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Total intravenous anesthesia for liver resections: anesthetic implications and safety
간절제술에 대한 전정맥마취 사용: 마취 관련 시사점 및 안전성

Selene Yan Ling Tan¹, Nian Chih Hwang¹,²
¹Department of Anesthesiology, Singapore General Hospital, ²Department of Cardiothoracic Anesthesia, National Heart Centre, Singapore

 지난 수십 년 동안 흡입마취제는 전신마취 유지에서 기본적으로 적용되어온 마취제이다. 그러나 전정맥마취(total intravenous anesthesia, TIVA)의 발전과 TIVA의 잠재적 이점의 근거들에 대한 보고가 점점 증가함에 따라, 마취통증의학과 의사들이 이러한 기존의 마취 패러다임에 대해 의문을 제기해야 할 때라고 사료된다. 프로포폴 기반 TIVA의 각성(emergence) 및 항구토 작용과 같은 이점들은 널리 알려져 있다. 면역 체계와 입환자 마취에 대한 TIVA의 잠재적인 이점에 대한 근거 또한 늘어나고 있으며, 흡입마취제는 프로포폴 기반 TIVA보다 지구 온난화에 영향을 미칠 확률이 실질적으로 더 높다는 근거도 보고되었다. 이와 같은 프로포폴 기반 TIVA의 강력한 잠재적 이점에도 불구하고 이 마취법의 광범위한 적용을 가로막는 장벽 또한 존재한다. TIVA의 기본 마취제로서 TIVA의 적용 가능성을 보다 엄밀하게 분석하기 위해, 본 리뷰에서는 복잡한 주요 개복수술, 특히 간절제술에서 프로포폴 기반 TIVA의 안전성 및 적용 가능성과 다양한 임상적 고려사항, 경제적 요인 및 수술실 회전율에 대하여 살펴볼 것이다.

Keywords: Desflurane; Hepatectomy; Inhalational anesthetics; Intravenous anesthetics; Sevoflurane; Volatile.
Combined cerebral and somatic near-infrared spectroscopy oximetry monitoring during liver surgery: an observational and non-interventional study

Yves Collin1,2,*, Tina Hu3,4,*, André Denault3,5, Annik Fortier6, William Beaubien-Souligny7, Réal Lapointe1, Franck Vandenbroucke-Menu1

1Department of Hepatobiliary-Pancreatic Surgery and Transplantation, Centre Hospitalier de l’Université de Montréal, Montreal, QC, 2Division of General Surgery, Department of Surgery, Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, QC, 3Intensive Care Unit, Centre Hospitalier de l’Université de Montréal, Montreal, QC, 4Faculty of Medicine, University of Toronto, Toronto, ON, 5Department of Anesthesiology and Intensive Care Unit, Montreal Heart Institute, Université de Montréal, Montreal, QC, 6Montreal Health Innovations Coordinating Center (MHICC), Montreal Heart Institute, Montreal, QC, 7Division of Nephrology, Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada

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Corresponding author:
André Denault, M.D., Ph.D., FRCPC
Department of Anesthesiology and Intensive Care Unit, Montreal Heart Institute, Université de Montréal, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada
Tel: +1-514-376-3330 Ext. 3732
Fax: +1-514-376-8784
Email: andre.denault@umontreal.ca
ORCID: https://orcid.org/0000-0003-0634-6291

*Yves Collin and Tina Hu contributed equally to this work as first co-authors.
Propofol abuse among healthcare workers: an analysis of criminal cases using the database of the Supreme Court of South Korea’s judgments

Hye-Yeon Cho¹, Yoonbin Hwang¹, SuHwan Shin², Susie Yoon¹,³, Ho-Jin Lee¹,³
¹Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, ²Department of Medical Law and Ethics, Graduate School, Yonsei University, ³Department of Anesthesiology and Pain Medicine, Seoul National University College of Medicine, Seoul, Korea

Keywords: Criminals; Health personnel; Illicit drugs; Intravenous administration; Legislation and jurisprudence; Propofol; Psychotropic drugs; Substance-related disorders.
Association of *HLA-DPA1* polymorphism with prolonged mechanical ventilation in patients undergoing liver transplantation

간이식 환자에서 장기간 기계환기와 *HLA-DPA1* 유전자 다형성의 연관성

Eun Jung Kim¹², Min-Soo Kim¹², Myoung Soo Kim³, Junhyun Nam¹, Seung Ho Choi¹²

¹Department of Anesthesiology and Pain Medicine, Severance Hospital, ²Anesthesia and Pain Research Institute, ³Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

배경: 장기간 기계환기(prolonged mechanical ventilation, PMV)는 간이식술 후 흔히 발생하는 합병증이다. 그러나 초기 발관의 임상 및 비용적 이점으로 인해 PMV에 대한 임상적 예측인자를 평가하기 위한 다양한 연구들이 수행되었다. 본 연구의 목적은 간이식을 받는 환자들의 PMV에 대한 후보 유전자 다형성(polymorphism)을 포함한 수술 전후 위험요인들의 영향을 확인하는 것이었다.

방법: 본 연구의 대상자는 간이식술을 받은 140명의 환자이다. 수술 후 기계환기 기간, 중환자실(ICU) 체류기간 및 입원기간, 30일 사망률을 살펴보았다. 환자 관련 임상요인 및 후보 유전자의 단일염기다형성(single nucleotide polymorphism, SNP)을 PMV에 대해 평가했고, 여기서 PMV는 48시간 초과의 기계환기를 정의하였다. 결과: 26명(19%)의 환자들에 대해 수술 후 48시간 이상 기계환기가 지속되었다. 수술 중 지속적 신체체액제(CRRT, continuous renal replacement therapy) 및 수술 후 혈청 젖산농도 상승은 비 PMV 그룹과 비교하여 PMV 그룹과 유의한 상관관계를 보였다(odd ratio [OR] = 24.731 [1.077, 567.915] vs. OR = 3.008 [1.497, 6.045]). 또한, 대립유전자 모델에서 *HLA-DPA1*의 rs8486 다형성과 PMV의 위험도 사이에 유의한 상관관계를 보였다(OR = 8.060 [1.451, 44.765]).

결론: *HLA-DPA1* 유전자에서 rs8486 다형성은 수술 중 CRRT 적용 및 수술 후 추적기간 동안 상승된 젖산농도와 더불어, 간이식 수혜자의 PMV 위험도에 독립적으로 영향을 미칠 수 있다.

Keywords: Artificial respiration; Genetic polymorphism; Genotype; HLA-DPA1 antigen; Liver transplantation; Postoperative care.
Epidemiologic study of epidural analgesia for lung cancer surgery from 2011 to 2018 in South Korea: a National Health Insurance Database cohort study

Tak Kyu Oh¹,², In-Ae Song¹

¹Department of Anesthesiology and Pain Medicine, ²Seoul National University Bundang Hospital, Seongnam, ³Seoul National University College of Medicine, Seoul, Korea

Keywords: Analgesia; Cohort studies; Epidemiology; Lung neoplasms; Pain management; Population; Postoperative pain; Thoracic surgery.
Prognostic value of left ventricular apical four-chamber longitudinal strain after heart valve surgery in real-world practice

Jae-Sik Nam, Ji-Hyun Chin, Hyun-Uk Kang, Juyoun Kim, Kyoung-Woon Joung, In-Cheol Choi

Department of Anesthesiology and Pain Medicine, Laboratory for Perioperative Outcomes Analysis and Research, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Keywords: Cardiac surgery; Echocardiography; Heart valve diseases; Morbidity; Mortality; Strain.

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Corresponding author:
Ji-Hyun Chin, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Laboratory for Perioperative Outcomes Analysis and Research, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
Tel: +82-2-3010-5632
Fax: +82-2-470-1363
Email: cjh@amc.seoul.kr
ORCID: https://orcid.org/0000-0001-9312-1685

Background: Left ventricular apical four-chamber longitudinal strain is a new index for evaluating cardiac function. However, the prognostic value of measuring left ventricular apical four-chamber longitudinal strain in actual clinical practice after heart valve surgery is still unclear. This study aimed to determine whether measuring left ventricular apical four-chamber longitudinal strain before heart valve surgery could predict surgical outcomes.

Methods: This cohort study was conducted from January 1, 2014, to December 31, 2018, at a tertiary care hospital in Korea. The primary outcome variable was all-cause mortality after surgery. The study population consisted of patients who underwent heart valve surgery. The primary predictor of interest was left ventricular apical four-chamber longitudinal strain. The secondary outcome variable was left ventricular ejection fraction (LVEF).

Results: Among the 1,773 patients enrolled, 132 patients (7.5%) died during the median follow-up period of 27.2 months. Patients with higher left ventricular apical four-chamber longitudinal strain had a statistically significant lower all-cause mortality rate (risk ratio = 0.94; 95% CI [0.90, 0.99]; P = 0.022). In contrast, LVEF was not significantly associated with all-cause mortality (risk ratio = 1.01; 95% CI [0.99, 1.03]; P = 0.222). In the multivariate analysis, left ventricular apical four-chamber longitudinal strain was found to be an independent predictor of all-cause mortality after adjusting for other factors (P = 0.022).

Conclusion: Measuring left ventricular apical four-chamber longitudinal strain before heart valve surgery may provide additional information to predict surgical outcomes in patients with heart valve diseases.
The state of anesthesia in South Korea: a national survey of the status of anesthetic service activity in 2014–2016

Eun-Su Choi, Hee-Won Jung, Woon Young Kim, Jae Hwan Kim, Yoon-Sook Lee

Department of Anesthesiology and Pain Medicine, Korea University Ansan Hospital, Ansan, Korea

Keywords: Anesthesia; Anesthesiologist; Health; Insurance; Non-anesthesiologists; Patient safety; Risk; Surgeons.
Use of a human patient simulator for apnea studies: a preliminary in vitro trial

Debendra Kumar Tripathy¹, Mridul Dhar¹, Bharat Bhushan Bhardwaj², K Hemanthkumar³, Praveen Talawar¹, Shalinee Rao³,⁴

¹Department of Anesthesiology and Critical Care, ²Department of Emergency Medicine, ³Advanced Center for Simulation and Skills, ⁴Department of Pathology, All India Institute of Medical Sciences, Rishikesh, India

Experimental Research Article

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Corresponding author: Mridul Dhar, M.D.
Department of Anesthesiology and Critical Care, All India Institute of Medical Sciences, Veerbhadra Road, Rishikesh 249203, India
Tel: +91-9717778374
Email: mridul.anaes@aiimsrishikesh.edu.in
ORCID: https://orcid.org/0000-0002-1913-2586

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Keywords: Apnea; Hypoxia; Nasal cannula; Oxygen inhalation therapy; Oxygen saturation; Patient simulation.
The evaluation of left ventricular (LV) systolic function is vital for guiding treatment strategies and predicting outcomes, especially for surgical treatments [1]. Traditionally, LV ejection fraction (LVEF) has been one of the most important markers for evaluating LV systolic function [2]. However, LVEF cannot discriminate between the different effects of load on myocardial contractility, resulting in falsely high LVEF in mitral regurgitation (MR) or falsely low LVEF in aortic stenosis and thus low accuracy for predicting treatment outcomes [3].

Recently, LV longitudinal strain (LVLS) was introduced as a new marker to evaluate LV systolic function and has been demonstrated to have postoperative prognostic value for various cardiac diseases [4–7]. LVLS has been found to be able to detect subtle ventricular dysfunction that LVEF cannot detect [8]. Several studies have reported that LVLS is independently associated with postoperative survival in valvular surgery, especially in corrective surgery for MR. Given the propensity for the LVEF to be overestimated in MR, impaired LV systolic function may be masked in patients with severe MR [9,10].

In this issue of the Korean Journal of Anesthesiology, Nam et al. [11] investigated the predictive value of apical four-chamber LVLS for postoperative survival in patients with various types of valvular heart disease. In this retrospective observational study of 1,773 patients, the authors demonstrated the long-term prognostic value of LVLS measured in the apical four-chamber view after heart valve surgery. During a median follow-up of 27 months, preoperative apical four-chamber LVLS was significantly associated with postoperative all-cause mortality, whereas LVEF was not. Moreover, LVLS showed a significant incremental prognostic value over LVEF and traditional prognostic factors (e.g., age, sex, Charlson comorbidity index, pulmonary hypertension, New York Heart Association [NYHA] classification, atrial fibrillation, and presence of valvular diseases) for predicting all-cause mortality. The authors showed that apical four-chamber LVLS might be a useful marker for predicting mortality after valvular surgery. This study provides an important rationale for incorporating longitudinal strain analyses into routine clinical practice.

This study shows a distinct view and has multiple advantages over previous studies. First, unlike the commonly used LVLS, measurements from one echocardiographic view (i.e., apical four-chamber view) were used. Measuring LVLS only in the apical four-chamber view without additional echocardiographic views (e.g., longitudinal two-chamber or three-chamber view) could thus have predictive value for postoperative outcomes with reasonable feasibility and reliability. Second, the relationship between LVLS and long-term mortality shown in this study was not limited to patients with MR. Patients with different valvular heart diseases and thus different pathophysiologies were analyzed together. Third, compared to previous studies [9,10,12], in this study, a relatively large number of patients who underwent valvular heart surgery were analyzed.
Although LVLS directly reflects myocardial shortening and is less dependent on loading conditions than LVEF [12], strain remains a load-dependent measure [13]. Despite some limitations, this study showed that apical four-chamber LVLS could be a useful alternative to conventional LV systolic function markers for predicting postoperative outcomes in patients undergoing heart valve surgery. An apical four-chamber LVLS can be easily implemented. In addition, it is useful when the imaging quality from the apical two- or three-chamber view is poor. Although LVEF remains a valuable marker of LV function, the addition of LVLS improves risk assessment.

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**Conflicts of Interest**

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

**References**

Total intravenous anesthesia for liver resections: anesthetic implications and safety

Selene Yan Ling Tan¹, Nian Chih Hwang¹,²

¹Department of Anesthesiology, Singapore General Hospital, ²Department of Cardiothoracic Anesthesia, National Heart Centre, Singapore

Inhalational anesthetics have been the default agents for general anesthesia maintenance for several decades. However, with advances in total intravenous anesthesia (TIVA) and a growing body of evidence on the potential benefits of TIVA, anesthesiologists need to question this paradigm. Some of the benefits of propofol-based TIVA, such as its antiemetic properties and patients’ smooth emergence, are widely acknowledged. A growing body of evidence suggests that TIVA may potentially benefit the immune system and cancer outcomes. From an existential health perspective, there is evidence that inhalational agents have a materially higher global warming potential than propofol-based TIVA. Despite the compelling potential benefits of propofol-based TIVA, there are barriers to its widespread adoption. To examine the applicability of TIVA as a mainstay agent more rigorously, we discuss the safety and applicability of propofol-based TIVA in the context of complex major abdominal surgery, specifically, liver resection surgery. We also discuss the use of propofol-based TIVA in liver resection surgery with a broad, integrated approach, addressing general and specific clinical considerations, economic factors, and operating room turnover.

Keywords: Desflurane; Hepatectomy; Inhalational anesthetics; Intravenous anesthetics; Sevoflurane; Volatile.

Introduction

Anesthesiologists are key players in advocating for patient safety and outcomes, as their actions can have immediate and long-term repercussions for patients [1,2]. The role of anesthesiologists is to provide optimal conditions for surgery, ameliorate the surgical stress response, prevent organ injury, and achieve quality postoperative analgesia [3–5]. In recent decades, volatile anesthetics have been the mainstay of our practice. However, a growing body of evidence suggests that total intravenous anesthesia (TIVA) may have benefits over inhalational anesthetics in terms of cancer outcomes, postoperative pain scores, and the surgical stress response [6]. Another supplementary benefit of TIVA is the much lower greenhouse gas impact of propofol compared to inhalational anesthetics; an impact that is four orders of magnitude lower than that of desflurane and nitrous oxide [7]. The theoretical advantages and disadvantages of TIVA over inhalational anesthetics in the general context have been clearly shown [8]. However, we have less certainty with regard to the pragmatic applications of TIVA in complex surgeries such as hepatic resection. The purpose of our narrative review is thus to examine the feasibility and safety of TIVA in a specific clinical context, such as anesthesia for hepatic resection. We aim to weigh the advantages and potential disadvantages of using TIVA in complex surgeries such as hepatic resection ma-
Potential advantages of TIVA for hepatic resection

Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) is one of the most common adverse effects of general anesthesia, with an incidence of 30–80% [9]. In the context of major abdominal surgery, careful attention should be paid to adequate PONV prophylaxis [10]. A multimodal approach within an enhanced recovery after surgery pathway allows the majority of patients to resume feeding on postoperative day 1 [11]. One of the recommended strategies for reducing the baseline risk of PONV is the preferential use of TIVA and avoidance of nitrous oxide and volatile anesthetics [12]. By conservative estimates, a patient presenting for hepatic resection will have at least four known risk factors for PONV: general anesthesia, postoperative opioids, long duration of anesthesia, and intra-abdominal surgery [12]. The use of volatile anesthetics for maintenance presents an additional risk factor. Consensus guidelines now recommend two modes of prophylaxis for patients with 1–2 risk factors and 3–4 modes of prophylaxis for patients with more than two risk factors [12]. In 2018, a meta-analysis demonstrated that TIVA reduces the relative risk of PONV by 39% (95% CI [31%, 47%]) compared with volatile anesthetics [13].

Postoperative delirium and confusion

Hepatic resection is a complex surgery that may be associated with a 20–50% risk of postoperative delirium [14]. Risk factors include advanced age, reduced serum albumin concentrations, cerebrovascular disorders, cardiovascular diseases, diabetes mellitus, benzodiazepine use, and a previous history of delirium [15]. Postoperative cognitive dysfunction (POCD) is characterized by acute and fluctuating impairments in attention and awareness. It is a serious complication that increases the length of hospital stay by 2–3 days and is associated with a 30-day mortality of 7–10% [14]. In a multicenter randomized controlled trial designed to study the incidence of postoperative delirium in two groups of patients assigned to light or deep anesthesia guided by bispectral index (BIS) monitoring, targeting light anesthesia was found to reduce the risk of POCD at 1 year (9% vs. 20% reduction based on an Abbreviated Mental Test score ≤ 6, P < 0.001) [16]. To date, however, studies have been equivocal, resulting in a lack of convincing evidence of any difference in the incidence of POCD between propofol-TIVA and inhalational anesthesia [17–21]. Nevertheless, current guidelines Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia recommend the use of processed electroencephalogram (pEEG) monitoring when a neuromuscular blocking drug is used with TIVA [22], which may be beneficial for avoiding excessive anesthetic depth. Intraoperative neuromonitoring is associated with a lower risk of delirium; however, the mechanism for this association is unknown and more studies are therefore needed [23,24].

Postoperative pain

In animal studies, propofol has been shown to decrease inflammatory cytokine concentrations and prevent the activation of N-methyl-D-aspartate receptors [25,26]. Some clinical studies have also suggested that propofol TIVA is associated with a reduction in postoperative pain [27,28]. A subgroup analysis in a recent retrospective cohort study found that propofol TIVA was associated with a clinically significant reduction in postoperative pain scores and opioid consumption in patients undergoing hepatobiliary and pancreatic surgery [29]. Another retrospective study found that propofol TIVA was associated with less pain during coughing and reduced morphine consumption in patients undergoing liver surgery [30]. Additionally, a scoping review of 16 clinical trials in 2020 compared the effects of propofol TIVA against inhalational anesthetics on postoperative pain scores and/or opioid consumption. The authors found that propofol TIVA had comparative benefits in nine clinical trials, resulted in worse outcomes in two clinical trials, and was no different from inhalational anesthetics in five clinical trials [31]. A meta-analysis reviewing the differences in postoperative analgesia between propofol TIVA and inhaled general anesthesia maintenance that was conducted before the aforementioned review found that propofol TIVA was associated with a statistically significant but minimal reduction in pain scores at 24 h [32].

