<td>7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.20 ± 0.40</td>
<td>1.01 ± 0.46</td>
<td>−16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/E’</td>
<td>9.4 ± 2.8</td>
<td>9.9 ± 2.9</td>
<td>5</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Pressure–volume curve relationships

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Changes (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mmHg)</td>
<td>17.6 ± 1.7</td>
<td>17.9 ± 1.7</td>
<td>2</td>
<td>0.017</td>
</tr>
<tr>
<td>LV E’a (mmHg/ml)</td>
<td>0.17 ± 0.04</td>
<td>0.18 ± 0.05</td>
<td>6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E’a (mmHg/ml)</td>
<td>1.47 ± 0.40</td>
<td>1.70 ± 0.50</td>
<td>16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV E’es (mmHg/ml)</td>
<td>2.68 ± 0.83</td>
<td>3.17 ± 1.05</td>
<td>18</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ventriculoarterial coupling (Ea/Ees)</td>
<td>0.56 ± 0.10</td>
<td>0.56 ± 0.18</td>
<td>0</td>
<td>0.912</td>
</tr>
<tr>
<td>SV/PP ratio (ml/mmHg)</td>
<td>1.82 ± 0.51</td>
<td>1.57 ± 0.52</td>
<td>−14</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or percentage. SBP: systolic blood pressure, DBP: diastolic blood pressure, ESP: end systolic pressure, ESV: end systolic volume, EDV: end diastolic volume, SV: stroke volume, LV: left ventricle, EF: ejection fraction, DTI: tissue doppler image, LVEDP: left ventricle end diastolic pressure, E’a: arterial elastance, E’es: end systolic elastance, PP: pulse pressure.

Table 3. Postoperative Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Changes (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>29 (12.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU stay length (days)</td>
<td>2 (1, 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay length (days)</td>
<td>22 (20, 29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-year mortality</td>
<td>8 (3.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (Q1, Q3). MACE: major adverse cardiovascular events, ICU: intensive care unit.

lower LV EF (65.0 ± 4.6 vs. 61.3 ± 8.5, P = 0.003) and S’ (9.2 ± 1.7 vs. 8.4 ± 2.1, P = 0.032) (Table 5). On multivariate regression analysis, high MELD score (odds ratio [OR]: 1.126, 95% CI [1.073, 1.182], P < 0.001) and higher postoperative E’a/E’es ratio (OR: 1.467; 95% CI [1.010, 2.049], P = 0.038) were identified as independent risk factors for longer postoperative hospital stays (Table 6). In patients with a prolonged hospital stay after LT, an increase in E’a without an increase in E’es led to a higher VAC; however, this was not observed in patients who were discharged within 42 days postoperatively (Fig. 2A).

Of these patients, 29 (12.1%) had MACE before hospital discharge (Table 3). MACE was significantly associated with the MELD score (P = 0.005), postoperative ESV (P = 0.002), EDV (P = 0.017), LV EF (P = 0.018), E/E’ (P = 0.009), LVEDP (P = 0.009), and E’a/E’es ratio (P = 0.008). Compared with patients with-

Table 4. Association of Postoperative Left Ventricular Pressure–volume Relationship Parameters with Length of Hospital Stay in Univariate Linear Regression Analysis

<table>
<thead>
<tr>
<th>Left ventricular pressure-volume relationship parameter</th>
<th>Postoperative hospital stay</th>
<th>β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mmHg)</td>
<td>0.005</td>
<td>0.937</td>
<td></td>
</tr>
<tr>
<td>E’a (mmHg/ml)</td>
<td>0.157</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>E’es (mmHg/ml)</td>
<td>−0.157</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>VAC</td>
<td>0.695</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>E’a (mmHg/ml)</td>
<td>−0.052</td>
<td>0.425</td>
<td></td>
</tr>
<tr>
<td>SV/PP (ml/mmHg)</td>
<td>−0.115</td>
<td>0.076</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Differences in E\textsubscript{a} (A), ventricular elastance (B), and VAC (C) between before and after LT. Throughout one month after LT, E\textsubscript{a} and E\textsubscript{es} were significantly increased (both P < 0.001). Therefore, E\textsubscript{a}/E\textsubscript{es} did not change significantly (P = 0.912). VAC: ventriculoarterial coupling, LT: liver transplantation, E\textsubscript{a}: arterial elastance, E\textsubscript{es}: end systolic elastance.

Discussion

This study investigated the characteristics of the pressure–volume relationship in patients undergoing LT and alterations in these parameters immediately after LT. We found that despite elevations in the arterial load in the 30 days following LT, VAC remained unaltered in normally discharged patients without postoperative MACE, patients with MACE had decreased E\textsubscript{es}, whereas E\textsubscript{a} was similar; therefore, E\textsubscript{a}/E\textsubscript{es} ratio increased, and the pressure–volume loop shifted to the right side (Fig. 2B). Patients with MACE had longer postoperative hospital stays (25.77 ± 14.32 days vs. 67.14 ± 97.11 days, P = 0.030). Multivariate regression analysis identified high MELD score (OR: 1.064, 95% CI [1.017, 1.113], P = 0.008), lower LV EF (OR: 1.514; 95% CI [1.079, 2.123], P = 0.016), and higher postoperative E\textsubscript{a}/E\textsubscript{es} ratio (OR: 6.347, 95% CI [1.672, 24.091], P = 0.007) as independent risk factors for postoperative MACE (Table 6).
*Kim et al. - Ventriculoarterial decoupling*

**Table 5. Comparison of Postoperative Echocardiographic Measurements between Patients Who Developed MACE and Increased Length of Hospital Stay, and Those Who Did Not**

<table>
<thead>
<tr>
<th>Ventriculo-arterial coupling</th>
<th>MACE</th>
<th>POD (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 211)</td>
<td>Yes (n = 29)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>119 ± 14</td>
<td>123 ± 14</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75 ± 10</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>ESP (mmHg)</td>
<td>107 ± 14</td>
<td>111 ± 13</td>
</tr>
</tbody>
</table>

Echocardiographic measurements

| SV (ml) | 66 ± 17 | 70 ± 16 | 0.275 |
| LV EF (%) | 65.9 ± 4.3 | 62.3 ± 9.5 | 0.011 |
| S' | 9.1 ± 1.6 | 9.1 ± 2.6 | 0.797 |
| E' | 7.0 ± 1.6 | 7.0 ± 2.1 | 0.816 |
| A' | 10.0 ± 2.0 | 9.8 ± 3.2 | 0.605 |
| E/A ratio | 1.02 ± 0.48 | 0.99 ± 0.30 | 0.816 |
| E/E' | 9.7 ± 2.4 | 11.3 ± 5.2 | 0.009 |
| LVEDP (mmHg) | 17.7 ± 1.4 | 18.7 ± 3.1 | 0.009 |

Pressure–volume curve relationships

| E_S (mmHg/ml) | 1.70 ± 0.51 | 1.68 ± 0.46 | 0.819 |
| E_E (mmHg/ml) | 3.22 ± 1.05 | 2.83 ± 1.02 | 0.060 |
| VAC | 0.55 ± 0.10 | 0.69 ± 0.45 | 0.008 |
| E' (mmHg/ml) | 0.18 ± 0.05 | 0.17 ± 0.03 | 0.311 |
| SV/PP (ml/mmHg) | 1.59 ± 0.54 | 1.43 ± 0.38 | 0.142 |


these results suggest that E_S is reflective of LV systolic function. On the ESP–volume line, E_S is quantified by the SV ejected from the ventricle against the arterial load that should be overcome by the LV. Compliance is elevated in patients with end-stage liver disease, and the SV/PP ratio reflects abnormalities in arterial compliance in these patients [10]. In addition, E_S is inversely correlated with TAC [14]. Our results showed that the SV/PP ratio was high inversely correlated with E_S, a measure of net arterial load, and may represent TAC in patients undergoing LT. Torregrosa et al. [4] found that cardiac alterations in cirrhosis were reversed within 6–12 months after LT by normalization of the systolic response. In addition, some studies have reported that TAC increased within 2–6 months after transplantation [15,16]. To our knowledge, this reversibility is generally observed within 30 days after transplantation, and LV systolic function increases concordantly with arterial stiffness, thereby maintaining VAC. This study is the first to analyze changes in arterial and ventricular elastance within one month of LT.

In the present study, the pressure–volume characteristics of patients with poor postoperative outcomes were fairly different from those of normally discharged patients without complications. Although studies have reported conflicting results, increases in the ventricular chamber size and volume have also been reported in patients with liver cirrhosis [17,18]. Our study found that the left ventricular ESV, EDV, and SV in patients with poor postoperative outcomes were higher than those in patients without complications. Alterations in LV volume and pressure are expected to contribute to the pressure–volume curve [19,20]. Consequently, a decrease in E_S and an increase in ESP, ESV, and EDV induced a pressure–volume curve shift to the right in patients who developed MACE and had longer postoperative hospital stays (Fig. 2). We also observed that VAC increased in patients with poor outcomes. This suggests that within one month after LT, the LV systolic function increased and matched the arterial load in normally discharged patients without complications; however, a relative increase in VAC adversely affected the clinical outcome. The E_S/E_E ratio is an important determinant of the net cardiac performance [21]. Contractility or arterial tone that is too high or too low decouples these processes and can lead to cardiac failure independent of myocardial ischemia or toxic effects. Both cardiac and ar-

https://doi.org/10.4097/kja.23266
### Table 6. Association of Postoperative Echocardiographic Parameters with Postoperative MACE and Prolonged Length of Hospital Stay in Univariate and Multivariate Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate OR</th>
<th>Univariate P value</th>
<th>Multivariate OR</th>
<th>Multivariate P value</th>
<th>POD ≥ 42 OR</th>
<th>POD ≥ 42 P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score</td>
<td>1.059</td>
<td>0.005</td>
<td>1.064</td>
<td>0.008</td>
<td>1.128</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ESP</td>
<td>1.023</td>
<td>0.109</td>
<td>1.011</td>
<td>0.442</td>
<td>1.037</td>
<td>0.010</td>
</tr>
<tr>
<td>ESV</td>
<td>1.046</td>
<td>0.002</td>
<td>1.037</td>
<td>0.294</td>
<td>1.008</td>
<td>0.249</td>
</tr>
<tr>
<td>EDV</td>
<td>1.017</td>
<td>0.017</td>
<td>0.983</td>
<td>0.170</td>
<td>0.983</td>
<td>0.170</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>0.918</td>
<td>0.018</td>
<td>1.514</td>
<td>0.016</td>
<td>0.887</td>
<td>0.003</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.889</td>
<td>0.816</td>
<td>1.222</td>
<td>0.588</td>
<td>0.732</td>
<td>0.032</td>
</tr>
<tr>
<td>S'</td>
<td>1.030</td>
<td>0.797</td>
<td>0.925</td>
<td>0.544</td>
<td>0.925</td>
<td>0.544</td>
</tr>
<tr>
<td>E'</td>
<td>0.973</td>
<td>0.816</td>
<td>0.802</td>
<td>0.049</td>
<td>0.802</td>
<td>0.049</td>
</tr>
<tr>
<td>A'</td>
<td>0.950</td>
<td>0.605</td>
<td>1.182</td>
<td>0.006</td>
<td>1.182</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>1.298</td>
<td>0.009</td>
<td>1.323</td>
<td>0.006</td>
<td>1.323</td>
<td>0.006</td>
</tr>
<tr>
<td>E_a (mmHg/ml)</td>
<td>0.912</td>
<td>0.819</td>
<td>1.404</td>
<td>0.368</td>
<td>1.404</td>
<td>0.368</td>
</tr>
<tr>
<td>E_es (mmHg/ml)</td>
<td>0.653</td>
<td>0.600</td>
<td>0.728</td>
<td>0.169</td>
<td>0.728</td>
<td>0.169</td>
</tr>
<tr>
<td>VAC</td>
<td>1.469</td>
<td>0.008</td>
<td>6.347</td>
<td>0.007</td>
<td>1.532</td>
<td>0.005</td>
</tr>
<tr>
<td>ESP = 0.9 × SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.467</td>
<td>0.038</td>
</tr>
<tr>
<td>E_a = ESP/SV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.467</td>
<td>0.038</td>
</tr>
<tr>
<td>E_es = ESP/ESV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.467</td>
<td>0.038</td>
</tr>
<tr>
<td>E_ed = EDP/EDV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.467</td>
<td>0.038</td>
</tr>
<tr>
<td>VAC = E_a/E_es</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.467</td>
<td>0.038</td>
</tr>
</tbody>
</table>


**Fig. 2.** Pressure–volume loops of the LV after LT (A) Prolonged postoperative hospital stay is significantly associated with higher VAC. (B) Compared with a patient without postoperative MACE (blue), the patient with MACE has decreased E_es, whereas E_a is similar; therefore, VAC increased and pressure–volume loop (red) is shifted to the right. POD: postoperative day, VAC: ventriculoarterial coupling, ESP: end-systolic pressure, SBP: systolic blood pressure, SV: stroke volume, ESV: end-systolic volume, EDP: end-diastolic pressure, EDV: end-diastolic volume, E_a: arterial elastance, E_es: end systolic elastance, E_ed: end diastolic elastance, MACE: major adverse cardiovascular events.

Ventricular decoupling can lead to acute hemodynamic decompensation that is classified according to the underlying pathophysiological mechanisms. Because acute hemodynamic impairment should be treated based on the etiological mechanism of cardiovascular dysfunction, it is very important to evaluate the VAC. Although alterations in the VAC and its components, E_a and E_es,
have been reported in aging, hypertension, and heart failure [22], data on patients with end-stage liver disease are lacking. This was the first study to examine changes in arterial and LV elastance after LT. According to our results, MACE within one month of LT seemed to develop due to ventriculoarterial decoupling because LV contractility did not increase in accordance with the arterial load. Additionally, these patients had longer postoperative hospital stays. In patients with cirrhotic cardiomyopathy, decoupling of the ventriculoarterial interaction after surgery can occur because of a reduction in the cardiac reserve. Collectively, these results suggest that perioperative assessment of the estimated VAC derived from echocardiography may be a valuable indicator of postoperative cardiovascular dysfunction and may help guide therapeutic strategies.

This study had some limitations. First, this was a retrospective study conducted at a single medical center. Therefore, the timing of the BP measurements and echocardiography was not controlled. Second, we did not measure E_a and E_es from the pressure–volume loops acquired during cardiac catheterization. However, this technique is invasive and its use in humans is limited; therefore, non-invasive assessments of E_a and E_es have been developed in previous studies [23,24]. Non-invasively obtained E_a/E_es ratios have been shown to closely approximate those obtained invasively [25]. Further prospective studies are needed to validate the gold-standard invasive methods. Third, E_es estimated by non-invasive single-beat determination using echocardiography when V_0 was designated as a volume axis intercept was considered reliable [6]. However, we simply regarded the ratio of ESP to ESV as E_es, assuming that V_0 was negligible compared with ESV [7]. If V_0 had been used in the calculations, the results would have differed. Further studies are needed to examine the pressure–volume relationship using V_0.

In conclusion, despite an elevated arterial load within 30 days after LT, VAC remained unaltered in patients discharged without MACE. Myocardial stiffness and contractility were increased to match the arterial load in patients without MACE. However, patients with postoperative MACE had significantly higher E_a/E_es ratios than those without MACE. Our results suggest that MACE within one month postoperatively seemed to develop due to ventriculoarterial decoupling because the LV contractility did not increase and match the arterial load. Therefore, perioperative assessment of the E_a/E_es ratio derived from echocardiography may be valuable for predicting postoperative cardiovascular dysfunction and guiding therapeutic strategies.

Funding
None.

Conflicts of Interest
No potential conflict of interest relevant to this article was reported.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions
Ji Yeon Kim (Writing – original draft)
Young-Jin Moon (Software; Validation)
Changjin Lee (Data curation)
Jin Ho Kim (Investigation)
Junghyun Park (Resources)
Jung-Won Kim (Conceptualization; Supervision; Writing – review & editing)

ORCID
Ji Yeon Kim, https://orcid.org/0009-0007-5802-3327
Young-Jin Moon, https://orcid.org/0000-0003-3719-1691
Changjin Lee, https://orcid.org/0000-0001-6560-994X
Jin Ho Kim, https://orcid.org/0009-0006-2246-5775
Junghyun Park, https://orcid.org/0009-0007-0594-9396
Jung-Won Kim, https://orcid.org/0009-0003-2949-7057

References
4. Torregrosa M, Aguadé S, Dos L, Segura R, Gómez A, Evange-
Association of preoperative blood glucose level with delirium after non-cardiac surgery in diabetic patients

Soo Jung Park¹,², Ah Ran Oh¹,³, Jong-Hwan Lee¹, Kwangmo Yang⁴, Jungchan Park¹

Department of Anesthesiology and Pain Medicine, ¹Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, ²Ajou University School of Medicine, Suwon, ³Kangwon National University Hospital, Chuncheon, ⁴Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Hyperglycemia has shown a negative association with cognitive dysfunction. We analyzed patients with high preoperative blood glucose level and hemoglobin A1c (HbA1c) level to determine the prevalence of postoperative delirium.

Methods: We reviewed a database of 23,532 patients with diabetes who underwent non-cardiac surgery. Acute hyperglycemia was defined as fasting blood glucose > 140 mg/dl or random glucose > 180 mg/dl within 24 h before surgery. Chronic hyperglycemia was defined as HbA1c level above 6.5% within three months before surgery. The incidence of delirium was compared according to the presence of acute and chronic hyperglycemia.

Results: Of the 23,532 diabetic patients, 21,585 had available preoperative blood glucose level within 24 h before surgery, and 18,452 patients reported levels indicating acute hyperglycemia. Of the 8,927 patients with available HbA1c level within three months before surgery, 5,522 had levels indicating chronic hyperglycemia. After adjustment with inverse probability weighting, acute hyperglycemia was related to higher incidence of delirium (hazard ratio: 1.33, 95% CI [1.10,1.62], P = 0.004 for delirium) compared with controls without acute hyperglycemia. On the other hand, chronic hyperglycemia did not correlate with postoperative delirium.

Conclusions: Preoperative acute hyperglycemia was associated with postoperative delirium, whereas chronic hyperglycemia was not significantly associated with postoperative delirium. Irrespective of chronic hyperglycemia, acute glycemic control in surgical patients could be crucial for preventing postoperative delirium.

Keywords: Blood glucose; Cognitive dysfunction; Emergence delirium; Glycated hemoglobin; Hyperglycemia; Mortality; Postoperative delirium.

Introduction

Delirium is a common complication following surgery and is described as a sudden change in mental state leading to fluctuations in consciousness or cognitive function [1]. Postoperative delirium, although typically temporary, has been linked to increased hospital stay, higher medical expenses, increased risk of complications, higher readmission rates, and even higher in-hospital mortality [2–5]. The development of postoperative delirium is thought to be due to a heightened susceptibility of the brain to external stressors, but the specific cause is not well understood. The interplay between risk factors and triggers makes it challenging to establish a protocol for preventing delirium.
Diabetes, a well-established risk factor for postoperative complications, is also linked to cognitive dysfunction, that could be caused by poor glycemic control [6]. Specifically, hyperglycemia is common in surgical patients, with a prevalence of 20% to 40%, and many of those patients have diabetes [7,8]. Increasing research suggests a correlation between perioperative hyperglycemia and negative clinical outcomes in surgical patients [8,9]. Theoretically, perioperative hyperglycemia leads to oxidative stress that can weaken the blood–brain barrier and result in neuronal inflammation [10]. The relationship between hyperglycemia and delirium has been shown in patients who are hospitalized, patients undergoing surgery [11,12], and those with poorly controlled diabetes [13]. Despite the need, a guideline for managing blood glucose levels in diabetic patients during surgery has not yet been established. In this study, we investigated the relation delirium and high blood glucose levels by conducting two separate analyses for acute and chronic hyperglycemia in diabetic patients undergoing non-cardiac surgery. Our results could aid in the development of future guidelines for managing blood glucose levels in the perioperative period.

Materials and Methods

The Institutional Review Board of Samsung Medical Center approved this study (SMC 2021-06-078) and waived the need for written informed consent from participants due to the nature of the study as explained below. This research was conducted in accordance with the Declaration of Helsinki, 2013 and results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data curation and study population

We conducted the analysis using the data from Non-cardiac Operation registry (NoCop) database for our institution. The NoCop registry is a single-center registry with de-identified data for 203,787 consecutive adult patients who underwent non-cardiac surgery, between January 2011 and June 2019. Data were extracted automatically using Clinical Data Warehouse that contains electronic hospital records for more than four million patients, including more than 900 million laboratory findings and 200 million prescriptions. The system can also pull data on mortalities from the National Population Registry of the Korea National Statistical Office using unique personal identification numbers.

Investigators independent of our study and blinded to the results used preoperative evaluation sheets and operation records to organize information about relevant variables. We also used International Classification of Diseases-10 codes to organize preoperative diagnoses. Non-diabetic patients and patients with preoperative diagnoses of delirium or dementia were excluded from this study. We divided our study population into groups and conducted two separate analyses after stratifying patients based on the presence of acute and chronic hyperglycemia. The acute hyperglycemia analyses considered patients with a blood glucose level measured within 24 h before surgery, and the chronic hyperglycemia analyses considered patients with a hemoglobin A1c (HbA1c) level measured within three months before surgery.

Definitions and study endpoints

Acute hyperglycemia was defined as at least one fasting blood glucose level above 140 mg/dl (7.77 mmol/L) or a random blood glucose level above 180 mg/dl (9.99 mmol/L) within 24 h before surgical incision. These levels were set according to the guidelines recommended by the American Diabetes Association and the American Association of Clinical Endocrinology [14]. Chronic hyperglycemia was defined as HbA1c level above 6.5% within three months before surgery [15]. Following institutional protocol, glucose concentrations were selectively measured during preoperative evaluation for patients with extensive medical histories or undergoing high-risk surgeries. Surgical risk was stratified according to the European Society of Cardiology/European Society of Anesthesiology guidelines on non-cardiac surgery [16]. According to these guidelines, surgeries were categorized into low risk, intermediate risk, and high risk based on the probability of cardiovascular risk occurrence: less than 1% as low risk, 1%–5% as intermediate risk, and over 5% as high risk. Patient physical status was classified by each attending anesthesiologist according to the American Society of Anesthesiologists Physical Status Classification System [17].

The primary endpoint was postoperative delirium, diagnosed by a psychiatrist using the Confusion Assessment Method (CAM), within 30 days after surgery. During postoperative care, patients with acute confusion or behavioral change were examined by the department of neuropsychology at the discretion of the attending clinician. For secondary endpoints, we analyzed mortality during one and three years of follow up.

Statistical analysis

For baseline characteristics, continuous variables are presented as means ± standard deviation (SD) or medians with interquartile ranges and were compared using a t-test or Mann-Whitney test, as appropriate. Categorical variables are reported as numbers.
and percentages and were compared using the Chi-square or Fisher’s exact test, as appropriate. Statistical significance was set at \( P < 0.05 \). We used inverse probability weighting (IPW) to balance the distribution of all available covariates between the groups while preserving the total number of patients. Specifically, we considered all available potential confounding factors in our analysis to evaluate the impact of hyperglycemia on postoperative delirium such as baseline characteristics (gender, age, and body mass index), and previous medical history such as hypertension, chronic kidney disease, cardiovascular conditions, and chronic obstructive pulmonary disease. We also retained blood test results, electrolyte levels, intraoperative event, and surgical risk. Stabilized weights of these variables inversely proportional to the marginal probability of hyperglycemia were used \([18]\). Through this method, the weights assigned to patients with higher values were the inverse of the propensity score, while patients with lower values received corresponding weights. The standardized mean difference was calculated to assess the balance of the covariates, and an absolute standardized difference value less than 10% was considered negligible. This diminished the confounding effect of relevant variables while estimating the effect of hyperglycemia on the outcomes. We then compared the risk of outcomes using a Cox proportional hazard regression model to compare the risk of outcomes between the two groups. The results were presented using hazard ratio (HRs) with 95% CIs. Kaplan-Meier curves were generated, and the log-rank test was used to compare the cumulative incidence of delirium. The log-rank test was employed to compare the curves between the hyperglycemia and non-hyperglycemia groups. All statistical analyses were performed using R 4.2.0 (http://www.R-project.org/), and the 'ipw' package was employed for IPW adjustment \([19]\).

**Results**

We excluded 413 patients with preoperative diagnoses of delirium or dementia and selected 23,532 (11.2% of the entire cohort) patients with diabetes. The baseline characteristics of patients with and without diabetes are presented in the supplemental material (Supplementary Table 1). The incidence of postoperative delirium in patients with diabetes (3.1%) was higher than that in patients without diabetes (1.2%). The flowchart of study patients is shown in Fig. 1.