Ischemic-reperfusion injury

Hemorrhage during liver resection is a significant threat to good clinical outcomes. However, while portal triad occlusion with complete clamping of the hepatic inflow is a useful means of minimizing intraoperative blood loss, ischemia and subsequent reperfusion injury of the liver is a primary concern [33]. Ischemic-reperfusion injury during liver resection involves Kupffer cells releasing reactive oxygen species (ROS) and proinflammatory mediators, which in turn leads to oxidative damage, induction of p53, apoptosis, and necrosis of hepatocytes and endothelial
cells [34]. Propofol is known to possess free radical-scavenging properties, as demonstrated by both in vivo and in vitro studies. This occurs either through direct chelation of ROS by propofol-derived phenoxyl radicals or by increasing the antioxidant defense capacity [35,36]. Propofol has also been shown to protect against hepatic ischemia-reperfusion injury by inhibiting B-cell leukemia/lymphoma 2 (BCL-2)/adenovirus E1B interacting protein 3 (BNIP3)-mediated oxidative stress [37]. One study that compared propofol infusion with isoflurane anesthesia during one-lung ventilation found that ROS production occurred to a lesser extent in the propofol group. The choice of anesthetic agent may alter the balance between antioxidant and oxidant concentrations. The total antioxidant status increased with time in the propofol group but not in the isoflurane group [38].

Acute kidney injury

Acute kidney injury (AKI) occurs in approximately 15% of patients undergoing liver resection surgery and is a potential cause of postoperative morbidity and mortality [39–41]. While many factors may contribute to the development of AKI, it is most frequently caused by acute tubular necrosis secondary to perioperative hypovolemia and hypotension. A recent single-center parallel randomized control study assessing perioperative renal function in patients anesthetized with either TIVA or sevoflurane found that sevoflurane anesthesia reduced urine output and sodium excretion and increased plasma renin concentrations compared with TIVA anesthesia [42]. The Volatile Anesthetic Protection Of Renal Transplants-1 (VAPOR-1) randomized controlled trial compared the impact of propofol vs. sevoflurane-based anesthesia during living donor kidney transplantation and found that while urinary biomarkers of kidney injury were increased on day 2 in the sevoflurane group, no significant differences in graft outcomes were seen. Notably, there was a lower acute rejection rate after two years in the sevoflurane group [43]. More studies, including the VAPOR-2 trial, will need to be evaluated before further conclusions can be reached.

Cancer outcomes

An observational study of 2,097 patients performed in the United States found that the most common indications for hepatic resection were secondary metastases (52%), primary hepatic malignancy (16%), biliary tract malignancy (10%), and benign hepatic tumors (5%) [44]. Given that most hepatic resections are performed for malignancies, another factor worth considering is the effect of anesthetic choice on cancer outcomes. While cancer outcomes are influenced by multiple factors, the choice of anesthetic is directly based on the anesthesiologist’s purview. A survey conducted on the practice patterns of anesthesiologists suggests that volatile-based anesthesia is a prevalent anesthetic technique in cancer surgery [45]. However, a developing body of evidence suggests that propofol-based TIVA may be linked to more favorable long-term cancer outcomes than volatile-based anesthesia [46–49]. Preclinical studies have demonstrated that volatile anesthetics affect innate and adaptive immune cell function and exert immunosuppressive effects. Mechanisms include decreased neutrophil recruitment and adhesion, reduced phagocytosis, decreased natural killer (NK) cell activity, and polarization of T lymphocytes toward a protumorigenic T helper 2 (Th2) cell population [50–52]. In comparison, propofol tends to maintain immune function and does not weaken the cytotoxic activity of NK cells [6]. Additionally, volatile anesthetics exhibit protumorigenic activity by increasing tumor growth, migration, and invasion in several types of cancers, including prostate, renal cell, ovarian, hepatocellular, and breast cancers. In contrast, propofol has been demonstrated to decrease tumor cell proliferation in breast, endometrial, prostate, lung, and gastric cancers; squamous cell carcinoma; glioblastoma; osteosarcoma; and leukemia [53]. A meta-analysis of TIVA vs. volatile anesthesia concluded that propofol TIVA may be associated with improved recurrence-free survival and overall survival in patients undergoing cancer surgery [47]. Despite evidence suggesting that TIVA may be the preferred anesthetic for patients undergoing cancer surgery, some degree of equipoise remains since the evidence currently available is derived from studies that are underpowered and/or flawed in their methodology. Currently, the Volatile Anesthesia and Perioperative Outcomes Related to Cancer trial, a large international multicenter randomized controlled trial, is in progress. Table 1 lists the studies comparing cancer outcomes in patients who received either TIVA or inhalational anesthesia for oncosurgery.

Safety and potential disadvantages of TIVA for hepatic resection

Hepatic blood flow

Hepatic resection has the potential to cause significant blood loss. Some strategies to reduce surgical blood loss include low central venous pressure (CVP), temporary inflow occlusion (Pringle maneuver), and other blood-loss-limiting surgical techniques [54]. Hence, the influence of TIVA versus inhalational anesthetic agents on hepatic blood flow should be examined. Propofol has been hypothesized to potentially increase hepatic blood flow and
alter hepatic oxygen consumption. A small animal study using a rabbit model compared the effects of intralipid and propofol infusions on hepatic blood flow and hepatic oxygenation and concluded that propofol increases total hepatic blood flow via increased hepatic portal venous flow and hepatic oxygen consumption; however, the hepatic oxygen balance was found to be preserved in this study [55]. A small crossover study was also performed in patients aged ≥ 18 years who were scheduled for general anesthesia (n = 20) in which patients were randomized to receive either propofol or desflurane under general anesthesia. Propofol was associated with notably higher blood flow in the right and middle hepatic veins than desflurane, as assessed by transesophageal echocardiography. However, this study had significant limitations, as neither baseline hepatic blood flow, total hepatic blood flow, nor hepatic oxygen consumption were directly measured. Additionally, the clinical implications of the findings regarding the balance between hepatic blood flow and hepatic oxygen consumption were not clear, including whether the net effects were beneficial or detrimental [56]. A more recent randomized controlled trial conducted by van Limmen et al. [57] in 2020 (n = 18), which compared the effects of propofol and sevoflurane on hepatic blood flow in patients undergoing pancreaticoduodenectomy, showed that hepatic blood flow was similar in both groups using a goal-directed hemodynamic therapy approach. Due to the paucity of data, however, more information is needed before conclusions can be drawn regarding the clinical effects of propofol on hepatic blood flow and metabolism in humans.

### Hemodynamic effects

Propofol has significant effects on the cardiovascular system that is more pronounced in elderly and frail patients [58]. Specifically, propofol causes a dose-dependent reduction in systemic blood pressure and cardiac output, primarily through vasodilatation and cardiovascular depression [59,60]. Therefore, if cardiac output is not adequately maintained, liver and kidney perfusion can be compromised [58]. Milne et al. [61] described the use of propofol TIVA target-controlled infusion (TCI) and remifentanil infusions to provide anesthesia for major hepatic resection. The authors reported low blood loss (ranging from 300 to 2,000 ml) and rapid patient recovery without any need for postoperative intensive care. The authors also postulated that propofol-induced vasodilatation was beneficial in reducing CVP and resulted in less venous distension in the liver, leading to reduced blood loss. More prospective randomized studies are required to investigate the hemodynamic effects of TIVA for hepatic resection.

### Accidental awareness under general anesthesia

The 5th National Audit Project (NAP 5) concluded that self-reported cases of accidental awareness under general anesthesia (AAGA) were more common with TIVA; however, most cases were avoidable. The most significant contributing factor was insufficient education and training [62]. Mistakes made during the delivery of TIVA may lead to overdosing, underdosing, and AAGA. According to NAP 5, the leading causes of AAGA were

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**Table 1.** Studies Comparing Total Intravenous Anesthesia vs. Inhalational Anesthesia in terms of Cancer Outcomes

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Method</th>
<th>Number of patients</th>
<th>Main findings</th>
<th>Main limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meng et al., 2020 [49]</td>
<td>Retrospective, cohort study</td>
<td>1,513</td>
<td>Patients receiving inhalational anesthesia have a lower 5-year overall survival rate than patients receiving TIVA [12.6% (95% CI, 9.0, 17.3) vs. 17.7% (95% CI, 11.3, 20.8), P = 0.024]</td>
<td>Not randomized, prospective study</td>
</tr>
<tr>
<td>Yap et al., 2019 [47]</td>
<td>Meta-analysis</td>
<td>7,866</td>
<td>Propofol-TIVA use may be associated with improved recurrence-free survival and overall survival in patients undergoing surgery</td>
<td>Inherent limitations of studies included in the meta-analysis</td>
</tr>
<tr>
<td>Yan et al., 2018 [48]</td>
<td>Prospective, randomized controlled study</td>
<td>50</td>
<td>In comparison with sevoflurane-based inhalational anesthesia, propofol/remifentanil-based TIVA can effectively inhibit the release of VEGF-C induced by breast surgery but did not seem to be beneficial in the short-term recurrence rate of breast cancer</td>
<td>Study may be underpowered</td>
</tr>
<tr>
<td>Wigmore et al., 2016 [46]</td>
<td>Retrospective, propensity-matched analysis</td>
<td>5,214</td>
<td>Volatile inhalational anesthesia was associated with a hazard ratio of 1.59 (1.30 to 1.95) for death on univariate analysis and 1.46 (1.29 to 1.66) after multivariable analysis of known confounders in the matched group</td>
<td>Not randomized, prospective study</td>
</tr>
</tbody>
</table>

TIVA: total intravenous anesthesia.
failure to administer the required dose of the drug and inadequate understanding of the underlying pharmacological principles of TIVA [22,62]. Recommendations include TCI, TIVA-specific administration sets, maintaining visibility of intravenous access whenever feasible, and pEEG monitoring when a neuromuscular blocker is used in conjunction with TIVA [22].

**Turnover time**

An international survey on the factors influencing the use of TIVA among anesthesiologists found that concerns about increased turnover time ranked highly on the list of reasons for not using TIVA. Of note, increased turnover time was of much lower importance amongst frequent users of TIVA when not selecting TIVA [63]. A few studies have compared the anesthetic turnover time for TIVA versus inhalational anesthesia. One retrospective study found that the time to extubation was shorter in patients receiving desflurane than in those receiving TCI-based propofol TIVA for open liver surgery [64]. Another comparison between propofol TIVA and desflurane anesthesia in patients undergoing functional endoscopic sinus surgery found that the propofol group emerged from anesthesia faster and had a lower risk of prolonged extubation time after anesthesia [65]. In two randomized clinical trials, BIS monitoring reduced propofol consumption and hastened recovery after propofol-TIVA in patients undergoing gynecological surgery [66,67]. Another randomized clinical trial comparing the effect of BIS titration in patients receiving propofol-alfentanil and nitrous oxide anesthesia concluded that titrating propofol with BIS monitoring was associated with reduced propofol administration, shorter time to extubation and improved quality of recovery [68]. Another potential consideration regarding the use of TIVA in hepatic resection is the impact of surgery on the hepatic metabolism of propofol. The liver is the predominant site for propofol metabolism. The majority of propofol (70%) is conjugated to propofol glucuronide by uridine 5'-diphosphate glucuronosyltransferase. Approximately 29% of propofol is hydroxylated to 2,6-diisopropyl-1,4-quinol (4-hydroxypropofol) [58]. Extrahepatic metabolism in the kidneys, small intestine, and lungs accounts for 40% of total propofol clearance. The liver is highly efficient in metabolizing propofol, with a blood extraction ratio of 0.9 [58]. Hence, recovery from TIVA may be delayed after hepatic resection surgery compared to non-hepatic surgery [69]. The impact of hepatic resection on total propofol clearance may be more significant for major hepatic resections, considering the duration of surgery, context-sensitive half time, and reduced propofol metabolism [70].

**Cost-effectiveness**

The cost-effectiveness of TIVA is another potential consideration for anesthesiologists deciding between TIVA and inhalational anesthesia [63]. While no relevant studies have been performed on TIVA for hepatic resection, a recent meta-analysis conducted in the United States compared the cost-effectiveness of TIVA versus inhalational anesthetics for non-cardiac surgery [71]. The results showed that general anesthesia maintenance with propofol TIVA was associated with a lower PONV rate, shorter stay in the post-anesthesia care unit, and reduced rescue antiemetic requirements, negating the greater costs for anesthetics, analgesics, and neuromuscular blockers for propofol TIVA. The results were consistent in both inpatient and ambulatory surgical settings [71]. With the availability of generic propofol and open-loop TCI systems, TIVA can potentially be much cheaper than sevoflurane and desflurane, even before factoring the costs that may arise from postoperative recovery [72].

**Conclusion**

TIVA is a promising technique for hepatic resection. Lack of familiarity with and experience in using TIVA for hepatic resection, however, are potential barriers to its use. Other potential barriers include concerns regarding AAGA, increased operating room turnover time, and hemodynamic stability in the context of a low-CVP anesthetic technique. However, TIVA may potentially improve the patient’s postoperative recovery profile, reduce PONV and postoperative opioid requirements, and have a positive impact on cancer outcomes. The learning curve associated with the use of TIVA, however, may be even steeper when applied to a complex, major abdominal procedure such as hepatic resection.

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**Conflicts of Interest**

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

**Author Contributions**

Selene Yan Ling Tan (Conceptualization; Data curation; Writing – original draft)
Nian Chih Hwang (Conceptualization; Writing – review & editing)

ORCID

Selene Yan Ling Tan, https://orcid.org/0000-0003-1716-1356
Nian Chih Hwang, https://orcid.org/0000-0002-1220-345X

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Combined cerebral and somatic near-infrared spectroscopy oximetry monitoring during liver surgery: an observational and non-interventional study

Yves Collin¹,²,* Tina Hu³,⁴,* André Denault³,⁵, Annik Fortier⁶, William Beaubien-Souligny⁷, Réal Lapointe¹, Franck Vandenbroucke-Menu¹

¹Department of Hepatobiliary-Pancreatic Surgery and Transplantation, Centre Hospitalier de l'Université de Montréal, Montreal, QC, ²Division of General Surgery, Department of Surgery, Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, QC, ³Intensive Care Unit, Centre Hospitalier de l'Université de Montréal, Montreal, QC, ⁴Faculty of Medicine, University of Toronto, Toronto, ON, ⁵Department of Anesthesiology and Intensive Care Unit, Montreal Heart Institute, Université de Montréal, Montreal, QC, ⁶Montreal Health Innovations Coordinating Center (MHICC), Montreal Heart Institute, Montreal, QC, ⁷Division of Nephrology, Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada

Background: Cerebral oximetry using near-infrared spectroscopy (NIRS) is used for monitoring cerebral oxygen saturation during cardiac surgery and is correlated with clinical outcomes. Our goal was to explore cerebral and somatic NIRS in liver resections as a predictor of post-operative complications.

Methods: Prospective observational and non-interventional study from a tertiary care university hospital including adult patients undergoing liver resection monitored using NIRS at four sites before and during surgery. Those sites were: frontotemporal left and right zones, right thigh, and right arm. Anesthesiologists and surgeons were blinded to oximetry values. Correlations were assessed between baseline oximetry values and cerebral-somatic desaturation load (threshold of 80% from baseline) values with peri-operative events and complications.

Results: Ninety patients were distributed equally among gender with a mean age of 59.7 ± 13.1 years. Lower baseline cerebral and/or somatic values were associated with increased risk of delirium, respiratory failure, surgical and renal complications, blood transfusions, and length of stay in the intensive care unit and in the hospital (P < 0.05). The severity of somatic desaturation below 80% was the only parameter associated with blood losses (P = 0.030) and length of hospital stay (P = 0.047).

Conclusions: Cerebral and somatic desaturation does occur in liver resection and can be used simultaneously during liver surgery. Both baseline cerebral and somatic NIRS values are correlated with complications and outcomes. However, thigh desaturation appears more sensitive than cerebral NIRS values in predicting some of these complications.

Keywords: Compartment syndromes; Hepatectomy; Intraoperative complications; Liver; Oximetry; Physiologic monitoring.
Introduction

Liver resections increase long-term survival in patients with colorectal cancer with liver metastasis [1]. Ongoing improvements in surgical and anesthetic techniques have significantly reduced mortality rates associated with liver resections. Nevertheless, it is still a major surgery that can lead to surgical bleeding and periods of hemodynamic instability. These hemodynamic fluctuations are a cause for medical concern because of their impact on tissue perfusion, which may lead to increased neurological and postoperative complications. The incidence of postoperative complications after liver resections is approximately 31% [2].

Monitoring of cerebral oxygen saturation using near-infrared spectroscopy (NIRS) [3], a non-invasive optical technique, is an efficient way to evaluate regional blood flow and tissue oxygen transport [4]. The association between pre-operative and intraoperative reduction in NIRS value with post-operative mortality, renal failure, and delirium has been established [5–16]. Although most studies have focused on monitoring cerebral oxygen saturation, few studies have explored the role of somatic NIRS monitoring. In patients with septic shock, reduction in systemic tissue oxygen saturation was predictive of mortality [17–19]. In addition, tissue hemoglobin oxygen saturation or somatic NIRS monitoring is the best predictor of outcome in trauma patients with massive transfusion [20] and is associated with worse outcome when combined with cerebral saturation in congenital heart disease [21,22]. In patients having sustained severe trauma, reduced somatic NIRS value have been associated with mortality, subsequent organ dysfunction, the need for massive transfusion, or emergent surgery [23–26]. We have recently reported our experience using cerebral and somatic NIRS in liver transplantation [27,28] and proposed a combined cerebral and somatic algorithm [29]. However, no studies have examined intraoperative cerebral and somatic oxygen saturation as a predictor of postoperative complications after hepatic surgery. The primary objective of this observational study was to determine the association between the systemic and/or cerebral desaturation and the number of postoperative adverse events in hepatic surgery. In addition, we wanted to describe several cases showing the promising role of this form of regional tissue oxygenation monitoring in liver resection surgery. Our hypothesis is that reductions in both cerebral and somatic NIRS will correlate with post-operative complications.

Materials and Methods

This prospective single-site observational and non-interventional study was approved by the Ethics Committee of the Centre Hospitalier de l’Université de Montréal, CHUM Protocol No. 10.192, and written informed consent was obtained from all patients. The study was registered with clinicaltrials.gov (NCT 01458262) and reported using the STROBE Checklist guidelines (Appendix 1). The study was supported by an unrestricted equipment grant from Covidien (Covidien/Medtronic Inc., USA). Patients younger than 18 years old and patients with pre-existing neurological disease were excluded. Patients were recruited from January 2012 to July 2013.

The INVOS oximeter system (INVOS 5100-PB, Covidien-Medtronic, USA) was used for all patients. Before anesthesia induction, sensors were placed on both the frontotemporal zones of patients’ heads and on the right thigh and right arm (opposite site of the intravenous line) and all four values displayed on a single screen on the NIRS monitor. The baseline values were obtained 1 min after sensors placing and signal stabilization. Validation of the use of both cerebral and somatic NIRS using this sensor was previously determined and reported in 53 healthy volunteers [30]. Normal left and right cerebral values were mean ± SD: 66.1 ± 9.4 and 66.6 ± 9.1 respectively, left and right arm: 74.1 ± 7.7 and 74.8 ± 8.5, and left and right thigh: 74.2 ± 8.0 and 74.1 ± 8.1. The same anesthesia induction technique (sufentanil, propofol, and rocuronium) was used for all patients. Anesthesia was maintained with desflurane in an air-oxygen mixture and rocuronium was administered as required. Monitoring included invasive arterial blood pressure monitoring, central venous pressure via central line, electrocardiogram, standard pulse oximetry, core temperature monitoring, and expired carbon dioxide measurement [31]. Every patient had indwelling urinary catheter and warming system. Only patients with hemoglobin ≥ 85 g/L, creatinine ≤ 104 µmol/L, and hemodynamic stability underwent phlebotomy before liver resection.

The technical details for the phlebotomy have been previously reported [32,33] and it was performed in 82 patients (91%) for an average of 273 ± 39 ml. All retrieved blood was re-transfused at the end. Vasopressors (phenylephrine and vasopressin) were used as required to manage blood pressure.

Patients were included if they underwent major liver resection that included right or left heptectomy with at least three or more segments. Liver parenchyma transection was performed using advanced bipolar coagulation and/or stapler. Hepatic pedicles were controlled within the liver parenchyma using a surgical stapler. Intermittent hilar clamping was used with a ratio of 15 min of clamping to 5 min of reperfusion on a case-to-case basis. Liver parenchyma hemostasis was obtained using argon coagulation and/or fibrin sealant. All cases were performed by open surgery.

Cerebral and somatic NIRS data were collected continuously...
starting before induction until 1 h after surgery. Basic monitoring data were also recorded through the surgery up to 1 h after the surgery. The anesthesiologist and the surgeon as well as all clinical personnel were completely blinded to all oximetry measurements, so its data were not used in patient care plan. The monitoring system was positioned in such a way that the information was always hidden from the treating team. One of the investigators (TH) was present in the operating room during all the cases to take note of the events during the surgical procedure. The severity of desaturation (cerebro-somatic desaturation load) was obtained by obtaining the product of the area between the 80% desaturation threshold and the oximetry curve and time as previously described [34,35].

Data were anonymized and compiled into a database. Patient demographics, surgery duration, intensive care unit (ICU) stay, and length of hospital stay (LOS) were measured. For every subject, the pre-operative American Society of Anesthesiologists (ASA) class, the co-morbidities, international normalized ratio, albumin, hemoglobin, platelet, and creatinine levels were recorded. The patient was monitored daily in the post-operative period and no change in care plan was undertaken based on oximetry data. All complications defined pre-operatively (Appendix 2) were recorded and graded according to Dindo-Clavien scale [36].

Statistical analysis

The primary outcome was to define the correlation coefficient between the number of systemic and/or cerebral desaturation phases and the number of postoperative adverse events. Continuous variables are presented as mean ± SD or as median and inter-quartile range (IQR) according to the normality of the distribution of the variables, while categorical variables are presented as frequency (percentages). The distribution of the continuous variables was assessed using plots (histograms, stem-and-leaf plots), normality tests (Shapiro-Wilk, Kolmogorov-Smirnov), and skewness and kurtosis indexes. Pearson’s (for normally distributed variables) and Spearman’s (for non-normal distribution) correlation coefficients were used to assess the relation between oximetry variables and continuous parameters of interest. Student t-tests and Mann-Whitney-Wilcoxon tests were used to compare oximetry measurements between categories of specific population baseline characteristics (sex, hypertension, smoking, etc.) and peri-operative variables (use of Pringle, etc.), and also between the presence versus absence of different complications (dichotomous variables for neurological, cardiac, respiratory, surgical, infectious, and hematological complications). Binary logistic regression was also used to study the relation between baseline oximetry values and the risk of these various complications. The same statistical analyses were performed accordingly to assess the relation between the severity of desaturation and the other parameters of interest. Measurement of cerebro-somatic desaturation load between the four sites of assessment were compared using a one-way repeated measures ANOVA and contrasts between groups (if the overall group test is statistically significant). Odds ratio (OR) and 95% CI were calculated. The original sample size calculation was based on a primary analysis involving a multiple linear regression model and requiring a total of 90 subjects. The primary analysis was then simplified and based on a simple Pearson correlation coefficient to assess the relation between oximetry variables and continuous parameters of interest. A sample size of 90 was still sufficient to detect a coefficient r of 0.3 (medium effect size) with a statistical power of 80% and a two-sided alpha of 0.05. For all tests, a two-sided P < 0.05 was considered significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., USA).

Results

Ninety patients (45 males and 45 females) scheduled for major liver resections (three or more segments) were included in the study. The mean age was 59.7 ± 13.1 years. Table 1 describes the baseline cerebral and somatic oximetry values, co-morbidities, and surgical indications of the patient population. Cerebral right (CR) and cerebral left (CL), somatic arm, and thigh NIRS values were successfully obtained and analyzed in most patients (90, 87, 89, and 89 patients). ASA 1 and 2 patients represent 84% of the cohort. Co-morbidities were present in 63 patients (70%). A total of 73 patients (81%) had previous abdominal surgery. The surgeries in this study included 32 right hepatectomies, 21 left hepatectomies, and 37 partial liver resections (of at least three segments). Median (Q1, Q3) operative time was 180 (140, 225) min and median blood loss was 350 (150, 600) ml. Median LOS was 7 (5, 10) days and median ICU stay was 2 (0, 2) days.

In the postoperative course, one patient died. Overall, 11 patients had severe complications (Dindo 3 or higher, 12.2%), 41 patients had mild complications (Dindo 1 or 2, 45.6%), and 38 patients (42.2%) had no complications. There were 9 neurologic, 6 cardiac, 16 respiratory, 35 surgical, 30 infectious, 5 renal, 10 hematologic, and 4 various complications (some patients had more than one complication; complications are detailed in Appendix 3).

Table 2 summarizes the relation between baseline NIRS value and population characteristics. Higher baseline somatic arm NIRS was observed in younger patients (correlation coefficient: −0.265, P = 0.013), patients with lower ASA (correlation coefficient:...
Table 1. Baseline Characteristics, Co-morbidities and Surgical Indications in the Population

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.7 ± 13.1</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>45/45</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.7 ± 18.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 9.6</td>
</tr>
<tr>
<td>ASA I–II</td>
<td>0.841</td>
</tr>
<tr>
<td>Baseline oximetry</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>CL</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>Arm</td>
<td>75 ± 8</td>
</tr>
<tr>
<td>Thigh</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (26.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (10.0)</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>8 (8.9)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8 (8.9)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>15 (16.7)</td>
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<tr>
<td>Previous abdominal surgery</td>
<td>73 (81)</td>
</tr>
<tr>
<td>Surgical indications</td>
<td></td>
</tr>
<tr>
<td>Malignancy*</td>
<td>71 (78.9)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>Colorectal liver metastases</td>
<td>51 (71.8)</td>
</tr>
<tr>
<td>Breast cancer liver metastases</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Melanoma liver metastases</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Neuroendocrine liver metastases</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Benign*</td>
<td>19 (21.1)</td>
</tr>
<tr>
<td>Liver abscess</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Ischemic cholangitis</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Hepatolithiasis</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Adenoma, focal nodular hyperplasia, hemangioma</td>
<td>14 (73.7)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number of patients or mean (%). *Percentages are presented over the section sub-total. Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. ASA: American Society Anesthesiology class, CR: cerebral right, CL: cerebral left.

-0.215, P = 0.047), and patients without co-morbidities (no co-morbidities NIRS = 77.4 ± 8.1%; presence NIRS = 73.4 ± 8.2%, P = 0.036). There was a significant difference in baseline values between men and women for arm (women: 77.4 ± 7.9%, men: 71.7 ± 7.9%, P = 0.001) and thigh (women: 76.5 ± 6.9%, men: 72.6 ± 8.2%, P = 0.018) measurements, but not for cerebral values.

The baseline values and the associated significant post-operative complications are shown in Table 3. Delirium was associated with lower baseline left cerebral saturation value (61.6 ± 6.3 vs. 67.7 ± 8.4, P = 0.041). Respiratory failure was associated with reduced bilateral cerebral and thigh saturations (CR and CL of 59.4 ± 8.2 and 59.7 ± 6.5 vs. 68.4 ± 8.8 and 68.2 ± 8.1, P = 0.004 and 0.002; thigh values: 69.5 ± 9.6 vs. 75.2 ± 7.3, P = 0.014). Both somatic values were lower in patients developing surgical complications (arm: 72.3 ± 8.6 vs. 76.0 ± 8.0, P = 0.049; thigh 71.6 ± 7.8 vs. 76.4 ± 7.3, P = 0.004) and renal complications (arm: 66.2 ± 4.8 vs. 75.1 ± 8.3, P = 0.014; thigh: 68.6 ± 4.1 vs. 74.9 ± 7.9, P = 0.032). Finally, a composite of all post-operative complications were only associated with reduced baseline thigh saturation values (72.5 ± 7.9 vs. 77 ± 7; P = 0.003).

Significant correlations between baseline NIRS values and peri-operative data are shown in Table 4. Baseline arm NIRS values were inversely associated with operating room bleeding values (P = 0.027), blood transfusion requirement values (P = 0.026), blood losses values (P = 0.046), and ICU LOS (P = 0.014). Lower baseline CR NIRS measurements were also associated with length of stay in ICU (P = 0.042). Lower baseline CL (P = 0.013) and thigh NIRS values (P = 0.009) correlated also with length of stay in ICU.

The cerebral desaturation load in relation to the peri-operative parameters and complications is shown in Table 5. Thigh desaturation (68 ± 328 %min) was more pronounced than cerebral (CR: 32 ± 151 %min; P = 0.005 and CL: 19 ± 84 %min; P = 0.021) or arm (37 ± 201 %min; P = 0.044) desaturation. The severity of thigh desaturation correlated directly with blood losses (P = 0.030) and LOS (P = 0.047) in the hospital. In addition, higher thigh desaturation load was associated with ileus (66 ± 366 vs. 72 ± 111; P = 0.005). No other correlation between the cerebral or somatic desaturation load and peri-operative parameters or complications was observed.

Using logistic regression, respiratory complications were associated with baseline CL (OR: 0.913, 95% CI [0.840, 0.992], P = 0.031) and thigh NIRS values (OR: 0.927, 95% CI [0.861, 0.999], P = 0.046). Surgical complications were associated only with baseline thigh NIRS values (OR: 0.925, 95% CI [0.869, 0.984], P = 0.013).

Examples of the directional and paradoxical changes observed in cerebral and somatic NIRS are shown in Figs. 1A and 1B. Parallel changes in all NIRS signals were seen during induction of anesthesia with pre-oxygenation (Fig. 1A) and bleeding and transfusion (Fig. 1B). Intraoperative hepatectomy, skin closure, and abdominal pressure were mostly associated with a reduction in thigh NIRS values (Figs. 2A and 2B). Acute respiratory failure was associated with more pronounced cerebral than somatic desaturation (Fig. 3). Examples of patients without (Figs. 4A and 4B) and
Table 2. Baseline Oximetry Measurements and Population Description Parameters

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (correlation coefficient)*</td>
<td>0.015 [0.891]</td>
<td>0.082 [0.451]</td>
<td>−0.265 [0.013]</td>
<td>−0.093 [0.384]</td>
</tr>
<tr>
<td>Gender (Mean M:F)</td>
<td>66.4:68.3 [0.332]</td>
<td>65.9:68.4 [0.158]</td>
<td>71.7:77.4 [0.001]</td>
<td>72.6:76.5 [0.018]</td>
</tr>
<tr>
<td>ASA score (correlation coefficient)</td>
<td>0.012 [0.914]</td>
<td>0.043 [0.699]</td>
<td>−0.215 [0.047]</td>
<td>0.040 [0.714]</td>
</tr>
<tr>
<td>Pre-op albumin (g/L) (correlation coefficient)</td>
<td>0.217 [0.040]</td>
<td>0.323 [0.002]</td>
<td>−0.049 [0.649]</td>
<td>0.093 [0.385]</td>
</tr>
<tr>
<td>Bilirubin (µmol/L) (correlation coefficient)</td>
<td>−0.046 [0.666]</td>
<td>−0.076 [0.484]</td>
<td>−0.287 [0.007]</td>
<td>−0.098 [0.359]</td>
</tr>
<tr>
<td>PALC (correlation coefficient)</td>
<td>−0.258 [0.014]</td>
<td>−0.266 [0.013]</td>
<td>−0.017 [0.874]</td>
<td>−0.102 [0.342]</td>
</tr>
<tr>
<td>Cancer (n = 69) (Mean N:Y)</td>
<td>66.5:67.5 [0.673]</td>
<td>65.9:67.5 [0.498]</td>
<td>76.8:74.0 [0.190]</td>
<td>76.2:74.1 [0.410]</td>
</tr>
<tr>
<td>Any co-morbidity (n = 63) (Mean N:Y)</td>
<td>67.0:67.4 [0.848]</td>
<td>67.7:66.9 [0.662]</td>
<td>77.4:73.4 [0.036]</td>
<td>75.0:74.3 [0.709]</td>
</tr>
<tr>
<td>Hypertension (n = 24) (Mean N:Y)</td>
<td>66.9:68.3 [0.532]</td>
<td>66.5:69.0 [0.220]</td>
<td>74.7:74.3 [0.844]</td>
<td>74.5:74.5 [0.984]</td>
</tr>
<tr>
<td>COPD (n = 8) (Mean N:Y)</td>
<td>67.6:64.8 [0.410]</td>
<td>67.4:64.3 [0.350]</td>
<td>74.7:74.0 [0.833]</td>
<td>74.7:72.7 [0.526]</td>
</tr>
<tr>
<td>Coronary artery disease (n = 8) (Mean N:Y)</td>
<td>67.9:61.8 [0.072]</td>
<td>67.6:63.1 [0.156]</td>
<td>75.1:69.8 [0.086]</td>
<td>75.0:69.5 [0.056]</td>
</tr>
<tr>
<td>Diabetes (n = 9) (Mean N:Y)</td>
<td>67.1:69.0 [0.566]</td>
<td>67.2:66.9 [0.922]</td>
<td>75.1:70.2 [0.098]</td>
<td>74.9:71.0 [0.155]</td>
</tr>
<tr>
<td>Chronic renal failure (n = 2) (Mean N:Y)</td>
<td>67.4:66.0 [0.838]</td>
<td>67.1:69.5 [0.691]</td>
<td>74.8:65.0 [0.101]</td>
<td>74.7:67.0 [0.170]</td>
</tr>
<tr>
<td>Cirrhosis (n = 5) (Mean N:Y)</td>
<td>67.1:70.6 [0.415]</td>
<td>67.2:67.0 [0.968]</td>
<td>75.0:68.8 [0.111]</td>
<td>74.6:73.6 [0.787]</td>
</tr>
<tr>
<td>Smoking (n = 15) (Mean N:Y)</td>
<td>68.1:63.4 [0.070]</td>
<td>67.9:63.5 [0.067]</td>
<td>75.3:71.4 [0.104]</td>
<td>75.4:70.4 [0.024]</td>
</tr>
<tr>
<td>Dyslipidemia (n = 15) (Mean N:Y)</td>
<td>67.4:66.9 [0.835]</td>
<td>67.4:65.7 [0.488]</td>
<td>75.3:70.8 [0.063]</td>
<td>75.1:71.8 [0.139]</td>
</tr>
</tbody>
</table>

Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. *Except for Age, means are expressed as % of saturation. CR: cerebral right, CL: cerebral left, ASA: American Society of Anesthesiologists, PALC: phosphatase alkaline, COPD: chronic obstructive pulmonary disease, n: number, N: no, Y: yes.

Table 3. Baseline Cerebral and Somatic Oximetry Values and Significant Post-operative Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number</th>
<th>CR</th>
<th>CL</th>
<th>Arm</th>
<th>Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td>81</td>
<td>67.8 ± 9.1</td>
<td>67.7 ± 8.4</td>
<td>74.8 ± 8.1</td>
<td>74.8 ± 8.0</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>63.1 ± 9.1</td>
<td>61.6 ± 6.3</td>
<td>72.5 ± 11.2</td>
<td>72.0 ± 5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diff (95% CI)</td>
<td>4.7 (–2.5, 11.9)</td>
<td>6.1 (0.6, 11.5)</td>
<td>2.3 (–7.1, 11.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P value</td>
<td>0.178</td>
<td>0.041</td>
<td>0.508</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>79</td>
<td>68.4 ± 8.8</td>
<td>68.2 ± 8.1</td>
<td>74.9 ± 8.4</td>
<td>75.2 ± 7.3</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>59.4 ± 8.2</td>
<td>59.7 ± 6.5</td>
<td>72.4 ± 8.2</td>
<td>69.5 ± 9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diff (95% CI)</td>
<td>8.9 (3.2, 14.7)</td>
<td>8.5 (3.9, 13.1)</td>
<td>2.5 (–3.1, 8.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P value</td>
<td>0.004</td>
<td>0.002</td>
<td>0.452</td>
</tr>
<tr>
<td>Surgical complications</td>
<td>56</td>
<td>68.2 ± 8.2</td>
<td>68.0 ± 7.7</td>
<td>76.0 ± 8.0</td>
<td>76.4 ± 7.3</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>65.9 ± 10.6</td>
<td>65.8 ± 9.4</td>
<td>72.3 ± 8.6</td>
<td>71.6 ± 7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diff (95% CI)</td>
<td>2.3 (–1.9, 6.5)</td>
<td>2.1 (–1.7, 6.0)</td>
<td>3.7 (–0.0, 7.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P value</td>
<td>0.125</td>
<td>0.198</td>
<td>0.049</td>
</tr>
<tr>
<td>Renal complications</td>
<td>85</td>
<td>67.8 ± 9.1</td>
<td>67.4 ± 8.4</td>
<td>75.1 ± 8.3</td>
<td>74.9 ± 7.9</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>59.6 ± 8.5</td>
<td>63.6 ± 7.4</td>
<td>66.2 ± 4.8</td>
<td>68.6 ± 4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diff (95% CI)</td>
<td>8.2 (–2.2, 18.5)</td>
<td>3.8 (–5.2, 12.8)</td>
<td>8.9 (3.1, 14.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P value</td>
<td>0.082</td>
<td>0.401</td>
<td>0.014</td>
</tr>
<tr>
<td>All complications</td>
<td>40</td>
<td>69.4 ± 7.7</td>
<td>68.9 ± 7.7</td>
<td>75.6 ± 8.7</td>
<td>77.0 ± 7.0</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>65.7 ± 10.0</td>
<td>65.7 ± 8.7</td>
<td>73.8 ± 8.1</td>
<td>72.5 ± 7.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diff (95% CI)</td>
<td>3.7 (0.0, 7.4)</td>
<td>3.2 (–0.3, 6.7)</td>
<td>1.9 (–1.7, 5.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P value</td>
<td>0.059</td>
<td>0.095</td>
<td>0.429</td>
</tr>
</tbody>
</table>

Values are presented as number of patients or mean ± SD. Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. CR: cerebral right, CL: cerebral left, Diff: Values are presented as mean ± SD. Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. CR: cerebral right, CL: cerebral left, Diff: difference.
with (Figs. 5A and 5B) post-operative complications are shown. In those patients with complications, greater signal variations, more frequent reductions below baseline NIRS values, and paradoxical cerebral and somatic changes were more frequently observed. Fig. 6 summarizes the most common patterns of cerebral and somatic desaturation observed in the current study.

**Discussion**

To our knowledge, this is the first observational and non-interventional study on the potential usefulness of combined cerebral and somatic NIRS in the setting of liver resections. It adds to previous observations we made in 10 liver transplantation patients [27]. We observed that both baseline cerebral and somatic values were associated with pre-operative variables, but also with post-operative complications. Somatic baseline values were higher than cerebral NIRS as previously reported [30]. In addition, higher somatic values were associated with younger age, lower ASA class, and lower co-morbidity burden. No gender difference was observed in cerebral NIRS values, in contrary to somatic arm and thigh values. Smokers had lower thigh NIRS values. An association with vascular disease could explain this difference as patients with (P = 0.056). Patients developing post-operative neurological, somatic NIRS in the setting of liver resections.