In patients with diabetes, 21,585 (91.7%) had available blood glucose levels measured within 24 h before surgery. Acute hyperglycemia was observed in 3,133 (14.5%) of those patients and was more prevalent in males and in patients with more comorbidities than average. The baseline characteristics of patients with and without acute hyperglycemia are summarized in Table 1. Compared with the group without acute hyperglycemia, the acute hyperglycemia group showed a significantly higher risk of delirium (2.6% vs. 6.2%, HR: 2.43, 95% CI [2.06, 2.87], \( P < 0.001 \)). The significance of the results persisted after adjustment with IPW (HR: 2.43, 95% CI [2.06, 2.87], \( P < 0.001 \)).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No acute hyperglycemia (n = 18,452)</th>
<th>Acute hyperglycemia (n = 3,133)</th>
<th>Before IPW</th>
<th>After IPW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P value</td>
<td>ASD</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>10,551 (57.2)</td>
<td>1,951 (62.3)</td>
<td>&lt; 0.001</td>
<td>10.4</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63.5 ± 11.1</td>
<td>63.8 ± 11.2</td>
<td>0.160</td>
<td>2.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.2 ± 3.7</td>
<td>24.5 ± 3.7</td>
<td>&lt; 0.001</td>
<td>20.2</td>
</tr>
<tr>
<td>Psychiatric disorder, any</td>
<td>930 (5.0)</td>
<td>214 (6.8)</td>
<td>&lt; 0.001</td>
<td>7.6</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>400 (2.2)</td>
<td>91 (2.9)</td>
<td>0.010</td>
<td>4.7</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>21 (0.1)</td>
<td>3 (0.1)</td>
<td>&gt; 0.990</td>
<td></td>
</tr>
<tr>
<td>Alcoholic use disorder</td>
<td>29 (0.2)</td>
<td>5 (0.2)</td>
<td>&gt; 0.990</td>
<td>0.1</td>
</tr>
<tr>
<td>Other substance abuse</td>
<td>5 (0.0)</td>
<td>1 (0.0)</td>
<td>&gt; 0.990</td>
<td>0.3</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>363 (2.0)</td>
<td>78 (2.5)</td>
<td>0.070</td>
<td>3.5</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>3 (0.0)</td>
<td>2 (0.1)</td>
<td>0.330</td>
<td>2.4</td>
</tr>
<tr>
<td>Current alcohol</td>
<td>2,986 (16.2)</td>
<td>496 (15.8)</td>
<td>0.640</td>
<td>1.0</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1,567 (8.5)</td>
<td>293 (9.4)</td>
<td>0.120</td>
<td>3.0</td>
</tr>
<tr>
<td>Previous disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11,208 (60.7)</td>
<td>1,901 (62.7)</td>
<td>0.960</td>
<td>0.1</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1,105 (6.0)</td>
<td>342 (10.9)</td>
<td>&lt; 0.001</td>
<td>17.8</td>
</tr>
<tr>
<td>Dialysis</td>
<td>237 (1.3)</td>
<td>113 (3.6)</td>
<td>&lt; 0.001</td>
<td>15.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>908 (4.9)</td>
<td>211 (6.7)</td>
<td>&lt; 0.001</td>
<td>7.7</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1,058 (5.7)</td>
<td>217 (6.9)</td>
<td>0.010</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart failure</td>
<td>171 (0.9)</td>
<td>49 (1.6)</td>
<td>0.001</td>
<td>5.7</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>521 (2.8)</td>
<td>119 (3.8)</td>
<td>0.004</td>
<td>5.4</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>165 (0.9)</td>
<td>54 (1.7)</td>
<td>&lt; 0.001</td>
<td>7.3</td>
</tr>
<tr>
<td>Aortic disease</td>
<td>114 (0.6)</td>
<td>14 (0.4)</td>
<td>0.310</td>
<td>2.3</td>
</tr>
<tr>
<td>Valvar heart disease</td>
<td>39 (0.2)</td>
<td>13 (0.4)</td>
<td>0.050</td>
<td>3.6</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>535 (2.9)</td>
<td>96 (3.1)</td>
<td>0.650</td>
<td>1.0</td>
</tr>
<tr>
<td>Preoperative blood laboratory tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/risk)</td>
<td>13.0 ± 1.9</td>
<td>12.5 ± 2.2</td>
<td>&lt; 0.001</td>
<td>24.1</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>97.2 ± 105.5</td>
<td>123.8 ± 158.9</td>
<td>&lt; 0.001</td>
<td>18.4</td>
</tr>
<tr>
<td>Preoperative electrolytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1,157 (6.3)</td>
<td>500 (16.0)</td>
<td>&lt; 0.001</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>134 (0.7)</td>
<td>29 (0.9)</td>
<td>0.280</td>
<td>2.2</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>344 (1.9)</td>
<td>126 (4.0)</td>
<td>&lt; 0.001</td>
<td>12.8</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>273 (1.5)</td>
<td>103 (3.3)</td>
<td>&lt; 0.001</td>
<td>11.9</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>580 (3.1)</td>
<td>209 (6.7)</td>
<td>&lt; 0.001</td>
<td>16.4</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>765 (4.1)</td>
<td>183 (5.8)</td>
<td>&lt; 0.001</td>
<td>7.8</td>
</tr>
<tr>
<td>Hypochloremia</td>
<td>696 (3.8)</td>
<td>318 (10.2)</td>
<td>&lt; 0.001</td>
<td>25.3</td>
</tr>
<tr>
<td>Hyperchloremia</td>
<td>2,296 (12.4)</td>
<td>406 (13.0)</td>
<td>0.430</td>
<td>1.5</td>
</tr>
<tr>
<td>Operative variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anesthesia</td>
<td>15,378 (83.3)</td>
<td>2,739 (87.4)</td>
<td>&lt; 0.001</td>
<td>11.6</td>
</tr>
<tr>
<td>Emergency operation</td>
<td>1,035 (5.6)</td>
<td>683 (21.8)</td>
<td>&lt; 0.001</td>
<td>48.4</td>
</tr>
<tr>
<td>Operation duration (min)</td>
<td>144.9 ± 105.6</td>
<td>151.8 ± 116.4</td>
<td>&lt; 0.001</td>
<td>6.2</td>
</tr>
<tr>
<td>Intraoperative transfusion</td>
<td>913 (4.9)</td>
<td>292 (9.3)</td>
<td>&lt; 0.001</td>
<td>17.0</td>
</tr>
<tr>
<td>Intraoperative inotropics infusion</td>
<td>2,303 (12.5)</td>
<td>659 (21.0)</td>
<td>&lt; 0.001</td>
<td>23.1</td>
</tr>
<tr>
<td>Surgical risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>5,880 (31.9)</td>
<td>715 (22.8)</td>
<td>&lt; 0.001</td>
<td>20.4</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10,646 (57.7)</td>
<td>2,037 (65.0)</td>
<td>&lt; 0.001</td>
<td>15.1</td>
</tr>
<tr>
<td>High</td>
<td>1,926 (10.4)</td>
<td>381 (12.2)</td>
<td>0.004</td>
<td>5.4</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No acute hyperglycemia (n = 18,452)</th>
<th>Acute hyperglycemia (n = 3,133)</th>
<th>Before IPW</th>
<th>After IPW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery types</td>
<td></td>
<td></td>
<td>P value</td>
<td>ASD</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>615 (3.3)</td>
<td>51 (1.6)</td>
<td>&lt; 0.001</td>
<td>46.4</td>
</tr>
<tr>
<td>Lung</td>
<td>983 (5.3)</td>
<td>340 (10.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>2,125 (11.5)</td>
<td>590 (18.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>711 (3.9)</td>
<td>78 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>1,616 (8.8)</td>
<td>170 (5.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>2,156 (11.7)</td>
<td>486 (15.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>1,639 (8.9)</td>
<td>250 (8.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urology</td>
<td>2,575 (14.0)</td>
<td>239 (7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecology</td>
<td>1,027 (5.6)</td>
<td>45 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone, skin, etc.</td>
<td>5,005 (27.1)</td>
<td>884 (28.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± SD. Surgical risk was stratified according to 2014 European Society of Cardiology/European Society of Anesthesiology guidelines. IPW: inverse probability weighting, ASD: absolute standardized difference. P value < 0.05 indicates statistical significance.

Table 2. Clinical Outcomes according to Acute Hyperglycemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No acute hyperglycemia (n = 18,452)</th>
<th>Acute hyperglycemia (n = 3,133)</th>
<th>Before IPW</th>
<th>After IPW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR 95% CI P value</td>
<td>Unadjusted HR 95% CI P value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>482 (2.6)</td>
<td>195 (6.2)</td>
<td>2.43</td>
<td>2.06, 2.87</td>
</tr>
<tr>
<td>One-year mortality</td>
<td>805 (4.4)</td>
<td>316 (10.1)</td>
<td>2.41</td>
<td>2.12, 2.75</td>
</tr>
<tr>
<td>Three-year mortality</td>
<td>1,671 (9.1)</td>
<td>554 (17.7)</td>
<td>2.07</td>
<td>1.88, 2.27</td>
</tr>
</tbody>
</table>

Values are presented as number (%). Delirium and mortality are presented with HR. IPW: inverse probability weighting, HR: hazard ratio. P value < 0.05 indicates statistical significance.

For chronic hyperglycemia analyses, we selected the 8,927 (37.9%) diabetic patients with available HbA1c level within three months before surgery. Baseline characteristics according to the presence of chronic hyperglycemia are shown in Table 3. Chronic hyperglycemia was not associated with delirium (3.5% vs. 3.3%, HR: 0.92, 95% CI [0.73, 1.16], P = 0.5 for delirium). The results persisted after adjustment with IPW (HR: 0.94, 95% CI [0.74, 1.19], P = 0.6) (Table 4). The Kaplan-Meier curves for delirium according to acute and chronic hyperglycemia are presented in Figs. 2 and 3. Acute hyperglycemia showed a significantly higher risk of delirium regardless of the presence of chronic hyperglycemia (HR: 2.11, 95% CI [1.54, 2.90], P < 0.001 for those without chronic hyperglycemia; HR: 2.87, 95% CI [1.82, 4.52], P < 0.001 for those with chronic hyperglycemia).

Discussion

We investigated the relationship between hyperglycemia and delirium in diabetic patients undergoing non-cardiac surgery using two distinct analyses for acute and chronic hyperglycemia. After selecting the diabetic patients for analysis, we compared the incidence of postoperative delirium according to the presence of diabetes, and delirium was more commonly found in diabetic patients. Among diabetic patients, acute hyperglycemia was significantly associated with postoperative delirium and one- and three-year mortality, whereas chronic hyperglycemia showed a significant association only with one-and three-year mortality.

Diabetes has long been reported as a risk factor for cognitive dysfunction. Particularly in surgical patients, the presence of diabetes has been shown to be associated with higher rates of postoperative delirium and hyperglycemia than in the general population [6,9,20]. Several other studies have focused on perioperative hyperglycemia and the risk of postoperative delirium [21–23]. Although some current guidelines recommend perioperative glycemic control [14,24,25], no treatment strategy has been optimized [7]. We conducted two distinct analyses for acute and chronic hyperglycemia and found that acute hyperglycemia was significantly...
Table 3. Baseline Characteristics according to Chronic Hyperglycemia in Patients with HbA1c within Three Months before Surgery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No chronic hyperglycemia (n = 3,405)</th>
<th>Chronic hyperglycemia (n = 5,522)</th>
<th>Before IPW</th>
<th>After IPW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P value ASD</td>
<td>P value ASD</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>1,784 (52.4)</td>
<td>3,027 (54.8)</td>
<td>0.030 4.9</td>
<td>0.900 0.3</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63.3 ± 12.7</td>
<td>63.2 ± 11.1</td>
<td>0.870 0.4</td>
<td>0.580 1.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3 ± 4.1</td>
<td>25.2 ± 3.8</td>
<td>0.290 2.3</td>
<td>0.960 0.1</td>
</tr>
<tr>
<td>Psychiatric disorder, any</td>
<td>282 (8.3)</td>
<td>380 (6.9)</td>
<td>0.020 5.3</td>
<td>0.930 0.2</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>123 (3.6)</td>
<td>160 (2.9)</td>
<td>0.070 4.0</td>
<td>0.990 &lt; 0.1</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>8 (0.2)</td>
<td>6 (0.1)</td>
<td>0.230 3.0</td>
<td>0.750 0.8</td>
</tr>
<tr>
<td>Alcoholic use disorder</td>
<td>4 (0.1)</td>
<td>14 (0.3)</td>
<td>0.250 3.2</td>
<td>0.790 0.7</td>
</tr>
<tr>
<td>Other substance abuse</td>
<td>0</td>
<td>3 (0.1)</td>
<td>0.440 3.3</td>
<td>0.170 2.6</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>113 (3.3)</td>
<td>151 (2.7)</td>
<td>0.130 3.4</td>
<td>0.990 &lt; 0.1</td>
</tr>
<tr>
<td>Current alcohol</td>
<td>495 (14.5)</td>
<td>859 (15.6)</td>
<td>0.200 2.8</td>
<td>0.940 0.2</td>
</tr>
<tr>
<td>Current smoking</td>
<td>257 (7.5)</td>
<td>490 (8.9)</td>
<td>0.030 4.8</td>
<td>0.970 0.1</td>
</tr>
<tr>
<td>Previous disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2,187 (64.2)</td>
<td>3,246 (58.8)</td>
<td>&lt; 0.001 11.2</td>
<td>0.850 0.4</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>487 (14.3)</td>
<td>503 (9.1)</td>
<td>&lt; 0.001 16.2</td>
<td>0.980 0.1</td>
</tr>
<tr>
<td>Dialysis</td>
<td>143 (4.2)</td>
<td>95 (1.7)</td>
<td>&lt; 0.001 14.7</td>
<td>0.960 0.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>188 (5.3)</td>
<td>293 (5.3)</td>
<td>0.700 1.0</td>
<td>0.910 0.2</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>226 (6.6)</td>
<td>386 (7.0)</td>
<td>0.550 1.4</td>
<td>0.920 0.2</td>
</tr>
<tr>
<td>Heart failure</td>
<td>63 (1.9)</td>
<td>78 (1.4)</td>
<td>0.130 3.5</td>
<td>0.850 0.4</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>112 (3.3)</td>
<td>187 (3.4)</td>
<td>0.850 0.5</td>
<td>0.940 0.2</td>
</tr>
<tr>
<td>Periphreral artery disease</td>
<td>33 (0.9)</td>
<td>67 (1.2)</td>
<td>0.340 2.4</td>
<td>0.990 &lt; 0.1</td>
</tr>
<tr>
<td>Aortic disease</td>
<td>32 (0.9)</td>
<td>26 (0.5)</td>
<td>0.010 5.6</td>
<td>0.890 0.3</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>13 (0.4)</td>
<td>16 (0.3)</td>
<td>0.580 1.6</td>
<td>0.990 &lt; 0.1</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>101 (3.0)</td>
<td>154 (2.8)</td>
<td>0.670 1.1</td>
<td>0.980 &lt; 0.1</td>
</tr>
<tr>
<td>Preoperative blood laboratory tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.4 ± 2.1</td>
<td>12.9 ± 2.1</td>
<td>&lt; 0.001 22.5</td>
<td>0.930 0.5</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>141.4 ± 185.6</td>
<td>106.1 ± 132.6</td>
<td>&lt; 0.001 19.7</td>
<td>0.990 &lt; 0.1</td>
</tr>
<tr>
<td>Preoperative electrolytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>248 (7.3)</td>
<td>541 (9.8)</td>
<td>&lt; 0.001 9.0</td>
<td>0.870 0.4</td>
</tr>
<tr>
<td>Hypertnatremia</td>
<td>42 (1.2)</td>
<td>31 (0.6)</td>
<td>0.001 7.1</td>
<td>0.920 0.2</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>96 (2.8)</td>
<td>122 (2.2)</td>
<td>0.080 3.9</td>
<td>0.940 0.2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>91 (2.7)</td>
<td>108 (2.0)</td>
<td>0.030 4.8</td>
<td>0.880 0.3</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>135 (4.0)</td>
<td>229 (4.1)</td>
<td>0.710 0.9</td>
<td>0.730 0.8</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>261 (7.7)</td>
<td>322 (5.8)</td>
<td>0.001 7.3</td>
<td>0.760 0.7</td>
</tr>
<tr>
<td>Hypochloremia</td>
<td>197 (5.8)</td>
<td>331 (6.0)</td>
<td>0.720 0.9</td>
<td>0.900 0.3</td>
</tr>
<tr>
<td>Hyperchloremia</td>
<td>509 (14.9)</td>
<td>626 (11.3)</td>
<td>&lt; 0.001 10.7</td>
<td>0.950 0.1</td>
</tr>
<tr>
<td>Operative variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anesthesia</td>
<td>2,448 (71.9)</td>
<td>4,526 (82.0)</td>
<td>&lt; 0.001 24.1</td>
<td>0.990 &lt; 0.1</td>
</tr>
<tr>
<td>Emergency operation</td>
<td>302 (8.9)</td>
<td>432 (7.8)</td>
<td>0.090 3.8</td>
<td>0.800 0.6</td>
</tr>
<tr>
<td>Operation duration (min)</td>
<td>139.9 ± 106.2</td>
<td>144.3 ± 104.5</td>
<td>0.050 4.2</td>
<td>0.960 0.1</td>
</tr>
<tr>
<td>Intraoperative transfusion</td>
<td>219 (6.4)</td>
<td>319 (5.8)</td>
<td>0.220 2.7</td>
<td>0.700 0.9</td>
</tr>
<tr>
<td>Intraoperative inotropic infusion</td>
<td>479 (14.1)</td>
<td>793 (14.4)</td>
<td>0.720 0.8</td>
<td>0.800 0.6</td>
</tr>
<tr>
<td>Surgical risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1,010 (29.7)</td>
<td>1,751 (31.7)</td>
<td>0.050 4.4</td>
<td>0.810 0.6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2,159 (63.4)</td>
<td>3,213 (58.2)</td>
<td>&lt; 0.001 10.7</td>
<td>0.750 0.7</td>
</tr>
<tr>
<td>High</td>
<td>236 (6.9)</td>
<td>558 (10.1)</td>
<td>&lt; 0.001 11.4</td>
<td>0.880 0.3</td>
</tr>
</tbody>
</table>

(Continued to the next page)
Table 3. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No chronic hyperglycemia (n = 3,405)</th>
<th>Chronic hyperglycemia (n = 5,522)</th>
<th>Before IPW</th>
<th>After IPW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>ASD</td>
<td>P value</td>
<td>ASD</td>
</tr>
<tr>
<td>Surgery types</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>109 (3.2)</td>
<td>214 (3.9)</td>
<td>&lt; 0.001</td>
<td>28.6</td>
</tr>
<tr>
<td>Lung</td>
<td>86 (2.5)</td>
<td>293 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>239 (7.0)</td>
<td>571 (10.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>35 (1.0)</td>
<td>93 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>224 (6.6)</td>
<td>445 (8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>280 (8.2)</td>
<td>594 (10.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>258 (7.6)</td>
<td>448 (8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urology</td>
<td>344 (10.1)</td>
<td>469 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecology</td>
<td>391 (11.5)</td>
<td>387 (7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone, skin, etc.</td>
<td>1,439 (42.3)</td>
<td>2,008 (36.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± SD. Surgical risk was stratified according to 2014 European Society of Cardiology/European Society of Anesthesiology guidelines. HbA1c: hemoglobin A1c, IPW: inverse probability weighting, ASD: absolute standardized difference. P value < 0.05 indicates statistical significance.

Table 4. Clinical Outcomes according to Chronic Hyperglycemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No chronic hyperglycemia (n = 3,405)</th>
<th>Chronic hyperglycemia (n = 5,522)</th>
<th>Before IPW</th>
<th>After IPW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR</td>
<td>95% CI</td>
<td>P value</td>
<td>IPW adjusted HR</td>
</tr>
<tr>
<td>Delirium</td>
<td>120 (3.5)</td>
<td>0.92</td>
<td>0.73, 1.16</td>
<td>0.5</td>
</tr>
<tr>
<td>One-year mortality</td>
<td>129 (3.8)</td>
<td>1.42</td>
<td>1.15, 1.74</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Three-year mortality</td>
<td>262 (7.7)</td>
<td>1.34</td>
<td>1.15, 1.55</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as number (%). Delirium and mortality are presented with HR. IPW: inverse probability weighting, HR: hazard ratio. P value < 0.05 indicates statistical significance.

Fig. 2. Kaplan-Meier curves of cumulative postoperative delirium during 30 days after surgery, separated by presence of acute hyperglycemia.
associated with postoperative delirium, whereas chronic hyperglycemia was not.

The association between acute hyperglycemia and postoperative delirium can be well explained. The first connection is neuro-inflammation that can be induced by hyperglycemia. Overactivation of glucose metabolism in hyperglycemic patients increases the generation of reactive oxygen species [26,27], as well as glycolytic intermediates, and the secretion of pro-inflammatory cytokines [28,29]. An imbalance between free radical generation and elimination causes oxidative stress to neuronal cells and increased inflammatory secretion. Second, hyperglycemia is related to blood–brain barrier destruction [10,26]. The blood-brain barrier is a selective diffusion barrier that maintains homeostasis in the central nervous system and restricts penetration of neurotoxic molecules. In an animal study, hyperglycemia was related to disruption of this barrier due to microvascular abnormalities [30]. Defects in the microvasculature of the brain could result in impaired neuronal function and increased delirium.

Unlike acute hyperglycemia, chronic hyperglycemia did not show a significant association with postoperative delirium. The relationship between chronic hyperglycemia and delirium was controversial in previous studies [21,31,32]. Although the presence of diabetes was consistently shown to be a risk factor for postoperative delirium, preoperative HbA1c level showed a significant association with postoperative delirium in one study [21] but not in another [32]. Our finding that chronic hyperglycemia was not associated with delirium can be explained by an increased tolerance to hyperglycemia [23]. Long-term exposure to high blood glucose can induce cell conditioning, such as control of the overflow of blood glucose into cells by regulating the expression of the glucose transporter in cell membranes to reduce glucose toxicity. Therefore, patients with chronic hyperglycemia within a certain range might be less vulnerable than others to the acute stress induced by surgery. However, chronic hyperglycemia has been reported to be a risk factor for cognitive dysfunction in long-term follow-up [12,33]. Thus, the clinical implication of our study is not that chronic hyperglycemia can be neglected, but that acute glycemic control might be important even in patients with chronic hyperglycemia.

Our study has several limitations. First, selection bias and information bias cannot be excluded from any observational study. Because our study was conducted in a single center where most of the patients are Asian, the results of this study cannot be generalized. Furthermore, residual confounding factors from unmeasured variables such as severity of diabetes and medication use, and intraoperative blood glucose level may have affected our results despite rigorous statistical adjustments. Second, we diagnosed delirium using the CAM score that might have underestimated the incidence of postoperative delirium. While the CAM score is widely used and validated, it relies on specific criteria and may not capture all nuances of delirium. Alternative scales, such as the Intensive Care Delirium Screening Checklist (ICDSC), offer advantages by utilizing dichotomous variables and incorporating non-verbal language assessments. These features could potentially provide a more comprehensive assessment of delirium. Also, we could not assess the severity or character of delirium because of the study design.
we were conducting a retrospective study. Third, we investigated only the preoperative glucose level. So, the effect of stress hyperglycemia that is common during surgery could not be considered. Despite those limitations, our results might be helpful in establishing guidelines for blood glucose management and prevention of delirium in diabetic patients.

In conclusion, preoperative acute hyperglycemia was associated with increased postoperative delirium and one- and three-year mortality, but chronic hyperglycemia did not show a significant association with postoperative delirium. Our findings underscore the potential importance of prioritizing acute glucose control before non-cardiac surgery regardless of long-term glucose control. Nevertheless, it is crucial to recognize that comprehensive care should encompass the management of chronic hyperglycemia, alongside acute glycemic control in diabetic patients undergoing non-cardiac surgery.

Funding
None.

Conflicts of Interest
No potential conflict of interest relevant to this article was reported.

Data Availability
The datasets generated during and/or analyzed during the current study are not publicly available due to the sensitive nature of some questions but are available from the corresponding author on reasonable request.

Author Contributions
Soo Jung Park (Conceptualization; Investigation; Writing – original draft)
Ah Ran Oh (Data curation; Formal analysis)
Jong-Hwan Lee (Methodology; Supervision)
Kwangmo Yang (Conceptualization)
Jungchan Park (Conceptualization)

ORCID
Soo Jung Park, https://orcid.org/0000-0001-9199-7157
Ah Ran Oh, https://orcid.org/0000-0002-8076-5104
Jong-Hwan Lee, https://orcid.org/0000-0001-8249-5550
Kwangmo Yang, https://orcid.org/0000-0002-7176-4935
Jungchan Park, https://orcid.org/0000-0002-7794-3547

Supplementary Material
Supplementary Table 1. Baseline Characteristics and Outcomes of Patients with and without Diabetes.

References


Effect of ultrafiltration on whole blood coagulation profile during cardiopulmonary bypass in cardiac surgery: a retrospective analysis

Jaemoon Lee¹, Dong-Kyu Lee², Won-Kyong Kwon¹, Sookyung Lee¹, Chung-Sik Oh¹, Klaus Görlinger³,⁴, Tae-Yop Kim¹

¹Department of Anesthesiology, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, ²Department of Anesthesiology and Pain Medicine, Dongguk University Ilsan Hospital, Goyang, Korea, ³Department of Anesthesiology and Intensive Care Medicine, University Hospital Essen, Essen, ⁴Medical Department, TEM Innovations GmbH/Werfen PBM, Munich, Germany

Background: Ultrafiltration (UF) would enhance coagulation profiles by concentrating coagulation elements during cardiopulmonary bypass (CPB) for cardiac surgery.

Methods: We retrospectively reviewed electronic medical records of 75 patients who had undergone cardiac surgery with rotational thromboelastometry-based coagulation management in a university hospital and analyzed the UF-induced changes in the maximum clot firmness (MCF) of extrinsically activated test with tissue factor (EXTEM) during CPB in 30 patients.

Results: The median volume of filtered-free water was 1,350 ml, and median hematocrit was significantly increased from 22.5% to 25.5%. As the primary measure, UF significantly increased the median MCF-EXTEM from 48.0 mm to 50.5 mm (P = 0.015, effect size r = 0.44). The area under the receiver operating characteristic curve pre-UF MCF-EXTEM for discrimination of any increase of MCF-EXTEM after applying UF was 0.89 (95% CI [0.77, 1.00], P < 0.001), and its cut-off value was 50.5 mm (specificity of 81.8% and sensitivity of 84.2% in Youden’s J statistic). In the secondary analyses using the cut-off value, UF significantly increased the median MCF-EXTEM from 40.5 mm to 42.5 mm in 18 patients with pre-UF MCF-EXTEM ≤ 50.5 mm. However, it did not increase MCF-EXTEM in 12 patients with pre-UF MCF-EXTEM > 50.5 mm. There was a significant interaction between pre-UF MCF-EXTEM values and applying UF (P < 0.001 for the subgroup, P = 0.046 for UF, P = 0.003 for interaction).

Conclusions: Applying UF improved clot firmness, and the improvement was more pronounced when pre-UF MCF-EXTEM had been reduced during CPB.

Keywords: Blood coagulation; Cardiac surgical procedures; Cardiopulmonary bypass; Retrospective studies; Thoracic surgery; Thrombelastography; Ultrafiltration.

Introduction

In cardiac surgery, intravenous (IV) priming fluids to the cardiopulmonary bypass (CPB) circuit and reservoir dilute all blood components. CPB-induced hemodilution can affect the overall coagulation performance and increase post-CPB bleeding [1].

Near the end of the CPB, ultrafiltration (UF) removes excessive free water from the patients and attenuates CPB-induced hemodilution. Applying UF has been regarded as effective in increasing hematocrit (Hct) and reducing red blood cell (RBC) transfusion...
UF may concentrate procoagulants and improve overall coagulation performance in adult cardiac surgery. However, in previous studies in adults, UF’s impacts on coagulation performance were inconsistent [3–5]. As UF concentrates all blood components, including procoagulants and anticoagulants, UF’s overall impact would be determined by the net balance of their concentrations.

Rotational thromboelastometry (ROTEM), a point-of-care viscoelastic test, has been used to analyze the coagulation performance of whole blood in various clinical settings, even during CPB [6]. While multiple ROTEM assays could specify the lack of each procoagulant, such as clotting factors, fibrinogen, and platelets, the maximum clot firmness (MCF) of extrinsically activated test with tissue factor (EXTEM) depicts clot strength with the combined contribution of platelets and fibrinogen [7].

We assumed that the possible changes of MCF-EXTEM after applying UF would indicate the overall impact of UF on the coagulation profile in patients undergoing cardiac surgery with CPB.

Therefore, we reviewed the electronic medical records (EMR) of cardiac surgery patients undergoing UF during CPB in a tertiary university hospital. We retrospectively analyzed the changes in MCF-EXTEM values before and after applying UF in these patients. The primary objective of our study was to determine whether applying UF affects MCF-EXTEM.

Materials and Methods

We retrospectively analyzed the EMR of 75 patients who underwent adult cardiac valve surgery in a tertiary university hospital (Konkuk University Medical Center) from 2019 to 2021. The Institutional Review Board approved the study (Institutional Review Board of Konkuk University Medical Center, IRB No: 2022-02-027). This study was registered on clinicaltrials.gov (NCT05 252559). The following eligibility criteria were employed: patients older than 19 years, getting moderate hypothermic CPB, and getting UF at the end of CPB. Patients with the following criteria were excluded: Re-do or Tri-do surgery, infective endocarditis, aortic dissection, packed RBC transfusion of more than three units during CPB, lacking EXTEM and fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D (FIBTEM) assay data before and after applying UF, and the filtered-free water volume of < 250 ml.