### Table 4. Baseline Saturation Values and Peri-operative Parameters

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical time (correlation coefficient)</td>
<td>-0.002 [0.985]</td>
<td>0.035 [0.748]</td>
<td>0.048 [0.661]</td>
<td>0.083 [0.443]</td>
</tr>
<tr>
<td>Use of Pringle (OR)</td>
<td>0.986 [0.565]</td>
<td>0.962 [0.178]</td>
<td>0.998 [0.950]</td>
<td>0.985 [0.595]</td>
</tr>
<tr>
<td>Total Pringle time (correlation coefficient)</td>
<td>-0.058 [0.767]</td>
<td>0.177 [0.377]</td>
<td>-0.024 [0.906]</td>
<td>0.084 [0.666]</td>
</tr>
<tr>
<td>Operating room blood transfusion (correlation coefficient)</td>
<td>-0.117 [0.273]</td>
<td>-0.071 [0.516]</td>
<td>-0.236 [0.027]</td>
<td>-0.060 [0.577]</td>
</tr>
<tr>
<td>Blood transfusion (hospital) (correlation coefficient)</td>
<td>-0.101 [0.344]</td>
<td>-0.051 [0.639]</td>
<td>-0.238 [0.026]</td>
<td>-0.140 [0.190]</td>
</tr>
<tr>
<td>Blood loss (correlation coefficient)</td>
<td>-0.196 [0.065]</td>
<td>-0.192 [0.074]</td>
<td>-0.213 [0.046]</td>
<td>-0.160 [0.135]</td>
</tr>
<tr>
<td>Length of stay in ICU (correlation coefficient)</td>
<td>-0.215 [0.042]</td>
<td>-0.141 [0.194]</td>
<td>-0.260 [0.014]</td>
<td>-0.075 [0.486]</td>
</tr>
<tr>
<td>LOS (correlation coefficient)</td>
<td>-0.196 [0.064]</td>
<td>-0.266 [0.013]</td>
<td>-0.072 [0.503]</td>
<td>-0.273 [0.009]</td>
</tr>
</tbody>
</table>

Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. The relation between baseline values and various peri-operative parameters is presented. OR or correlation coefficient are presented when appropriate. CR: cerebral right, CL: cerebral left, ICU: intensive care unit, LOS: length of hospital stay.

### Table 5. Cerebro-somatic Desaturation Load Values, Peri-operative Parameters and Complications

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebro-somatic desaturation load below 80% (%min)</td>
<td>32 ± 151 (n = 90)</td>
<td>19 ± 84 (n = 87)</td>
<td>37 ± 201 (n = 88)</td>
<td>68 ± 328* (n = 89)</td>
</tr>
<tr>
<td>Surgical clamping time (correlation coefficient)</td>
<td>-0.177 [0.358]</td>
<td>0.021 [0.918]</td>
<td>-0.510 [0.007]</td>
<td>-0.005 [0.980]</td>
</tr>
<tr>
<td>Blood loss (correlation coefficient)</td>
<td>0.104 [0.329]</td>
<td>0.049 [0.652]</td>
<td>0.013 [0.905]</td>
<td>0.230 [0.030]</td>
</tr>
<tr>
<td>Length of stay in ICU (correlation coefficient)</td>
<td>0.128 [0.229]</td>
<td>-0.046 [0.675]</td>
<td>-0.056 [0.606]</td>
<td>-0.030 [0.765]</td>
</tr>
<tr>
<td>LOS (correlation coefficient)</td>
<td>-0.110 [0.302]</td>
<td>-0.030 [0.768]</td>
<td>0.071 [0.508]</td>
<td>0.211 [0.047]</td>
</tr>
</tbody>
</table>

Complications (OR [95% CI])

- **Neurological**
  - 0.831 [0.275, 2.508] [0.742]
  - 1.000 [0.994, 1.008] [0.728]
  - 0.992 [0.959, 1.026] [0.664]
  - 1.000 [0.998, 1.002] [0.849]

- **Cardiac**
  - 0.829 [0.209, 3.279] [0.789]
  - 1.000 [0.995, 1.010] [0.565]
  - 0.870 [0.381, 1.987] [0.741]
  - 0.967 [0.836, 1.118] [0.648]

- **Respiratory**
  - 1.000 [0.999, 1.005] [0.149]
  - 0.997 [0.986, 1.009] [0.633]
  - 0.998 [0.991, 1.006] [0.670]
  - 1.000 [0.998, 1.002] [0.981]

- **Surgical**
  - 1.000 [0.998, 1.003] [0.702]
  - 1.000 [0.995, 1.006] [0.838]
  - 1.000 [0.998, 1.007] [0.300]
  - 1.000 [0.998, 1.001] [0.652]

- **Infectious**
  - 1.000 [0.997, 1.003] [0.897]
  - 0.997 [0.990, 1.005] [0.481]
  - 1.000 [0.997, 1.015] [0.184]
  - 1.000 [0.999, 1.001] [0.948]

- **Hematological**
  - 1.000 [0.999, 1.005] [0.213]
  - 1.000 [0.995, 1.008] [0.638]
  - 0.975 [0.869, 1.094] [0.665]
  - 1.000 [0.998, 1.002] [0.953]

Three patients were excluded for the CL and one patient for both the arm and thigh baseline oximetry measurement. *The somatic load desaturation was higher than the CR (P = 0.005), CL (P = 0.021), and arm (P = 0.044). CR: cerebral right, CL: cerebral left, ICU: intensive care unit, LOS: length of hospital stay.
respiratory, renal, and surgical complications had lower baseline cerebral as reported previously [10,11,13,37] but also lower somatic NIRS values that have not been reported. Interestingly, in patients undergoing liver resection, lower somatic NIRS values were more commonly associated than cerebral NIRS values in patients developing those complications, which have not been reported in the literature before. Finally, in terms of the severity of intraoperative desaturation, thigh desaturation was more commonly observed and was the only NIRS variable associated with blood losses and prolonged LOS in the hospital. Therefore, this study suggests that, when considering only desaturation load during surgery, somatic oximetry may be superior to cerebral oximetry for the prediction of post-operative outcomes in some types of non-cardiac surgeries such as liver surgery.

While very few papers have studied the use of cerebral NIRS monitoring during liver surgery or transplantation [12,38–41], most clinical studies with NIRS monitoring comes from the cardiac surgical environment [5,6,9–13,34,42–44]. The mean cumulative cerebral desaturation load during liver surgery in this study (Left: 19 ± 84 %min, Right: 32 ± 151 %min) appeared to be

Fig. 1. Cerebral and somatic regional oxygen saturation (rSO$_2$) during oxygenation and bleeding (A) Prior to hepatectomy in a 64-year-old man (patient #24), a significant increase in both cerebral and somatic rSO$_2$ signals was observed shortly following the induction of anesthesia and pre-oxygenation. (B) Intraoperative bleeding in a 78-year-old woman (patient #88) during right hepatectomy. Note the proportional reduction on all rSO$_2$ signals and their increase during transfusion.

Fig. 2. Cerebral and somatic regional oxygen saturation (rSO$_2$) during extubation and abdominal pressure (A) rSO$_2$ signals following skin closure in a 67-year-old woman (patient #13) with previous abdominal surgery following cholecystectomy and hepatectomy of segments 4, 5, and 8. More pronounced reduction in thigh oximetry was observed compared to arm and cerebral signals following skin closure and extubation. The difference normalized within 2 h. (B) Localized changes in thigh oximetry during abdominal pressure in a 72-year-old woman (patient #59) during hepatectomy of segment 1. Note the minimal changes in the other oximetry signals.
greatly inferior to what was previously observed in cardiac surgery (100–400 %min) [35]. In patients undergoing liver resection, an association between baseline cerebral desaturation, neurological and respiratory complications, ICU length of stay as well as the total LOS was observed. Hypothetically, this could be explained by the baseline cerebral oximetry measurement, which will be influenced by the physiological cardiopulmonary and hematological reserve of the patient, with sicker patients staying longer in the hospital after liver resection. Another variable that could play a role would be altered autoregulation of patients with liver disease [38,39]; however, only five patients had cirrhosis in our group.

The most interesting findings of our study were the dynamic patterns observed with combined use of cerebral and somatic sensors positioned at the arm and thigh in relationship with clinical events. The combined use of both somatic and cerebral NIRS parameters has been reported in cardiac surgical patients for fluid challenge [45] and as a predictor of post-operative delirium [46]. Most of its use has been in pediatric cardiac surgical patients [21,47,48]. Combining cerebral and somatic NIRS is useful to discriminate if a reduction in ScO2 results from a central or peripheral process as we previously proposed [29,49]. For instance, if brain and somatic desaturation are present simultaneously, the etiology is unlikely to be cerebral in nature and could be hemorrhagic shock as we observed in Fig. 1B.

In our study, baseline systemic values (arm and/or thigh) predicted more post-operative complications, especially direct surgical complications, compared to cerebral values. During a state of relative hypoperfusion, blood flow will be preferentially maintained to organs such as the brain, heart, liver, and kidney at the expense of muscles. Therefore, early in shock, cerebral autoregulation will be maintained, but signs of hypoperfusion could be detected earlier in the muscles that are monitored with somatic NIRS. In addition, NIRS signals are very sensitive to cerebral venous congestion [50] and right ventricular diastolic dysfunction [51]. In the presence of venous congestion or hypervolemia, complications such as delirium, respiratory insufficiency, ileus, and cardio-renal failure will be observed [50,52]. This may explain why liver manipulation and abdominal pressure, by causing transient vena cava occlusion, will lead to lower limb congestion and the Pringle maneuver will similarly cause bowel venous congestion (Figs. 2A and 2B). Bowel congestion could lead to an inflammatory reaction similar to what is described in the cardio-intestinal syndrome [53]. The frequent observation of reduced thigh NIRS value during caval obstruction as reported previously in liver transplantation [54] and the increase in lower extremity NIRS during treatment of abdominal compartment syndrome [49] could support this hypothesis. In our patient population, an association with reduced somatic NIRS and post-operative complications was present. If such complications occur, then longer ICU and hospital LOS may be observed.

**Fig. 3.** Cerebral and somatic regional oxygen saturation (rSO2) during respiratory failure. Post-operative brain desaturation in a 66-year-old woman (patient #91) with portal hypertension with acute respiratory failure requiring re-intubation. The patient had a hepatectomy of segments 5, 6, 7, and 8. Note that the change in brain desaturation was more pronounced than the somatic signals during respiratory failure.
There are several limitations from our study. This is a single center study with a limited sample size that limits the validity of the findings. Our study is however the first and largest observational and non-interventional study in liver resection that lays the basis for future potential interventional trials. As shown by other authors, we observed an association with reduced baseline oxime values, intraoperative desaturation, and outcome. The impact of brain and somatic desaturation correction remains debatable [55-58]. The determination of the number of patients in whom cerebral and somatic desaturation would occur in liver resection was undetermined and never reported. Therefore, our study can be used as a pilot study to determine in more detail the number of patients in whom cerebral and somatic desaturation would occur in liver resection.

Fig. 4. Unchanged cerebral and somatic regional oxygen saturation (rSO₂) (A) 69-year-old man (patient #42) in whom surgical findings led to a cancellation of the hepatectomy. The patient did not develop any post-op complications. (B) 53-year-old woman (patient #86) with hepatectomy of segments 2, 3, 4, and 7. The patient did not develop any complications post-operatively. A: arm, CL: cerebral left, CR: cerebral right, ICU: intensive care unit, T: thigh.
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patients in order to perform a more precisely powered study. Furthermore, because we did not systematically assess the clinical implications of desaturation patterns associated with intra-operative events, the qualitative observations reported remain only hypothesis-generating and will require validation. Therefore, the benefit and clinical impact of monitoring cerebral and somatic NIRS in
non-cardiac surgery remain to be proven. While our data does not provide causative explanation for the findings because of the observational nature of this study, it certainly provides interesting findings justifying more research in the field. In fact, our work seems to suggest that both cerebral and somatic NIRS could be used at baseline before surgery to establish some patients at risk. Our findings suggest that somatic monitoring may be as important, if not more, than cerebral monitoring to predict surgical outcome in liver surgery. It is also possible that lower baseline cerebral or somatic saturation are associated with sicker patients at higher risk of complications such as delirium as reported for cerebral saturation \[11,46\]. We did not explore in detail the mechanism of reduced NIRS values, but it may represent a relatively easy method to identify those high-risk patients at the bedside. A multicenter trial with a larger cohort of patient would be required in order to identify the most important determinants that influence cerebro-somatic NIRS measurement in liver surgery.

In conclusion, combining cerebral and somatic oxygenation monitoring with NIRS is a promising tool for liver resection cases. Baseline NIRS values and intraoperative somatic desaturations may have a prognosis value for post-operative outcomes. It may identify higher risk patients. The extent to which interventions can correct cerebral and somatic desaturation in liver resection and its possible impact on clinical outcomes is still to be elucidated.

Acknowledgements

Our group would like to sincerely acknowledge Dr. Roxanne Allard, Dr. Fabio Payette, and Dr. Andrée Cloutier for their input in the preparation of this work.

Funding

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Conflicts of Interest

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

Author Contributions

Yves Collin (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing)
Tina Hu (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing)
André Denault (Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing)
Annik Fortier (Conceptualization; Formal analysis; Methodology; Writing – review & editing)
William Beaubien-Souligny (Formal analysis; Writing – original draft; Writing – review & editing)
Réal Lapointe (Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing)
Franck Vandenbroucke-Menu (Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing)
References


### Appendix 1. STROBE Statement—Checklist of Items That Should Be Included in Reports of Observational Studies

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>5</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
<td>6</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>State specific objectives, including any prespecified hypotheses</td>
<td>6–7</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Present key elements of study design early in the paper</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 8–9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</td>
<td>8–9</td>
</tr>
<tr>
<td></td>
<td>Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Case-control study—For matched studies, give matching criteria and the number of controls per case</td>
<td>8</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
<td>9–10 + Appendix 2</td>
</tr>
<tr>
<td></td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
<td>8–11</td>
</tr>
<tr>
<td><strong>Data sources/measurement</strong></td>
<td>Describe any efforts to address potential sources of bias</td>
<td>8–10</td>
</tr>
<tr>
<td><strong>Bias</strong></td>
<td>Explain how the study size was arrived at</td>
<td>8–9</td>
</tr>
<tr>
<td><strong>Study size</strong></td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Quantitative variables</strong></td>
<td>Describe all statistical methods, including those used to control for confounding</td>
<td>9–10</td>
</tr>
<tr>
<td></td>
<td>Describe any methods used to examine subgroups and interactions</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Explain how missing data were addressed</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(d) Cohort study—If applicable, explain how loss to follow-up was addressed</td>
<td>9–10</td>
</tr>
<tr>
<td></td>
<td>Case-control study—If applicable, explain how matching of cases and controls was addressed</td>
<td>9–10</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy</td>
<td>9–10</td>
</tr>
<tr>
<td><strong>Statistical methods</strong></td>
<td>Describe any sensitivity analyses</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</td>
<td>12 + Tables 1 and 2</td>
</tr>
<tr>
<td></td>
<td>Give reasons for non-participation at each stage</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Consider use of a flow diagram</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders</td>
<td>Tables 1 and 2</td>
</tr>
<tr>
<td><strong>Descriptive data</strong></td>
<td>Indicate number of participants with missing data for each variable of interest</td>
<td>12</td>
</tr>
<tr>
<td><strong>Statistical methods</strong></td>
<td>Summarise follow-up time (eg, average and total amount)</td>
<td>12</td>
</tr>
</tbody>
</table>

(Continued to the next page)
### Appendix 1. Continued

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
<th>PAGE</th>
</tr>
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<tbody>
<tr>
<td><strong>Outcome data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15*</td>
<td><strong>Cohort study</strong>—Report numbers of outcome events or summary measures over time. <strong>Case-control study</strong>—Report numbers in each exposure category, or summary measures of exposure. <strong>Cross-sectional study</strong>—Report numbers of outcome events or summary measures.</td>
<td>12 + Appendix 3</td>
</tr>
<tr>
<td><strong>Main results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included.</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(b) Report category boundaries when continuous variables were categorized.</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Other analyses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses.</td>
<td>Tables 4 and 5</td>
</tr>
<tr>
<td><strong>Discussion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Key results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Summarise key results with reference to study objectives.</td>
<td>15</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.</td>
<td>17–18</td>
</tr>
<tr>
<td><strong>Interpretation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.</td>
<td>16–18</td>
</tr>
<tr>
<td><strong>Generalisability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Discuss the generalisability (external validity) of the study results.</td>
<td>16–18</td>
</tr>
<tr>
<td><strong>Other information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Funding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.</td>
<td>2</td>
</tr>
</tbody>
</table>

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

### Appendix 2. Definitions of Variables

<table>
<thead>
<tr>
<th><strong>Demographic Factors</strong></th>
<th><strong>Preoperative Variables</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight/Height$^2$</td>
<td>Body mass index (kg/m$^2$)</td>
</tr>
<tr>
<td></td>
<td>American Society of Anesthesiologists class</td>
</tr>
<tr>
<td></td>
<td>Child-Pugh score</td>
</tr>
<tr>
<td></td>
<td>Model for End-Stage Liver Disease (MELD) score</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Perioperative Variables</strong></th>
<th><strong>Postoperative Variables</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral desaturation</td>
<td>Neurological</td>
</tr>
<tr>
<td>Area under the threshold spent beneath the absolute threshold limit of 80% of the baseline rSO$_2$ value multiplied by time. (6)</td>
<td>Delirium</td>
</tr>
<tr>
<td>Cerebral desaturation load (%min)</td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cardiac complications</strong></th>
<th><strong>Respiratory complications</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Supraventricular tachyarrhythmia characterized by uncoordinated atrial activation as shown on an electrocardiogram and requires electrical or pharmacological cardioversion. (9)</td>
<td>Embolus identified as obstructing a vessel as diagnosed by pulmonary angiography. (10)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Empyema</td>
</tr>
<tr>
<td>Myocardial infarction with persistent Q wave</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Cardiac arrest/cardiogenic shock</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Need for vasopressors and inotropic agents, intra-aortic balloon-pump, or ventricular-assist device for &gt; 48 hours.</td>
<td>Pneumothorax</td>
</tr>
</tbody>
</table>

| **Surgical complications** | |
|--------------------------||
| Liver failure | Increased MELD score > 9. |
| Biliary fistula | Presence of bile in drainage fluid, drainage ≥ 50 mL/day on the third day after the operation, and drainage for 3 days consistently. (11) |
| Ileus | Impairment in gastrointestinal mobility for over 6 days after the surgery. (12) |
| Revision surgery | Follow-up surgery is required. |

(Continued to the next page)
**Infectious complications**

- **Wound infection**: Infection from surgical procedure requiring antibiotic therapy.
- **Clostridium Difficile**: Documented infection using toxin assay.
- **Intra-abdominal abscess**: Localized collection of pus or gastrointestinal content inside abdominal cavity requiring antibiotics or percutaneous drainage. (13)
- **Infected ascites**: Documented peritoneal fluid with positive culture.
- **Peritonitis**: Presence of free pus or gastrointestinal content in the peritoneal cavity requiring antibiotics or surgical treatment. (13)
- **Urinary tract infection**: Documented urine with positive culture.
- **Sepsis and septic shock**: Non-specific systemic inflammatory symptoms with evidence of microbial basis. (14) Severe sepsis is defined as sepsis with organ dysfunction and septic shock is defined as sepsis with hypotension despite adequate volume resuscitation. (14)
- **Fungemia**: Positive fungal blood culture.