Anesthesia induction, maintenance, and CPB

Electrocardiogram, bispectral index, and pulse oximetry were applied upon the patient’s arrival in the operation room. A 20–22 G catheter was placed in the radial or femoral artery for monitoring invasive blood pressure (BP). Anesthesia was maintained with sevoflurane or propofol-remifentanil-rocuronium infusions. Central venous pressure, pulmonary arterial pressure, cardiac index (CI), mixed venous O2 saturation (Vigilance II™ monitor, Edwards), and cerebral O2 saturation (INVOS™ 5100C Regional Oximeter, Medtronic) were monitored. Before and after applying CPB, O2 and medical air (FiO2 0.4–0.6) were ventilated to maintain normocapnia. Intraoperative transesophageal echocardiogram (TEE) was performed according to the institutional protocol. Acetate-buffered balanced crystalloid solutions and phenylephrine were infused to maintain the mean BP of 80%–120% of the pre-induction value. The main surgical procedure was performed under CPB with moderate hypothermia (28–29°C). The CPB pump was primed with 1,500 to 1,700 ml of acetate-buffered balanced crystalloid, 100 ml of 20% mannitol, and 100 ml of 20% albumin. A single aortic and two venous cannulas were placed in the aorta and right atrium for CPB. Unfractionated heparin 300 IU/kg was administered for initiating anticoagulation during CPB, and additional dosages were issued under the monitoring of activated coagulation time (ACT). The ACT was maintained at above 400 s before the initiation and during the maintenance of CPB.

CPB was conducted with a non-pulsatile centrifugal pump, polyvinyl chloride tubing, and a membrane oxygenator with hollow polypropylene fibers. The pump flow rate was adjusted to 2.0 to 2.5 L/min/m2 to maintain a mean BP (MBP) of 55 to 70 mmHg. During CPB, continuous positive airway pressure of 5–7 mmHg was applied to the patient’s lung, and the α-stat strategy managed PaCO2. After cross-clamping the aorta, the cold, bloodless crystalloid cardioplegic solution was administered through antegrade and/or retrograde coronary perfusion, repeated every 30 min.

UF was started during rewarming, with a flow rate of 200 ml/min/m2 through a hemoconcentration with tubing and adapter set (Hemocor HPH™, Medivatos Inc.), placed in the inlet connected to the arterial line and the outlet connected to the venous line, and continued until the almost end of CPB.

CPB was weaned with or without inotropic support when the core temperature reached 36°C. The same ventilation strategy applied during the pre-CBP period was restored during the post-CBP period. Intraoperative fluid management was performed upon TEE monitoring. Dobutamine, epinephrine, or milrinone was infused as a first-line inotropic agent for weaning from CPB, as needed. Its infusion rate was adjusted and supplemented with norepinephrine infusion to achieve a CI of > 2.0 L/min/m2 and MBP of > 65 mmHg.

Intraoperative bleeding from the surgical site was salvaged and
returned to the patients using a sucker and a cell saver system during the entire surgical procedure. Especially after completing UF and weaning from CPB, the residual blood in the CPB circuit and reservoir underwent the cell saver process and was washed and reinfused to the patients.

The threshold for transfusion of packed RBCs was a Hct of < 18%–21% or the decline of \( rSO_2 > 20\% \) during the CPB period and a Hct of < 24%–28% or \( rSO_2 \) decline > 20% during the post-CPB period, respectively. Protamine 3 mg/kg was administered to neutralize the heparin effect after weaning from CPB.

Fresh frozen plasma, fibrinogen concentrate, cryoprecipitate, or platelets were administered upon ROTEM analyses, indicating coagulation dysfunction with ongoing bleeding. After surgery, patients were transferred to the intensive care unit and managed according to institutional protocols.

**ROTEM analyses and data acquisition**

In all patients, an arterial blood sample of 1 ml underwent routine ROTEM assays (ROTEM® sigma, TEM Innovations) consisting of EXTEM and FIBTEM at the following time points: immediately after anesthesia induction (pre-CPB), immediately before applying UF (pre-UF), immediately after completing UF (post-UF), and after CPB-weaning and protamine neutralization (post-CPB).

For the present study, the changes in the clotting time of EXTEM (CT-EXTEM), clot formation time of EXTEM (CFT-EXTEM), MCF-EXTEM, and clot amplitude at 5 min and maximum clot formation in FIBTEM (A5-FIBTEM and MCF-FIBTEM), and lysis index at 30 min of EXTEM (LI30-EXTEM) were analyzed. The changes of PLTEM, which is to estimate platelet count (calculated by EXTEM – FIBTEM), and MCF -PLTEM were also analyzed.

**Study objectives**

The primary objective of this study is to ascertain the impact of UF on MCF-EXTEM in patients undergoing cardiac surgery with CPB. The secondary objective of this study is to figure out the relationship between the positive MCF-EXTEM response and the application of UF in these patients. The positive response was defined as any elevation in MCF-EXTEM following the application of UF compared to pre-UF MCF-EXTEM values.

**Statistical analysis**

Results were expressed as mean ± standard deviation (SD), median (Q1, Q3), or number (%) according to the data type. Statistical analysis was performed using R version 4.2.1™ (R Development Core Team, 2022). Before statistical analysis, normality was checked for the continuous variables with a visual check of Q-Q plots and histograms. Comparative analysis was done using nonparametric statistical methods, such as the Wilcoxon signed-rank test. Results included P values and effect size r. Kendall's tau-b was applied to figure out the relationship between the amount of filtered-free water and the UF-induced changes in Hct and ROTEM parameter values. A two-sided P value below 0.05 was considered statistically significant.

We performed a Wilcoxon signed-rank test to compare the values of MCF-EXTEM before and after applying UF as the study’s primary objective. Additionally, we conducted a receiver-operator curve (ROC) analysis to evaluate the discrimination ability toward positive MCF-EXTEM response by applying UF as the secondary measure. The area under the receiver operating curve (AUROC) and a 95% CI were estimated with the DeLong algorithm and R package PROC [8]. The optimal cut-off value of pre-UF MCF-EXTEM to the positive response was estimated with Youden’s J statistic. To elucidate the relationship between pre-UF MCF-EXTEM and UF application, we divided all patients into two subgroups according to the estimated cut-off value of pre-UF MCF-EXTEM (more than and less than or equal to the cut-off value). We performed a comparative analysis to determine whether UF affected CFT-EXTEM and others, such as CF-EXTEM, A5-FIBTEM, MCF-FIBTEM, MCF-PLTEM, and LI30-EXTEM, in each subgroup. To investigate the interaction between the grouping by pre-UF MCF-EXTEM values and the UF effect simultaneously, non-parametric repeated measured Analysis of variance (ANOVA) with one repeated factor and one between factor analysis (FLD-F1 model) was applied (R package ’nparLD’) [9]. ANOVA-type statistics were used for all tests. As a measure of relative effect, we used the relative treatment effect (RTE). The RTE means effect measurement that can be interpreted as follows: an RTE of 0.5 represents no effect; an RTE greater than 0.5 indicates a tendency for subjects in a subgroup to generally have higher scores compared to the average individual within the whole sample; an RTE value of 0.7 for a subgroup means that there is a 70% estimated probability that a randomly chosen individual from this subset will have a higher score than a randomly selected individual from the entire dataset; and conversely, an RTE of 0.2 for a subgroup means a 20% estimated probability that a randomly chosen individual from the whole dataset will have a lower score than a randomly selected individual from this subset. Additionally, in the two subgroups, the median difference and corresponding quartiles between pre-UF MCF-EXTEM and post-UF MCF-EXTEM were estimated by bootstrap with a resampling number of 3000.
Results

Out of the EMR data of 75 eligible patients, those of 45 patients were excluded due to the exclusion criteria. Finally, we included the EMR data of 30 patients for the statistical analysis (Fig. 1).

Detailed demographic data and information on transfusion are described in Table 1. The mean CPB duration was 206 min, and the median volume of filtered free water (Q1, Q3) was 1,350 (1,200–1,925) ml. By applying UF, median Hct values were significantly increased from 22.5% to 25.5% (P < 0.001, Table 2).

As the primary outcome of our study, UF significantly increased median MCF-EXTEM (Q1, Q3), and its change was moderately affected by UF (48.0 [38.8, 54.0] mm for pre-UF, 50.5 [40.0, 56.0] mm for post-UF, P = 0.015, effect size r = 0.44). UF did not significantly change CT-EXTEM, CFT-EXTEM, A5-FIBTEM, MCF-FIBTEM, MCF-PLTEM, and LI30-EXTEM (Table 2). However, no significant correlation existed between the amount of filtered-free water and the changes in ROTEM parameters, even MCF-EXTEM (Supplementary Table 1).

The estimated AUROC of discriminating the positive response of the pre-UF MCF-EXTEM by the application of UF was 0.89 (95% CI [0.77, 1.00], P < 0.001). In the ROC analysis, the estimated cut-off value of pre-UF MCF-EXTEM to discriminate the positive response to applying UF was 50.5 mm, with a sensitivity of 84.2% and a specificity of 81.8% (Fig. 2A).

As the secondary outcome of this study, pre- and post-UF MCF-EXTEM values in patients with pre-UF MCF-EXTEM ≤ 50.5 mm (n = 18) were 40.5 (33.8, 45.8) mm and 42.5 (38.5, 53.0) mm.

Fig. 1. Schema of data collection and analyses. UF: ultrafiltration, ROTEM: rotational thromboelastometry, Packed RBC: packed red blood cell, CPB: cardiopulmonary bypass, Pre-UF: immediately before applying UF, Post-UF: immediately after applying UF, MCF-EXTEM: maximum clot firmness of EXTEM, AUROC: area under the receiver operating curve, EXTEM: extrinsically-activated test with tissue factor.

https://doi.org/10.4097/kja.23698
mm, respectively (estimated median difference and quartiles = 2.0 [0.0, 5.0] mm). For the patients of pre-UF MCF-EXTEM ≤ 50.5 mm (n = 12), the pre- and post-UF MCF-EXTEM values were 57.5 (52.8, 60.3) mm and 56.0 (51.0, 48.8) mm, respectively (estimated median difference and quartiles = −1.0 [−2.5, 2.0] mm). UF had a significant effect on the changes of Hct and MCF-EXTEM, and its effect had an interaction with subgroups (Hct: P = 0.031 for the subgroup, P < 0.001 for UF, P = 0.032 for interaction; MCF-EXTEM: P < 0.001 for the subgroup, P = 0.046 for UF, P = 0.003 for interaction, Fig. 2B). CT-EXTEM was not changed by applying UF. CFT-EXTEM, A5-FIBTEM, MCF-FIBTEM, and MCF-PLTEM represented a significant difference between the subgroups, and it was not revealed in the interaction with applying UF statistically (Table 3).

The RTE of applying UF (pre- vs. post-UF) and the reduction of pre-UF MCF-EXTEM (≤ 50.5 mm vs. > 50.5 mm) on Hct and ROTEM parameter values are illustrated in Fig. 3 and presented in Supplementary Table 2. The RTE of pre-UF MCF-EXTEM ≤ 50.5 mm increased from 0.26 to 0.39 following the application of UF. Meanwhile, the RTE of pre-UF MCF-EXTEM > 50.5 mm remained unchanged, shifting only marginally from 0.77 to 0.75 after UF.

### Discussion

As the primary objective, applying UF significantly increased MCF-EXTEM at the end of CPB for cardiac surgery. MCF-EXTEM depicts the degree of clot firmness that was the contribution of platelet and fibrinogen [7]. The observed change in MCF-EXTEM was approximately 2.5 mm, but it would be clinically relevant in affecting the decision-making for coagulation management. Furthermore, in the analyses employing the cut-off value of ROC, applying UF increased MCF-EXTEM in patients with reduced pre-UF MCF-EXTEM value, while it did not in patients with sustained pre-UF MCF-EXTEM value.

Without a doubt, UF would concentrate all blood components, including RBCs, fibrinogen, platelets, and clotting factors. Howev-

---

**Table 1. Demographic Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>163.3 ± 9.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63 ± 12</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.7 ± 15.5</td>
</tr>
<tr>
<td>MV surgery</td>
<td>17</td>
</tr>
<tr>
<td>AV surgery</td>
<td>8</td>
</tr>
<tr>
<td>MV and TV surgery</td>
<td>3</td>
</tr>
<tr>
<td>MV and AV surgery</td>
<td>2</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>206 ± 72</td>
</tr>
<tr>
<td>Filtered free water (ml)</td>
<td>1,350 (1,200, 1,925)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number of patients or median (Q1, Q3). MV: mitral valve, AV: aortic valve, TV: tricuspid valve, CPB: cardiopulmonary bypass, RBC: red blood cell.

**Table 2. The Changes of Hct and ROTEM Parameters after Anesthesia Induction, before and after Applying UF, and after Weaning from CPB and Protamine Neutralization (n = 30)**

<table>
<thead>
<tr>
<th></th>
<th>Pre-CPB</th>
<th>Pre-UF</th>
<th>Post-UF</th>
<th>Post-CPB</th>
<th>Pre-UF vs. Post-UF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct (%)</td>
<td>34.0 (31.0, 39.0)</td>
<td>22.5 (19, 25)</td>
<td>25.5 (23.8, 28.3)</td>
<td>27.0 (24.8, 29.3)</td>
<td>4.565 &lt; 0.001* 0.83</td>
</tr>
<tr>
<td>CT-EXTEM (s)</td>
<td>69.5 (59, 84.3)</td>
<td>82.5 (72.8, 104.3)</td>
<td>82.0 (71.8, 87.3)</td>
<td>100.0 (77.5, 112.8)</td>
<td>−0.695 0.487 0.13</td>
</tr>
<tr>
<td>CFT-EXTEM (s)</td>
<td>81.5 (51.0, 98.0)</td>
<td>105 (70.0, 185.8)</td>
<td>97.0 (69.0, 165.8)</td>
<td>121.5 (104.5, 200.5)</td>
<td>−0.751 0.453 0.14</td>
</tr>
<tr>
<td>MCF-EXTEM (mm)</td>
<td>62.5 (57.8, 71.3)</td>
<td>48.0 (38.8, 54)</td>
<td>50.5 (40, 56)</td>
<td>53.0 (41.8, 57.8)</td>
<td>2.431 0.015* 0.44</td>
</tr>
<tr>
<td>A5-FIBTEM (mm)</td>
<td>18.5 (12.8, 24.8)</td>
<td>9.0 (6.8, 12.0)</td>
<td>9.5 (8.5, 15.8)</td>
<td>10.5 (6.8, 16)</td>
<td>1.150 0.250 0.21</td>
</tr>
<tr>
<td>MCF-FIBTEM (mm)</td>
<td>20.0 (13.2, 25.8)</td>
<td>10.5 (8, 13.3)</td>
<td>10.5 (8.8, 17.5)</td>
<td>11.5 (7, 18.3)</td>
<td>0.422 0.673 0.08</td>
</tr>
<tr>
<td>MCF-PLTEM (mm)</td>
<td>46.5 (41.5, 48.8)</td>
<td>38.0 (28.5, 42.5)</td>
<td>38.5 (31.5, 46.0)</td>
<td>38.5 (32.0, 45.8)</td>
<td>−1.725 0.084 −0.31</td>
</tr>
<tr>
<td>LI30-EXTEM (%)</td>
<td>100 (100, 100)</td>
<td>100 (100, 100)</td>
<td>100 (100, 100)</td>
<td>100 (100, 100)</td>
<td>0.000 &gt; 0.99 0.00</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). Hct: hematocrit, ROTEM: rotational thromboelastometry, UF: ultrafiltration, CPB: cardiopulmonary bypass, CT-EXTEM: clotting time of EXTEM, CFT-EXTEM: clot formation time of EXTEM, MCF-EXTEM: maximum clot firmness of EXTEM, A5-FIBTEM and MCF-FIBTEM: clot amplitude at 5 min after clot initiation and maximum clot firmness in FIBTEM, MCF-PLTEM: lysis index at 30 min of EXTEM, Pre-CPB: before induction, Pre-UF: immediately before applying ultrafiltration, Post-UF: immediately after applying ultrafiltration, Post-CPB: after weaning from CPB and The comparisons of Pre-UF vs. Post-UF were made by Wilcoxon Signed Ranks Tests. Z: estimated statistics, r: effect size. *two-sided P < 0.05.
Our study showed that, despite the significant MCF-EXTEM increase, UF could not demonstrate substantial increases of CT-EXTEM, MCF-FIBTEM, and MCF-PLTEM, depicting the specific contributions of clotting factors, fibrinogen, and platelets, respectively.

As aforementioned, the apparent increase in MCF-EXTEM is due to the combined effect of increased platelet and fibrinogen levels. However, unless the degree of fibrinogen or platelet dilution reaches a certain level, even an intense degree of UF-induced fibrinogen or platelet concentration will not increase MCF-FIBTEM or MCF-PLTEM values. Our results with the increased MCF-PLTEM and MCF-EXTEM without changes in MCF-FIBTEM agreed with a previous study in which the impact of UF on platelet function in cardiac surgery are variable [1].

Fig. 2. The estimation of a positive response of MCF-EXTEM to applying UF and sub-group analyses of actual MCF-EXTEM changes employing the estimated cut-off values. A positive response was defined as any increase of MCF-EXTEM after applying UF. (A) The receiver operating characteristic analysis of the changes in MCF-EXTEM speculated that the estimated AUROC to discriminate a significant increase in MCF-EXTEM to applying UF was 0.89 (95% CI [0.77, 1.00], P < 0.001). The estimated cut-off value of pre-UF MCF-EXTEM to predict the positive response was 50.5 mm, with a sensitivity of 84.2% and a specificity of 81.8%. (B) Analyses employing the cut-off value, UF significantly increased MCF-EXTEM (40.5 [33.8, 45.8] mm vs. 42.5 [38.5, 53.0] mm) when pre-UF MCF-EXTEM was reduced (≤ 50.5 mm, n = 18/30), and UF did not affect MCF-EXTEM when pre-UF MCF-EXTEM was maintained (> 50.5 mm, n = 12 / 30; P < 0.001 for the between-groups, P = 0.046 for UF, P = 0.003 for interaction). EXTEM: extrinsically-activated test with tissue factor, MCF-EXTEM: maximum clot firmness of EXTEM, UF: ultrafiltration, Pre-UF: immediately before applying UF, Post-UF: immediately after applying UF, AUROC: area under the receiver operating curve.

Not only UF-induced hemococoncentration but also CPB-induced hemodilution affect fibrinogen and platelet levels, the key factors of optimal clot formation and polymerization [12–14] and post-CPB coagulation management [7,15]. Therefore, the direct effects of CPB-induced hemodilution on all blood elements may have to be considered for interpreting our results regarding UF-induced change. The degree of diluting each element or compromising the element’s activity seems proportional to the extent of hemodilution or infused IV fluid [16,17]. However, still, dilution thresholds for inducing an apparent change in each element’s activity were variable [18].

In our study, CPB induced 30%–40% hemodilution, reducing Hct from 34.0% to 22.5%. The reduced pre-UF amplitudes of all EXTEM, PLTEM, and FIBTEM tracings confirmed that this CPB-induced hemodilution reduced fibrinogen and platelet levels [19]. The A5-FIBTEM value was reduced to 9.0 mm, comparable to the 100–125 mg/dl fibrinogen level [13,14]. However, a previous study showed that, even in an intense CPB-hemodilution, platelet level was well maintained, presumably due to the sequestered platelets from the spleen and lungs [20].

Applying CPB itself also alters the fibrinogen/fibrin cascade, resulting in reduced fibrin synthesis, consumption, and degradation [21–23]. At the same time, it increases the level of fibrinogen deg-
radiation products, interfering with fibrin formation, till the post-CPB period [24]. Dilution of RBC also reduces fibrin’s activity [25].

In addition to hemodilution- and UF-induced changes in the levels of pro-coagulants, that of anti-coagulants could be a critical determinant of overall coagulation performance. CPB reduced antithrombin (AT) activity and other protease inhibitors [16,17] and paradoxically induced a prothrombotic state [26]. Systemic heparinization also directly affects AT activity, probably relieving CPB-induced prothrombotic status [27]. Applying UF also increases the heparin concentration [28].

The amount of filtered water exceeding a certain level would be an important factor for providing tangible UF-induced changes in MCF-EXTEM. However, in our study, there was no significant correlation between the volume of filtered free water and the degree of MCF-EXTEM changes. As in our study, even a massive filtration could not resolve the extreme hemodilution status in some patients. In this context, the degree of CPB-induced hemodilution before applying UF is also a critical factor in expecting a positive response to applying UF.

Meanwhile, pre-UF values of MCF-EXTEM could discriminate the positive response to UF with high sensitivity and specificity in ROC analysis, and its estimated cut-off value for predicting the positive response was 50.5 mm. The cut-off value was similar to the lower limit of the reference value of MCF-EXTEM for sufficient clot firmness (ranges of 50-70 mm) in a ROTEM-guided bleeding management [7].

In the subgroup analyses employing the cut-off value (> or ≤ 50.5 mm), UF could provide tangible increases in EXTEM assays in the patients with the already reduced pre-UF MCF-EXTEM (≤ 50.5 mm). By contrast, in patients with sustained pre-UF MCF-EXTEM values (> 50.5 mm), UF could not affect MCF-EXTEM. These dichotomized results suggest that UF increases MCF-EXTEM only in patients with reduced pre-UF MCF-EXTEM (the RTE of pre-UF:post-UF with MCF-EXTEM ≤ 50.5 mm = 0.26:0.39, Fig. 3). These results may potentially explain why previous studies could not consistently demonstrate a response to UF-induced changes in coagulation performance [5,12].

The absence of MCF-FIBTEM change, even in patients with reduced pre-UF MCF-EXTEM, supports the idea that the UF-induced increase in fibrinogen level might be less than a certain level to produce enhanced MCF-FIBTEM.

As in our study, it would be beneficial to perform a viscoelastic test near the end of CPB in predicting the efficacy and volume of UF as part of coagulation management [6]. ROTEM analyses before the end of CPB could prompt the preparation and administration of blood products or factor concentrates.

Our study did not analyze the possible relationship between UF and post-CPB bleeding nor determine the changes in platelet count and function before and after applying UF, despite the subgroup results suggesting the UF-induced increase in platelet

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-UF</th>
<th>Post-UF</th>
<th>Pre-UF</th>
<th>Post-UF</th>
<th>Effect of reduction in MCF-EXTEM ≤ 50.5 mm or not</th>
<th>Effect of applying UF</th>
<th>Interaction between two factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct (%)</td>
<td>20.5 (19.0, 23.0)</td>
<td>25.0 (23.0, 27.3)</td>
<td>24.5 (21.5, 26.0)</td>
<td>26.0 (24.0, 30.0)</td>
<td>0.031*</td>
<td>&lt; 0.001*</td>
<td>0.032*</td>
</tr>
<tr>
<td>CT-EXTEM (s)</td>
<td>87.0 (73.5, 113.0)</td>
<td>84.0 (75.0, 95.5)</td>
<td>82.0 (72.3, 89.0)</td>
<td>78.5 (66.0, 83.5)</td>
<td>0.067</td>
<td>0.389</td>
<td>0.627</td>
</tr>
<tr>
<td>CFT-EXTEM (s)</td>
<td>152.5 (92.5, 263.8)</td>
<td>119.5 (73.0, 309.0)</td>
<td>70.0 (58.0, 103.3)</td>
<td>82.0 (62.0, 114.8)</td>
<td>0.003*</td>
<td>0.681</td>
<td>0.043*</td>
</tr>
<tr>
<td>MCF-EXTEM (mm)</td>
<td>40.5 (33.8, 45.8)</td>
<td>42.5 (38.5, 53.0)</td>
<td>57.5 (52.3, 60.8)</td>
<td>56.0 (51.0, 60.8)</td>
<td>&lt; 0.001*</td>
<td>0.046*</td>
<td>0.003*</td>
</tr>
<tr>
<td>A5-FIBTEM (mm)</td>
<td>7.0 (5.5, 16.8)</td>
<td>9.0 (6.8, 18.3)</td>
<td>10.5 (9.0, 11.8)</td>
<td>10.0 (9.0, 13.0)</td>
<td>0.003*</td>
<td>0.117</td>
<td>0.642</td>
</tr>
<tr>
<td>MCF-FIBTEM (mm)</td>
<td>8.0 (6.5, 18.0)</td>
<td>10.0 (6.8, 22.0)</td>
<td>11.5 (10.3, 13.0)</td>
<td>12.0 (10.0, 14.8)</td>
<td>0.012*</td>
<td>0.427</td>
<td>0.151</td>
</tr>
<tr>
<td>MCF-PLTEM (mm)</td>
<td>29.5 (25.0, 37.8)</td>
<td>33.5 (29.5, 39.3)</td>
<td>42.5 (40.0, 50.0)</td>
<td>43.0 (39.5, 48.8)</td>
<td>&lt; 0.001*</td>
<td>0.204</td>
<td>0.272</td>
</tr>
<tr>
<td>LI30-EXTEM (%)</td>
<td>100 (100, 100)</td>
<td>100 (100, 100)</td>
<td>100 (100, 100)</td>
<td>100 (100, 100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). ROTEM: rotational thromboelastometry, UF: ultrafiltration, Pre-UF: immediately before applying UF, Post-UF: immediately after applying UF, Hct: hematocrit, EXTEM: extrinsically-activated test with tissue factor, FIBTEM: fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D, PLTEM: calculated value for estimating platelet contribution (PLTEM = EXTEM – FIBTEM) CT-EXTEM: clotting time of EXTEM, CFT-EXTEM: clot formation time of EXTEM, MCF-EXTEM: maximum clot firmness of EXTEM, A5-FIBTEM and MCF-FIBTEM: clot amplitude at 5 min after clot initiation and maximum clot firmness in FIBTEM, MCF-PLTEM: calculated value for estimating platelet contribution (MCF-PLTEM = MCF-EXTEM – MCF-FIBTEM), LI-30 EXTEM: lysis index at 30 min of EXTEM, ANOVA: Analysis of variance, and Nonparametric RM ANOVA with one repeated and one between factors. *two-side P value < 0.05.
Fig. 3. The RTE of non-parametric repeated measures ANOVA with one repeated and one between factors (F1-LD-F1 model) for analyses employing the cut-off value. The black line indicates the subgroup of pre-UF MCF-EXTEM ≤ 50.5 mm (n = 18), the grey line indicates the subgroup of pre-UF MCF-EXTEM > 50.5 mm (n = 12). The dots and bars indicate RTE values and their 95% CI. RTE: relative treatment effect, ANOVA: Analysis of variance, Hct: hematocrit, UF: ultrafiltration, Pre-UF: immediately before applying UF, Post-UF: immediately after applying UF, EXTEM: extrinsically-activated test with tissue factor, FIBTEM: fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin D, PLTEM: calculated value for estimating platelet contribution (PLTEM = EXTEM – FIBTEM), MCF-EXTEM: maximum clot firmness of EXTEM, CT-EXTEM: clotting time of EXTEM, CFT-EXTEM: clot formation time of EXTEM, A5-FIBTEM and MCF-FIBTEM: clot amplitude at 5 min after clot initiation and MCF in FIBTEM, MCF-PLTEM: calculated value for estimating platelet contribution (= MCF-EXTEM – MCF-FIBTEM), and LI-30 EXTEM: lysis index at 30 min of EXTEM.

https://doi.org/10.4097/kja.23698
count. UF’s contribution by eliminating CPB-induced proinflammatory cytokines was not accounted for [29]. UF did not affect clot initiation, as indicated by the CT-EXTEM change in our study. Still, CT-EXTEM could be insensitive and not affected until the hemodilution of > 60%–70% in a previous report [12].

Our study demonstrated that UF during CPB improved coagulation performance, especially in patients with CPB-induced dilutional coagulopathy. A prospective study is warranted to confirm whether the cut-off value during CPB can be used to expect the UF’s positive impact as a part of the ROTEM-guided algorithm for managing coagulation during cardiac surgery [7].

Funding

This study was supported by the Konkuk University Medical Centre Research Grant 2020.

Conflicts of Interest

Klaus Görlinger works as the Medical Director of TEM innovations GmbH/Werfen PBM, Munich, Germany since 2012.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Jaemoon Lee (Conceptualization; Data curation; Formal analysis; Writing – original draft)
Dong-Kyu Lee (Conceptualization; Data curation; Formal analysis)
Won-Kyoun Kwon (Conceptualization; Data curation; Formal analysis)
Sookyung Lee (Data curation; Formal analysis)
Chung-Sik Oh (Conceptualization; Data curation; Formal analysis)
Tae-Yop Kim (Conceptualization; Data curation; Formal analysis; Funding acquisition; Writing – review & editing)

ORCID

Jaemoon Lee, https://orcid.org/0000-0001-5974-2955

Dong-Kyu Lee, https://orcid.org/0000-0002-4068-2363
Won-Kyoun Kwon, https://orcid.org/0000-0001-5753-2479
Sookyung Lee, https://orcid.org/0009-0003-2105-2539
Chung-Sik Oh, https://orcid.org/0000-0001-8874-5186
Klaus Görlinger, https://orcid.org/0000-0002-7315-9528
Tae-Yop Kim, https://orcid.org/0000-0003-0806-8969

Supplementary Materials

Supplementary Table 1. Correlation analysis between changes in ROTEM parameters and the amount of filtered-free water.
Supplementary Table 2. The RTE values of non-parametric repeated measures ANOVA with one repeated and one between factors (F1-LD-F1 model) for analyses employing the cut-off value.

References

Association between De Ritis ratio and intraoperative blood transfusion in patients undergoing surgical clipping of unruptured intracranial aneurysms: a single center, retrospective, propensity score-matched study

Ji-Hoon Sim*, Chan-Sik Kim*, Seungil Ha, Hyunkook Kim, Yong-Seok Park, Joung Uk Kim

Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Although elective surgery for unruptured intracranial aneurysms (UIA) has increased, few studies have evaluated the risk factors for transfusion during UIA surgery. We evaluated the association between the preoperative De Ritis ratio (aspartate transaminase/alanine transaminase) and the incidence of intraoperative transfusion in patients who had undergone surgical UIA clipping.

Methods: Patients who underwent surgical clipping of UIA were stratified into two groups according to the preoperative De Ritis ratio cutoff levels (< 1.54 and ≥ 1.54), and the propensity score (PS)-matching analysis was performed to compare the incidence of intraoperative transfusion. Logistic regression analyses were performed to determine the risk factors for intraoperative transfusion. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses were performed to verify the improvement in the intraoperative transfusion predictive model upon addition of the De Ritis ratio.

Results: Intraoperative transfusion incidence was 15.4% (77/502). We observed significant differences in the incidence of intraoperative transfusion (16.2% vs. 39.7%, P = 0.004) between the groups after matching. In the logistic regression analyses, the De Ritis ratio ≥ 1.54 was an independent risk factor for transfusion (odds ratio [OR]: 3.04, 95% CI [1.53, 6.03], P = 0.002). Preoperative hemoglobin (Hb) value was a risk factor for transfusion (OR: 0.33, 95% CI [0.24, 0.47], P < 0.001). NRI and IDI analyses showed that the De Ritis ratio improved the intraoperative blood transfusion predictive models (P = 0.031 and P = 0.049, respectively).

Conclusions: De Ritis ratio maybe a significant risk factor for intraoperative transfusion in UIA surgery.

Keywords: Alanine transaminase; Aspartate aminotransferases; Blood coagulation; Blood transfusion; Intracranial aneurysm; Propensity score.

Introduction

Intracranial aneurysm is an abnormal enlargement of a cerebral artery, usually occurring at the arterial bifurcation or circle of Willis [1], and is one of the major diseases affecting 2%–5% of the global population [2–4]. Recently, the widespread use of noninva-
sive imaging methods such as magnetic resonance imaging has increased the diagnosis of incidentally discovered unruptured intracranial aneurysms (UIAs) [5]. This has led to increased prophylactic endovascular therapy or elective surgical clipping of asymptomatic UIA to prevent subarachnoid hemorrhage (SAH) [6]. However, despite the fact that both surgical and endovascular treatment for UIA carry a risk of up to 5% mortality and morbidity [7], few studies have investigated the predictors and risk factors for bleeding and transfusion during UIA surgery [8], and available information is limited.

The De Ritis ratio is a prognostic biomarker that can be easily calculated by dividing the serum levels of aspartate aminotransferase (AST) by the alanine aminotransferase (ALT) in blood tests [9,10]. The De Ritis ratio is a predictor of survival and complications in patients undergoing some surgeries as well as various cancers [11–13]. Recent studies have reported the relationship between serum aminotransferase (AST and ALT) level and intracerebral hemorrhage (ICH) [14,15], and the De Ritis ratio may be associated with vascular diseases [16,17]. However, to date, no study has reported the association between the De Ritis ratio and incidence of intraoperative transfusion during intracranial aneurysm surgery. Therefore, in this study, we evaluated the correlation between the preoperative De Ritis ratio and the incidence of intraoperative transfusion in patients who underwent surgical clipping of UIA.

**Materials and Methods**

**Study design and population**

Patients over 18 years of age who underwent surgical clipping of UIAs between January 2018 and April 2020 were enrolled in this study. The Institutional Review Board of Asan Medical Center (Republic of Korea; protocol number: 2022-0755) approved our study, and the need for written informed consent was waived due to its retrospective nature. The exclusion criteria were as follows: patients undergoing revision surgery; patients with hemotologic disease; patients with ongoing medication of anticoagulants, such as antiplatelet agents and warfarin; and patients with incomplete data or missing AST/ALT values.

**Anesthetic technique**

Three anesthesiologists were involved in the anesthesia for neurosurgery during the study period, and they performed as one neuroanesthesia team, with the same anesthesia protocol. For general anesthesia, routine monitors, including noninvasive blood pressure, electrocardiography, and pulse oximetry, were used. Following local infiltration with lidocaine, an arterial catheter was inserted into a radial artery for continuous blood pressure monitoring. For anesthesia induction, 2 mg/kg of propofol and 0.6 mg/kg of rocuronium were administered intravenously. To maintain anesthesia after intubation, propofol and remifentanil were infused using a target-controlled infusion pump (Orchestra®, Fresenius Vial), increasing the effect-site concentration to 2.5–3.0 μg/ml and 10–12 ng/ml, respectively. The Marsh and Minto model were used for target-controlled infusion of propofol and remifentanil, respectively. To prevent hypotension, phenylephrine (0.5–3.0 mg/h) was continuously infused to maintain the mean arterial pressure above 65–70 mmHg. During anesthesia, crystalloid solutions (0.9% normal saline or plasma solution) or colloid solutions (5% albumin) were administered. During surgery, when the plasma hemoglobin (Hb) level reduced to less than 8 g/dl, packed red blood cell (RBC) transfusion was performed, and the Hb level was maintained at more 10 g/dl in patients with coronary artery disease. Hemodynamic instability due to acute massive blood loss was also an indication for transfusion.

**Clinical data collection and outcome assessments**

Demographic data and pre and intraoperative variables were collected through an electronic medical record system. Demographic and preoperative data included age, height, weight, body mass index (BMI), sex, and aneurysm location and number. Data on comorbid diseases such as diabetes mellitus (DM), hypertension (HTN), cardiovascular disease (CVD), cerebrovascular accident (CVA), and chronic kidney disease (CKD) were also collected.

Laboratory variables included preoperative Hb, platelet count, white blood cell, prothrombin time (PT), activated partial thromboplastin clotting time, RBC distribution width, and creatinine, protein, albumin, blood urea nitrogen, C-reactive protein, AST, ALT, sodium, and potassium levels. All patients’ laboratory blood tests were performed within 14 days prior to surgery. Intraoperative variables included operation time, surgeon who performed the surgery, total crystalloids, urine output, albumin use, mannitol use, RBC transfusion, and RBC unit.

The study outcome was the comparison of the intraoperative transfusion incidence according to the preoperative De Ritis ratio cutoff level (< 1.54 and ≥ 1.54) before and after the propensity score (PS) analysis. Analysis of the risk factors for intraoperative transfusion and evaluation of the association between the preoperative De Ritis ratio and intraoperative transfusion were also the study’s objectives. Additionally, receiver operating characteristic (ROC), net reclassification improvement (NRI), and integrated
discrimination improvement (IDI) analysis were employed to evaluate the improvement of model power when adding the De Ritis ratio to the risk model of intraoperative blood transfusion.

Statistical analysis

Data are appropriately presented as means and standard deviations (SDs), median of interquartile ranges, or numbers with ratios. Categorical data was analyzed using the chi-square test or Fisher’s exact test, and continuous data was evaluated using the unpaired t-test or Mann–Whitney U test. To reduce the impact of potential confounders, a PS-matching analysis was performed using 14 variables: age, height, weight, BMI, sex, DM, HTN, CVD, CVA, CKD, Hb level, and aneurysm location, number, and maximum size (Table 1). The criteria for selecting variables for inclusion in the PS model were based on perioperative variables that may influence intraoperative blood transfusion based on the knowledge gained from the existing literature [8,18]. Absolute standardized mean differences were calculated to detect imbalances between the two groups before and after matching. We chose 1:1 PS matching using the nearest neighbor method with a caliper of 0.2. After performing 1:1 PS matching, continuous variables were compared by paired t-test or Wilcoxon signed-rank tests, and categorical variables were compared using the McNemar test. We also used multivariate logistic regression analysis to determine risk factors for intraoperative blood transfusion.

All variables with P values < 0.1 in univariate analysis were included in the multivariate analysis. A ROC curve analysis was used to determine the cutoff value of the De Ritis ratio for intraoperative transfusion. In addition, NRI and IDI analyses were used to evaluate the predictive value of the preoperative De Ritis ratio for intraoperative blood transfusion discrimination. NRI and IDI are statistical methods used to assess the improvement in predictive performance when a novel biomarker is added to a model containing standard biomarkers [19]. Any P value < 0.05 was considered statistically significant. Data manipulation and statistical analysis were performed using IBM SPSS Statistics version 22.0 for Windows (IBM Corp.) and R version 3.1.2 (R Foundation for Statistical Computing).

Results

Of the 530 enrolled patients, 29 were excluded because they did not fulfill the study criteria. Hence, a total of 501 patients were enrolled in this study (Fig. 1).

Table 1 shows the baseline characteristics and perioperative variables of the study population. The mean age and BMI of the

Table 1. Baseline Characteristics & Perioperative Variables of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 501)</th>
<th>Before matching</th>
<th>After matching</th>
<th>P value</th>
<th>SMD</th>
<th>De Ritis ratio &lt; 1.54</th>
<th>P value</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61.5 ± 8.2</td>
<td>60.9 ± 7.8</td>
<td>61.0 ± 8.2</td>
<td>0.534</td>
<td>0.142</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.1 (152.7, 164.0)</td>
<td>158.0 (153.0, 164.6)</td>
<td>155.6 (151.5, 160.8)</td>
<td>0.018</td>
<td>0.329</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.5 (56.5, 70.2)</td>
<td>63.1 (56.9, 71.9)</td>
<td>57.5 (52.0, 62.2)</td>
<td>&lt; 0.001</td>
<td>0.681</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.0 (23.1, 27.0)</td>
<td>25.2 (23.3, 27.2)</td>
<td>23.2 (22.5, 25.2)</td>
<td>&lt; 0.001</td>
<td>0.633</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (F)</td>
<td>344 (68.7)</td>
<td>306 (61.2)</td>
<td>348 (69.3)</td>
<td>0.218</td>
<td>0.200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>61 (12.2)</td>
<td>56 (11.2)</td>
<td>57 (11.4)</td>
<td>1.000</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>208 (41.5)</td>
<td>181 (36.7)</td>
<td>207 (35.4)</td>
<td>1.000</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>21 (4.2)</td>
<td>19 (3.8)</td>
<td>22 (3.4)</td>
<td>1.000</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>30 (6.0)</td>
<td>26 (5.2)</td>
<td>32 (4.8)</td>
<td>1.000</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>5 (1.0)</td>
<td>4 (0.8)</td>
<td>6 (0.9)</td>
<td>1.000</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm location</td>
<td>104 (20.8)</td>
<td>91 (18.2)</td>
<td>105 (20.9)</td>
<td>1.000</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>206 (41.2)</td>
<td>181 (36.0)</td>
<td>218 (39.3)</td>
<td>1.000</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>198 (39.5)</td>
<td>178 (35.5)</td>
<td>209 (33.7)</td>
<td>1.000</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA and others</td>
<td>29 (5.8)</td>
<td>25 (5.0)</td>
<td>30 (4.9)</td>
<td>1.000</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

https://doi.org/10.4097/kja.23415

(Continued to the next page)
Table 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>Before matching</th>
<th></th>
<th></th>
<th>After matching</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>De Ritis ratio</td>
<td>De Ritis ratio</td>
<td>P value</td>
<td>SMD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 501)</td>
<td>&lt; 1.54</td>
<td>≥ 1.54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 430)</td>
<td>(n = 71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm number</td>
<td>319 (63.7)</td>
<td>282 (65.6)</td>
<td>37 (21.2)</td>
<td>0.026</td>
<td>0.454</td>
<td></td>
</tr>
<tr>
<td></td>
<td>117 (23.4)</td>
<td>91 (21.2)</td>
<td>26 (36.6)</td>
<td>21.2 ± 6.2</td>
<td>162.2 ± 55.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48 (9.6)</td>
<td>40 (9.3)</td>
<td>8 (11.3)</td>
<td>9 (13.2)</td>
<td>7 (10.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (2.0)</td>
<td>10 (2.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (1.4)</td>
<td>7 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm maximum size (mm)</td>
<td>4.5 (3.4, 6.0)</td>
<td>4.6 (3.4, 6.0)</td>
<td>4.5 (3.7, 6.0)</td>
<td>0.712</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.940</td>
<td>2 (2.9)</td>
<td>3.8 ± 0.3</td>
<td>0.006</td>
<td>0.998</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 (35.3)</td>
<td>24 (35.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (13.2)</td>
<td>7 (10.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.9 (12.2, 13.9)</td>
<td>13.0 (12.3, 14.0)</td>
<td>12.2 (11.7, 12.9)</td>
<td>&lt; 0.001</td>
<td>0.613</td>
<td>12.6 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>233.0 (197.0, 267.0)</td>
<td>236.0 (201.0, 268.0)</td>
<td>216.0 (191.0, 240.5)</td>
<td>0.013</td>
<td>0.175</td>
<td>242.8 ± 61.5</td>
</tr>
<tr>
<td></td>
<td>5.8 (4.9, 6.8)</td>
<td>5.9 (5.0, 6.9)</td>
<td>5.5 (4.8, 6.5)</td>
<td>0.043</td>
<td>0.279</td>
<td>6.3 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>1.0 (0.9, 1.0)</td>
<td>1.0 (0.9, 1.0)</td>
<td>1.0 (0.9, 1.0)</td>
<td>0.025</td>
<td>0.244</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>26.2 (25.0, 27.6)</td>
<td>26.2 (25.0, 27.6)</td>
<td>26.4 (24.8, 27.6)</td>
<td>0.623</td>
<td>0.124</td>
<td>26.9 ± 4.2</td>
</tr>
<tr>
<td></td>
<td>0.8 (0.7, 0.9)</td>
<td>0.8 (0.7, 0.9)</td>
<td>0.7 (0.7, 0.8)</td>
<td>0.950</td>
<td>0.058</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>7.0 (6.7, 7.3)</td>
<td>7.0 (6.8, 7.3)</td>
<td>7.0 (6.6, 7.3)</td>
<td>0.400</td>
<td>0.166</td>
<td>7.0 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>3.9 (3.7, 4.1)</td>
<td>3.9 (3.7, 4.1)</td>
<td>3.8 (3.7, 4.0)</td>
<td>0.172</td>
<td>0.174</td>
<td>3.8 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>210 (180.0, 250.0)</td>
<td>210 (180.0, 250.0)</td>
<td>200 (170.0, 240.0)</td>
<td>0.068</td>
<td>0.243</td>
<td>23.6 ± 9.4</td>
</tr>
<tr>
<td></td>
<td>180 (140.0, 260.0)</td>
<td>200 (150.0, 270.0)</td>
<td>11.0 (9.0, 13.0)</td>
<td>&lt; 0.001</td>
<td>1.332</td>
<td>22.8 ± 13.4</td>
</tr>
<tr>
<td></td>
<td>142.0 (140.0, 143.0)</td>
<td>141.0 (140.0, 143.0)</td>
<td>142.0 (140.5, 143.0)</td>
<td>0.073</td>
<td>0.260</td>
<td>141.2 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>4.2 (4.0, 4.5)</td>
<td>4.2 (4.0, 4.5)</td>
<td>4.2 (4.1, 4.5)</td>
<td>0.788</td>
<td>0.037</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>0.466</td>
<td>0.022</td>
<td>0.466</td>
<td>0.022</td>
<td>0.466</td>
<td>0.466</td>
</tr>
<tr>
<td></td>
<td>0.644</td>
<td>0.077</td>
<td>0.644</td>
<td>0.077</td>
<td>0.644</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>0.594</td>
<td>0.122</td>
<td>0.594</td>
<td>0.122</td>
<td>0.594</td>
<td>0.122</td>
</tr>
<tr>
<td></td>
<td>1450.0 (1160.0, 196.0)</td>
<td>1470.0 (1160.0, 198.0)</td>
<td>1400.0 (1140.0, 188.5)</td>
<td>0.466</td>
<td>0.022</td>
<td>162.2 ± 55.2</td>
</tr>
<tr>
<td></td>
<td>178 (35.5)</td>
<td>155 (30.9)</td>
<td>23 (4.6)</td>
<td>27 (19.9)</td>
<td>41 (30.1)</td>
<td>162.2 ± 72.2</td>
</tr>
<tr>
<td></td>
<td>323 (64.5)</td>
<td>275 (54.9)</td>
<td>48 (9.6)</td>
<td>23 (16.9)</td>
<td>45 (33.1)</td>
<td>0.998 &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>600.0 (310.0, 960.0)</td>
<td>600.0 (310.0, 960.0)</td>
<td>650.0 (330.0, 1025.0)</td>
<td>0.479</td>
<td>0.116</td>
<td>695.6 ± 488.3</td>
</tr>
<tr>
<td></td>
<td>4 (0.8)</td>
<td>2 (0.5)</td>
<td>2 (2.8)</td>
<td>0.179</td>
<td>0.186</td>
<td>748.0 ± 534.7</td>
</tr>
<tr>
<td></td>
<td>10 (2.0)</td>
<td>8 (1.9)</td>
<td>2 (2.8)</td>
<td>0.940</td>
<td>0.195</td>
<td>0.537 0.106</td>
</tr>
<tr>
<td></td>
<td>77 (15.4)</td>
<td>49 (11.4)</td>
<td>28 (39.4)</td>
<td>&lt; 0.001</td>
<td>0.680</td>
<td>0.476 0.246</td>
</tr>
<tr>
<td></td>
<td>0.2 ± 0.4</td>
<td>0.1 ± 0.4</td>
<td>0.5 ± 0.6</td>
<td>&lt; 0.001</td>
<td>0.577</td>
<td>0.2 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>0.023</td>
<td>0.2 ± 0.4</td>
<td>0.4 ± 0.6</td>
<td>0.013</td>
<td>0.430</td>
<td></td>
</tr>
</tbody>
</table>

patients were 61.5 years and 25.0 kg/m², respectively, and the majority were women (68.7%). Of the 502 patients, 61 (12.2%) had DM, 300 (59.9%) had HTN, 25 (5.0%) had CVD, 21 (4.2%) had CVA, and 8 (1.6%) had CKD. Most patients belonged to American Society of Anesthesiologists (ASA) class 2 (61.0%) and 3 (38.2%), while five patients belonged to ASA class 4 (0.8%). The middle cerebral arteries were the most common site for aneurysm (41.5%), and the median of the maximum aneurysmal size was 4.5 mm (Table 1). Two surgeons with more than 10 years of experience in neurovascular surgery performed aneurysm clipping during the study period. No significant statistical differences were observed in the De Ritis ratio groups between the two surgeons, even after PS matching. The incidence of intraoperative transfusion was 15.4% (77/502) and the average packed RBC transfusion volume was 1.0 unit in transfused patients. The average packed RBC transfusion volume across all patients was 0.2 unit (Table 1). Intraoperative aneurysm rupture did not occur in any of the cases. After 1:1 PS matching, all baseline characteristics and perioperative variables after matching showed no significant differences between the group with the De Ritis ratio < 1.54 (n = 68) and those with ≥ 1.54 (n = 68) (Table 1).

ROC curve analysis exhibits a preoperative De Ritis ratio cutoff value of 1.54 for intraoperative transfusion (area under the curve [AUC]: 0.661, sensitivity: 36.36%, specificity: 89.86%; Fig. 2). Using the cutoff value, 71 patients (14.2%) were categorized as part of the high De Ritis ratio group; and 430 patients (85.8%) as part of the low De Ritis ratio group (Table 1). Patients in the high De Ritis ratio group were older (P = 0.001), had a lower BMI (P < 0.001), and had a higher proportion of women. (P = 0.016). They also had higher aneurysm numbers (P = 0.026). Concerning laboratory variables, patients in the high De Ritis ratio group had lower Hb (P < 0.001) and platelet levels (P = 0.013) (Table 1).

**Study outcomes**

After PS-matched analysis, the incidences of intraoperative transfusion (39.7% vs. 16.2%, P = 0.004) and volume of RBC transfusion (0.4 ± 0.6 vs. 0.2 ± 0.4, P = 0.013) were significantly higher in the high De Ritis ratio group than in the low De Ritis group (Table 1).

In the multivariate analysis, the preoperative De Ritis ratio was identified as an independent risk factor for intraoperative transfusion (odds ratio [OR]: 3.04, 95% CI [1.53, 6.03], P = 0.002; Table 2). Additionally, the preoperative Hb value was also a risk factor for intraoperative transfusion (OR: 0.33, 95% CI [0.24, 0.47], P < 0.001; Table 2).

---

**Fig. 1.** Flowchart of the retrospective study. AST: aspartate aminotransferase, ALT: alanine aminotransferase.
The addition of the De Ritis ratio to the clinical predictive model for intraoperative transfusion, consisting of age, BMI, sex, CVD, preoperative Hb and albumin levels, and PT, showed no significant improvement in the AUC (P = 0.483) but significant improvement in discrimination measured by NRI (0.265, 95% CI [0.024, 0.507], P = 0.031) and IDI (0.027, 95% CI [0.000, 0.055], P = 0.049; Table 3).

**Discussion**

Our study demonstrated that the preoperative De Ritis ratio was an independent risk factor for intraoperative transfusion in patients who underwent UIA clipping. After scores-matching analysis, a significant difference was observed in the incidence of intraoperative transfusion according to the preoperative De Ritis ratio cutoff level. Additionally, the De Ritis ratio improved the predictive model for intraoperative blood transfusion in NRI and IDI analyses. These results suggest that the preoperative De Ritis ratio, together with previously well-known Hb levels, may be a significant risk factor for intraoperative transfusion in UIA surgery.

Only a few studies report the incidence and risk factors for intraoperative blood transfusion for the clipping of UIA. One study reported an incidence of intraoperative transfusion of 24.5% and identified older age, lower hematocrit level on admission, preoperative aneurysm rupture, severe intraventricular hemorrhage, and larger aneurysm size as preoperative factors associated with intraoperative transfusion [20]. Another study has reported an in-

![De Ritis ratio ROC curve](https://doi.org/10.4097/kja.23415)
Table 3. Improvement in AUC, NRI, and IDI by Addition of De Ritis ratio to Clinical Predictive Models

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC (95% CI)</th>
<th>P value</th>
<th>NRI (95% CI)</th>
<th>P value</th>
<th>IDI (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1*</td>
<td>0.839 (0.804, 0.870)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1* + De Ritis ratio</td>
<td>0.845 (0.794, 0.896)</td>
<td>0.483</td>
<td>0.265 (0.024, 0.507)</td>
<td>0.031</td>
<td>0.027 (0.000, 0.055)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). AUC: area under the curve, NRI: net reclassification improvement, IDI: integrated discrimination improvement, BMI: body mass index, CVD: cardiovascular disease, PT: prothrombin time, INR: international normalized ratio, Hb: hemoglobin, *Model 1 = age + BMI + sex + CVD + Hb + PT, INR + albumin.

Although UIA clipping surgeries are increasing with the advancement of imaging techniques, little is known about biomarkers that can predict bleeding and transfusion during UIA clipping surgery. Our study has a clinical value by demonstrating an association between a novel biomarker, the De Ritis ratio, and blood transfusion during UIA clipping surgery. While few studies have shown an association between AST or ALT levels and bleeding, studies linking them to intraoperative bleeding are rare. In a study that analyzed the national health insurance data for more than 100,000 cases, serum aminotransferase level was a significant predictor of ICH [14]. According to another international study on the East Asian population, elevated ALT levels were associated with an increased risk of ICH [15]. Although there is a known correlation between liver dysfunction and bleeding tendencies [25,26], the exact mechanism for the effect of abnormalities in aminotransferase levels on bleeding is not well understood. Along with the abnormalities in coagulation due to the changes in liver function, one can also consider changes in the physical properties of the blood vessels themselves. Brachial-ankle pulse wave velocity, a measure of arterial stiffness, is significantly associated with liver disease and various liver enzymes, particularly AST/ALT [17,27]. Although the exact mechanism by which the De Ritis ratio affects bleeding during aneurysm clipping surgery is unknown, it is believed that it may influence intraoperative blood transfusions through impaired coagulation resulting from liver dysfunction and changes in the physical properties of blood vessels, as described earlier.

There are some limitations to our study. First, due to the retrospective study design, unexpected bias cannot be ruled out, and it may be challenging to determine causality beyond correlations between variables. To overcome the limitations of this retrospective study, we performed PS matching and found that significant differences were observed in the incidence and volume of transfusions between the two groups even after matching. Second, we were unable to provide a precise mechanism for the association that the De Ritis ratio shows with blood transfusion during UIA clipping surgery. Further studies are needed to elucidate this mechanism. Third, to date, no study has accurately reported the cutoff value of the De Ritis ratio for intraoperative transfusion. More well-designed studies are required for accurate validation of the preoperative De Ritis ratio cutoff value that could predict transfusion and surgical outcomes. Fourth, there may have been differences in the determination of transfusion among the anesthesiologists that could cause provider bias, although the anesthesiologists performed as one neuroanesthesia team with no significant difference in practice. Lastly, due to the nature of the surgery...
itself and the retrospective nature of the study, the exact value of the estimated blood loss was difficult to measure and was excluded as an outcome variable. Future prospective studies on this topic will require accurate measurement and recording of this variable.

In conclusion, the De Ritis ratio might be a significant risk factor for intraoperative blood transfusion in patients undergoing UIA clipping surgery and has the potential to be a useful index for intraoperative anesthetic management in this patient population.