**Hematological complications**

- **Bleeding**: Blood loss requiring red blood cells, fresh frozen plasma, cryoprecipitate, and platelets. Massive blood loss is defined as the loss of one blood volume = 70 ml/kg or 5 liters in an adult patient within 24 hours or the loss of 0.5 blood volumes within 3 hours. (15)
- **Thrombophlebitis**: Inflammation of a cannulated vein requiring heparin, antibiotics, or anti-inflammatory medications. (16)
- **Renal failure**: Dialysis requirement or doubling of baseline serum creatinine level, or serum creatinine level > 150 μmol/L (1.7 mg/dl). (2)

**Other complications**

- **Excessive weight gain**: ≥ 20 kg compared to pre-operative weight.
- **Upper gastrointestinal bleeding**: Blood loss from upper gastrointestinal tract documented by gastroscopy.

**Miscellaneous Variables**

- **Length of time in the ICU**: Length of time from date of surgery to the date when patient left the ICU.
- **Length of hospital stay**: Length of time from date of surgery to the date when patient left the hospital.
- **Clavien-Dindo classification of postoperative complications**: All complications were given a grade, which ranged from Grade I (a deviation from the normal postoperative course without the need of pharmacological treatment or surgical interventions), Grade II (requiring pharmacological treatment), Grade III (requiring surgical, endoscopic, or radiological intervention), Grade IV (life-threatening complication), and Grade V (death of patient). (17)

CK: creatinine kinase, CT: computed tomography, FiO₂: inspired fraction of oxygen, ICU: intensive care unit, PaO₂: arterial oxygen partial pressure, rSO₂: regional brain or somatic saturation.

**References**


### Appendix 3. Detailed Complications Observed in the Studied Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Absence</th>
<th>DINDO 1-2</th>
<th>DINDO 3 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>81 (90)</td>
<td>9 (10)</td>
<td></td>
</tr>
<tr>
<td>Convulsion</td>
<td>89 (99)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>87 (97)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>89 (99)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>88 (98)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>81 (90)</td>
<td>9 (10)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>87 (97)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Empyema</td>
<td>89 (99)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>79 (88)</td>
<td>9 (10)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Gastro-intestinal complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>89 (99)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Biliary leak</td>
<td>76 (84)</td>
<td>12 (13)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Stress ulcer</td>
<td>88 (98)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Infected ascites</td>
<td>89 (99)</td>
<td>1 (1)</td>
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<tr>
<td>Ileus</td>
<td>71 (79)</td>
<td>19 (21)</td>
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<tr>
<td>Portal vein thrombosis</td>
<td>89 (99)</td>
<td>1 (1)</td>
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<tr>
<td><strong>Infectious complications</strong></td>
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<tr>
<td>Urinary tract infection</td>
<td>88 (98)</td>
<td>2 (2)</td>
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<tr>
<td>Abdominal abscess</td>
<td>88 (98)</td>
<td>2 (2)</td>
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<tr>
<td>Wound infection</td>
<td>81 (90)</td>
<td>9 (10)</td>
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<tr>
<td>Clostridium Difficile infection</td>
<td>87 (97)</td>
<td>3 (3)</td>
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<tr>
<td>Sepsis</td>
<td>87 (97)</td>
<td>3 (3)</td>
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<tr>
<td>Septic shock</td>
<td>89 (99)</td>
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<tr>
<td>Fungiemia</td>
<td>88 (98)</td>
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<tr>
<td>DCS1</td>
<td>89 (99)</td>
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<td><strong>Hematological complications</strong></td>
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<td>Pancytopenia</td>
<td>80 (89)</td>
<td>9 (10)</td>
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<tr>
<td>Deep vein thrombosis</td>
<td>89 (99)</td>
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<td><strong>Renal complications</strong></td>
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<tr>
<td>Volume overload</td>
<td>80 (89)</td>
<td>9 (10)</td>
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<tr>
<td>Renal failure</td>
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<td>4 (4)</td>
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<tr>
<td><strong>Surgical complications</strong></td>
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<tr>
<td>Various complications</td>
<td>55 (61)</td>
<td>30 (33)</td>
<td>5 (6)</td>
</tr>
<tr>
<td><strong>Total number of patients with complications</strong></td>
<td>38 (42.2)</td>
<td>41 (45.5)</td>
<td>11 (12.2)*</td>
</tr>
</tbody>
</table>

*Patient may have more than one complication.
Propofol abuse among healthcare workers: an analysis of criminal cases using the database of the Supreme Court of South Korea’s judgments

Hye-Yeon Cho¹, Yoonbin Hwang¹, SuHwan Shin², Susie Yoon¹,³, Ho-Jin Lee¹,³
¹Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, ²Department of Medical Law and Ethics, Graduate School, Yonsei University, ³Department of Anesthesiology and Pain Medicine, Seoul National University College of Medicine, Seoul, Korea

Background: Due to its abuse potential, propofol has been classified as a controlled substance since February 2011 in South Korea. Healthcare workers are exposed to propofol abuse considering their easy access to this substance in hospitals. Therefore, we aimed to investigate propofol abuse among healthcare workers through the database of the Supreme Court in South Korea.

Methods: We retrospectively analyzed adjudicated criminal cases related to propofol abuse among healthcare workers from January 1, 2013, to December 31, 2020, using the database of the Supreme Court of South Korea’s judgments. We collected the clinical characteristics and punishment-related information of healthcare workers who abused propofol.

Results: Of the 194 cases collected using the search term ‘propofol,’ 20 were included in the final analysis. The most common healthcare workers who abused propofol were nursing aides (n = 15). Among them, 40% (n = 8) of the defendants had previously been punished for substance abuse, and 35% (n = 7) had a history of psychological disease. Of the defendants, 65% (n = 13) self-administered propofol more than twice, and the median number of self-administrations was three. Except for two, the defendants were sentenced to imprisonment, including suspended sentences, and the median values of their duration of prison and probation were 9 months and 24 months.

Conclusions: Despite propofol being strongly regulated as a controlled substance in South Korea, its abuse among healthcare workers remains. Healthcare workers should be vigilant against its abuse among themselves.

Keywords: Criminals; Health personnel; Illicit drugs; Intravenous administration; Legislation and jurisprudence; Propofol; Psychotropic drugs; Substance-related disorders.

Introduction

Propofol has been the most widely used intravenous hypnotic agent for general anesthesia and sedation; however, it has a risk of abuse [1]. It is known to activate the mesocorticolimbic dopaminergic system through the gamma-aminobutyric acid A receptor, which can contribute to abuse potential [1]. In a prospective study conducted in Korean patients receiving gastric endoscopy, propofol showed a high euphoria effect, which is higher than that of marijuana [2]. According to the practice guidelines for propofol sedation by the Korean Society of Anesthesiologists (KSA), physicians should be acquainted
with its abuse potential and carefully evaluate the presence of psychological dependence before administration [3]. Against this backdrop, for the first time worldwide, propofol has been classified as a controlled substance in Korea since February 2011 [4,5]. Moreover, on February 9, 2018, the Korean Ministry of Food and Drug Safety classified propofol as a psychoactive drug of priority control [6]. Currently, details of propofol from manufacturing to sales are required to be reported in the narcotics information management system in South Korea.

Since an anesthesiologist’s first propofol abuse case was reported in 1992 [7], several propofol abuse cases among healthcare workers have been reported [8]. Healthcare workers are more likely to be exposed to propofol abuse than laypeople considering their easy access to this substance in hospitals [4]. They can directly acquire propofol at the hospital where they work or use the remaining propofol after administering it to patients [9]. In the previous peer-reviewed literature between 1992 and 2009, 45 cases of propofol abuse have been reported, of which 40 (89%) were identified in healthcare professionals [8]. In the retrospective cohort study regarding substance use disorder (SUD) among anesthesiology residents in the United States from 1975 to 2009, 384 (2.2%) individuals had confirmed SUD during their residency [10]. Eleven of these individuals reported that the substance used during their initial episode of abuse was propofol [10]. In another retrospective study regarding SUD among anesthesiologists conducted from 2004 to 2013 in Australia and New Zealand, propofol was the most commonly abused medication among anesthesiologists (n = 18/44; 41%) [11].

However, to our knowledge, few studies conducted before 2011—when propofol was not classified as a controlled substance [12,13]—have addressed propofol abuse among healthcare workers in South Korea. According to the recent report published by the Korean Supreme Prosecutors’ Office, the number of medical personnel who committed a crime related to psychoactive drugs increased from 55 in 2016 to 196 in 2020 [14]. Therefore, we aimed to investigate the current state and specific characteristics of propofol abuse among healthcare workers by analyzing adjudicated criminal cases. Further, we aimed to discuss our role as anesthesiologists in preventing its abuse through this study.

Materials and Methods

Adjudicated criminal cases that are publicly accessible in the database of the Supreme Court of Korea’s judgments were analyzed. Criminal cases closed from January 1, 2013, can be searched on the Internet through the public service of the Supreme Court of Korea [15]. Without personally identifiable information, the details of each case were provided to the researcher. All criminal cases that were sentenced from January 1, 2013, to December 31, 2020, were searched using the term ‘propofol.’ We included the cases in which the defendant was a healthcare worker and propofol abuser. We excluded cases unrelated to propofol abuse by healthcare workers based on the authors’ judgment (HY Cho and H-J Lee). After the initial analysis, we judged that there were cases indirectly related to propofol abuse among the cases excluded from this study. Therefore, we additionally classified the excluded cases as follows: propofol abuse of non-healthcare workers, sale of propofol by non-physicians for financial benefit, propofol administration by physicians for financial benefit, violation of medical service, propofol theft by non-healthcare workers, and crimes where propofol was not the main issue of the case. This study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB no. 2111-125-1275), which waived the need for informed consent due to the nature of the study.

In each lawsuit text, a detailed description of the case and the court decisions regarding criminal punishment were observed. The judgment texts were reviewed by two board-certified anesthesiologists (HY Cho and H-J Lee), who collected the following information independently: type of violation, the criminal record of drug abuse, history of psychological diseases, route of propofol acquisition, number of propofol administrations, use of illegal drugs other than propofol, and punishment-related information (prison sentence, suspended sentence, and penalty). In the case of a disagreement between the two authors, the decision was made after a discussion with a third author (SH Shin).

Using the MedCalc Statistical Software version 18.6 (MedCalc Software bvba, Belgium), descriptive statistics were used. Continuous and categorical data are described as median (Q1, Q3) or mean ± SD and percentages, respectively.

Results

There were 194 cases during the study period, 20 of which were related to propofol abuse by healthcare workers (Fig. 1). Among the excluded cases, 19 involved physicians administering propofol to their patients for financial benefit. In the two cases, the physician was fined Korean Won 5,000,000 for neglecting the management of propofol.

Characteristics of the cases are presented in Table 1. The most common healthcare workers who abused propofol were nursing aides (n = 15/20; 75%). The most common location for propofol abuse was a residential area in 65% (n = 13) cases. Of the defendants, 40% (n = 8) had previously been punished for substance abuse.
abuse, and 65% (n = 13) of the defendants self-administered propofol more than twice (maximum number of self-administrations, 39). The median number of propofol self-administration was three and stolen propofol ampules was 11 (maximum number of stolen propofol ampules, 65). The proportion of defendants who self-administered other drugs with propofol simultaneously (benzodiazepine, n = 5; ketamine, n = 2; fentanyl, n = 2; nalbuphine, n = 1) was 40% (n = 8). In four of the 15 cases of propofol abuse by nursing aides, the residual propofol was stolen after its administration to the patient, while in 11 cases, it was stolen directly from the storage by obtaining its password or stealing the key. There were three physicians who had abused propofol; two of them had a history of conviction for substance abuse (propofol, methamphetamine). Further, two of them had self-administered propofol for stress relief and the third to resolve sleep disturbance.

Judgment statuses are shown in Table 2. The defendants in all cases were punished for violating the narcotics control act, and a theft charge was added in the cases of nursing aides who were not eligible for the management of propofol. Three defendants who had a criminal history of the same offense within the last three years were imprisoned without suspension, and their duration of imprisonment was 4, 12, and 18 months, respectively. The median additional collection amount was 31,796 Korean won—an additional charge for stolen propofol.

**Discussion**

Although the recognition of the abuse potential of propofol has

<table>
<thead>
<tr>
<th>Table 2. Judicial Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Months from first administration to the judgment</td>
</tr>
<tr>
<td>Prison/probation</td>
</tr>
<tr>
<td>Duration of prison (months)</td>
</tr>
<tr>
<td>Duration of probation (months)</td>
</tr>
<tr>
<td>Additional collection amount (Korean Won)</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), number (%) or mean ± SD. *Three cases had a criminal history of the same offense that existed within the last three years.
increased and the control over it has also been strengthened, propofol abuse among healthcare workers still occurs in South Korea. Additionally, although not included in our analyses, other problems associated with propofol abuse, such as propofol trading by a physician, neglect of its management, and propofol theft, were also identified in this study. Considering the increased use of propofol as a sedative agent [16], healthcare workers should be wary of its abuse potential.

Previous studies have reported propofol abuse by non-healthcare professionals as well as healthcare professionals in South Korea. The first study regarding propofol abuse in South Korea was conducted among healthcare professionals working in the operating room [12]. This study was a nationwide survey of 95 councilors of the KSA working at 61 hospitals. In this study, nine propofol abusers working at seven hospitals were identified (anesthesiology resident, n = 4; non-anesthesiology resident, n = 2; nurse in anesthesiology, n = 1; not described, n = 2). In the autopsy study related to propofol abuse in South Korea, nine of the 16 subjects were healthcare professionals (three physicians and six nurses) [17]. Among them, the cause of death in 14 subjects was drug intoxication, and that in two subjects was hanging. In another structured survey conducted on 38 non-healthcare professional propofol abusers, stress relief was the most common reason for the first-time administration of propofol, and most of them had received propofol two or three times a week during the last 12 months [18]. Although our study could not investigate the reason for the first administration of propofol in all cases, the most common cause of its first administration was also stress relief. Additionally, as repeated abuse of controlled substances increases the probability of being apprehended, it was noted that propofol administration continued after the first one in 65% of abusers in our study.

Our study included information related to punishment for propofol abuse that was not covered in previous studies [12,17,18]. The recidivism and number and dosage of abused drugs act as important factors in the judgment regarding drug abuse cases [19]. If the defendant is currently under probation for another criminal offense, a prison sentence is inevitable. In our study, all three imprisoned defendants were under probation due to another drug abuse. Additionally, the probation period is judged to be one and half to two times longer than the prison period in South Korea, and in this study, the mean value of the prison period was 8.5 months and the median value of the total period including the probation and prison periods was 24 months. Additional collection charge was imposed on the defendant according to the price of propofol, which was administered and could not be confiscated.

Recently, a notification system was introduced to notify doctors who inappropriately prescribed propofol based on the predefined criteria regarding propofol prescription to reduce propofol abuse [20]. The predefined criteria included that propofol should be prescribed and administered only for general anesthesia or sedation, and the number of propofol administrations for sedation should not exceed once a month. It also included the appropriate dose of propofol for general anesthesia and sedation [21]. This strong regulation can increase physicians’ awareness of propofol abuse and reduce propofol abuse caused by inappropriate prescription and administration. After implementing this system, the number of inappropriate prescriptions based on the predefined criteria decreased by 64% from 3,815 to 1,371 [22]. However, because this strong regulation can limit the use of propofol in clinical practice, which has advantages as an anesthetic or sedative agent, its advantages and disadvantages should be discussed.

Our results suggest that the following precautionary measures are needed to reduce propofol abuse by healthcare workers. First, handlers of antipsychotics should pay more attention to its management. Despite antipsychotics being stored in a locked place according to the Narcotics Control Act in South Korea, propofol was stored in an uncontrolled place in half of our cases (Table 1). Additionally, we could identify two cases in which doctors were fined for neglecting the management of propofol in the excluded cases. An exhaustive monitoring system is also needed for the remaining amount of propofol after administration to the patient. In four cases in this study, defendants self-administered the remaining propofol after administration to the patient (Table 1). Propofol handlers should pay special attention to the remaining amount of propofol after administration. Second, a systematic treatment and rehabilitation program with the active support of the government should be prepared. In the aforementioned study, five out of the nine propofol abusers had a previous history of drug abuse other than propofol, and only two of the nine abusers participated in the relapse prevention program [12]. In another study, the relapse rate of SUD related to hypnotics in anesthesiology residents has been reported to be 29% [10]. The recidivism rate of the abuse of psychotropic substances has been reported to be 37.2% in South Korea [14], and in our study, 40% of the defendants had a history of substance abuse. Active treatment and rehabilitation of addicted healthcare workers will help prevent their recurrence of substance abuse. However, conflicting results have also been reported for its effectiveness [23,24], and their cost-effectiveness should be discussed. Finally, to fundamentally prevent substance abuse, periodic education on the seriousness of substance abuse is also needed for healthcare workers.

This study has some limitations. First, the judicial cases ana-
Analyzed did not always contain detailed clinical information, such as the reasons for the first abuse and previous history of psychological disease. Second, our results could not represent all propofol abuse by healthcare workers. The mortality rate of propofol abuse has been reported to be as high as 28% to 38% [1,25], and healthcare workers who died from propofol abuse could not be included in this study. Additionally, we hypothesized that the number of medical personnel legally punished for propofol abuse does not accurately represent the number of medical personnel who actually abuse propofol. According to the aforementioned study, it is estimated that all propofol abusers were not legally punished [12]. As a result, the small number of cases in this study made it difficult to perform additional analyses other than descriptive statistics. Further, the results of our study should be interpreted cautiously because the aforementioned limitation might have resulted in biased results for a specific department of occupation.

In conclusion, our study identified several propofol abuse cases by healthcare workers in South Korea. Despite an increased awareness of propofol abuse and strengthening the regulation on the management of propofol in South Korea, its abuse is steadily occurring. Healthcare workers should be vigilant against the abuse risk of propofol and continue to strive to prevent its abuse among their colleagues.

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None.

Conflicts of Interest

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

Author Contributions

Hye-Yeon Cho (Data curation; Formal analysis; Writing – original draft)
Yoonbin Hwang (Data curation)
SuHwan Shin (Conceptualization; Methodology)
Susie Yoon (Writing – review & editing)
Ho-Jin Lee (Conceptualization; Methodology; Writing – review & editing)

References


Association of *HLA-DPA1* polymorphism with prolonged mechanical ventilation in patients undergoing liver transplantation

Eun Jung Kim¹,², Min-Soo Kim¹,², Myoung Soo Kim³, Junhyun Nam¹, Seung Ho Choi¹,²

¹Department of Anesthesiology and Pain Medicine, Severance Hospital, ²Anesthesia and Pain Research Institute, ³Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

**Background:** Prolonged mechanical ventilation (PMV) is a common complication after liver transplantation surgery. However, owing to the clinical and economic benefits of early extubation, many efforts have been used to assess the clinical predictors for PMV. The aim of our study was to explore the impact of perioperative risk factors, including candidate gene polymorphisms, for PMV in patients undergoing liver transplantation.

**Methods:** One hundred forty patients who underwent liver transplantation surgery were enrolled. The duration of mechanical ventilation after surgery was examined, along with the length of intensive care unit and hospital stay, and 30-day mortality. Patient-related clinical factors and single nucleotide polymorphisms of candidate genes were assessed with regard to PMV, which was defined as mechanical ventilation for > 48 h.

**Results:** Twenty-six (19%) patients continued to receive mechanical ventilation at 48 h after surgery. Intraoperative continuous renal replacement therapy (CRRT) and an elevated serum lactate level during the postoperative period were significantly associated with the PMV group, compared to the non-PMV group (odds ratio [OR] = 24.731 [1.077, 567.915] versus OR = 3.008 [1.497, 6.045]). A significant association existed between the HLA-DPA1 rs8486 polymorphism and the risk of PMV under the allele model (OR = 8.060 [1.451, 44.765]).

**Conclusions:** The rs8486 polymorphism in *HLA-DPA1* can independently affect the risk of PMV in liver transplantation recipients, along with intraoperative CRRT application, and elevated lactate level during the postoperative period.

**Keywords:** Artificial respiration; Genetic polymorphism; Genotype; HLA-DPA1 antigen; Liver transplantation; Postoperative care.

**Introduction**

Preoperative comorbidities, challenging surgical procedures, and complex postoperative management are the factors that make enhanced recovery after surgery difficult for liver transplantation patients. Early weaning from mechanical ventilation alleviates pulmonary complications such as atelectasis, intrapulmonary shunting, and pneumonia, and effectively improves patients’ recovery [1]. For graft survival matter, immediate extubation effectively promotes venous return to the heart and increases cardiac output and hepatic arterial blood flow, thereby helping to improve early graft function [2]. However, despite the clinical strength of early weaning from mechanical ventilation, identifying pa-
Patients who are likely to receive prolonged mechanical ventilation (PMV) remains very difficult [3].

Patients undergoing PMV represent up to 15% of all patients requiring weaning from mechanical ventilation [4]. Patients who undergo PMV often have advanced chronic respiratory failure and/or other comorbidities, and eventually account for longer intensive care unit (ICU) stays and greater financial burden. Thus, emerging interests focusing on reducing the need for PMV and on predicting candidate patients who are at risk for developing PMV are needed. In 2005, a consensus conference led by the National Association for Medical Direction of Respiratory Care (NAMDC) defined PMV as mechanical ventilation for ≥ 21 consecutive days for ≥ 6 h/days with invasive (i.e., via endotracheal tube or tracheostomy) and/or noninvasive (i.e., facial/nasal interface) methods of delivery [5]. However, a great diversity exists in the definition of PMV in many published studies [6–10]. In most critical care and postoperative patient management-based studies, PMV has been variously defined as duration of mechanical ventilation of > 24 h [6], > 48 h [7], > 14 days [8], to as long as > 29 days [9], or as the need for mechanical ventilator support during post-ICU care [10].

Various studies have identified patient-related clinical factors that contribute to the development of PMV such as an excessive amount of red blood cells or fresh frozen plasma transfusion, low preoperative platelet count (i.e., < 10 × 10^9/L), elevated serum lactate level at the end of surgery, followed by the type of surgery such as coronary artery bypass graft, aortic dissection repair, open heart surgery, and, most importantly, liver transplantation surgery [5,11–15]. In particular, the extravascular lung water index and pulmonary vascular permeability index measured at the end of surgery have been validated as independent predictors of PMV in patients undergoing liver transplantation surgery [14]. However, in addition to traditional clinical predictor studies [5,11–15], genetic research focusing on candidate gene polymorphism is being widely conducted to develop a disease prediction model in various clinical situations [16–27].

Medford et al. [28] conducted a study on the development of acute respiratory distress syndrome (ARDS) in critical patients and showed the statistical correlation of the ARDS incidence with the genetic polymorphisms of vascular endothelial growth factor (VEGF). The study demonstrated higher incidence of ARDS with VEGF polymorphism to be responsible for the increase in microvascular permeability and worsening of clinical statuses of patients with ARDS. Kotsaki et al. [24] had identified the association of the early progression of ventilator-related pneumonia in intubated patients with the proof of less proinflammatory cytokine production followed by lipopolysaccharide stimulation in wild type patients, showing the role of single nucleotide polymorphisms (SNPs) within the promoter region of the tumor necrosis factor (TNF) gene for the susceptibility of the host to infection. Other studies had also identified the novel candidate genes in association with the development of acute lung injury and ARDS phenotypes, although the underlying mechanisms of pathogenesis associated with lung injury are still being answered [16,19,25,26].

The assessment of genetic polymorphisms responsible for a patient’s risk of requiring PMV is a challenging task. The early detection of the specific polymorphic genes associated with PMV in patients undergoing liver transplantation surgery could prove to be a useful tool or future biomarkers in postoperative patient management. Moreover, identifying the genetic polymorphisms in this patient population could aid in implementing a personalized treatment strategy for individual patients, based on individual frailty. Therefore, the aim of this study was to determine the perioperative risk factors that affect PMV occurrence after liver transplantation surgery. We particularly sought to investigate the role of candidate gene polymorphisms as independent predictors of PMV after liver transplantation surgery.

**Materials and Methods**

**Patients**

In this prospective observational study, we recruited patients between the ages of 20 years and 65 years who were scheduled to undergo living donor liver transplantation surgery. Study approval was obtained from the Institutional Review Board (no. 4-2014-0989) of Yonsei University Health System (Seoul, Korea). Written informed consent was obtained from 140 adult patients (January 2015–January 2018; ClinicalTrials.gov Identifier: NCT02402634). This clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. Patients undergoing mechanical ventilation before surgery, patients currently or previously diagnosed with respiratory disease, and patients with musculoskeletal disorders that may be accompanied by a decreased breathing ability were excluded. Preoperative neurologic evaluations were performed by neurologists, including evaluation for hepatic encephalopathy.

**Anesthesia protocols**

Anesthesia was inducted with propofol (1.5 mg/kg), sufentanyl (1 μg/kg), and rocuronium (0.6–0.8 mg/kg) for muscle relaxation. After endotracheal intubation, desflurane (6–8%) was adminis-
Mechanical ventilation weaning and extubation

All patients had been discharged to ICU and were administered mechanical ventilation for hemodynamic monitoring on the day of surgery. Chest radiography and arterial blood gas analysis were conducted at least twice daily to observe the initial changes closely. All recipients were ventilated by using a lung-protective ventilation strategy, which consisted of PEEP and low tidal volume (i.e., 6–8 ml/ideal body weight) with permissive hypercapnia. If a patient was hemodynamically stable and oxygenation had improved adequately (i.e., SpO\textsubscript{2} > 90%, FiO\textsubscript{2} ≤ 0.5, and PEEP ≤ 5 cmH\textsubscript{2}O), then mechanical ventilator weaning was attempted as soon as possible. All recipients underwent the 1-hour t-tube challenge test to assess the possibility of weaning success and to predict potential complications associated with spontaneous breathing trials.

Mechanical ventilation weaning and extubation for every patient were administered by the same intensive care team. The duration of mechanical ventilation after surgery was examined along with the length of ICU and hospital stay, 30-day mortality, and of which PMV was defined as mechanical ventilation for > 48 h.

Single nucleotide polymorphism selection and sample collection

Thirteen established candidate SNPs from 11 genes were selected, based on literature reviews on the genetic involvement in inflammatory-related pulmonary disease. They included rs581000 in the growth arrest and DNA damage inducible alpha (GADD45A) gene; rs18000896 of the interleukin-10 (IL10) gene; rs6721961 of the nuclear factor erythroid 2-related factor 2 (NFE2L2) gene; rs2241880 of the autophagy related 16 like 1 (ATG16L1) gene; rs4073 of the CXCL motif chemokine ligand (CXCL8) gene; rs909253 of the lymphotoxin alpha (LTA) gene; rs1799964 and rs1800629 of the TNF gene; rs8486 of the major histocompatibility complex, class II alpha 1 (HLA-DPA1) gene; rs3025039 of the VEGF A gene; rs1800796 of the interleukin-6 (IL6) gene; and rs187238 and rs1946518 of the interleukin-18 (IL18) gene [16–27].

Approximately 2 ml of fasting blood was collected after anesthetic induction prior to surgery from each participant and stored at –80°C. Genomic DNA was prepared from blood samples by using the QuickGene Whole DNA Blood Kit S (Kurabo, Japan), based on the manufacturer’s instructions. All SNPs were genotyped with a single base primer extension assay by using ABI PRISM SNPShot Multiplex kit (Applied Biosystems, USA), based on the instructions.

Statistical analysis

Statistical analyses were conducted using SPSS version 25.0 (IBM Corp., USA) and SAS software, version 9.1.3 (SAS Institute, Inc., USA). Testing for Hardy–Weinberg equilibrium and allelic association analyses were conducted using the Chi-square test or Fisher’s exact test. The association analyses of PMV with perioperative clinical factors and SNPs are presented with ORs and 95% CIs, using logistic regression models with Bonferroni correction, as appropriate. A value of P < 0.05 was statistically significant.

Results

Baseline characteristics

The baseline characteristics of 140 recipients are summarized in
Table 1. Twenty-six (19%) recipients continued to receive mechanical ventilation at 48 h after surgery, while 114 recipients were weaned from mechanical ventilation within 48 h after surgery. The mean age of the PMV group and non-PMV group was 53.5 ± 11.7 and 55.7 ± 8.4 yr, respectively. Statistically significant between-group differences existed in sex distribution (the female-to-male ratio of the PMV group and non-PMV group were 1.36 and 0.36, respectively with P = 0.002). The preoperative model for end-stage liver disease (MELD) score, presence of underlying diabetes, coagulopathy, intraoperative continuous renal replacement therapy (CRRT), and smoking status were also significantly different between the two groups: the MELD score, prevalence of coagulopathy, and use of intraoperative CRRT were higher in the PMV group, and the prevalence of underlying diabetes and smoking history was higher in the non-PMV group. Detailed differences of other perioperative parameters between the two groups were shown in Supplementary Table 1. However, no significant difference was observed with respect to the presence of congestive heart failure, chronic obstructive pulmonary disease, preoperative respiratory complications, and the duration of surgery.

SNP genotypes with PMV

Genotype frequency of all candidate SNPs were in Hardy-Weinberg equilibrium (P > 0.05) (Table 2). Significant differences in the genotype frequency of rs1800629 and rs8486 were noted between the PMV and non-PMV groups: the PMV group had a higher frequency of A and C alleles (P = 0.025 and P = 0.002, respectively) and a lower frequency of GG and TT genotypes in the rs1800629 and rs8486 polymorphisms (P = 0.045 and P = 0.004, respectively) (Supplementary Table 2).

Dominant, recessive, codominant, and allele models were adopted to evaluate the associations of the candidate gene polymorphisms with PMV, patient demographics, and perioperative data (Table 3). The stepwise logistic regression analysis revealed that a mutation at rs8486 in the HLA-DPA1 gene (OR: 8.060, 95% CI [1.451, 44.765], P = 0.017), the use of intraoperative CRRT (OR: 24.731, 95% CI [1.077, 567.915], P = 0.045), and the level of serum lactate in postoperative 24 h (OR: 3.008, 95% CI [1.497, 6.045], P = 0.002) were significantly associated with a higher risk for PMV (Table 4).

Discussion

We examined the association between candidate gene polymorphisms, related perioperative clinical factors, and the risk of PMV in liver transplantation recipients. Our results suggested that the application of intraoperative CRRT, an elevated serum lactate level during the postoperative period, and the minor allele of the rs8486 gene polymorphism in HLA-DPA1 were risk factors for the development of PMV in liver transplantation recipients. Previous studies [15,29] have also highlighted the high inci-
Table 2. The Overall Description and the Distribution of Alleles and Genotypes for Selected SNP

<table>
<thead>
<tr>
<th>rs number</th>
<th>Gene</th>
<th>Position</th>
<th>Allele frequency</th>
<th>Genotype frequency</th>
<th>HWE P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs581000</td>
<td>GADD45A</td>
<td>chr1: 68150271</td>
<td>G 167 (60.9) C 107 (39.1)</td>
<td>GG 52 (38.0) CG 63 (46.0) CC 22 (16.1)</td>
<td>0.721</td>
</tr>
<tr>
<td>rs4129267</td>
<td>IL6R</td>
<td>chr1: 154426264</td>
<td>T 141 (50.7) C 137 (49.3)</td>
<td>TT 35 (25.2) CT 71 (51.1) CC 33 (23.7)</td>
<td>0.869</td>
</tr>
<tr>
<td>rs2228145</td>
<td>IL6R</td>
<td>chr1: 154426970</td>
<td>G 141 (50.7) T 137 (49.3)</td>
<td>GG 35 (25.2) GT 71 (51.1) TT 33 (23.7)</td>
<td>0.869</td>
</tr>
<tr>
<td>rs1800896</td>
<td>IL10</td>
<td>chr1: 206946897</td>
<td>A 263 (93.9) G 17 (6.1)</td>
<td>AA 123 (87.9) AG 17 (12.1) GG 0</td>
<td>1.000</td>
</tr>
<tr>
<td>rs6721961</td>
<td>NFE2L2</td>
<td>chr2: 178130037</td>
<td>C 201 (71.8) A 79 (28.2)</td>
<td>CC 76 (54.3) AC 49 (35.0) AA 15 (10.7)</td>
<td>0.143</td>
</tr>
<tr>
<td>rs2241880</td>
<td>ATG16L1</td>
<td>chr2: 234183368</td>
<td>A 161 (57.9) G 117 (42.1)</td>
<td>AA 44 (31.7) AG 73 (52.5) GG 22 (15.8)</td>
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</tr>
<tr>
<td>rs4073</td>
<td>CXCL8</td>
<td>chr4: 74606024</td>
<td>T 78 (27.9) C 202 (72.1)</td>
<td>TT 75 (53.6) CT 50 (35.7) CC 15 (10.7)</td>
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</tr>
<tr>
<td>rs909253</td>
<td>NFE2L2</td>
<td>chr6: 31540313</td>
<td>A 161 (57.9) G 117 (42.1)</td>
<td>AA 44 (31.7) AG 73 (52.5) GG 22 (15.8)</td>
<td>0.152</td>
</tr>
<tr>
<td>rs1799964</td>
<td>TNF</td>
<td>chr6: 31542308</td>
<td>T 202 (72.7) C 76 (27.3)</td>
<td>TT 73 (52.5) CT 56 (40.3) CC 10 (7.2)</td>
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<tr>
<td>rs1800629</td>
<td>TNF</td>
<td>chr6: 31543031</td>
<td>G 262 (94.9) A 14 (5.1)</td>
<td>GG 125 (90.6) GA 12 (8.7) AA 1 (0.7)</td>
<td>0.294</td>
</tr>
<tr>
<td>rs8486</td>
<td>HLA-DPA1</td>
<td>chr6: 33065191</td>
<td>T 187 (66.8) C 93 (33.2)</td>
<td>TT 62 (44.3) CT 57 (40.7) CC 21 (15.0)</td>
<td>0.200</td>
</tr>
<tr>
<td>rs3025039</td>
<td>VEGF A</td>
<td>chr6: 43752536</td>
<td>C 228 (82.0) T 50 (18.0)</td>
<td>CC 93 (66.9) TT 42 (30.2) TT 4 (2.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>rs2097677</td>
<td>chr7: 22693220</td>
<td>G 205 (73.2) A 75 (26.8)</td>
<td>GG 78 (55.7) GA 49 (35.0) AA 13 (9.3)</td>
<td>0.204</td>
<td></td>
</tr>
<tr>
<td>rs1800796</td>
<td>IL6</td>
<td>chr7: 22766246</td>
<td>C 208 (74.8) G 70 (25.2)</td>
<td>CC 74 (53.2) CG 60 (43.2) GG 5 (3.6)</td>
<td>0.113</td>
</tr>
<tr>
<td>rs187238</td>
<td>IL18</td>
<td>chr11: 112034988</td>
<td>G 245 (88.1) C 33 (11.9)</td>
<td>GG 107 (77.0) GC 31 (22.3) CC 1 (0.7)</td>
<td>0.700</td>
</tr>
<tr>
<td>rs1946518</td>
<td>IL18</td>
<td>chr11: 112035458</td>
<td>C 139 (50.4) A 137 (49.6)</td>
<td>CC 32 (23.2) AC 75 (54.3) AA 31 (22.5)</td>
<td>0.393</td>
</tr>
</tbody>
</table>

Values are presented as the number (%). SNP: single nucleotide polymorphisms, HWE: Hardy–Weinberg equilibrium, GADD45A: growth arrest and DNA damage inducible alpha, IL: interleukin, NFE2L2: nuclear factor erythroid 2-related factor 2, ATG16L1: autophagy related 16 like 1, CXCL 8: C-X-motif C chemokine ligand 8, LTA: lymphotoxin alpha, TNF: tumor necrosis factor, HLA-DPA1: major histocompatibility complex, class II alpha 1, VEGF A: vascular endothelial growth factor A.

Table 3. Association Analyses between PMV and rs8486

<table>
<thead>
<tr>
<th>Variables</th>
<th>Genotype</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rs8486</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT vs. CT vs. CC</td>
<td>TT vs. CT + CC</td>
</tr>
<tr>
<td>Mechanical ventilation time &gt; 48 h</td>
<td>5 (19.2) 14 (53.9) 7 (26.9)</td>
<td>0.005 0.007 0.066</td>
</tr>
<tr>
<td>Mechanical ventilation time (h)</td>
<td>25.03 ± 7.43 62.98 ± 23.64 45.9 ± 13.43</td>
<td>0.245 0.033 0.065</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± SD. PMV: prolonged mechanical ventilation, h: hours.

https://doi.org/10.4097/kja.22014
Numerous studies have shown that the susceptibility of respiratory-related diseases is affected by polymorphisms in many genes, including GADD45A, IL-10, NFE2L2, TNF-α, VEGF A, IL-6, IL-18, and HLA-DPA1 [16,18,19,23–27]. The HLA region, located on chromosome 6, is characterized by high gene density, variability, and extensive linkage disequilibrium. The HLA region encodes hundreds of genes with an immunological function and proteins with critical roles in immunity such as antigen processing and presentation, and self-recognition by immune cells such as ligand receptors, cytokines, signaling factors, heat shock proteins, and transcription regulators. The HLA region is also involved in many biological processes such as histocompatibility, inflammation, ligands for immune cell receptors, and the complement cascade [32,33]. The role of HLA as an immune-inhibitory molecule has been investigated in the field of inflammatory conditions; neoplasms such as hematolymphoid neoplasms, visceral carcinomas, dermal-based neoplasms; and, recently, in the pathogenesis of respiratory syndrome outbreaks in coronavirus disease 2019 [34] for which a strong association has been demonstrated between HLA ligands and increased susceptibility to respiratory infection. In addition, the SNP rs8486 polymorphism has a functional consequence such as the 3’-UTR variant; therefore, genetic variation in the 3’-UTR variant can also affect gene expression that interferes with micro-RNA binding [35]. The result of minor allele of rs8486 gene polymorphism to be the risk factor for the develop-

Table 4. Univariate and Multivariate Logistic Regression Models for Liver Transplantation Recipients with PMV

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR [95% CI]</td>
<td>P value</td>
</tr>
<tr>
<td>rs8486 allele</td>
<td>2.58 [1.397, 4.762]</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Patient demographics

| Sex (M)            | 0.262 [0.108, 0.633] | 0.003 | 0.431 [0.049, 3.822] | 0.450 |
| Height             | 0.942 [0.894, 0.993] | 0.027 | 0.907 [0.799, 1.030] | 0.133 |
| MELD score         | 1.098 [1.043, 1.156] | < 0.001 | 1.129 [0.998, 1.277] | 0.053 |
| DM                 | 0.112 [0.015, 0.863] | 0.036 | 0.112 [0.009, 1.373] | 0.087 |
| Coagulopathy       | 3.175 [1.164, 8.657] | 0.024 | 0.338 [0.045, 2.546] | 0.292 |
| CRRT               | 13.333 [2.424, 73.335] | 0.003 | 24.731 [1.077, 567.915] | 0.045 |
| Smoking Hx         | 0.379 [0.158, 0.909] | 0.030 | 2.166 [0.366, 12.824] | 0.394 |

Perioperative data

| Transfused RBC (ml/kg/h) | 1.336 [1.123, 1.589] | 0.001 | 1.267 [0.802, 2.000] | 0.311 |
| Transfused FFP (ml/kg/h) | 2.631 [1.490, 4.646] | 0.001 | 3.352 [0.821, 13.679] | 0.092 |
| Transfused PLT (ml/kg/h) | 3.309 [1.354, 8.088] | 0.009 | 0.129 [0.016, 1.010] | 0.051 |
| Blood loss (ml/kg/h)     | 1.118 [1.027, 1.217] | 0.010 | 0.888 [0.709, 1.113] | 0.303 |
| Lactate 24 h             | 1.587 [1.114, 2.260] | 0.011 | 3.008 [1.497, 6.045] | 0.002 |
| Preoperative INR         | 2.306 [1.235, 4.305] | 0.009 | 0.687 [0.168, 2.805] | 0.601 |
| Preoperative Hct (%)     | 0.902 [0.830, 0.980] | 0.015 | 0.969 [0.849, 1.107] | 0.645 |

ment of PMV in liver transplantation recipients is in collusion with the likelihood of minor alleles to become risk alleles in the published genome wide association study on complex diseases [36]. However, functionality of such changes requires empirical confirmation in further studies.