**Funding**

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (Ministry of Science and ICT) (Grant number: RS-2022-00165755). This study was also supported by grants (2023IE0008 and 2023IP0134) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Republic of Korea.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Data Availability**

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

**Author Contributions**

Ji-Hoon Sim (Data curation; Formal analysis; Funding acquisition; Methodology; Resources; Validation; Writing – original draft)
Chan-Sik Kim (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft)
Seungil Ha (Data curation; Formal analysis; Investigation; Methodology; Project administration)
Hyunkook Kim (Formal analysis; Investigation; Methodology; Resources; Validation)
Yong-Seok Park (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – review & editing)
Joung Uk Kim (Data curation; Supervision; Validation; Visualization)

**ORCID**

Ji-Hoon Sim, https://orcid.org/0000-0002-7790-1961
Chan-Sik Kim, https://orcid.org/0000-0002-5038-0203
Seungil Ha, https://orcid.org/0000-0003-1984-5110
Hyunkook Kim, https://orcid.org/0009-0002-3687-5389
Yong-Seok Park, https://orcid.org/0000-0002-3752-2211
Joung Uk Kim, https://orcid.org/0000-0001-9631-9849

**References**


Background: Open inguinal hernia repair (OIH R) surgery is a common surgical procedure, and ultrasound guided interfascial plane blocks can also be included in current approaches to postoperative multimodal analgesia regimens. This study aimed to compare the postoperative analgesic efficacy of the erector spinae plane block (ESPB) and transversalis fascia plane block (TFPB) in patients undergoing OIH R.

Methods: This prospective, randomized, assessor-blinded comparative study was conducted in the postoperative recovery room and ward of a tertiary hospital. A total of 80 patients with American Society of Anesthesiologists physical status I–III were enrolled and allocated equally to either the ESPB or TFPB group. The patients received standard multimodal analgesia in addition to an ultrasound-guided ESPB or TFPB. During the first 24 h postoperatively, tramadol consumption was assessed and pain levels at rest and during movement were compared using numeric rating scale (NRS) scores at 1, 3, 6, 9, 12, 18, and 24 h postoperatively.

Results: The results showed no difference in NRS scores at any time point between the groups, except for NRS at rest in the third hour. However, tramadol consumption was lower in the TFPB group than in the ESPB group overall (88 ± 75.2 vs. 131 ± 93.7 mg, respectively; P = 0.027, mean difference: −43, 95% CI [−80.82, −5.18]).

Conclusions: The TFPB leads to lower tramadol requirements in the first 24 h postoperatively than the ESPB in patients undergoing OIH R.

Keywords: Analgesia; Chronic pain; Herniorrhaphy; Inguinal hernia; Nerve block; Regional anesthesia; Ultrasonography.

Introduction

Regional anesthesia techniques, particularly with the development and incorporation of ultrasonography technology into anesthesia practice, have become popular and widely used by anesthesiologists over the past few decades, both as effective anesthesia techniques and as essential components of multimodal analgesia [1–3].

Approximately 20 million open or laparoscopic inguinal hernia repairs are performed annually, making it one of the most common operations conducted in general surgery [4]. Effective pain management is crucial for both types of surgeries, though patients under-
going open inguinal hernia repair (OIHR) often experience nociceptive pain initially and can potentially develop moderate to severe long-term chronic pain due to factors such as nerve damage. Some studies report an incidence of chronic pain up to 20% within 1–5 years of OIHR performed using a Liechtenstein incision [5]. While some publications suggest that incorporating regional anesthesia techniques into conventional analgesic approaches can mitigate chronic postoperative pain, evidence supporting this claim remains limited [5,6].

Opioids, non-steroidal anti-inflammatory drugs, and other analgesics are conventionally recommended to manage postoperative pain post-OIHR. However, procedure-specific pain management (PROSPECT) guidelines recommend a multimodal analgesic approach for postoperative pain management, including regional nerve techniques such as infiltrative analgesia, ilioinguinal/iliohypogastric (II-IH) nerve block, and transversus abdominalis plane block [7,8].

In OIHR surgery, the subcostal nerve (T12), ilioinguinal nerve (L1), iliohypogastric nerve (T12-L1), and sometimes the genitofemoral nerve (L1-L2) provide sensory innervation to the incision area [9–11]. According to the literature, II-IH and transversus abdominalis plane (TAP) blocks are used most frequently to treat postoperative pain following OIHR surgery [12]. To provide a wider sensory block to the inguinal region, some clinicians have chosen to apply blocks more proximal than the TAP and II-IH blocks. While the transversalis fascia plane block (TFPB) inhibits both the lateral cutaneous branches of the IH and subcostal nerves, it also inhibits sensory transmission to the T12-L1 dermatomes. This technique, originally only used for analgesia in iliac crest harvesting, has since been applied in a variety of surgeries including inguinal hernia repair, cesarean section, and varicocelectomy [13–15]. Numerous studies have also been conducted on the quadratus lumborum block and erector spinae plane block (ESPB), among others, which have become increasingly popular for adult and pediatric lower abdominal surgery [16–18].

The ultrasound-guided TFPB is a regional anesthesia technique defined by Hebbard that targets the T12-L1 dermatomes [19]. Similar to the techniques mentioned above, the TFPB has been used for inguinal region and lower abdominal surgeries owing to the target region of the block, and has been the subject of various clinical studies [20,21]. Although both the TFPB and ESPB have been found to reduce postoperative analgesic consumption in OIHR, no study has compared analgesic consumption between these two techniques in inguinal hernia repair surgery.

We hypothesized that these two techniques, which provide sensory block in similar anatomical regions, would show comparable reduction in analgesic requirements. This randomized controlled trial aimed to compare the effects of ESPB and TFPB on the analgesic requirement in the first 24 h after unilateral OIHR surgery. A secondary aim was to compare the pain scores between the two techniques within the same timeframe.

Materials and Methods

Study design

The design of this study was randomized, prospective, comparative, and assessor-blinded. The principles outlined in the Declaration of Helsinki, 2013 were adhered to throughout this research project, which was conducted at a tertiary hospital between May 2022 and November 2022. This study was approved by the local ethics committee (No. OMU-KAEK 2021/558) and the Medicines and Medical Devices Agency (No. 22-AKD-05) of the Turkish Ministry of Health and registered at ClinicalTrials.gov (No. NCT05344105).

This study included patients aged 18–65 years with an American Society of Anesthesiologists (ASA) physical status I–III scheduled to undergo elective unilateral open inguinal hernia surgery under spinal anesthesia. Patients with a body mass index (BMI) > 35 kg/m², coagulopathy, local infection or hematoma in the block target area, an allergy to local anesthetic (LA) agents or one of the drugs used in the study, history of chronic opioid and corticosteroid use as well as those who refused to participate, were unable to use the controlled analgesia system, had a psychiatric disorder, or were taking drugs that could affect the perception of pain, such as gabapentin/pregabalin, were excluded from the study. To further standardize the study, patients with surgical times < 30 min or > 180 min were excluded.

Randomization and blinding

While being transferred to the postoperative care unit (PACU), the patients were randomly allocated to the TFPB and ESPB groups by the anesthesia assistant using sequentially numbered opaque envelopes (n = 40 per group).

The healthcare professional responsible for randomization, who was not involved in patient evaluation, was the sole participant in this step. Each patient was assigned a randomized identification number that was used for all data collection and evaluation processes. Microsoft Excel 2010 was used to create the randomization ID numbers. The anesthesiologist responsible for data collection was blinded to the study group. A separate specialist who was not involved in data collection or analysis performed each block.
Anesthesia administration procedure

All patients received anesthesia and perioperative analgesia according to the same protocol. Intraoperative monitoring included electrocardiography, non-invasive blood pressure monitoring, and peripheral oxygen saturation measurements. To provide surgical anesthesia, a 26-gauge (G) spinal needle was inserted from the midline at the L3–L4/L4–L5 level and spinal anesthesia, consisting of 2.5–3 ml of 0.5% heavy bupivacaine, was administered to all patients in the seated position. No adjunctive medication was added to the spinal anesthesia. Patients were subjected to a pin-prick test after spinal anesthesia, and surgery was started after sensory block at the T10 level was achieved. The surgical team did not administer infiltrative analgesia to the surgical site. Twenty minutes before the end of surgery, 1 g paracetamol and 50 mg dexketoprofen were administered to all patients as part of the perioperative analgesia plan.

Block administration

All blocks were performed in a sterile environment at the end of the surgery in the block performance room. Each block was performed unilaterally using a low-frequency ultrasound device (3–5 MHz, Esoate MyLab™30Gold) at the same LA volume and concentration (30 ml of 0.25% bupivacaine).

TFPB application

Sonographic imaging was performed in the supine or lateral position when the supine image was insufficient. To identify the skin, subcutaneous tissue, external oblique muscle, internal oblique muscle, transversus abdominis muscle, deep fascia of the transversus abdominis muscle, retroperitoneal adipose tissue, peritoneum, and quadratus lumborum muscle, the transducer was placed such that it rested on the iliac crest in the transverse plane and was angled slightly caudally. A 21-G 100-mm needle (SonoPlex STIM, Pajunk) was advanced just as deep as the lateral end of the transversus abdominis muscle using the out-of-plane technique, and 30 ml of LA was injected.

ESPB application

With the patient in the lateral decubitus position, the transducer was placed 2–3 cm lateral to the spinous process of the T12 vertebra, and the erector spinae muscle and transverse process were visualized. Using the out-of-plane technique, the tip of the 21-G 100-mm needle was advanced in the interfacial plane deep to the erector spinae muscle, and 30 ml of LA was injected.

Standard postoperative analgesia protocol and pain evaluation process

All patients underwent identical analgesic protocols. After surgery, 1 g of paracetamol and 50 mg of dexketoprofen were administered intravenously at 8- and 12-h intervals, respectively. Tramadol-based patient-controlled analgesia (PCA), prepared at a concentration of 4 mg/ml in a total volume of 100 ml, was also administered. The bolus dose was adjusted to 10 mg and the lockout time was set to 20 min, with no basal infusion. In the recovery room, the PCA was initiated immediately after the block was performed, and the patient was instructed to request analgesia if the numeric rating scale (NRS) score was > 4. If the NRS score remained > 4 despite the use of PCA in the first 24 h, 25 mg of intravenous meperidine was planned as a rescue analgesic. The total amount of tramadol consumed was recorded at 1, 3, 6, 9, 12, 18, and 24 h postoperatively.

The NRS was used to assess pain at 1, 3, 6, 9, 12, 18, and 24 h postoperatively at rest and while coughing. The NRS is a one-dimensional scale that can be used to assess pain intensity in adults. It is a segmented numerical version of the visual analog scale and involves choosing an integer (ranging from 0 to 10) that most accurately reflects the current level of pain, where 0 represents no pain and 10 represents the most excruciating pain imaginable.

Outcome measurements

The primary outcome was opioid (tramadol) consumption within the first 24 h. The NRS scores obtained while at rest (NRS-rest) and while coughing (NRS-dynamic) served as secondary outcome measures. Six hours after surgery, symptoms such as nausea, vomiting, time to first analgesia request, and quadriceps muscle weakness were noted. Quadriceps muscle weakness was assessed as follows: with the hip joint at 45° and the knee joint at 90° of flexion, the patient was instructed to extend the knee joint first against gravity and then against applied resistance. The patient's ability to extend the knees was assessed using a 3-point scale (0 = normal strength [the knee can be extended to full extension both against gravity and applied force], 1 = paresis [the knee can be extended against gravity but not against applied resistance], and 2 = paralysis [the knee cannot be extended]). Scores of 1 and 2 were considered to reflect quadriceps weakness.
Sample size and statistical analyses

In our pilot study involving 10 patients, we observed that the 24-h tramadol consumption in the TFPB group was 108 ± 41.47 mg. To detect a statistically significant 30% reduction in tramadol consumption with an alpha level of 0.05 and a beta level of 0.10, we calculated that a minimum of 35 participants per group would be required. To account for potential dropouts, we included a minimum of 40 patients in each group, which represented a 15% increase in the sample size.

The Statistical Package for Social Sciences (SPSS Statistics for Windows, version 22.0; IBM Corp.) was used for statistical analyses. The Kolmogorov-Smirnov test was used to determine data normality. Descriptive data are presented as mean and standard deviation (SD), mean difference (MD) and 95% CI, or median (Q1, Q3). Continuous variables with equal variances were assessed using the t-test, whereas non-normally distributed data were analyzed using the Mann-Whitney U test. Categorical variables were evaluated using the chi-square or Fisher’s exact test. The time to first analgesia requirement was analyzed using the t-test and Kaplan-Meier analysis. The threshold for statistical significance was set at P < 0.05. The Bonferroni correction was used to analyze NRS scores, with statistical significance adjusted to P < 0.0071 owing to measurements from seven time points.

Results

Eighty-four patients agreed to participate in the study, four of which were excluded: two for inadequate/failed spinal block and two for PCA device failure. Therefore, 40 patients per group were included in the study. The CONSORT flow diagram for this study is shown in Fig. 1.

Males comprised the majority of patients in both groups (TFPB group: 38/40 and ESPB group: 35/40). The ASA classification; average age, height, weight, and BMI of the patients; and surgical times were similar between the groups, as shown in Table 1 (P > 0.05).

When the mean 24-h tramadol requirements of the groups were compared, the TFPB group was found to have a lower tramadol requirement than the ESPB group, with a statistically significant difference (88 ± 75.2 vs. 131 ± 93.7 mg, MD: −43, 95% CI [−80.82, −5.18], P = 0.027).

As shown in Table 2 and Fig. 2, the cumulative amount of tramadol consumed in the TFPB group was significantly lower than that consumed in the ESPB group at all time points, with the exception of the first hour. In addition, when we used time intervals rather than time points of cumulative tramadol and repeated the

---

**Fig. 1.** Consolidated Standards of Reporting Trials (CONSORT) diagram of the study. TFPB: transversalis fascia plane block, ESPB: erector spinae plane block.
comparisons, the use of tramadol for hours 1–3 was statistically significantly lower in the TFPB group than in the ESPB group (10.5 ± 20.24 vs. 24.5 ± 31.86 mg, MD: −14, 95% CI [25.88, −2.12], P = 0.018). No significant differences in the amount of tramadol required was found between hours 3–6, 6–9, 9–12, 12–18, or 18–24 (P > 0.05).

**Table 1.** Comparison of Age, Gender, ASA Classification, Height, Weight, Body Mass Index, Surgical Time, and Time to First Analgesia Requirement between the TFPB and ESPB Groups

<table>
<thead>
<tr>
<th>Patients and clinical data</th>
<th>TFPB group (n = 40)</th>
<th>ESPB group (n = 40)</th>
<th>P value</th>
<th>Mean difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.2 ± 12.6</td>
<td>48.9 ± 11.1</td>
<td>0.910†</td>
<td>0.3</td>
<td>−4.99, 5.59</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>38/2</td>
<td>35/5</td>
<td>0.216‡</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>ASA PS (I/II/III)</td>
<td>7/29/4</td>
<td>5/31/4</td>
<td>0.819‡</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.72 ± 0.04</td>
<td>1.71 ± 0.06</td>
<td>0.384†</td>
<td>0.01</td>
<td>−0.01, 0.03</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.4 ± 8.5</td>
<td>79.1 ± 9.7</td>
<td>0.732†</td>
<td>−0.7</td>
<td>−4.76, 3.36</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 ± 3.0</td>
<td>27.0 ± 2.9</td>
<td>0.451†</td>
<td>−0.5</td>
<td>−1.82, 0.81</td>
</tr>
<tr>
<td>Surgical time (min)</td>
<td>52.1 ± 11.4</td>
<td>53.4 ± 12.0</td>
<td>0.621†</td>
<td>−1.3</td>
<td>−6.52, 3.91</td>
</tr>
<tr>
<td>Patients not requiring rescue analgesia via PCA</td>
<td>10 (25.0)</td>
<td>3 (7.5)</td>
<td>0.033†</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Time to first analgesia* (min)</td>
<td>264.8 ± 140.1</td>
<td>209.2 ± 110.6</td>
<td>0.053†</td>
<td>55.6</td>
<td>−0.59, 111.79</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number of patients or number (%). TFPB: transversalis fascia plane block, ESPB: erector spinae plane block, ASA PS: American Society of Anesthesiologists physical status, BMI: body mass index, PCA: patient-controlled analgesia, N/A: not applicable.

*Patients not requiring analgesia via PCA were excluded from the t-test. †t-test, ‡Fisher’s exact test.

**Table 2.** Comparison of Cumulative Tramadol Consumption at Different Time Points between the TFPB and ESPB Groups

<table>
<thead>
<tr>
<th>Cumulative tramadol consumption</th>
<th>TFPB group (n = 40)</th>
<th>ESPB group (n = 40)</th>
<th>P value</th>
<th>Mean difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0.323</td>
<td>0.9</td>
<td>−0.98, 2.98</td>
</tr>
<tr>
<td>3 h</td>
<td>0 (0, 10)</td>
<td>0 (20, 40)</td>
<td>0.041*</td>
<td>−13</td>
<td>−25.47, −0.53</td>
</tr>
<tr>
<td>6 h</td>
<td>0 (20, 50)</td>
<td>20 (40, 80)</td>
<td>0.013*</td>
<td>−25</td>
<td>−43.66, −5.33</td>
</tr>
<tr>
<td>9 h</td>
<td>0 (40, 100)</td>
<td>80 (40, 140)</td>
<td>0.017*</td>
<td>−32</td>
<td>−59.21, −5.79</td>
</tr>
<tr>
<td>12 h</td>
<td>50 (10, 120)</td>
<td>90 (40, 160)</td>
<td>0.032*</td>
<td>−34</td>
<td>−64.97, −3.03</td>
</tr>
<tr>
<td>18 h</td>
<td>80 (10, 120)</td>
<td>100 (60, 180)</td>
<td>0.025*</td>
<td>−39</td>
<td>−73.86, −5.14</td>
</tr>
<tr>
<td>24 h</td>
<td>80 (10, 140)</td>
<td>110 (60, 180)</td>
<td>0.027*</td>
<td>−43</td>
<td>−80.82, −5.18</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). TFPB: transversalis fascia plane block, ESPB: erector spinae plane block. *Statistically significant difference.

In our study, patients in the TFPB group who underwent unilateral OIHR surgery under spinal anesthesia required significantly less tramadol for postoperative analgesia than those in the ESPB group. The NRS scores were comparable across most timeframes. Since the scheduled analgesia was adequate in the TFPB group, the proportion of patients who did not request an additional PCA rescue dose in the first 24 h was 25%, whereas it was 7% in the

Discussion

In our study, patients in the TFPB group who underwent unilateral OIHR surgery under spinal anesthesia required significantly less tramadol for postoperative analgesia than those in the ESPB group. The NRS scores were comparable across most timeframes. Since the scheduled analgesia was adequate in the TFPB group, the proportion of patients who did not request an additional PCA rescue dose in the first 24 h was 25%, whereas it was 7% in the
As mentioned, available studies for both techniques included in this study are limited. In OIHR, the TFPB has only been used in a few studies. Lopez-Gonzalez et al. [22] conducted a retrospective observational study in which 30 ml of 0.25% levobupivacaine was administered through the TFPB and anterior TAP block at the conclusion of unilateral OIHR surgery performed under general anesthesia and found comparable postoperative analgesic outcomes for both techniques. Fouad et al. [15] compared the postoperative analgesic effects of the TFPB and anterior quadratus lumborum block and found both to be effective and comparable in inguinal hernia surgery. One controlled study examined the postoperative analgesic effect of a preemptive TFPB in patients undergoing OIHR and concluded that it reduces both postoperative analgesic requirements and pain intensity following pediatric inguinal herniorrhaphy [23].

The ESPB, introduced by Forero in 2016 [24], involves administering LA in the interfacial plane between the transverse process of the vertebrae and the erector spinae muscle group with the goal of blocking both the dorsal and ventral rami. The ESPB can be adapted to various spinal levels, potentially producing paravertebral block-like effects [24,25], and has been used for postoperative pain management as part of multimodal analgesia for nearly all types of operations (except for distal extremities and cephalic operations) with positive results [25,26].

Previous studies have shown the efficacy of ESPB after OIHR surgery in both adult and pediatric patients [27,28]. El-Emam and El Motlb [27] administered ESPB to children at a volume of 0.5 ml...
ml/kg from the L1 transverse process and found a lower rescue analgesic requirement, lower FLACC scores, and a longer time to first analgesic request compared to the II-IH block in OIHR. Sakae et al. [28] performed ESPB at T8 level with 20 ml ropivacaine (0.5%) LA, determined that it did not reduce the rescue analgesic requirement, and reported that it was ineffective for OIHR. Given the volume and concentration of ESPB used in that study [28], we did not expect it to be effective for OIHR.

In our study, we observed that TFPB outperformed ESPB in terms of the postoperative analgesic requirement in patients undergoing OIHR under spinal anesthesia, whereas the effects on pain scores and first analgesic requirement were comparable. Despite differences in the clinical study methodology, tramadol requirements in both groups were comparable or lower than those in regional anesthesia studies in the same patient group [29,30]. The TFPB group required 33% less tramadol than the ESPB group; however, this difference may not be clinically significant. To date, no minimum clinically important difference (MCID) studies have been conducted for OIHR, and no data have been provided regarding the threshold at which change in opioid requirements or NRS scores would be significant. As a result, we could not make any definitive statements regarding the clinical significance of this statistical difference between the groups. However, asserting the clinical significance of this difference, which is equivalent to an oral morphine dose of approximately 13 mg, may not be reasonable given the currently available literature (generally, a reduction ≥ 30 mg or > 40% is considered significant). For a stronger claim, the MCID for OIHR surgery should be calculated along with the concept-specific MCID, which is already recommended for similar types of surgeries [31,32].

As mentioned, ESPB is a popular, easy, and safe technique that is frequently used for both acute and chronic pain, and successful applications for perioperative analgesia have been reported for both open and laparoscopic inguinal hernia surgeries. The possible mechanism of action is explained as the transition of LA to the paravertebral area when applied to the posterior of the transverse process. However, clinical, cadaveric, and radiological studies have shown that for many interfacial plane blocks, this same distribution is not always observed [33,34]. Although the ESPB sometimes results in limited sensory block in the paraspinous region, it also sometimes works as a multilevel paravertebral block [35,36].

Conversely, the TFPB application point is very close to the nerve tissue and is a more target-specific block. The differences in tramadol requirements between the groups may have resulted from these anatomical differences. When we reanalyzed tramadol consumption using time intervals instead of cumulative tramadol consumption, we determined that the statistical difference was found in the 1–3 h interval and the main difference in the subsequent measurements was due to the difference at this interval. Although the LA is applied directly adjacent to the nerve in TFPB, it is applied far from these neuronal structures in ESPB and reaches the target via leakage from the fascial planes. This may also help explain the difference determined clinically earlier.

Performance-oriented characteristics, such as ease of sonoana-

Table 3. Comparison of NRS Scores at Rest (Static) and During Movement (Dynamic) at Different Time Points between the TFPB and ESPB Groups

<table>
<thead>
<tr>
<th></th>
<th>TFPB group (n = 40)</th>
<th>ESPB group (n = 40)</th>
<th>P value</th>
<th>Mean difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS-at rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>0.5 (0, 2)</td>
<td>0.5 (0, 1.5)</td>
<td>0.875</td>
<td>0</td>
<td>−0.35, 0.41</td>
</tr>
<tr>
<td>3 h</td>
<td>1 (0.5, 2)</td>
<td>2 (1, 2)</td>
<td>&lt;0.001*</td>
<td>−0.3</td>
<td>−0.81, 0.04</td>
</tr>
<tr>
<td>6 h</td>
<td>1.5 (1, 2)</td>
<td>2 (1, 2)</td>
<td>0.027</td>
<td>−0.3</td>
<td>−0.85, −0.05</td>
</tr>
<tr>
<td>9 h</td>
<td>1 (1, 2)</td>
<td>2 (1, 2)</td>
<td>0.279</td>
<td>−0.2</td>
<td>−0.57, 0.17</td>
</tr>
<tr>
<td>12 h</td>
<td>1 (1, 2)</td>
<td>1 (1, 2)</td>
<td>0.324</td>
<td>−0.2</td>
<td>−0.54, 0.18</td>
</tr>
<tr>
<td>18 h</td>
<td>1 (1, 2)</td>
<td>1 (1, 2)</td>
<td>0.573</td>
<td>0.1</td>
<td>−0.25, 0.45</td>
</tr>
<tr>
<td>24 h</td>
<td>1 (1, 2)</td>
<td>1 (1, 2)</td>
<td>0.467</td>
<td>−0.1</td>
<td>−0.48, 0.22</td>
</tr>
<tr>
<td>NRS-with movement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>2 (0, 3)</td>
<td>1.5 (0, 3)</td>
<td>0.748</td>
<td>0.1</td>
<td>−0.52, 0.72</td>
</tr>
<tr>
<td>3 h</td>
<td>2 (1, 3)</td>
<td>3 (2, 3)</td>
<td>0.276</td>
<td>−0.4</td>
<td>−0.91, 0.27</td>
</tr>
<tr>
<td>6 h</td>
<td>3 (2, 3)</td>
<td>3 (2, 3)</td>
<td>0.098</td>
<td>−0.4</td>
<td>−0.83, 0.07</td>
</tr>
<tr>
<td>9 h</td>
<td>3 (2, 3)</td>
<td>3 (2, 3)</td>
<td>0.249</td>
<td>−0.2</td>
<td>−0.68, 0.18</td>
</tr>
<tr>
<td>12 h</td>
<td>2 (2, 3)</td>
<td>3 (2, 3)</td>
<td>0.05</td>
<td>−0.4</td>
<td>−0.85, −0.01</td>
</tr>
<tr>
<td>18 h</td>
<td>2 (2, 3)</td>
<td>2 (2, 3)</td>
<td>0.709</td>
<td>−0.2</td>
<td>−0.48, 0.32</td>
</tr>
<tr>
<td>24 h</td>
<td>2(1, 3)</td>
<td>2 (2, 2)</td>
<td>0.412</td>
<td>−0.1</td>
<td>−0.51, 0.21</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). TFPB: transversalis fascia plane block, ESPB: erector spinae plane block, NRS: numeric rating scale.

*Statistically significant difference.
tomical visualization and identification, necessity of positioning, and block onset time, are also important, as well as whether the technique used in regional anesthesia is effective as an analgesic. In our study, we placed all patients undergoing ESPB in the lateral decubitus position, which increased the time required to perform the block. However, we were able to perform this technique in the supine position in 37 of the 40 patients who received the TFPB. This not only saves practitioner time but also eliminates the need for an additional healthcare professional to maintain the patient under spinal anesthesia in the lateral position. The block performance time for the TFPB was significantly shorter and the effort required was lower. However, this was not documented in detail as it was not one of our outcomes.

Ten patients in the TFPB group and three patients in the ESPB group did not require any tramadol from their PCA devices, with a statistically significant difference.

Quadriceps weakness was a secondary outcome of our study. We found quadriceps weakness in one patient in the ESPB group when the groups were assessed at 6 h after the block, which persisted until 9 h postoperatively. At 6 h postoperatively, no quadriceps weakness was found in the TFPB group. Transient quadriceps weakness has been reported anecdotally in the literature after the administration of a TFPB or ESPB at or below the T11 level, though it usually resolves within 24 h [37,38]. As with all regional anesthesia techniques, complications such as intravascular injection, systemic anesthetic toxicity, and injury to adjacent tissues can be observed. Practitioners must be aware of this complication and potential side effects of LA spread.