Our study successfully demonstrated a significant relationship of rs8486 SNP encoding HLA-DPA1 with PMV and with the duration of mechanical ventilation after liver transplantation surgery. The candidate gene search was conducted using a published gene database and with a focus on respiratory-related infection and innate inflammatory-related genes. However, our patients’ data only showed a significant relationship with the sole HLA-DPA1 gene, along with clinical factors such as an elevated postoperative serum lactate level and intraoperative CRRT. SNP rs1800629, which encodes the traditional inflammatory cytokine TNF-α had a significant relationship before multivariate regression; however, it ultimately failed to show a correlation, along with clinical factors. A race-specific gene database search was conducted with the necessary statistical confirmation; however, the small number of patients may have limited the achievement of statistical significance in this study.

In addition to genetic factors, an elevated serum lactate level and the application of intraoperative CRRT had a significant effect on the occurrence of PMV. Serum lactate levels have especially been emphasized as a good predictor for delayed endotracheal extubation among liver transplantation recipients [37]. It has also been highlighted as a significant risk factor for increasing the postoperative risk of morbidity and mortality [38] and prolonging the length of hospital stay [39]. These findings are consistent with the findings of this study. Hyperlactatemia could be caused by the higher production and lower clearance of lactate because of a pathologic process such as decreased renal function and could result in the application of CRRT. The origin of hyperlactatemia after liver transplantation surgery can be multifactorial and includes primary nonfunction of the newly grafted liver, substantial surgical blood loss with hypoperfusion, high-dose vasopressor use, acute kidney injury and oliguria, and organ ischemia and reperfusion during surgical procedures [40,41]. Organ ischemia induced by lower perfusion and lower oxygen utilization during the anhepatic phase are associated with an elevated level of lactate into the systemic circulation because of decreased washout and subsequent metabolic acidosis during reperfusion. Such an imbalance of oxygen supply and organ consumption results in a poor patient outcome, including PMV. A previously published study has confirmed that longer ventilation time and the need for reintubation and tracheostomy were associated with postoperative hyperlactatemia after major surgery [39].

CRRT can be applied to patients with refractory renal dysfunction to manage uncontrolled metabolic acidosis, electrolyte imbalance, volume overload, and brain edema, accompanied by hemodynamic instability. Many institutions apply intraoperative CRRT for liver transplantation recipients with severe preoperative renal dysfunction to prevent critical uremic challenges and to facilitate fluid management during surgery. Its application is regarded as a successful management method during liver transplantation surgery [42,43]. Despite the clinical advantages of CRRT, underlying hemodynamic instability and decreased renal function of patients receiving CRRT make applying intraoperative CRRT as the prominent risk factor for morbidity, mortality, and other poor outcomes such as PMV in patients undergoing liver transplantation surgery. Previously published studies have likewise reported a greater number of patients who received CRRT in the PMV group posttransplant [15], and a higher risk of respiratory failure requiring intubation among critically ill patients who needed CRRT [44]. However, other renal-related factors such as the duration of CRRT, severity of underlying renal dysfunction, and modality of renal replacement therapy also have a role in postoperative mechanical ventilator care or intensive care; therefore, further in-depth analysis and study are required to clearly demonstrate the effect of CRRT on PMV.

A high MELD score and coagulopathy are also well-known risk factors for posttransplantation and postsurgery morbidity and mortality [45,46]. Such risk factors could contribute to the decreased diffusion capacities and could possibly affect the onset of respiratory complications and PMV among transplantation recipients [46,47]. With regard to coagulopathy, excessive fluid administration and positive fluid balance significantly lower respiratory compliance, which is highly suggestive of the occurrence of post-liver transplantation acute lung injury and severe ARDS caused by volume overload, massive blood transfusion, severe ischemia–reperfusion syndrome, and systemic infection [48].

A history of diabetes has an inconsistent effect on PMV. Such various results with less statistically significant finding are probably because of diverse confounding factors of diabetes such as the type and duration of diabetes, glycosylated hemoglobin (HbA1c) levels, type of medications, and the use of insulin. Patients diagnosed with diabetes in our group had a median (Q1, Q3) duration of diabetes of 7 (2, 10) years. Each patient had regularly taken an antidiabetic medication with an average HbA1c level of 6.5 ± 1.4%. Such differences in the patient population could have resulted in the discrepancy toward PMV and respiratory complications reported in other previously published studies [21,49]. The same explanation could be adopted for smoking history in that non-smoking patients were more often in the PMV group.

https://doi.org/10.4097/kja.22014
The current study had several limitations. First, the small sample size and the homogeneity of the study group limit in-depth subgroup analysis and applying the results universally to different ethnic groups. However, various genetic studies are actively being conducted that especially target Caucasians. Therefore, we believe that genetic information focusing on Asian populations is also significant in the field of patient management. Moreover, further studies with a larger sample size are needed to verify the findings, along with in-depth statistical approach to show the diagnostic probabilities.

Second, novel technologies are being rapidly introduced in the field of genetic studies; therefore, more affluent genomic information could have been obtained by means of genome-wide studies using genotyping arrays or exome whole genome sequencing. However, these latest technologies have the limitations of high costs and statistical burden.

This study identified the rs8486 polymorphism in HLA-DPA1 as a gene associated with PMV in liver transplantation recipients, as were intraoperative CRRT application, and an elevated lactate level during the postoperative period.

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Conflicts of Interest

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

Author Contributions

Eun Jung Kim (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Visualization; Writing – original draft; Writing – review & editing)
Min-Soo Kim (Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Validation; Writing – review & editing)
Myoung Soo Kim (Data curation; Supervision; Writing – review & editing)
Junhyun Nam (Data curation; Methodology; Writing – review & editing)
Seung Ho Choi (Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. Perioperative findings of the liver transplantation recipients
Supplementary Table 2. Single nucleotide polymorphism genotypes in the PMV and non-PMV groups

ORCID

Eun Jung Kim, https://orcid.org/0000-0002-5693-1336
Min-Soo Kim, https://orcid.org/0000-0001-8760-4568
Myoung Soo Kim, https://orcid.org/0000-0002-8975-8381
Junhyun Nam, https://orcid.org/0000-0001-7646-2672
Seung Ho Choi, https://orcid.org/0000-0001-8442-4406

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Epidemiologic study of epidural analgesia for lung cancer surgery from 2011 to 2018 in South Korea: a National Health Insurance Database cohort study

Tak Kyu Oh¹,², In-Ae Song¹

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

Background: Epidural analgesia is commonly used for pain control during lung cancer surgery. However, the clinical trends in epidural analgesia, associated factors, and their association with clinical outcomes remain controversial. Therefore, we aimed to investigate the trends, associated factors, and their association with the clinical outcomes of epidural analgesia for lung cancer surgery.

Methods: The National Health Insurance Database was used as the data source in a nationwide cohort study. All adult patients who underwent lung cancer surgery between 2011 and 2018 were included.

Results: A total of 60,031 adult patients who underwent surgery for lung cancer were included. Of these, a total of 24,786 patients (41.3%) received epidural analgesia with a mean value of 1.5 days (standard deviation: 2.0 days). Male sex, increased Charlson comorbidity index (CCI), concurrent musculoskeletal disease, and a wider surgical extent were associated with higher odds of epidural analgesia for lung cancer surgery. Compared to open thoracotomy, video-assisted thoracoscopic surgery (VATS) was associated with lower odds of epidural analgesia for lung cancer surgery. Moreover, epidural analgesia was not associated with 30-day mortality, fatal respiratory events, or one-year mortality after lung cancer surgery.

Conclusions: From 2011 to 2018, 41.3% of patients with lung cancer in South Korea received epidural analgesia for lung cancer surgery. Some factors (male sex, increased CCI, concurrent musculoskeletal disease, wider surgical extent, and VATS) were associated with the use of epidural analgesia in lung cancer surgery. However, epidural analgesia was not associated with clinical outcomes after lung cancer surgery.

Keywords: Analgesia; Cohort studies; Epidemiology; Lung neoplasms; Pain management; Population; Postoperative pain; Thoracic surgery.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide [1]. According to global cancer statistics from 185 countries in 2020 [2], 2,206,771 individuals were newly diagnosed with lung cancer, and 1,796,144 patients died due to lung cancer in 2020. As the global incidence, death, and economic burden of lung cancer have increased [3], effective management of lung cancer remains a significant public health issue.

For the treatment of lung cancer, surgical procedures are first considered with curative
Epidural analgesia for lung surgery

Materials and Methods

Study design and ethical statement

The study protocol was approved by the Institutional Review Board (IRB) (IRB approval number: X-2008-630-902). The National Health Insurance Scheme (NHIS) approved the data sharing protocol for this study (NHIS approval number: NHIS-2021-1-041). The requirement for informed consent was waived by the IRB because the data were analyzed retrospectively in an anonymous form after masking the individual and sensitive information of the study population.

Data source and study population

The NHIS database was used as the national registration database. The NHIS database contains all disease diagnoses and prescription information regarding the procedures and/or drugs in South Korea. The government supports financial expenses for treatment or medical examinations after registration of disease diagnoses and prescriptions. Moreover, the NHIS database contains demographic and socio-economic information of the South Korean population. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes is used to register any disease in the NHIS database.

This study included all adult patients (≥18 years old) who were diagnosed with lung cancer (C34 of ICD-10 code) and underwent lung cancer surgery between January 1, 2011, and December 31, 2018, in South Korea. In South Korea, the government covers almost all expenses (approximately 95%) involved in the treatment and examination of lung cancer after the registration of ICD-10 codes (C34); thus, all patients with lung cancer who underwent lung cancer surgery were included in the NHIS database.

Epidural analgesia for lung cancer surgery

As the main independent variable, information on the administration of epidural analgesia during lung cancer surgery for pain control was collected. The prescription code for epidural patient-controlled analgesia (PCA) was used to extract data. Patients who received epidural PCA after lung cancer surgery were considered the epidural analgesia group, and the other patients were considered the control group.

Study outcomes

First, the proportion of patients who received epidural analgesia from 2011 to 2018 after lung cancer surgery was examined. Second, the factors associated with epidural analgesia in patients who underwent lung cancer surgery were examined. Third, the association of epidural analgesia with 30-day mortality, development of fatal respiratory events, and one-year mortality after lung cancer surgery was investigated. A fatal respiratory event was defined as a diagnosis of acute respiratory distress syndrome (ARDS) (J80 of ICD-10 code) or respiratory failure (J96 of ICD-10 code) during hospitalization following lung cancer surgery.

Collected variables

Age and sex were collected as demographic information. To reflect socioeconomic status, household income level, employment status, and residence locality at the time of lung cancer surgery were collected. The annual household income level in South Korea is registered by considering the individual’s annual income and property to determine their insurance premium. All patients were divided into four groups based on the quartile ratio of the household income level. Employment status did not include self-employed people, and all patients were divided into two groups according to their residence: urban areas (capital or other metropolitan cities) and rural areas (all other areas). For sur-


gery-related information, the type of surgery, use of VATS or open thoracotomy, and a redo-case of surgery were collected for this study. Surgery type was divided into five groups: wedge resection, segmentectomy, lobectomy, bilobectomy, and pneumonectomy. If a patient underwent wedge resection in addition to segmentectomy, the patient was included in the segmentectomy group, whereas a patient who underwent segmentectomy in addition to lobectomy was included in the lobectomy group. As a high case volume was strongly associated with improved survival outcomes after lung cancer surgery [12], the annual number of lung cancer surgery cases in each hospital in South Korea was calculated. The patients were then divided into four groups using quartile ratios, based on the case load of the hospital in which the lung cancer surgery was performed (Q1: ≤ 74, Q2: 75– 276, Q3: 277–921, and Q4: ≥ 922). In addition, all patients were divided into two groups according to the hospital in which the lung cancer surgery was performed: a tertiary general hospital group and a general hospital group. The total cost of hospitalization (United States Dollar [USD]) and length of hospital stay (days) were recorded. For comorbid stats related information, the Charlson comorbidity index (CCI) at the time of lung cancer surgery was calculated using the ICD-10 codes of individual diseases (Supplementary Table 1), which were registered within one year before the date of the lung cancer surgery. Concurrent musculoskeletal disease (M* of ICD-10 code) and preoperative chronic analgesic (opioid, paracetamol, non-steroidal anti-inflammatory drugs, gabapentin, or pregabalin) use (≥ 90 days) were collected as covariates. In addition, the underlying disability before lung cancer surgery was collected because all individuals with any disability should be registered in the NHIS database to receive various benefits from the social welfare system in South Korea. The disabilities were divided into six grades based on severity (grade 1, most severe; grade 6, mildest). Patients with grades 1, 2, or 3 constituted the severe disability group, while those with grades 4, 5, or 6 constituted the mild-to-moderate disability group.

Statistical analysis

The clinicopathological characteristics of all patients are presented as mean values with standard deviations (SDs) for continuous variables and numbers with percentages for categorical variables. For comparison of clinicopathological characteristics between the epidural analgesia and control groups, t-test and chi-square test were used. Next, we constructed a multivariable logistic regression model to examine the factors associated with epidural analgesia. All variables were included in the multivariable model for adjustment, and the Hosmer–Lemeshow test was used to confirm if the goodness of fit in the model was appropriate.

For secondary analyses, multivariable logistic models were constructed to investigate whether epidural analgesia was associated with 30-day mortality or development of fatal respiratory events after lung cancer surgery. We also fitted a multivariable Cox regression model to examine whether epidural analgesia was associated with the one-year mortality risk after lung cancer surgery. The results of logistic regression were presented as odds ratios (ORs) with 95% CIs, whereas those of Cox regression were presented as hazard ratios (HRs) with 95% CIs. There was no multicollinearity between the variables in the model with variance inflation factors < 2.0. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., USA) and R software (version 3.6.2; R Foundation for Statistical Computing, Austria). Statistical significance was set at P < 0.05.

Results

Study population

A total of 60,031 adult patients who were diagnosed with lung cancer and underwent lung cancer surgery between January 1, 2011, and December 31, 2018, were included in the analysis. Clinicopathological characteristics of the patients are shown in Table 1. The mean age of the patients was 65.6 years (SD: 9.9 years), and 61.3% (36,778/60,031) were men. The epidural analgesia group included 24,786 patients (41.3%), and they received epidural analgesia for a mean duration of 1.5 days (SD: 2.0 days).

Trend of epidural analgesia for lung cancer surgery in South Korea

Fig. 1 shows the trends in epidural analgesia use for lung cancer surgery in South Korea. In 2011, 45.2% (2,477/5,479) of patients received epidural analgesia, which gradually increased until 2016 (64.7%, 5,406/8,360). However, the proportion of epidural analgesics decreased by 20.8% (1,889/9,076) in 2017 and 12.0% (1,198/9,959) in 2018. Table 2 shows the results of the comparison of clinicopathological characteristics between the epidural analgesia and control groups. The epidural analgesia group had a higher proportion of lobectomy (17,055/24,786; 68.8% vs. 23,733/35,245; 67.3%), bilobectomy (972/24,786; 3.9% vs. 985/35,245; 2.8%), and pneumonectomy (928/24,786; 3.7% vs. 828/35,245; 2.3%) than the control group (P < 0.001).

https://doi.org/10.4097/kja.22089
Table 1. Clinicopathological Characteristics of the Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.6 ± 9.9</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>36,778 (61.3)</td>
</tr>
<tr>
<td>Household income level</td>
<td></td>
</tr>
<tr>
<td>Q1 (lowest)</td>
<td>12,207 (20.3)</td>
</tr>
<tr>
<td>Q2</td>
<td>9,149 (15.2)</td>
</tr>
<tr>
<td>Q3</td>
<td>13,361 (22.3)</td>
</tr>
<tr>
<td>Q4 (highest)</td>
<td>24,057 (40.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1,257 (2.1)</td>
</tr>
<tr>
<td>Having a job at surgery</td>
<td>37,808 (63.0)</td>
</tr>
<tr>
<td>Residence at surgery</td>
<td></td>
</tr>
<tr>
<td>Urban area</td>
<td>23,803 (39.7)</td>
</tr>
<tr>
<td>Rural area</td>
<td>36,228 (60.3)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Wedge resection</td>
<td>11,489 (19.1)</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>4,041 (6.7)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>40,788 (67.9)</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>1,957 (3.3)</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>1,756 (2.9)</td>
</tr>
<tr>
<td>VATS</td>
<td>48,888 (81.4)</td>
</tr>
<tr>
<td>CCI at surgery</td>
<td>6.2 ± 3.0</td>
</tr>
<tr>
<td>Concurrent musculoskeletal disease</td>
<td>4,532 (7.5)</td>
</tr>
<tr>
<td>Preoperative chronic analgesics use</td>
<td></td>
</tr>
<tr>
<td>Opioid</td>
<td>3,291 (5.5)</td>
</tr>
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<td>Paracetamol</td>
<td>236 (0.4)</td>
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<tr>
<td>NSAIDs</td>
<td>220 (0.4)</td>
</tr>
<tr>
<td>Gabapentin or pregabalin</td>
<td>1,725 (2.9)</td>
</tr>
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<td>Having a disability at surgery</td>
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</tr>
<tr>
<td>Mild to moderate</td>
<td>5,433 (9.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>1,784 (3.0)</td>
</tr>
<tr>
<td>Redo case</td>
<td>2,786 (4.6)</td>
</tr>
<tr>
<td>Annual case volume of lung cancer surgery</td>
<td></td>
</tr>
<tr>
<td>Q1: ≤ 74</td>
<td>15,108 (25.2)</td>
</tr>
<tr>
<td>Q2: 75–276</td>
<td>13,807 (23.0)</td>
</tr>
<tr>
<td>Q3: 277–921</td>
<td>14,868 (24.8)</td>
</tr>
<tr>
<td>Q4: ≥ 922</td>
<td>16,248 (27.1)</td>
</tr>
<tr>
<td>Type of hospital</td>
<td></td>
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<tr>
<td>Tertiary general hospital</td>
<td>46,648 (77.7)</td>
</tr>
<tr>
<td>General hospital</td>
<td>13,383 (22.3)</td>
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<tr>
<td>Duration of epidural analgesia, day</td>
<td>1.5 ± 2.0</td>
</tr>
<tr>
<td>Fatal respiratory event</td>
<td>285 (0.5)</td>
</tr>
<tr>
<td>Postoperative ARDS</td>
<td>156 (0.3)</td>
</tr>
<tr>
<td>Postoperative respiratory failure</td>
<td>135 (0.2)</td>
</tr>
<tr>
<td>Total cost for hospitalization (USD)</td>
<td>8,890.5 ± 4,334.4</td>
</tr>
<tr>
<td>LOS (day)</td>
<td>11.6 ± 7.9</td>
</tr>
<tr>
<td>Postoperative 30-day mortality</td>
<td>446 (0.7)</td>
</tr>
<tr>
<td>Postoperative one-year mortality</td>
<td>4,407 (7.3)</td>
</tr>
<tr>
<td>Year of surgery</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>5,479 (9.1)</td>
</tr>
<tr>
<td>2012</td>
<td>6,164 (10.3)</td>
</tr>
<tr>
<td>2013</td>
<td>6,640 (11.1)</td>
</tr>
<tr>
<td>2014</td>
<td>7,050 (11.7)</td>
</tr>
<tr>
<td>2015</td>
<td>7,303 (12.2)</td>
</tr>
<tr>
<td>2016</td>
<td>8,260 (13.9)</td>
</tr>
<tr>
<td>2017</td>
<td>9,076 (15.1)</td>
</tr>
<tr>
<td>2018</td>
<td>9,959 (16.6)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). VATS: video-assisted thoracoscopic surgery, CCI: Charlson comorbidity index, NSAIDs: non-steroidal anti-inflammatory drugs, ARDS: acute respiratory distress syndrome, USD: United States dollars, LOS: length of hospital stays.