This study also had some limitations. The first limitation was that neither cutaneous blockage mapping nor dermatomal sensory analysis were conducted after regional anesthesia. We chose not to perform these measurements because the patients included in the study underwent surgery under spinal anesthesia and because doing so might have been confusing in the event of prolonged spinal anesthesia. A recent Delphi consensus advised that block characteristics such as sensory testing of the block and block duration should be noted and reported [39]. Compared with peripheral nerve block studies, determining the duration of facial plane blocks is significantly more difficult. Instead, we assessed the time to first analgesic request, which was ≥ 3.5 h for both block groups. The Delphi consensus study also suggests recording and reporting patient satisfaction. Although we conducted patient satisfaction surveys, such as the QoR-15, and almost all our patients provided positive feedback, the fact that this was not documented is a significant limitation. As our work was planned prior to the release of this Delphi consensus, we were unable to follow these and similar recommendations, but we recommend that those who work on regional anesthesia in the future consider the consensus recommendations.

Although the lack of a control group can be considered a limitation, our research was defined and conducted as a comparative study, as previous controlled/observational studies have demonstrated the effectiveness of both blocks. In studies investigating the postoperative analgesic efficacy of facial plane blocks, patients may undergo surgery under general or spinal anesthesia [40]. In our clinic, spinal anesthesia is often preferred as the main method of administration in patients with OIHR. Considering our clinical practice, we believe that it would be more appropriate to add a facial block after spinal anesthesia, rather than administering spinal anesthesia alone. Another limitation is that we did not evaluate and note the duration of spinal anesthesia in some timeframes. Unfortunately, this concern is common in similar studies investigating the effectiveness of interfacial plane blocks performed at the end of surgeries performed under spinal anesthesia. Features such as the type and volume of LA in the spinal anesthesia, and the duration of surgery were kept similar, and all blocks were performed at the end of surgery, thus minimizing the effects of spinal anesthesia duration on pain and analgesic consumption. A non-inferiority/superiority or equivalence trial may have been more appropriate. However, because of the absence of an established gold standard for both the ESPB and TFPB techniques and the lack of prior comparative studies, this particular methodology was not employed.

In the absence of spinal morphine, our study revealed that patients who underwent unilateral OIHR under spinal anesthesia experienced a lower cumulative analgesic requirement during the 24-h postoperative period when ultrasound-guided TFPB was added as part of the multimodal analgesia than when ESPB was added.

**Acknowledgements**

We would like to thank Naci Murat from the Ondokuz Mayis University Faculty of Engineering/Industrial engineering for his contributions to the statistical evaluation of this study.

**Funding**

This study was funded by the Interventional Clinical Research Ethics Committee of Samsun Research and Education Hospital (No. EHK/2022-97).

**Conflicts of Interest**

No potential conflict of interest relevant to this article was re-


**Data Availability**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Author Contributions**

Hale Kefeli Çelik (Conceptualization; Data curation; Funding acquisition; Methodology; Writing – original draft; Writing – review & editing)
Serkan Tulgar (Conceptualization; Data curation; Methodology; Supervision; Writing – original draft; Writing – review & editing)
Ömer Faruk Bük (Data curation; Investigation; Writing – review & editing)
Kadem Koç (Data curation; Methodology; Writing – review & editing)
Murat Ünal (Data curation; Investigation; Writing – review & editing)
Caner Genç (Data curation; Investigation; Writing – review & editing)
Mustafa Süren (Conceptualization; Methodology; Supervision; Writing – review & editing)

**ORCID**

Hale Kefeli Celik, https://orcid.org/0000-0002-0850-4524
Serkan Tulgar, https://orcid.org/0000-0003-1996-7505
Ömer Faruk Bük, https://orcid.org/0000-0003-4559-2735
Kadem Koç, https://orcid.org/0000-0002-7957-5135
Murat Ünal, https://orcid.org/0000-0002-5524-9175
Caner Genç, https://orcid.org/0000-0002-2987-6909
Mustafa Süren, https://orcid.org/0000-0001-6999-6510

**References**


Learning with our peers: peer-led versus instructor-led debriefing for simulated crises, a randomized controlled trial

Morgan Jaffrelot¹,²,³, Sylvain Boet⁴,⁵,⁶,⁷, Yolande Floch⁵, Nitan Garg⁴, Daniel Dubois⁴, Violaine Laparra², Lionel Touffet², M. Dylan Bould⁵,⁶,⁸

¹University of Ottawa Skills and Simulation Center and Academy for Innovation in Medical Education, University of Ottawa, Ottawa, ON, Canada, ²Simulation Center, University of Western Brittany and University Hospital of Brest, ³Education and Health Promotion Laboratory EA 3412, Paris 13-Sorbonne Paris Cité University, France, ⁴Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, ⁵The Ottawa Hospital Research Institute, ⁶Department of Innovation in Medical Education, Faculty of Medicine, University of Ottawa, ⁷Institut du Savoir Montfort, ⁸Department of Pediatric Anesthesia, Children’s Hospital of Eastern Ontario, Ottawa, ON, Canada

Background: Although peer-assisted learning is known to be effective for reciprocal learning in medical education, it has been understudied in simulation. We aimed to assess the effectiveness of peer-led compared to instructor-led debriefing for non-technical skill development in simulated crisis scenarios.

Methods: Sixty-one undergraduate medical students were randomized into the control group (instructor-led debriefing) or an intervention group (peer debriefer or peer debriefee group). After the pre-test simulation, the participants underwent two more simulation scenarios, each followed by a debriefing session. After the second debriefing session, the participants underwent an immediate post-test simulation on the same day and a retention post-test simulation two months later. Non-technical skills for the pre-test, immediate post-test, and retention tests were assessed by two blinded raters using the Ottawa Global Rating Scale (OGRS).

Results: The participants’ non-technical skill performance significantly improved in all groups from the pre-test to the immediate post-test, with changes in the OGRS scores of 15.0 (95% CI [11.4, 18.7]) in the instructor-led group, 15.3 (11.5, 19.0) in the peer-debriefee group, and 17.6 (13.9, 21.4) in the peer-debriefer group. No significant differences in performance were found, after adjusting for the year of medical school training, among debriefing modalities (P = 0.147) or between the immediate post-test and retention test (P = 0.358).

Conclusions: Peer-led debriefing was as effective as instructor-led debriefing at improving undergraduate medical students’ non-technical skill performance in simulated crisis situations. Peer debriefers also improved their simulated clinical skills. The peer debriefing model is a feasible alternative to the traditional, costlier instructor model.

Keywords: Critical care; Education; Feedback; Peer group; Professional competence; Simulation training.

Introduction

Full-scale, high-fidelity, manikin-based simulation is recognized as a powerful educa-
tional tool for developing the skills and competencies of healthcare professionals [1]. This modality of simulation is particularly useful for teaching critical care skills [2] and the principles of crisis resource management (CRM) [3]. Various studies have demonstrated the efficacy of manikin-based simulation in teaching non-technical skills, such as communication and teamwork, and improving patient-level outcomes [4]. Poor development of these non-technical skills increases the likelihood of human error and threatens patient safety, particularly in crisis situations. In a simulated environment, clinical skills can be safely practiced and assessed without risk to patients [5]. Furthermore, studies have shown that technical skills are correlated with non-technical skills, i.e., that when non-technical skills improve technical skills improve as well and vice-versa [6].

In simulation-based medical education, debriefing, “the feedback process that encourages learners to reflect on their performance” [7], is key for the success of experiential learning [8,9]. Debriefing is most commonly facilitated by an expert whose goal is to help learners identify and close gaps in their knowledge and skills in a safe learning environment. However, the wider implementation of simulation-based education may be limited by instructor availability and associated time costs [10].

Peer-assisted learning (PAL), in which trainees provide feedback to other trainees, is well-described in medical education, although data in the simulation literature is limited [11]. PAL creates a low-risk, informal environment in which feedback is provided by individuals at similar cognitive phases of skill acquisition and thus encourages reciprocity in learning. The potential benefits of PAL include increased accountability, critical thinking, increased self-disclosure (i.e., accepting vulnerability discussing their own performance challenges), and a reduced need for instructor availability [11]. Self-debriefing [7] and within-team debriefing [12] have been shown to be effective alternatives to instructor-led debriefing for CRM skill development in a simulation environment. Previous studies of peer debriefing have mainly assessed learners’ acceptance and satisfaction [13]. Our study aimed to compare the effect on learning between participating as a peer debriefer, and participating as a debrievee of a peer or instructor (control). To the best of our knowledge, no previous study has examined the effects that being a peer debriefer have on learning. Considering that teaching has been described as one of the most effective strategies for learning [14], we hypothesized that peer debriefers would acquire the same level of CRM skills as the peers that they debriefed and the control group. We also hypothesized that skill retention would be superior in the peer debriefer group.

Materials and Methods

Study population and orientation

Institutional Research Ethics Board approval was obtained (20120938-01H) from the Centre Hospitalier Universitaire de Brest in France and Ottawa in Canada and was conducted in accordance with the Helsinki Declaration-2013. Fourth- and fifth-year medical students from the University of Brest were recruited for this study. Informed consent was obtained from all the participants. To preclude unwanted divulgence of study details among potential participants, a confidentiality agreement was also obtained. All participants underwent a 30-min orientation to familiarize themselves with the key concepts and simulation equipment. They were shown a standardized teaching video on the principles of patient simulation, CRM, and non-technical skills [15]. They were then introduced to the Laerdal SimMan 3G simulator manikin (Laerdal Medical France), monitors (Laerdal Medical France) and the simulation room. All participants completed a demographic questionnaire after their orientation and were recruited in 2013.

Study design

This study had a prospective, randomized, controlled, repeated-measures design. After orientation, all participants individually participated in a high-fidelity simulated hypotensive crisis scenario (pre-test). The study day was randomized to either be a control day (instructor group) or an intervention day (debriefer/debrievee groups) and allocation was based on the availability of the participant for scheduling on particular days. Participants in the control group (n = 21) individually completed two subsequent simulation scenarios, each followed by instructor-led debriefing. The participants in the peer debriefing group (n = 40) were randomized into either the peer debriefee/learner (PL) or the peer debriefer/teacher (PT) group using sealed envelopes, with stratification according to year, so that participants were paired with another participant of the same year (Fig. 1). The PL then completed two successive simulated crisis scenarios, followed by a peer-led debriefing. PTs only observed their peers; they did not manage the scenarios themselves. The PT used a debriefing form developed from the best practice guide. The guide was structured around three aspects: (i) actions observed, (ii) use of good judgement, and (iii) exploring and closing the gaps observed [16,17]. This orientation was used to guide the debriefing. In the second scenario, partner pairings were randomly changed to ensure that the participants were not debriefed twice by the same
The debriefing session was limited to 20 min for all groups. After the second debriefing, all participants, including peer debriefers, participated independently in an immediate post-test scenario, followed by a retention post-test two months later.

Two trained confederates (i.e., actors playing the role of other healthcare professionals in the scenarios) were used for each scenario. Their roles were scripted, and they only performed tasks when directed by the participant as it was critical that the confederates avoid offering crisis management advice. The pre-test, immediate post-test, and retention post-test scenarios simulated intra-abdominal hemorrhagic shock, whereas the two training scenarios simulated anaphylactic and septic shock in a random order. Each scenario lasted for five minutes. To evaluate skill performance, all scenarios were video recorded and overlaid with the patient’s vital signs before being sent to the video raters.

**Simulation scenarios**

The scenarios were created and determined to be of comparable difficulty through an iterative review by emergency simulation faculty and students. Shock was chosen as the theme because it is a realistic critical situation that students may need to manage in the first few minutes in actual clinical scenarios. These scenarios encompass many standardized procedures and decision-making processes. All non-technical CRM skills can be assessed during these short clinical scenarios. To avoid sequencing effects, the scenario order was randomized for each participant and equally allocated between the groups.

**Outcome measures**

Our primary outcome was the change in non-technical skill performance of peer debriefers, as measured by the Ottawa Global Rating Scale (OGRS). The secondary outcome was the relative effectiveness of receiving instructor-led debriefing versus being a peer debriefee versus being a peer debriefer on non-technical skill performance in a CRM simulation session. The assessment was performed immediately after debriefing and again two months later. The OGRS has been shown to be a valid and reliable tool for assessing emergency physicians’ non-technical skills [18]. The OGRS encompasses five main skill categories: leadership, problem solving, situational awareness, resource utilization, and communi-
cation. Each category is scored out of seven, with seven being the maximum and one being the minimum score. Several behavioral descriptors are included for each category to assist the scorer in selecting the most appropriate score. For instance, a lower leadership score would be represented by “loses calm and control during most of the crisis; unable to make firm decisions, etc.” whereas a higher score corresponds to “remains calm and in control during the entire crisis; makes prompt and firm decisions without delay, etc.” The scores were summed to provide a total OGRS score ranging from 5 to 35 [18].

Two raters with extensive experience in simulation and CRM principles were trained to evaluate all video data collected from the participants. Raters’ training consisted of (i) familiarization with the OGRS, (ii) scoring of 12 training videos on simulated crises comparable to those used in the current study, and (iii) discussion of the individual ratings of these videos as a group until the raters and principal investigator reached a consensus. The training process for the raters took six hours, and validation was established when the raters reached substantial agreement on their ratings of the training videos. Once the desired inter-rater reliability was reached, the two raters rated the data videos independently in random order, blinded to the participants’ randomization, test phase, and level of training. Of note, only the raters were asked to score participants’ performances. During the debriefing, the debriefers (either instructor or peer debriefers) made comments or asked participants questions to foster reflection in their minds, but they did not score their performance using the OGRS.

**Statistical analysis**

Demographic data were analyzed using the chi-square and Mann-Whitney U tests. Inter-rater reliability was assessed using the intraclass correlation coefficient of the total OGRS score. An a priori 2-sided P value of 0.05 was used for all statistical comparisons. SPSS (version 23.0) was used for all analyses.

We used a repeated-measures general linear model (GLM), accounting for the covariate of the participant’s level of training (year 4 or 5). For the main analysis of the primary outcome measure, the total OGRS score was treated as the dependent variable. The independent variables were the test phase (pre-test vs. post-test vs. retention-test) for the within-subject analysis and the type of debriefing (peer debriefer vs. peer debriefee vs. instructor debriefing) for the between-subject analysis. We also controlled for the level of undergraduate training by including it as a covariate in the GLM. This approach allowed us to compare the effects of the type of debriefing and the test phase on skill performance. Moreover, we were able to examine interactions between these three variables in cases for which pre-test performance was found to be significantly different between the two groups. We used the estimated marginal means to compare groups for the pre-test, post-test, and retention tests. Sidak’s test was used for post hoc comparisons.

As previously published data using the OGRS have referred to post-graduate trainees, pilot data for undergraduates were not available at the time of study planning. Therefore, we performed a sample size calculation based on the expected effect size. In the fields of psychology and education, a Cohen’s $f$ effect size > 0.4 is considered large and acceptable for a given teaching intervention. Therefore, based on the analysis described above, we relied on an F-test to calculate the sample size using G*Power software (version 3.12). We calculated a total sample size of 45 based on an effect size of 0.4, a 2-tailed $\alpha$ of 0.05, a power of 0.80, three groups and three timepoints for measurements, and a correlation among repeated measures of 0.5. We thus intended to recruit 60 participants to allow for 25% attrition at the time of the retention test, equating to 20 participants per group.

**Results**

**Demographics**

Sixty-one participants were recruited and completed the study. A summary of the participants’ characteristics is presented in Table 1. A significant difference in the medical school year was found between the groups; therefore, we added this covariate to the analysis.

<table>
<thead>
<tr>
<th>Table 1. Participant Demographics (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristic</td>
</tr>
<tr>
<td>Year of medical school (4/5)*</td>
</tr>
<tr>
<td>Gender (F/M)</td>
</tr>
<tr>
<td>Absence of previous experience of a crisis event in clinical practice</td>
</tr>
</tbody>
</table>

*In France, medical students undergo 6 years of medical school before post-graduate training.
Inter-rater reliability

We achieved an almost perfect overall inter-rater reliability for the total OGRS score of 0.95 (P < 0.001). Due to the high level of agreement among the raters, the mean OGRS score was used for the analysis.

Primary outcome

The peer debriefers demonstrated a statistically significant improvement in their total OGRS scores between the pre-test and post-test and between the pre-test and retention test (P < 0.001). The overall OGRS scores also significantly improved between the pre-test and post-test and between the pre-test and retention test for the control group and peer debriefees (P < 0.001). For the pre-test, post-test, and retention-test phases, no significant differences in the mean total OGRS scores were found among the debriefing modalities (P = 0.147) when the year of medical school training covariate was accounted for.

Estimated marginal means for the change in total OGRS score between the pre-test and post-test were 15.0 (95% CI [11.4, 18.7]) for the instructor debriefing group, 15.3 (95% CI [11.5, 19.0]) for the debriefee group, and 17.6 (95% CI [13.9, 21.4]) for the debriefer group. Estimated marginal means for the change in the total OGRS score between the pre-test and retention test were 12.8 (95% CI [9.1, 16.4]) for the instructor debriefing group, 14.8 (95% CI [11.0, 18.6]) for the debriefee group, and 16.3 (95% CI [12.6, 20.1]) for the debriefer group. No significant differences in performance were found between the post-test and retention test (P = 0.358).

Of note, for the main analysis, the normality was non-significant (P > 0.05) based on the Kolmogorov-Smirnov test, except for the peer-debriefee group and only for the pre-test (P = 0.039). The sphericity assumption was not violated (Mauchly’s W test) and was not significant (P > 0.95).

These results indicate that participants experienced significant and comparable improvement from pre-test to post-test, irrespective of the intervention (instructor vs. peer debriefing), and that the improvement was retained for at least two months (Table 2).

Discussion

Our study aimed to investigate the relative efficacy of participating as a peer debriefer compared with receiving peer- or instructor-led debriefing on non-technical skill performance during CRM. Our results demonstrate that non-technical skill performance during simulated crisis scenarios improved for peer debriefers similarly to that for participants who received instructor debriefing. Non-technical skill performance improved regardless of the debriefing modality and was retained for at least two months.

This lack of difference in non-technical skill performance improvement between peer debriefers and participants who received instructor- or peer-led debriefing highlights the educational benefit of PAL to both teachers and learners. Active engagement through reviewing peers may facilitate student learning [19]. Furthermore, trainees’ involvement in feedback and assessment processes may contribute to the development of facilitation and communication skills, lifelong learning competencies, and critical thinking and reflection [20]. This result aligns with other randomized controlled trials’ findings that observing a simulated performance is effective for students’ learning of crisis management skills to the same extent as participants who are active in the simulation as long as observers actively participate in the debriefing process [21,22]. Our study adds more evidence to the literature, showing that debriefing is a critical component of learning in simulation-based education.

Regardless of group allocation, students’ performance did not decline after two months. This suggests that, after three short scenarios, the participants achieved a high level of performance of non-technical skills for managing the first five minutes of a crisis situation, even in the two groups without an instructor. Of note, we did not examine the content of the debriefings, and peer assessors may utilize a different approach to debriefing than instructors [20]. Moreover, faculty and peer assessors do not apply the same strategies to assess and observe situations. Students may have dif-

Table 2. Ottawa Global Rating Scale Scores according to Group and Test Phase

<table>
<thead>
<tr>
<th>Group allocation</th>
<th>Pre-test Mean ± SD</th>
<th>95% CI</th>
<th>Post-test Mean ± SD</th>
<th>95% CI</th>
<th>Retention post-test Mean ± SD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instructor debriefing</td>
<td>14.3 ± 6.2</td>
<td>12.0, 16.4</td>
<td>29.3 ± 4.2*</td>
<td>27.1, 31.5</td>
<td>27.0 ± 6.2*</td>
<td>24.9, 29.2</td>
</tr>
<tr>
<td>Peer debriefee</td>
<td>11.1 ± 4.0</td>
<td>8.9, 13.4</td>
<td>26.4 ± 6.2*</td>
<td>24.1, 28.6</td>
<td>25.9 ± 5.4*</td>
<td>23.7, 28.1</td>
</tr>
<tr>
<td>Peer debriefer</td>
<td>10.5 ± 4.6</td>
<td>8.2, 12.7</td>
<td>28.1 ± 3.8*</td>
<td>25.8, 30.3</td>
<td>26.8 ± 3.9*</td>
<td>24.6, 29.0</td>
</tr>
</tbody>
</table>

Ottawa global rating scale scores ranges from 5 (minimum) to 35 (maximum). *P < 0.001 compared to Pre-test score.

https://doi.org/10.4097/kja.23317
different interests when observing the performance of their peers, and matching and modeling peer performance could be a powerful tool to help students bridge the gap between the learning and application contexts [23]. However, analyzing qualitative differences in debriefing styles between participants and instructors [24] was beyond the scope of this study but could be the subject of future investigations. The retention test, similar to the pre- and post-tests, consisted of a hypotensive shock scenario. Therefore, future studies should determine whether peer debriefing is as effective as instructor debriefing when learned non-technical skills are transferred to other CRM scenarios. Given the homogeneity of the scenarios, it could also be argued that any improvement in non-technical skills across all three groups was the result of practice alone rather than from benefits derived from debriefing. First, we assessed non-technical skills as opposed to knowledge of medical management. Second, we did not include a control group of participants who completed scenarios without feedback. A previous study showed that residents who managed simulation scenarios without debriefing did not demonstrate improvements in their non-technical skills [8]. Therefore, we decided to compare peer debriefing with the currently accepted gold standard of instructor debriefing. Overall, our results challenge the traditional view that expert instructors must facilitate simulation debriefing. Although our study was not statistically powered to conclude that both peer-debriefers and peer-debriefee strategies were as effective as instructor debriefing, our results suggest that PAL strategies may be a valuable adjunctive tool to expert-facilitated simulation debriefing. The scores for the non-technical skills studied were high. This indicates that the participants improved quickly and developed a high level of fundamental skills. This is particularly interesting considering that students in undergraduate courses have been found to feel uncomfortable giving feedback to others as they consider themselves not competent enough to assess their peers [25]. None of the students had experience leading a crisis situation; thus, for most of them, this was an opportunity to experience shock in its multiple dimensions for the first time. The debriefers focused on two new tasks: both educational and medical learning. We are not suggesting that having an expert instructor present for debriefing is not necessary [26]; however, we recommend considering when it is the most essential. Established alternatives to instructor debriefing (self-debriefing, within-team debriefing) [7,12,27] should encourage further development in curriculum design.

Our study had several limitations. Despite a retention of 100% of the participants, a relatively small number of fourth- and fifth-year undergraduate medical students from the University of Brest were enrolled in this single-center study. Since medical curricula and resultant attitudes towards simulation vary across institutions, our findings may not be generalizable to all medical students or higher-level trainees such as residents. In our study, only peer debriefers observed their peers completing two scenarios following the pre-test; none of the other participants had the opportunity to observe their peers in the hot seat. Accordingly, peer debriefers had less time to practice, which may explain the non-superiority of this group in post-test and retention test performance. In addition, we cannot determine whether the impact of the peer debriefers’ assessments on the learning of non-technical skills was due to the observation of their peers, facilitation of debriefing, or both. Finally, the implications of our study may vary across countries and organizations. While most centers in North America need to compensate instructors for their time, other countries or centers may pay instructors salaries. Additionally, despite the significant upfront costs of purchasing a manikin for simulation, it can be used virtually 24/7 and lasts for many years. Therefore, the recurrent cost of instructors’ time is the main barrier to conducting simulations in centers that need to pay for instructors.

In conclusion, all participants’ performance of non-technical skills in simulated crisis scenarios, as measured by the OGRS, improved and was retained for at least two months in this study. We found no difference in the degree of improvement in the performance of non-technical skills among the participants, regardless of whether they provided debriefing to their peers or were debriefed by a peer or instructor. These findings suggest the potential role of PAL in teaching non-technical skills in CRM. The use of peer assessment may help offset the limited availability of expert instructors, which is a barrier to the wider implementation of simulation-based medical education. Moreover, the educational benefit for peer debriefers demonstrated in our study makes a compelling argument for the incorporation of peer assessment activities into medical curricula. This is consistent with data from previous randomized controlled trials investigating alternative approaches to instructor debriefing, and PAL may play a role alongside the gold-standard of expert instructor debriefing.

Acknowledgements

We would like to thank Guy Bescond, Julien Cabon, and Sophie Fleureau for their technical support during the simulation sessions and the confederates and medical students of the University of Brest (France) for their participation in this study. We would also like to thank the Center de SIMulation en santé (CESIM) for their assistance with data collection and Ashlee-Ann Pigford and Hladkowicz for their administrative and technical support throughout the research project.
**Funding**

This study was supported by a research grant from the Academy of Innovation in Medical Education at the University of Ottawa, Canada. Dr. Boet was supported by The Ottawa Hospital Anesthesia Alternate Funds Association and the Faculty of Medicine, University of Ottawa with a Tier 2 clinical research chair.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Data Availability**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Author Contributions**

Morgan Jaffrelot (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)

Sylvain Boet (Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)

Yolande Floch (Conceptualization; Resources; Writing – review & editing)

Nitan Garg (Investigation; Resources; Writing – review & editing)

Daniel Dubois (Investigation; Resources; Writing – original draft; Writing – review & editing)

Violaine Laparra (Investigation; Resources; Writing – review & editing)

Lionel Touffet (Investigation; Resources; Writing – review & editing)

M. Dylan Bould (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)

**ORCID**

Morgan Jaffrelot, https://orcid.org/0009-0007-4577-4586

Sylvain Boet, https://orcid.org/0000-0002-1679-818X

Yolande Floch, https://orcid.org/0009-0009-7573-837X

Nitan Garg, https://orcid.org/0000-0002-0259-8996

Daniel Dubois, https://orcid.org/0000-0002-7088-5110

Violaine Laparra, https://orcid.org/0009-0003-2928-7105

Lionel Touffet, https://orcid.org/0009-0007-6781-856X

M. Dylan Bould, https://orcid.org/0000-0003-1675-466X

**References**


Use of oxygen reserve index during bronchoscopic balloon dilation for subglottic stenosis in a patient with left ventricular assist device implantation
-a case report-

Jimin Lee¹, Minwoo Chung¹, Eui-Suk Sung³, Jung-Pil Yoon¹,², Yeong Min Yoo¹,², Jaesang Bae¹, Hee Young Kim¹,²

¹Department of Anesthesia and Pain Medicine, Pusan National University Yangsan Hospital, ²Department of Anesthesia and Pain Medicine, Pusan National University School of Medicine, ³Department of Otolaryngology-Head and Neck Surgery, Pusan National University Yangsan Hospital, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Yangsan, Korea

Background: Monitoring the oxygenation status is crucial during general anesthesia to ensure patient safety. Although noninvasive pulse oximetry is commonly used to monitor percutaneous oxygen saturation (SpO₂), it may not accurately reflect changes in oxygen partial pressure when the latter is excessively high or low. The oxygen reserve index (ORi) provides real-time information about the oxygen reserve status.

Case: We present a case of successful management of subglottic stenosis using balloon bronchoscopy in an infant with a left ventricular assist device implantation under ORi monitoring to predict hypoxemia during the surgical procedure.

Conclusions: Utilizing ORi monitoring during anesthesia for procedures involving apnea in critically ill infants can help predict impending desaturation before a drop in SpO₂ occurs, allowing anesthesiologists to effectively anticipate and manage the apnea period. Continuous ORi monitoring offers valuable insights during surgical procedures, especially in infants with compromised respiratory and cardiovascular functions.

Keywords: Acquired subglottic stenosis; Bronchoscopic surgical procedure; Bronchoscopy; Dilation; Hypoxia; Laryngostenosis; Oxygen.

Monitoring oxygenation status during general anesthesia is essential for respiratory management. Most anesthesiologists use noninvasive pulse oximetry to monitor percutaneous oxygen saturation (SpO₂) to detect hypoxemia and adjust the inspired oxygen concentration without invasive tests such as arterial blood gas analysis [1]. However, in cases where the actual oxygen partial pressure is excessively high or low, the SpO₂ reading can still appear close to 100%. Once the SpO₂ reading begins to decrease, it indicates a significant drop in the oxygen partial pressure, and the rate of decrease in SpO₂ accelerates rapidly, increasing the risk of hypoxemia [2,3]. The oxygen reserve index (ORi) (Masimo Corp.) is a time indicator of oxygen reserves. It not only displays oxygen saturation, but also indicates the oxygen reserve status on a scale of 0.00 (no reserve) to 1.00 (much reserve) that is different from noninvasive pulse oximetry [4].

We report a case of successful management of subglottic stenosis using balloon bron-
choscopy in an infant with left ventricular assist device (LVAD) implantation under ORi monitoring to predict hypoxemia during the surgical procedure.

Case Report

This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (IRB No. 05-2022-215), and written informed consent for publication was obtained from the parents as the patient was a minor. A male infant was diagnosed with dilated cardiomyopathy at two months of age and underwent implantation of a LVAD (Berlin EXCOR®, 10 ml; Berlin Heart AG). Following extubation at three months of age, the patient developed mild hoarseness and later presented with nasal flaring, chest retraction, and stridor. Reintubation was performed using an uncuffed endotracheal tube (ETT) with an internal diameter (ID) of 3.5 mm for two days. Beta-agonist inhalation therapy was initiated; however, the patient’s condition progressed to grade 3 stenosis (Fig. 1). Tracheostomy was considered, but the parents objected. Alternatively, bronchoscopic balloon dilation was planned.

At the time of admission to the operating room, the patient was five months old, with a length of 57 cm and weight of 5.9 kg. SpO₂ was maintained at 100% with 1 L/min of oxygen via a nasal cannula. The blood pressure was 119/63 mmHg and the heart rate was 172 beats/min. To monitor the risk of rapid desaturation during surgery, a sensor (rainbow® sensor, R2–25, Revision L, Masimo Corp.) for measuring ORi was attached to the patient’s right big toe. ORi was monitored using the own system (Root® with Radical-7® system; Masimo Corp.). During anesthesia induction, oxygen was continuously supplied at a rate of 5 L/min through a nasal cannula, and an additional 5 L/min was administered using a mask. An intravenous injection with 8 mg of ketamine, 4 mg of rocuronium, and 10 μg of fentanyl was administered. The procedure was anticipated to be difficult because of involuntary movement caused by surgical stimulation; therefore, a neuromuscular blocker was administered despite predicting the occurrence of apnea. Subsequently, a laryngeal mask airway (LMA) #1 (i-gel®; Intersurgical Ltd.) was inserted. Anesthesia was maintained with an infusion of 4–12 mg/kg/h of 1% propofol, and the bispectral index was maintained at 33–37.

After achieving SpO₂ of 100% and ORi of 1, LMA was removed and a suspension laryngoscope was inserted into the glottis by the surgeon. Bronchoscopic balloon dilation was started when ORi reached 1, and continued for approximately 30 s, even after ORi reached 0. Apneic oxygenation was performed using oxygen supplied at a rate of 5 L/min through the nasal cannula during the procedure. Mechanical ventilation via ETTs with IDs of 5.0 and 6.0 mm was also attempted, but resulted in near apnea. The total time for the first procedural attempt was approximately 3–4 min, with 3 min from ORi 1 to 0 and 30 s from ORi 0 to SpO₂ 80% (Fig. 2A). The apnea period was extended to ensure sufficient procedural time, even after the ORi reached 0. As a result, despite initiating ventilation with 100% oxygen when SpO₂ was 80%, there was a temporary drop in SpO₂ by 40% to 60% after approximately 30 s. Fortunately, there was no hemodynamic instability, such as bradycardia or hypotension. When the ORi reached 0, the LMA was reinserted and rescue ventilation was performed with 100% oxygen. It took approximately 1 min to reach SpO₂ above 97% and approximately 3 min for ORi to change from 0 to 1. The procedure was performed four times, with each trial lasting for 1 min 30 s at pressures of 760, 1140, 1520, and 1900 mmHg, respec-

Fig. 1. Bronchoscopic view of subglottic lesion. (A) Preoperative diagnosis is grade 3 subglottic stenosis. (B, C) The lesion improves to grade 1 subglottic stenosis after bronchoscopic balloon dilatation.
tively. Each trial also had a temporary drop in SpO\textsubscript{2} by 40% to 60% similar to the first attempt (Fig. 2B) although there was no hemodynamic instability.

The lesion improved to grade 1 subglottic stenosis (Fig. 1), and the procedure was successfully completed. The infusion of propofol was discontinued, and sugammadex (Bridion\textsuperscript{®}; MSD) 20 mg was administered to reverse the neuromuscular block because the “train of four” count was 0 after the end of the surgery, and about 4 mg/kg of sugammadex was considered reasonable. It was confirmed that the “train of four” ratio was > 90%. LMA was subsequently removed after smooth, spontaneous breathing was confirmed. The patient was shifted to the ward under the supervision of an attending pediatrician.

**Discussion**

In anesthesia for procedures that cause apnea, the ability to predict impending desaturation before a drop in oxygen saturation occurs is crucial for ensuring patient safety, especially in vulnerable populations such as neonates and infants with poor respiratory and cardiovascular function. Such patients have limited physiological reserves and are susceptible to oxygenation issues.

Neonates and infants have distinct characteristics in their respiratory and cardiovascular systems that make them vulnerable to oxygenation problems; their airways are anatomically different, with a narrow upper airway and relatively large epiglottis. Additionally, their laryngeal cartilages are not fully developed, leading to frequent obstructions during inspiration. Newborns and infants have narrower airways than adults, making them more prone to ventilation and diffusion impairments. Moreover, they have a lower functional residual capacity, low oxygen reserve, poor tolerance to apnea, and susceptibility toward hypoxemia and atelectasis. Furthermore, apnea in these populations, especially in children with reduced cardiopulmonary function, can rapidly lead to desaturation and systemic circulatory crises [5].

Once the partial pressure of arterial oxygen (PaO\textsubscript{2}) reaches 80 mmHg or higher, SpO\textsubscript{2} tends to remain close to 100%. Beyond this point, further increases in PaO\textsubscript{2} do not result in an increase in SpO\textsubscript{2}, as the hemoglobin is already fully saturated with oxygen. Consequently, SpO\textsubscript{2} cannot reliably predict PaO\textsubscript{2} or reflect the oxygen reserves after complete oxygenation of hemoglobin [6]. When SpO\textsubscript{2} starts to decrease, it indicates that PaO\textsubscript{2} has undergone a steep decline in the oxygen–hemoglobin dissociation curve. Therefore, even if immediate actions are taken to improve...
oxygenation when SpO₂ begins to drop, rapid decrease in PaO₂ can lead to a sharp decline in SpO₂ and hypoxemia [2]. Although arterial blood gas analysis provides an accurate measurement of PaO₂, its invasive and intermittent nature limits its ability to monitor sustained hypoxemia continuously [7).

ORi is a novel noninvasive parameter that reflects real-time oxygen reserves. It is represented as a value between 0 and 1, where 0 represents no oxygen reserve and 1 represents maximum oxygen reserve. ORi reflects PaO₂ values in the range of 100 to < 200 mmHg [8,9]. Previous studies in adult and pediatric patients have shown that ORi decreases approximately 30 s before the onset of SpO₂ decline, providing sufficient time for interventions to prevent hypoxemia [6,10]. A study by Szmuk et al. [6] focused on changes in ORi and SpO₂ in 25 relatively healthy pediatric patients after performing preoxygenation and endotracheal intubation, and disconnecting the anesthesia circuit from the ETT. This may not be directly applicable to vulnerable patients with compromised respiratory and cardiovascular functions because relatively healthy pediatric patients maintained SpO₂ levels during apnea periods. However, continuous monitoring of changes in ORi can help determine whether a patient has a full oxygen reserve. By observing the depletion of the oxygen reserve and the start of a decrease in SpO₂, it is possible to predict hypoxia during the procedure, and anesthesiologists can provide information on when to stop the procedure. ORi increases from 0.0 to 1.0 even after SpO₂ reaches 100%, indicating that the capacity of the oxygen reserve has reached its maximum value that can present the optimal timing for procedures such as balloon bronchoscopy to ensure patient safety. However, there was a time gap between balloon bronchoscopy and the initiation of ventilation in the current case, prompting reoxygenation after ORi reached 0. This resulted in a temporary but significant decrease in SpO₂ to levels as low as 45%. From this point of view, it was somewhat disappointing not to apply a transnasal humidified rapid-insufflation ventilatory exchange using a high-flow nasal cannula.

ORi has a significant correlation with PaO₂ values in the range of 100 to < 200 mmHg. When PaO₂ is > 100 mmHg, the ORi value is ≥ 0.24, and when PaO₂ is > 150 mmHg, the ORi value is ≥ 0.55 [9]. If the balloon bronchoscopic procedure had been interrupted and reoxygenation initiated when ORi fell between 0.24 and 0.55, in addition to the ORi alarm of downward trends, it could have prevented the infant from experiencing further desaturation.

In premature neonates, infants, and children, apnea induced by anesthesia or airway-related surgical procedures can lead to rapid desaturation because they have lower oxygen reserves and consume more oxygen than adults [5]. In infants with poor respiratory and cardiovascular functions, the severity of desaturation is even more pronounced and can potentially result in bradycardia and cardiac arrest [11,12]. By utilizing ORi, it is possible to predict expected desaturation during procedures involving apnea in critically ill infants, allowing anesthesiologists to anticipate and manage the apnea period effectively. This helps protect patients from severe hypoxemia. Additionally, real-time estimation of PaO₂ can be achieved using ORi that is beneficial not only in cases of decreased PaO₂ but also in critically ill neonates and infants to prevent complications such as absorption atelectasis, pulmonary injury, and retinal injury caused by excessively high PaO₂ levels [13,14].

Funding

This work was supported by a 2023 research grant from Pusan National University Yangsan Hospital.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

Jimin Lee (Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing)
Minwoo Chung (Writing – review & editing)
Eui-Suk Sung (Writing – review & editing)
Jung-Pil Yoon (Writing – review & editing)
Yeong Min Yoo (Writing – review & editing)
Jaesang Bae (Writing – review & editing)
Hee Young Kim (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Supervision; Writing – original draft; Writing – review & editing)

ORCID

Jimin Lee, https://orcid.org/0000-0003-2751-3212
Minwoo Chung, https://orcid.org/0000-0002-3302-0150
Eui-Suk Sung, https://orcid.org/0000-0001-8752-3426

https://doi.org/10.4097/kja.23568
References

Venous air emboli during esophagoscopy confirmed by computed tomographic pulmonary angiography -a case report-

Thadakorn Tantisarasart¹, Thara Tantichamnankul¹, Chanatthee Kitsiripant¹, Panjai Choochuen²

Departments of ¹Anesthesiology, ²Radiology, Prince of Songkla University, Songkhla, Thailand

Background: Esophagogastroduodenoscopy (EGD) is vital for the diagnosis and treatment of various gastrointestinal conditions but carries a low risk of venous air embolism (VAE). We report a case of VAE during EGD, confirmed by computed tomographic pulmonary angiography (CTPA).

Case: A 56-year-old male with a history of hypopharyngeal cancer underwent EGD for dysphagia-related esophageal dilation. Signs of VAE were noted, prompting swift interventions, including oxygen therapy, positional changes, and CTPA. CTPA revealed the Mercedes-Benz sign, pneumomediastinum, and a minimal pneumothorax. The patient's oxygen saturation improved within 30 min before undergoing CTPA, and he was discharged on postoperative day 4.

Conclusions: Timely recognition of VAE, resulting in appropriate interventions supported by CTPA, resulted in favorable patient outcomes.

Keywords: Air embolism; Anesthesia; Computed tomography angiography; Digestive system endoscopy; Esophageal stenosis; Esophagogastroduodenoscopy; Hypopharyngeal neoplasms.

Esophagogastroduodenoscopy (EGD) is a crucial procedure in gastroenterology that allows for various gastrointestinal conditions to be appropriately diagnosed, treated, and monitored. Although EGD offers invaluable information and therapeutic options, venous air embolism (VAE) is a rare but severe potential complication. As VAEs can disrupt blood flow and cause serious cardiovascular and pulmonary complications, including cardiac arrest and acute respiratory distress, clinicians must be extremely vigilant. This case report highlights the importance of promptly recognizing and managing VAE during EGD to prevent the potential adverse outcomes associated with this rare but serious complication. The aim of this case report is thus to enhance clinicians’ understanding of VAE and to emphasize the importance of its consideration during EGD procedures.

This case report obtained written informed consent from a guardian and was approved by the Human Research Ethics Committee of Faculty of Medicine, Prince of Songkla University.

Case Report

A 56-year-old male patient (weight: 62 kg, height: 175 cm) who had previously un-
dergone chemotherapy and radiation therapy for hypopharyngeal cancer developed a complete cervical esophageal stricture after undergoing external beam radiotherapy. Airway assessments revealed no limitations in mouth, jaw, or neck movement and a Mallampati score of II. The patient underwent a scheduled esophagogastroduodenoscopy in the gastrointestinal suite four months later to dilate the esophagus and facilitate oral feeding despite the presence of a gastrostomy. The gastrointestinal suite was equipped with a pre-use checked anesthesia machine and monitor, an emergency cart, and a defibrillator.

Initially, the attending anesthesiologist administered intravenous ketamine (50 mg), midazolam (2 mg), and fentanyl (50 µg). However, because of difficulties in maintaining the airway, the attending anesthesiologist decided to switch to general anesthesia using an oroendotracheal tube. Anesthesia was maintained using sevoflurane 2.0–3.0 vol% with a mixture of 40% oxygen. Mechanical ventilation was provided at a tidal volume of 500 ml, a rate of 12 breaths/min, and a positive end-expiratory pressure of 5 mmHg. Intraprocedural monitoring included electrocardiography, noninvasive blood pressure, pulse oximetry (SpO₂), and end-tidal carbon dioxide concentration (ETCO₂). Air insufflation was also used during the procedure. Endoscopy revealed complete stenosis 10 cm from the incisor, with a distal site 35 cm from the gastrostomy site. The esophageal stricture was successfully dilated using the rendezvous technique.

Approximately 45 min into the endoscopy, the patient's oxygen saturation dropped abruptly from 100% to 85% and the ETCO₂ decreased from 30 to 10 mmHg. The patient had a blood pressure of 110/85 mmHg and a heart rate of 105 beats/min in normal sinus rhythm. Subcutaneous emphysema was identified in the right chest wall, while lung examinations yielded normal results. The surgical team was promptly notified and the procedure was halted.

CTPA was conducted to rule out a pulmonary embolism while an adequate depth of anesthesia was maintained using midazolam and sevoflurane at a minimum alveolar anesthetic concentration (MAC) of 0.5. CTPA results revealed minimal air bubbles in the pulmonary trunk, forming a tri-radiate offshoot artifact (dynamic Mercedes-Benz sign) attributed to pulsation (Fig. 1) [1]. Diffuse pneumomediastinum and minimal right pneumothorax were also observed (Fig. 2). Mechanical ventilation was continued until postoperative day 2, and the patient was discharged on postoperative day 4.

https://doi.org/10.4097/kja.23722

Fig. 1. (A) Axial and (B) coronal CT pulmonary angiography (CTPA) images showing minimal air bubbles in the pulmonary trunk (arrow), indicating a tri-radiate offshoot artifact (dynamic Mercedes-Benz sign) due to pulsation.

Fig. 2. Axial CT image using lung window setting showing diffuse pneumomediastinum and minimal right pneumothorax.
Discussion

Endoscopic procedures often require sedation. Adverse events experienced under non-operating room anesthesia are similar to those experienced in the operating room, but the frequency and implications differ. Anesthesiologists encounter challenges in unfamiliar environments, such as limited space, confusion regarding the location of critical equipment and supplies, and restricted access to both the patient and airway. Ensuring patient safety is pivotal for anesthesiologists, encompassing appropriate collaboration with the team, management of a mobile anesthesia cart adequately equipped for emergencies, and the implementation of an effective system of communication during emergencies. Adequate anesthesia manpower is also crucial for patient safety. Anesthesiologists that practice regularly have been shown to be more efficient than non-regular anesthesiologists, as demonstrated by higher mean oxygen saturation, lower operating room turnaround time, and lower operating room costs [2].

EGD is a versatile procedure with diagnostic and therapeutic applications including the management of complex conditions (e.g., esophageal strictures) that often involve the rendezvous technique. Although complications associated with esophageal dilation are relatively rare, they can include esophageal or hypopharyngeal perforation, abdominal wall infection, stomach wall dehiscence, and pneumothorax [3]. Although rare, VAE is a severe and potentially fatal complication that is primarily iatrogenic and has been documented in various medical procedures, including sitting craniotomy, pars plana vitrectomy, cesarean delivery, and gastrointestinal procedures such as endoscopic retrograde cholangiopancreatography and EGD [4].

Clinical manifestations of VAE are diverse and can involve both the cardiovascular and neurological systems. However, in certain instances, the effects may be obscured by anesthesia, making prompt recognition difficult. The severity of VAE is closely linked to the rate and volume of air introduced into the circulatory system. Smaller volumes may cause subclinical effects, whereas larger volumes can significantly disturb a patient’s hemodynamics. The symptoms of VAE are nonspecific, meaning that even the smallest suspicion should prompt a thorough investigation and diagnosis. Several risk factors are associated with VAE, including inflammatory conditions of the bile duct, hepatic abscesses, inflammatory bowel diseases, necrotizing enterocolitis, and gastrointestinal tumors. Procedural factors that can increase the risk of VAE include air insufflation and the use of nitrous oxide [5]. Most cases of VAE occur in conjunction with a disruption in the mucosal barrier, such as an ulceration, dilation, biopsy, or sphincterotomy.

In this patient, VAE likely occurred due to direct air entry into the exposed blood vessels during esophageal stricture dilation, resulting in a connection between the esophageal lumen and venous circulation [6,7]. Additionally, the use of high-pressure air insufflation during the procedure may have facilitated air entry [8]. Notably, the insufflation pressure was not continuously monitored. Furthermore, exposure of the endoscope to radiation may have resulted in inflammatory changes, predisposing the esophagus to VAE [3]. A rapid reduction in ETCO₂ is a highly sensitive indicator of VAE at a threshold of 0.25 ml/kg of air and can be used to identify VAE in patients without hemodynamic compromise [9]. In cases of suspected VAE, a pulmonary embolism must be excluded, particularly in patients with underlying cancers. Therefore, the use of diagnostic tools, such as CTPA, is recommended. CTPA exhibits high sensitivity (83%) and specificity (96%) for detecting pulmonary embolisms [10]. Despite immediate bowel decompression and initial management with 100% oxygen, hemodynamic maintenance, and Trendelenburg positioning, air persisted in the pulmonary artery for an hour. The time to resolution of symptomatic air embolisms can vary from 5 to 12 h [11,12]. The rate of air resorption may depend on the initial size and volume of the pulmonary embolism. The precise volume of air that can cause hemodynamic disturbances is uncertain; however, even small amounts (e.g., 50–100 ml) can be fatal in humans [12]. VAE can also be diagnosed with point-of-care ultrasonography (POCUS) using transesophageal echocardiography (TEE), which can be conducted at the bedside and provides information on signs of cardiopulmonary compromise [13]. However, the volume of air required for the detection of VAE by TEE is larger than that for CTPA, and the sensitivity may vary depending on the operator’s experience and interpretive errors [13]. Thus, small symptomatic pulmonary air embolisms may be missed on TEE.

Our CTPA findings showed minimal air bubbles in the pulmonary trunk as a tri-radiate offshore artifact (dynamic Mercedes-Benz sign) in the upper section of the anatomic structures. This differs from respiratory artifacts, which have a distinct appearance in the middle or lower sections of vessels and typically appear as lines or other long shapes [14]. To optimize diagnosis, we adjusted the images to a relatively high window width (400–1600 HU) and a window center at approximately 40 HU with a lung window setting ranging from 1200 to −400 HU [15]. These settings can be used to clearly distinguish air bubbles representing a tri-radiate offshore artifact from other artifacts.

Anesthesiologists play a crucial role in the prevention and management of VAE during endoscopic procedures. Prevention of VAE is paramount and can be effectively addressed using prophylactic measures including the identification of high-risk patients, maintenance of adequate venous pressure, and vigilant monitor-
ing for signs of VAE. Continuous monitoring of vital signs, ETCO\(_2\) levels, and central venous pressure coupled with awareness of the patient's medical history can facilitate the early detection of VAE. In terms of procedural factors, opting for carbon dioxide (CO\(_2\)) insufflation over air insufflation is a viable strategy for eliminating the risk of VAE. CO\(_2\) has a significantly greater solubility than air (by approximately 50 times). This increased solubility widens the safety margin for inadvertent entry of gas into the circulatory system \[4\]. However, procedures during EGD may be limited when the Trendelenburg position or a posture that elevates the patient's upper body above heart level is used.

In summary, EGD is a valuable procedure with various diagnostic and therapeutic applications, including complex cases such as esophageal strictures. However, the infrequent occurrence of VAE underscores the importance of vigilant monitoring, early detection, and prompt intervention to ensure patient safety. CTPA plays a pivotal role in the diagnosis and management of VAE, particularly in patients with underlying cancers.

**Funding**

None.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Data Availability**

All data generated or analyzed during this study are included in this published article.

**Author Contributions**

Thadakorn Tantisarasart (Writing – original draft; Writing – review & editing)
Thara Tantichamnankul (Writing – review & editing)
Chanatthee Kitsiripant (Writing – review & editing)
Panjai Choochuen (Writing – review & editing)

**ORCID**

Thadakorn Tantisarasart, https://orcid.org/0000-0002-2448-3276
Thara Tantichamnankul, https://orcid.org/0009-0008-8462-6292
Chanatthee Kitsiripant, https://orcid.org/0000-0003-1504-9336
Panjai Choochuen, https://orcid.org/0000-0002-2137-3055

**References**

Dear Editor,

We are intrigued by the paper titled “Usefulness of C-curved stylet for intubation with the C-MAC® Miller videolaryngoscope in neonates and infants: a prospective randomized controlled trial” [1]. However, we have specific concerns that require further discussion.

The feasibility of endotracheal intubation depends on the radius of the endotracheal tube (ETT) curvature that clinically ranges between 12.05 and 15.78 cm [2]. Technical variations may arise based on the patient’s anatomical structure, the characteristics of the laryngoscope utilized, and the proficiency of the medical provider. To mitigate these differences, the ease of ETT insertion can be adjusted by employing a stylet [3,4]. The authors describe how applying a stylet transforms the ETT into either a hockey stick-curved or a C-curved type. They suggested that in neonates and infants, modifying the ETT shape into a C-curve may reduce tube handling time compared to the conventional hockey stick-shaped tube during intubation using a C-MAC® video-laryngoscope Miller blade [1].

Generally, there are two types of Hockey sticks: field or ice hockey. Players or goalies use different shapes. Hockey players need to decide the type of curve (e.g., toe, mid, or heel), depth of curve (e.g., slight, moderate, or deep), and face angle (e.g., neutral, slightly open, or open), depending on their age, position, and preference. Similarly, anesthesiologist need to decide the angle and curve of the ETT for endotracheal intubation. We are curious about the difference between the hockey stick-curved and the C-curved type. The authors do not provide detailed explanation of the specific shape applied. Should we understand it as a general concept? We assume that the difference is only the tip of the tube that is connected to the breathing circuit being straight or curved.

The tip length of the hockey stick-curved tube or the radius of the C-curved type tube is an important aspect. We would like to know the changes in the length or angle when the hockey stick-curved tube was initially attempted and subsequently modified. Additionally, we are interested in the initial and final radius of the C-curved type tube (Figs. 1A and B). This paper does not provide clear explanation about the specific length or angle for the first attempt of endotracheal intubation. Can we conclude that the C-curve type tube is effective when using the C-MAC® video-laryngoscope Miller blade without further explanation?

Although this explanation can be understood in general concept, we guess a more detailed explanation would be helpful for clinical application. In the process of preparing for ETT, there is no explanation of the changes such as an increase or decrease in the length of the hockey stick-curved tube and/or the radius of the C-curved tube before and during intubation. In particular, the authors used a cuffed ETT; however, when using an uncuffed ETT for pediatric patients, there is also the issue of determining the appropriate point and angle of the hockey-stick shape (Figs. 1A and B). In pediatric patients, especially neonate and infants, even a slight deviation of 1 mm in the bending portion can greatly affect the difficulty of intubation in neonates and infants. The time required for endotracheal intubation is important, but so is the management of the ETT shape to ensure easy, rapid, and safe intubation. Moreover, how the medical provider holds and inserts the ETT is also crucial. With direct laryngoscopy, there is a straight pathway from the teeth to the larynx, generally allowing for a straightforward tube. While using a video-laryngoscope, we cannot see the entire length of the tube, and the ease of insertion depends on the angle of the laryngoscope blade and the length of tube tip that meets in front of the glottis. As endotracheal intubation involves exposing the glottis with a direct- or video-laryngoscope and subsequent alignment of the laryngoscope blade tip and tube tip at the glottis, differences may occur depending on the instrument type and skillfulness. Successful endotracheal intubation depends on the view of the glottis (full, partial, or none), the ease of tracheal intubation (easy, difficult, or unachievable), and the specific device used to facilitate tracheal intubation [5].

We believe that ensuring correct formation and maintenance of the shape of the ETT before endotracheal intubation is crucial for achieving easy, rapid, and non-traumatic intubation, leading to good exposure of the glottis.

Fig. 1. Shape of hockey stick and C-shape. (A) Hockey stick shape, (B) C-shape of endotracheal tube.
Response to “Comment on Usefulness of C-curved stylet for intubation with the C-MAC® Miller videolaryngoscope in neonates and infants: a prospective randomized controlled trial”

Thank you for the insightful comments made by Park et al. [1] on our previous article. As mentioned in the “Limitations” section [2], the success of intubation using a videolaryngoscope depends on the type of endotracheal tube (ETT) and videolaryngoscope, skill of the medical practitioner, and stylet angle. In our study, all intubations were performed using a cuffed ETT (ShileyTM, Hi-Contour Oral/Nasal Tracheal Tube, Covidien) ID 3.0 mm and C-MAC® Miller videolaryngoscope (Karl Storz) for neonate and infant populations. Therefore, to generalize our results to a larger population, further investigations are needed.

To maintain ETT angle consistency throughout the study, we created ETT templates for both the hockey-stick- and C-curved ETTs [2]. However, we now recognize that our explanation was insufficient. The C-curved stylet is shaped like a circular quarter with a radius of approximately 13 cm. The angle between the ETT tip and end (connector part) was approximately 90° (Fig. 1A). The hockey-stick-curved stylet...
stylet was bent 3 cm upstream from the tube tip (approximately 2 cm upstream of the distal end of the cuff; Fig. 1B).

**Jung-Bin Park, Ji-Hyun Lee**  
Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Corresponding author: Ji-Hyun Lee, M.D., Ph.D.  
Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea  
Tel: +82-2-2072-3661 Fax: +82-2-747-8364  
Email: muslab6@snu.ac.kr

Received: November 17, 2023; Accepted: November 28, 2023

**Author Contributions**: Jung-Bin Park (Conceptualization; Investigation; Methodology; Writing – original draft); Ji-Hyun Lee (Conceptualization; Investigation; Methodology; Writing – review & editing)

**ORCID**: Jung-Bin Park, https://orcid.org/0000-0002-8816-5605; Ji-Hyun Lee, https://orcid.org/0000-0002-8384-8191

**References**

1. Park DH, Chung JD, Jeong CY, Yang HS. Comment on “Usefulness of C-curved stylet for intubation with the C-MAC® Miller videolaryngoscope in neonates and infants: a prospective randomized controlled trial”. Korean J Anesthesiol 2024; 77: 282-3.


Korean J Anesthesiol 2024;77(2):283-284  
https://doi.org/10.4097/kja.23842

**Funding**: None.

**Conflicts of Interest**: Ji-Hyun Lee has been an editor of the Korean Journal of Anesthesiology since 2021. However, she was not involved in the review process for this article, including peer reviewer selection, evaluation, and decision-making. No other potential conflict of interest relevant to this article was reported.
Corrigendum

The article by Kang P, et al. entitled, “Association of the perfusion index with postoperative acute kidney injury: a retrospective study” (Korean J Anesthesiol 2023;76(4):348-356) was published error in the Project Number.

Before correction:
This work was supported by the Korea Medical Device Development Fund grant funded by the government of Republic of Korea (in particular, the Ministry of Science and ICT; the Ministry of Trade, Industry and Energy; the Ministry of Health and Welfare; and the Ministry of Food and Drug Safety) (Project Number: 202011823).

The correct information is found below:
This work was supported by the Korea Medical Device Development Fund grant funded by the government of Republic of Korea (in particular, the Ministry of Science and ICT; the Ministry of Trade, Industry and Energy; the Ministry of Health and Welfare; and the Ministry of Food and Drug Safety) (Project Number: 202011B23).

The authors apologize for any inconvenience these mistakes may have caused.

Association of the perfusion index with postoperative acute kidney injury: a retrospective study

Pyoyoon Kang¹, Jung-bin Park¹, Hyun-Kyu Yoon¹, Sang-Hwan Ji¹, Young-Eun Jang¹, Eun-Hee Kim¹, Ji-Hyun Lee¹, Hyung Chul Lee¹, Jin-Tae Kim¹,², Hee-Soo Kim¹,²

Department of Anesthesiology and Pain Medicine, ¹Seoul National University Hospital, ²Seoul National University College of Medicine, Seoul, Korea

Korean Journal of Anesthesiology 2023;76(4):348-356
DOI: https://doi.org/10.4097/kja.22620

The article by Kang P, et al. entitled, “Association of the perfusion index with postoperative acute kidney injury: a retrospective study” (Korean J Anesthesiol 2023;76(4):348-356) was published error in the Project Number.

Before correction:
This work was supported by the Korea Medical Device Development Fund grant funded by the government of Republic of Korea (in particular, the Ministry of Science and ICT; the Ministry of Trade, Industry and Energy; the Ministry of Health and Welfare; and the Ministry of Food and Drug Safety) (Project Number: 202011823).

The correct information is found below:
This work was supported by the Korea Medical Device Development Fund grant funded by the government of Republic of Korea (in particular, the Ministry of Science and ICT; the Ministry of Trade, Industry and Energy; the Ministry of Health and Welfare; and the Ministry of Food and Drug Safety) (Project Number: 202011B23).

The authors apologize for any inconvenience these mistakes may have caused.
Notice

The Korean Society of Anesthesiologists
Editorial Board / Tel: +82-2-792-5128 / Fax: +82-2-792-4089 / Email: journal@anesthesia.or.kr

1. On-line manuscript review process

1) All proposed manuscripts for publication in the Korean Journal of Anesthesiology will be processed exclusively online. Please use the “Questions and Answers” section of our website (http://www.editorialmanager.com/kja) for any concerns you may have vis-à-vis problems, questions, or suggestions for improvement. You may also direct them to the attention of the electronic manuscripts processing manager (editorial manager) (M2PI, +82-2-6966-4930).

2) Processing publication-related inquiries for newly submitted manuscripts through the main number of the KJA would cause undue burden for the KJA in its general duties. As such, these inquiries should be made entirely online in the “Questions & Answers” section of the website. Requests and orders - including the expected date of publication and the status of manuscript under review - should be made online, and responses shall be provided without delay upon confirmation.

2. Information and regulation for submitting manuscripts

1) The corresponding author will be notified by e-mail whenever there is any change in the status of a submitted manuscript. Authors could also obtain this information directly through the website. The KJA will respond to all review inquiries. However, the expected Volume and Number cannot be provided, if it has not yet been confirmed; as such, we would not be able to entertain inquiries on this matter.

2) Doctoral and Master's dissertations should abide by the manuscript submission guidelines of the KJA and should accompany a scanned file of the thesis title and the signature(s) of the examiner(s). This information should be entered in the “Paper Information” section during the online submission process.

3) The corresponding author should be a faculty. The corresponding author will be notified by e-mail whenever there is any change in the status of a submitted manuscript, and any resubmission can only be made by the corresponding author.

4) A manuscript needs to be resubmitted if there is a change in the makeup of the manuscript authorship; thus, special care should be taken when registering authors.

5) Manuscript review is terminated after two reviews, but a member of the review committee may request for a 3rd review.
Instructions to authors

Enacted March 24, 1995
Recently revised (28th) December 1, 2023

The Korean Journal of Anesthesiology (KJA) is an international, English-language, open-access, and peer-reviewed journal for anesthesiology, critical care, and pain medicine. As an official scientific journal of the Korean Society of Anesthesiologists (KSA), the KJA published monthly until 2014 and now publish bimonthly in 2015 (on the first day of February, April, June, August, October, and December). Its abbreviated title is "Korean J Anesthesiol." The KJA publishes definitive articles that can improve clinical care or guide further research in the field of anesthesiology. Additionally, KJA gladly reviews and publishes negative results for which publication will benefit clinical practice and promote further research activity. Manuscripts for submission to the KJA should be written according to the following policies. The KJA follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, available at: www.icmje.org/, if otherwise not described below.

Editorial Policy

The Editor assumes that all authors listed in a manuscript have agreed with the following policy of the KJA on submission of manuscript. Except for the negotiated secondary publication, manuscript submitted to the KJA must be previously unpublished and not be under consideration for publication elsewhere. Under any circumstances, the identities of the referees will not be revealed. If a new author should be added or an author should be deleted after the submission, it is the responsibility of the corresponding author to ensure that the author concerned are aware of and agree to the change in authorship. The KJA has no responsibility for such changes. Minimum publication charges and additional fee for reprints will due on every manuscript. Color illustrations are charged to the authors. All published manuscripts become the permanent property of the KSA and may not be published elsewhere without written permission.

General information

1. Publication types

The KJA focuses on Original articles (Clinical trial/Experimental research, Meta-analysis), Case reports, Reviews, Letters to the editor, Statistical round, and Editorials.

2. Language

Manuscripts submitted to the KJA should be compiled in English. Spellings should abide by American spellings. Medical terminology should be written based on the most recent edition of Dorland’s Illustrated Medical Dictionary. Accepted manuscripts are requested to be proofread by professional English editors.

3. Submission of manuscript

In addition to members of the KSA, any researcher throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Authors are requested to submit their papers electronically by using the online manuscript submission system, available at: https://www.editorialmanager.com/kja/default.aspx. Authors, reviewers, and editors send and receive all correspondences through this system.

4. Peer review process

Under any circumstances, the identities of the reviewers will not be revealed and the reviewers will be blinded to the names of the authors and the institutions from which the manuscripts have been sent. Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer’s opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer’s opinion. The author’s revisions should be completed within 30 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication again. To extend the revision period to more than 30 days, the author should negotiate with the Editorial Board. The manuscript review process should be finished the second review. If the authors wish further review, the Editorial Board may consider it. The Editorial Board will make a final decision on the approval for publication of the submitted manuscripts and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data need professional statistical review by a statistician. The review and publication processes that are not described in the Instructions for Authors will be incorporated into the Editorial Policy Statements approved by the Council of Science Ed-
itors Board of Directors, available at: www.councilscienceeditors.org/.

5. Article processing charge and publication fee
There is no charge for submitting and processing a paper until policy change. But, the KJA charges a publication fee for each printed page of KRW. Publication fees are waived if the affiliation of corresponding author is outside Korea.

6. Copyrights
Copyrights of all published materials are owned by the KSA. On behalf of co-author(s), corresponding author must complete and submit the journal’s copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (http://www.icmje.org/recommendations/). A copy of the form (https://ekja.org/authors/copyright_transfer_agreement.php) is made available to the submitting author within the Editorial Manager submission process.

7. Open access
KJA is an open access journal. Accepted peer-reviewed articles are freely available on the journal website for any user, worldwide, immediately upon publication without additional charge. Articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. To use the tables or figures of KJA in other periodicals, books or media for scholarly, educational purposes, the process of permission request to the publisher of KJA is not necessary. This is in accordance with the Budapest Open Access Initiative definition of open access. It also follows the open access policy of PubMed Central at United States National Library of Medicine (http://www.ncbi.nlm.nih.gov/pmc/). All the content of the journal is available immediately upon publication without embargo period.

Research and publication ethics
For the policies on research and publication ethics that are not stated in these instructions, the Good Publication Practice Guidelines for Medical Journals, available at: https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13, or the Guide-lines on Good Publication, available at: publicationethics.org/, can be applied.

1. Conflict-of-interest statement
Conflict of interest exists when an author or the author’s institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having a great potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and the background of the completed research.

2. Statement of informed consent and Institutional Review Board approval
If the study in the article is on human subjects or human-originated material, informed consent for the study and the Institutional Review Board (IRB) approval number needs to be provided. Copies of written informed consents and IRB approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to make potential ethical issues clear.

3. Statement of human and animal right
Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2013) (available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Authors should indicate whether the procedures were conducted in accordance with the Helsinki Declaration-2013 in the Text. Clinical studies that do not meet
the Helsinki Declaration will not be considered for publication. Human subjects should not be identifiable, such that patients’ names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

4. Registration of the clinical trial research
Any researches that deals with clinical trial should be registered with the primary national clinical trial registration site such as Korea Clinical Research Information Service (cris.nih.go.kr/) or other sites accredited by WHO or International Committee of Medical Journal Editor such as ClinicalTrials.gov (clinicaltrials.gov/).

5. Reporting guidelines
The KJA recommends a submitted manuscript to follow reporting guidelines appropriate for various study types. Good sources for reporting guidelines are the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network (www.equator-network.org/) and the U.S. National Library of Medicine’s (NLM’s) Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html). The appropriate checklist (and flow diagram, if applicable) must be included with each submission.

6. Authorship
Authorship credit should be based on: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; AND 2) drafting the article or revising it critically for important intellectual content; AND 3) final approval of the version to be published; AND 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these 4 conditions. If the number of authors is equal to or greater than 2, there should be a list of each author’s role in the submitted paper. Authors are obliged to participate in peer review process. All others who contributed to the work who are not authors should be named in the Acknowledgements section. KJA has a strict policy on changes to authorship after acceptance of the article and will only consider changes in the most extraordinary situations once the article is accepted.

7. Plagiarism and duplicate publication
Plagiarism is the use of previously published material without attribution. The KJA editorial office screens all submitted manuscripts for plagiarism, using a sophisticated software program, prior to peer review. When plagiarism is detected at any time before publication, the KJA editorial office will take appropriate action as directed by the standards set forth by the Committee on Publication Ethics (COPE). For additional information, please visit http://www.publicationethics.org. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access.

8. Secondary publication
It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, available at: www.icmje.org/.

9. Feedback after publication
If the authors or readers find any errors, or contents that should be revised, it can be requested from the Editorial Board. The Editorial Board may consider erratum, corrigendum or a retraction. If there are any revisions to the article, there will be a CrossMark description to announce the final draft. If there is a reader’s opinion on the published article with the form of Letter to the editor, it will be forwarded to the authors. The authors can reply to the reader’s letter. Letter to the editor and the author’s reply may be also published.

9-1. Process to manage the research and publication misconduct
When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author’s idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of KJA will discuss the suspected cases and reach a decision. KJA will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

9-2. Policy of Article withdrawal, retraction, and replacement
1) Article withdrawal
Articles in Press (articles that have been accepted for publication but which have not been formally published and will not yet have the complete volume/issue/page information) that include errors, or are discovered to be accidental duplicates of
A preprint is a preliminary version of a scientific article that is posted online at publicly accessible repositories before undergoing a formal peer review in a traditional academic journal.

Authors are encouraged to submit the final versions of their preprints to KJA without treating them as duplicate submissions or publications. During the manuscript submission process, authors should disclose the preprint's DOI to exclude it from the estimation of the similarity index for the final manuscript. We will conceal the preprint's DOI to blind peer reviewers to the authors' list. Any differences between the authors' list of the final manuscript submitted to KJA and the preprint should be minimal and will require a thorough explanation. After acceptance for publication, authors will be asked to update the meta-information of the preprint to point to the DOI of the final published article in KJA.

Articles published without peer review, including preprints, abstracts of conferences, and American Society of Anesthesiologists (ASA) refresher course lectures, may not be included in the references.

**Manuscript preparation**

1. **Word processors and format of manuscript**
   A manuscript must be written in proper and clear English. The manuscript, including tables and their footnotes, and figure legends, must be typed in one double space. Materials should be prepared with a standard 12-point typeface or greater (Times New Roman typeface is preferred). The manuscript should be in the following sequence: cover letter (optional), title page file, manuscript (title and running title, abstract and keywords, introduction, materials and methods, results, discussion, references, tables, and figure legends), figures, other submission elements. All pages should be numbered consecutively starting from the title page. All numbers should be written in Arabic numerals throughout the manuscripts. Our preferred file format is DOCX or DOC. A single PDF file that contains all materials in a file including figures and figure legends is acceptable. In that case, authors should add line numbers throughout the document. Manuscript containing anything in headers and footers, except of page numbers, will be returned to authors. If your PDF submission is accepted, you will be asked to upload your final document file in DOCX or DOC format as well. Make sure to update your PDF file with the most recent version of your manuscript.

2. **Abbreviation of terminology**
   Abbreviations should be avoided as much as possible. When they are used, full expression of the abbreviations followed by the abbreviated word in parentheses should be given at the first use. Common abbreviations, however, may be used, such as DNA. Abbreviation can be used if it is listed as a MeSH subject heading (http://www.ncbi.nlm.nih.gov/mesh).
3. **Word-spacing**

1) Leave 1 space for each side, using arithmetic marks as +, −, ×, etc.

Leave no space for hyphen between words.

2) Leave 1 space after “,” and “;”. Leave 2 spaces after “.” and “:”.

3) Using parentheses, leave 1 space each side.

4) Brackets in parentheses, apply square brackets.

4. **Citations**

1) If a citation has 2 authors, write as “Hirota and Lambert.” If there are more than 3 authors, apply ‘et al.’ at the end of the first author’s surname. Ex) Kim et al. [1].

2) Citation should be applied after the last word or author’s surname.

3) Apply citation before a comma or period.

4) Identify reference by several or coupled Arabic numbers, enclosed in square brackets on the line as [1,3,5].

5. **Arrangement of manuscript**

All articles should be arranged in the following order.

- Cover letter (optional)
- Title Page file, uploaded separately
- Manuscript, as a single file in word processing format (eg, .doc), consisting of Title and running title, Abstract (if required for the article type; see relevant section), Body Text, Referenc-es, Tables, Figure Legends, if any (in numerical order, on the same page); be sure to number all pages of the manuscript file
- Figures (each Figure should be a separate file in figure file format)
- Other submission elements (Supplemental Digital Content, etc.)

Each new section’s title should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page. Page numbers should be placed at the middle of the bottom of page. For survey-based clinical studies, the original survey document does not need to be included in the body of the manuscript but may be supplemented in an appendix.

6. **Statistical Analysis**

1) Describe the statistical tests employed in the study with enough detail so that readers can reproduce the same results if the original data are available. The name and version of the statistical package should be provided.

2) Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.¹

3) The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should describe whether the basic statistical assumptions are met.²,³

4) For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality.

5) When analyzing a categorical variable, if the number of events and sample is small, exact test or asymptotic method with appropriate adjustments should be used. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and number of events are sufficiently large.

6) The Korean Journal of Anesthesiology (KJA) strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.⁴

7) Except for study designs that require a one-tailed test, for example, non-inferiority trials, the P values should be two-tailed. A P value should be expressed up to three decimal places (not as “P < 0.05”). If the value is less than 0.001, it should be described as “P < 0.001” but never as “P = 0.000.” For large P value greater than 0.1, the values can be rounded off to one decimal place, for example, P = 0.1, P = 0.9.

8) A priori sample size calculation should be described in detail.⁵ Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent.

---

In the case of multiple comparisons, an adjusted level of significance is acceptable.

9) It is recommended using mean ± SD or median (Q1, Q3) format to present representative values of continuous variables. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean ± SD of body weight in patients measured on a scale that is accurate to 0.1 kg should be expressed as 65.45 ± 2.52 kg.

10) Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.

7. Organization of manuscript

1) Clinical or Experimental research

(1) Title page

① Title

Title should be concise and precise. For the title, only the first letter of the first word should be capitalized.

② Author information

First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.

③ Running title

A running title of no more than 40 characters, including letters and spaces, should be described. If inappropriate, the editorial board may revise it.

④ Corresponding Author

Name, mailing address, phone number, and e-mail address of the corresponding author

⑤ Previous presentation in conferences

Title of the conference, date of presentation, and the location of the conference may be described.

⑥ Conflict of interest

It should be disclosed here according to the statement in the Research and publication ethics regardless of existence of conflict of interest. If the authors have nothing to disclose, please state: “No potential conflict of interest relevant to this article was reported.”

⑦ Funding

Funding to the research should be provided here. Providing a FundRef ID is recommended including the name of the funding agency, country and if available, the number of the grant provided by the funding agency. If the funding agency does not have a FundRef ID, please ask that agency to contact the FundRef registry (e-mail: fundref.registry@crossref.org). Additional detailed policy of FundRef description is available from http://www.crossref.org/fundref/.

⑧ Acknowledgments

Any persons that contributed to the study or the manuscript, but not meeting the requirements of an authorship could be placed here. For mentioning any persons or any organizations in this section, there should be a written permission from them.

⑨ IRB number

⑩ Clinical trial registration number

If any of these elements are not applicable to your submission, write “not applicable” after the number and topic; for example, “Prior Presentations: Not applicable.”

(2) Manuscript

① Title and Running title

② Abstract

All manuscripts should contain a structured abstract that is written only in English. Provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Quotation of references is not available in the abstract. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.

③ Introduction

The introduction should address the purpose of the article concisely and include background reports that are relevant to the purpose of the paper.

④ Materials and Methods

- The materials and methods section should include sufficient details of the design, subjects, and methods of the article in order, as well as the data analysis methods and con-

---

6Lee S and Lee DK. What is the proper way to apply the multiple comparison test? Korean J Anesthesiol 2018; 71: 353-60.

7http://www.amamanualofstyle.com/
trol of bias in the study. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others.

- When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the IRB for the study and the IRB approval number needs to be provided. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by Institutional Board for the Care and Use of Laboratory Animals. "American Society of Anesthesiologists physical status classification" should not be abbreviated. As a rule, subsection titles are not recommended.

- Clearly describe the selection of observational or experimental participants. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). For additional information, please visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/.

- Reports of randomized trials must conform to the revised CONSORT guidelines and should be submitted with the CONSORT flow diagram. The CONSORT checklist should be submitted as a separate file along with the manuscript. The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org or EQUATOR Network (https://www.equator-network.org/home/).

- Units
  Laboratory information should be reported in International System of Units [SI]. Please refer to A Guide for Biological and Medical Editors and Authors, 6th Edn. Baron DN and Clarke HM, ed. (2008), CRC Press. or visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/.

- Exceptions
  A. The unit for volume is "L", others in "dl, ml, μl".
  B. The units for pressure are mmHg or cmH₂O.
  C. Use Celsius for temperature
  D. Units for concentration are M, mM, μM.
  E. When more than 2 items are presented, diagonal slashes are acceptable for simple units. Negative exponents should not be used.
  F. Leave 1 space between number and units.

- Exception) 5%, 36°C
- Machines and Equipment
  According to the 11th edition of the American Medical Association, provide the model name and manufacturer’s name without the country.
- Drug Names
  Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide ® or ™ as a superscript and the manufacturer's name.
- Ions
  Ex) Na⁺ [O], Mg²⁺ [O], Mg⁺⁺ [X], Mg⁺² [X]
- Statistics
  Statistical methods must be described with enough detail so that readers can reproduce the same results if the original data available. The KJA strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. A sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint.

- Results
  Results should be presented in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all of the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. Citation of tables and figures should be provided as Table 1 and Fig. 1.

- Discussion
  The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat the results in detail or other information that is given in the Introduction or the Results section. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the Discussion section.

- References
References should be obviously related to documents and should not exceed 50. For exceeding the number of references, it should be negotiated with the Editorial Board. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide footnotes in the body text section. All of the references should be stated in English, including author, title, name of journal, etc.

If necessary, the editorial board may request original documents of the references.


Six authors can be listed. If more than 6 authors are listed, only list 6 names with 'et al.'

Provide the start and final page numbers of the cited reference.

Abstracts of conferences are not allowed to be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.

Description format

A. Regular journal
Author name. Title of journal. Name of journal published year; volume: start page-final page.
Ex) '2006; 7(Suppl 1): 64-96' '2007; 76: H232-8'
B. Monographs
C. Chapter
D. Electronic documents
E. Online journal article
F. Papers that have been submitted and accepted for publication should be included in the list, with the phrase ‘in press’ replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction.

Table

- Type or print each table on a separate sheet of paper.
- Number tables consecutively in the order of their first citation in the text.
- Supply a brief title
- Tables should be more than 4 rows and should not be over 1 page.
- Except for titles and first letters, all of the text in the tables should be written in small alphabetic letters.
- In demographic data, sex would be provided as M/F, and age in yr. Data of year, weight, height, and any other units would be provided with 1 decimal place.
- “±” sign in the upper column of table should be lined up with the lower column.
- Footnotes should be provided consecutively in order of the cited tables or statistics.
- Marks for footnote should be given in order of *, †, ‡, §, ¶, **, ††, ‡‡... When marks are used to explain items of the table, indicate them with superscripts.
- Define all abbreviations except those approved by the International System of Units. Define all abbreviations every
time they are repeated.

5 Legends for figures and photographs
   • All of the figures and photographs should be described in the text separately.
   • The description order is the same as in the footnotes in tables and should be in recognizable sentences.
   • Define all abbreviations every time they are repeated.

(3) Figures and illustrations
   ① The KJA publishes in full color, and encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.
   ② Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to clearly frame the image. Axis labels should be large enough to be easily readable, and printed in black.
   ③ Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files. Width of figure should be 84 mm (one column). Contrast of photos or graphs should be at least 600 dpi. Contrast of line drawings should be at least 1,200 dpi. Number figures as “Fig. (Arabic numeral)” in the order of their citation. (ex. Fig. 1).
   ④ Photographs should be submitted individually. If Figure 1 is divided into A, B, C and D, do not combine it into 1, but submit each of them separately. Authors should submit line drawings in black and white.
   ⑤ In horizontal and vertical legends, the letter of the first English word should be capitalized.
   ⑥ Connections between numbers should be denoted by “-” not “--”. Do not space the numbers (ex. 2–4).
   ⑦ Figures (line drawings) should be clearly printed in black and white.
   ⑧ Figures should be explained briefly in the footnotes. The format is the same as the table format.
   ⑨ An individual should not be recognizable in the photographs or X-ray films unless written consent of the subject has been obtained and is provided at the time of submission.
   ⑩ Pathological samples should be pictured with a measuring stick.

(4) Other submission elements (Video submission)
The KJA publishes supplemental video (movie) clip(s) that will be available online. Not only recording of the abstract, text, audio or video files, but also data files should be added here.

Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and be discussed in the text. Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) in the video clips. However, all identifying information, including patient name and/or ID number, hospital name, and date of the procedure, should be removed.

Video clips should contain succinct teaching points that must be supported by the current literature or standard reference texts, preferably those most accessible to the general reader. The adequacy of the teaching points will be evaluated during the review process and finally confirmed by the editorial board at the end of the review process.

Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.

① The video clip(s) should have simple file names (e.g., Video 1***, Video 2***) and include the appropriate extension (e.g., .mov, .mpg).
② The maximum number of video clips is 20.
③ The video clip(s) should be playable on both Windows and MAC computers. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.
④ Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.
⑤ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

2) Systematic review and meta-analysis
Systematic reviews are systematic, critical assessments of literature and data sources in order to answer a specific question, and/or includes a statistical technique leading to a quantitative summary of results and examining sources of differences in results among studies, if any. The subtitle should include the phrase “A systematic review” and/or “A Meta-analysis.”
Organization of systematic review and meta-analysis: Same as clinical and experimental studies, except,
   • All systematic reviews and meta-analyses should be regist-
tered at an appropriate online public registry (eg, PROSPERO; http://www.crd.york.ac.uk/PROSPERO/), and registration information should be included with the submission.

- Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/). Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.

- No limitation the number of the references.

3) Case Reports

A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or population, that is so unusual that a clinical trial is not feasible.

Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.

(1) Title page: Same as clinical and experimental studies.

(2) Manuscript

① Title and Running title.

② Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.

③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.

④ Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.

⑤ Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.

⑥ References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board.

⑦ Tables and figures: Proportional to clinical and experimental studies.

4) Reviews

Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts equal to or less than 250 words in English. Figures and tables should be provided in English. References should be obviously related to documents and should not exceed 100. For exceeding the number of references, it should be negotiated with the Editorial Board. Body text should not exceed 30 A4 pages, and the number of figures and tables should be equal to or less than 6.

5) Letters to the Editor

Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. Book reviews as well as news of scientific societies and scientific meetings in Korea or abroad can be included. Letters to the editor of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.

Cover pages should be formatted as those of clinical research papers. The body text should not exceed 1,000 words and should have no more than 5 references. For exceeding the number of references, it should be negotiated with the Editorial Board. A figure or a table may be used. A maximum of five au-
thors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.

6) Statistical Round
A Statistical Round is a narrative review of the application of contemporary quantitative sciences to issues of concern to anesthetia researchers. A Statistical Round involves a focused discussion on one or more unique or interesting statistical analysis methods that has previously been published in this journal or expresses the general policies or opinions of the Statistical Round Board. They are solicited by the Statistical Round Board and reviewed by the Statistical Editor. There are no word limits to or rules regarding the structure of a Statistical Round. They should have an unstructured abstract of no more than 250 words in English. All articles in a Statistical Round will be published in English and translated into Korean for the convenience of Korean readers. The Korean version of the Statistical Round will be published only on the Web page of the Journal (https://ekja.org). The inclusion of sample datasets as Web (Supplemental) content is encouraged.

8. Recently revised instructions for authors are applied from December 2023 submissions.