**Fig. 1.** The trends of epidural analgesia for lung cancer surgery from 2011 through 2018 in South Korea.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Epidural analgesia (n = 24,786)</th>
<th>Control group (n = 35,245)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.7 ± 9.8</td>
<td>65.6 ± 10.0</td>
<td>0.034</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>15,885 (64.1)</td>
<td>20,893 (59.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Household income level</td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Q1 (lowest)</td>
<td>5,118 (20.6)</td>
<td>7,089 (20.1)</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>3,857 (15.6)</td>
<td>5,292 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>5,566 (22.5)</td>
<td>7,795 (22.1)</td>
<td></td>
</tr>
<tr>
<td>Q4 (highest)</td>
<td>9,713 (39.2)</td>
<td>14,344 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>532 (2.1)</td>
<td>725 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Having a job at surgery</td>
<td>15,297 (61.7)</td>
<td>22,511 (63.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Residence at surgery</td>
<td></td>
<td></td>
<td>0.145</td>
</tr>
<tr>
<td>Urban area</td>
<td>9,914 (40.0)</td>
<td>13,889 (39.4)</td>
<td></td>
</tr>
<tr>
<td>Rural area</td>
<td>14,872 (60.0)</td>
<td>21,356 (60.6)</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Wedge resection</td>
<td>4,336 (17.5)</td>
<td>7,153 (20.3)</td>
<td></td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>1,495 (6.0)</td>
<td>2,546 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>17,055 (68.8)</td>
<td>23,733 (67.3)</td>
<td></td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>972 (3.9)</td>
<td>985 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>928 (3.7)</td>
<td>828 (2.3)</td>
<td></td>
</tr>
<tr>
<td>VATS</td>
<td>1,8948 (76.4)</td>
<td>29,940 (84.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CCI at surgery</td>
<td>6.5 ± 3.1</td>
<td>5.9 ± 3.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Concurrent musculoskeletal disease</td>
<td>2,116 (8.5)</td>
<td>2,416 (6.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preoperative chronic analgesics use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid</td>
<td>1,407 (5.7)</td>
<td>1,884 (5.3)</td>
<td>0.079</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>84 (0.3)</td>
<td>152 (0.4)</td>
<td>0.075</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>74 (0.3)</td>
<td>146 (0.4)</td>
<td>0.021</td>
</tr>
<tr>
<td>Gabapentin or pregabalin</td>
<td>665 (2.7)</td>
<td>1,060 (3.0)</td>
<td>0.019</td>
</tr>
<tr>
<td>Having a disability at surgery</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td>2,375 (9.6)</td>
<td>3,058 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>790 (3.2)</td>
<td>994 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Redo case</td>
<td>996 (4.0)</td>
<td>1,790 (5.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Annual case volume of lung cancer surgery</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Q1: ≤ 74</td>
<td>7,257 (29.3)</td>
<td>7,851 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Q2: 75–276</td>
<td>5,743 (23.2)</td>
<td>8,065 (22.9)</td>
<td></td>
</tr>
<tr>
<td>Q3: 277–921</td>
<td>5,799 (23.4)</td>
<td>9,069 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Q4: ≥ 922</td>
<td>5,988 (24.2)</td>
<td>10,260 (29.1)</td>
<td></td>
</tr>
<tr>
<td>Type of hospital</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tertiary general hospital</td>
<td>20,236 (81.6)</td>
<td>26,412 (74.9)</td>
<td></td>
</tr>
<tr>
<td>General hospital</td>
<td>4,550 (18.4)</td>
<td>8,833 (25.1)</td>
<td></td>
</tr>
<tr>
<td>Fatal respiratory event</td>
<td>140 (0.6)</td>
<td>145 (0.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Total cost for hospitalization (USD)</td>
<td>8,981.7 ± 4,718.2</td>
<td>8,826.3 ± 4,041.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LOS (day)</td>
<td>12.5 ± 8.7</td>
<td>11.0 ± 7.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Postoperative 30 days mortality</td>
<td>218 (0.9)</td>
<td>228 (0.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Year of surgery</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2011</td>
<td>2,477 (10.0)</td>
<td>3,002 (8.5)</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>2,976 (12.0)</td>
<td>3,188 (9.0)</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>3,181 (12.8)</td>
<td>3,459 (9.8)</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>3,696 (14.9)</td>
<td>3,354 (9.5)</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>3,963 (16.0)</td>
<td>3,340 (9.5)</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>5,406 (21.8)</td>
<td>2,954 (8.4)</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>1,889 (7.6)</td>
<td>7,187 (20.4)</td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>1,198 (4.8)</td>
<td>8,761 (24.9)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). VATS: video-assisted thoracoscopic surgery, CCI: Charlson comorbidity index, NSAIDs: non-steroidal anti-inflammatory drugs, USD: United States dollars, LOS: length of hospital stays.
Associated factors with application of epidural analgesia

Table 3 shows the results of the multivariate logistic regression model for the application of epidural analgesia. Male sex (OR: 1.17, 95% CI [1.12, 1.21], P < 0.001), increased CCI (OR: 1.06, 95% CI [1.06, 1.07], P < 0.001), and concurrent musculoskeletal disease (OR: 1.46, 95% CI [1.36, 1.57], P < 0.001) were associated with higher odds of epidural analgesia for lung cancer surgery. Compared to wedge resection, segmentectomy (OR: 1.13, 95% CI [1.04, 1.23], P = 0.003), lobectomy (OR: 1.21, 95% CI [1.16, 1.27], P < 0.001), bilobectomy (OR: 1.52, 95% CI [1.37, 1.69], P < 0.001), and pneumonectomy (OR: 1.68, 95% CI [1.50, 1.88], P < 0.001) were associated with higher odds of epidural analgesia for lung cancer surgery. Compared to open thoracotomy, VATS was associated with lower odds of epidural analgesia for lung cancer surgery (OR: 0.73, 95% CI [0.70, 0.77], P < 0.001).

Thirty-day mortality, fatal respiratory event, and one-year mortality

Table 4 shows the results of the analyses regarding 30-day mortality, fatal respiratory events, and one-year mortality associated with epidural analgesia for lung cancer surgery. The epidural analgesia group showed no significant difference in the odds of 30-day mortality (OR: 1.07, 95% CI [0.87, 1.32], P = 0.522), fatal respiratory events (OR: 1.12, 95% CI [0.87, 1.45], P = 0.388), and one-year mortality risk (HR: 1.01, 95% CI [0.94, 1.07], P = 0.840). However, epidural analgesia might influence the management of acute and chronic pain control and patient satisfaction following lung cancer surgery. Unfortunately, these details are not available in the NHIS dataset.

Discussion

According to the results of this population-based cohort study in South Korea, 41.3% patients received epidural analgesia for lung cancer surgery. Even though there has been a recent decreased rate of epidural analgesia with the increase of VATS, our study suggested that epidural analgesia might still be a good option in case of increased CCI, concurrent musculoskeletal disease, and wider surgical extent. Moreover, clinical outcomes were assessed, such as 30-day mortality, fatal respiratory events, and one-year mortality.

The most clinically relevant points in this study were the associated factors for the application of epidural analgesia because it reflects the favoring of epidural analgesia among anesthesiologists and surgeons for pain control of lung cancer surgery using re-
Table 4. Analyses regarding 30-day Mortality, Fatal Respiratory Events, and One-year Mortality Associated with Epidural Analgesia for Lung Cancer Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR, HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality (model 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epidural analgesia group</td>
<td>1.07 (0.87, 1.32)</td>
<td>0.522</td>
</tr>
<tr>
<td>Fatal respiratory event (model 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epidural analgesia group</td>
<td>1.12 (0.87, 1.45)</td>
<td>0.388</td>
</tr>
<tr>
<td>One-year mortality (model 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epidural analgesia group</td>
<td>1.01 (0.94, 1.07)</td>
<td>0.840</td>
</tr>
</tbody>
</table>

All covariates were adjusted. OR: odds ratio, HR: hazard ratio.

al-world data. Although the risks and benefits of thoracic epidural analgesia for pain control have been documented [13], there was insufficient information on the cases in which epidural analgesia was frequently performed for pain control of lung cancer surgery. Moreover, we also showed that epidural analgesia might not affect important clinical outcomes after lung cancer surgery such as 30-day mortality, fatal respiratory events, and one-year mortality. This is the first study to describe the factors associated with the use of epidural analgesia for lung cancer surgery using real-world data based on a national registration database.

The efficacy of epidural analgesia in lung cancer surgery remains controversial [14]. As the thoracic epidural technique is a high-risk procedure that may cause dural puncture, epidural hematoma, or nerve damage [15], IV analgesia has been used for postoperative pain control in VATS as a less invasive technique. Kim et al. [16] reported that IV and epidural analgesia are equally effective for pain control in VATS lobectomy. Moreover, paravertebral block could be used instead of epidural analgesia for effective pain control in VATS lobectomy. In South Korea, the proportion of VATS among lung cancer surgeries has increased from 64.5% (3,535/5,479) in 2011 to 91.4% (9,106/9,959) in 2018 (Supplementary Fig. 1). The increasing trend of VATS in South Korea may have affected the decrease in epidural analgesia since 2016.

A wider surgical extent, such as pneumonectomy, bilobectomy, and lobectomy, might affect the preference for epidural analgesia in South Korea. In addition to postoperative pain control, epidural analgesia protects against pneumonia after lung cancer surgery [18]. Pneumonectomy for lung cancer is a high-risk procedure, and epidural analgesia lowers the risk of respiratory complications after pneumonectomy [19]. Thus, the anesthesiologists and thoracic surgeons used epidural analgesia for lobectomy, bilobectomy, and pneumonectomy more than for wedge resection and segmentectomy. Similarly, increased CCI with comorbid status might affect the clinician’s preference for epidural analgesia because patients with many underlying diseases have a high risk of pneumonia after lung cancer surgery [20]. Therefore, patients with lung cancer in addition to many other underlying diseases need epidural analgesia to prevent pneumonia after lung cancer surgery.

Importantly, epidural analgesia was not associated with clinical outcomes after lung cancer surgery, such as 30-day mortality, fatal respiratory events, or one-year mortality. This is a clinically important result because epidural analgesia is known to reduce pulmonary complications after lung cancer surgery [19,20]. A retrospective cohort study from a single medical center in Taiwan reported that thoracic epidural analgesia was not associated with better recurrence-free or overall survival in patients who underwent lung cancer surgery [21]. Moreover, in a recent randomized trial by Xu et al. [22] epidural analgesia did not improve overall, recurrence-free, or cancer-specific survival after major lung cancer surgery. In addition to the previous reports [21,22], the present epidemiological study conducted in South Korea also showed that the impact of epidural analgesia on clinical outcomes after lung cancer surgery was not significant.

This study had several limitations. First, preoperative lung function was not evaluated because of a lack of data in the NHIS database. For example, the forced expiratory volume per second was not used in this study. Second, lifestyle factors, such as alcohol consumption and smoking history, were not evaluated due to a lack of data sources. Third, the tumor stage of lung cancer was not provided in this study, which could have affected the use of epidural anesthesia and mortality after lung cancer surgery. Finally, generalizability might be limited because medical and insurance systems differ according to the country. For example, patients with lung cancer in South Korea had to pay approximately 5% of the total treatment expense, including epidural analgesia, due to financial support from the NHIS.

In conclusion, from 2011 to 2018, 41.3% of patients with lung cancer in South Korea received epidural analgesia for lung cancer surgery. Some factors (male sex, increased CCI, concurrent musculoskeletal disease, wider surgical extent, and VATS) were associated with the use of epidural analgesia in lung cancer surgery. Moreover, epidural analgesia was not associated with clinical outcomes (30-day mortality, fatal respiratory events, or one-year mortality) after lung cancer surgery. However, considering the limitations of this study, it is not clearly known if the effect could be similar to that of epidural analgesia if appropriate pain control is performed in patients who did not receive epidural analgesia. Therefore, future study is needed for evaluating the effect of epidural analgesia on clinical outcomes after lung cancer surgery.
Funding

None.

Conflicts of Interest

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

Author Contributions

Tak Kyu Oh (Conceptualization; Data curation; Formal analysis; Writing – original draft)
In-Ae Song (Conceptualization; Methodology; Project administration; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. The ICD-10 codes
Supplementary Fig. 1. The trends of VATS from 2011 through 2018 in South Korea

ORCID

Tak Kyu Oh, https://orcid.org/0000-0002-4027-4423
In-Ae Song, https://orcid.org/0000-0002-7814-4253

References


Prognostic value of left ventricular apical four-chamber longitudinal strain after heart valve surgery in real-world practice

Jae-Sik Nam, Ji-Hyun Chin, Hyun-Uk Kang, Juyoun Kim, Kyoung-Woon Joung, In-Cheol Choi

Department of Anesthesiology and Pain Medicine, Laboratory for Perioperative Outcomes Analysis and Research, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Left ventricular longitudinal strain is an emerging marker of ventricular systolic function. However, the prognostic value of apical four-chamber longitudinal strain after heart valve surgery in real-world clinical practice is uncertain. The authors investigated whether left ventricular apical four-chamber longitudinal strain measured in real-world practice is helpful for predicting postoperative outcomes in patients undergoing heart valve surgery.

Methods: This observational cohort study was conducted in patients who underwent heart valve surgery between January 2014 and December 2018 at a tertiary hospital in South Korea. The exposure of interest was preoperative left ventricular apical four-chamber longitudinal strain. The primary outcome was postoperative all-cause mortality.

Results: Among 1,773 study patients (median age, 63 years; female, 45.9%), 132 (7.4%) died during a median follow-up of 27.2 months. Preoperative left ventricular apical four-chamber longitudinal strain was significantly associated with all-cause mortality (adjusted hazard ratio, 0.94 per 1% increment in absolute value; 95% CI [0.90, 0.99], P = 0.022), whereas left ventricular ejection fraction (LVEF) was not significantly associated with all-cause mortality (adjusted hazard ratio: 1.01, 95% CI [0.99, 1.03], P = 0.222). Moreover, combining left ventricular apical four-chamber longitudinal strain to the LVEF and conventional prognostic factors enhance the prognostic model for all-cause mortality (P = 0.022).

Conclusions: In patients undergoing heart valve surgery without coronary artery disease, left ventricular apical four-chamber longitudinal strain measured in real-world clinical practice was independently associated with postoperative survival. Left ventricular longitudinal strain measurement may be helpful for outcome prediction after valve surgery.

Keywords: Cardiac surgery; Echocardiography; Heart valve diseases; Morbidity; Mortality; Strain.

Introduction

In patients with advanced valvular heart disease, surgical treatment is one of the key management options. However, considering that cardiac surgery entails substantial operative risks, accurate prediction of both the risks and benefits of surgery in each patient is crucial. Evaluating the left ventricular systolic function carries a vital role in making treatment decisions; specifically, left ventricular ejection fraction (LVEF) has been a cor-
nerstone in determining surgical intervention and risk prediction [1–4].

Left ventricular longitudinal strain has recently gained interest as a marker of left ventricular systolic function. Strain is a mechanical term representing the degree of deformation relative to the material’s reference length; accordingly, left ventricular longitudinal strain directly reflects longitudinal myocardial shortening during a cardiac cycle. Recently, left ventricular longitudinal strain has shown significant prognostic value in a variety of cardiac diseases, such as heart failure [5,6], acute myocardial infarction [7], and cardiomyopathy [8].

In terms of valvular surgery, several studies have shown that left ventricular longitudinal strain was independently associated with long-term postoperative survival [9,10]. However, as previous studies were exclusively conducted in patients with mitral regurgitation (MR), the prognostic value of left ventricular longitudinal strain in patients with other types of heart conditions is less clear. Furthermore, strain analyses in previous studies [9,10] were performed post-hoc using stored echocardiography data for research purposes. Hence, it is unclear whether left ventricular longitudinal strain can confer significant incremental prognostic values over conventional risk factors in real-world clinical settings. In addition, while the above-mentioned studies used global left ventricular longitudinal strain, several reports have demonstrated the feasibility and reliability of left ventricular apical four-chamber longitudinal strain [11,12].

Thus, we investigated whether left ventricular apical four-chamber longitudinal strain measured in clinical practice can be helpful for predicting postoperative survival in patients with various types of valvular heart diseases including MR. We also examined the predictive value of left ventricular longitudinal strain for postoperative complications.

Materials and Methods

Design and participants

This observational cohort study was conducted at a tertiary hospital (Asan Medical Center) in South Korea. All patients who underwent heart valve surgery at our institution between January 2014 and December 2018 were screened for eligibility. We excluded patients under 20 years of age, those who underwent urgent or emergent surgery, and those who underwent combined coronary artery bypass surgery. Patients who did not undergo left ventricular longitudinal strain analysis preoperatively were also excluded.

The Institutional Review Board (AMC IRB no. 2020–1630) approved the study protocol and waived the need for informed consent considering the retrospective nature of the study. Clinical data of the study population was collected from the electronic medical record and institutional echocardiography database. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [13].

Echocardiography and strain analysis

All candidates for heart valve surgery were preoperatively evaluated with transthoracic echocardiography using standard machines and techniques in accordance with the American Society of Echocardiography guidelines [14]. At our institution, the incorporation of left ventricular longitudinal strain measurement as a part of transthoracic echocardiography began in late 2013. This new policy encouraged the provision of formal left ventricular longitudinal strain reporting. In the initial phase of the left ventricular longitudinal strain reporting, speckle tracking analysis was performed with EchoPAC (GE Healthcare, USA) or QLAB (Philips Healthcare, The Netherlands) according to the availability of ultrasound machines. Afterward, they have been replaced by a vendor-independent software, Image-Arena™ (TomTec, Germany) since 2015. In this transitional phase, only the apical four-chamber longitudinal strain was measured and reported, thus highlighting the expansion of strain reporting against resource limitation. Strain measurements were performed by experienced sonographers. After acquiring an adequate apical four-chamber view, the region of interest is automatically traced by strain software. Endocardial border tracing was manually adjusted if appropriate. A four-chamber strain curve throughout the cardiac cycle was derived and peak longitudinal strain value was calculated from the average of the six segments. This strain reporting policy was phased in over six years, and the final strain analysis implementation with global longitudinal strain was adopted in 2020; however, the data acquired in the final phase was not included in this study.

Study exposure and outcomes

The primary exposure of this study was left ventricular four-chamber longitudinal strain measured from the last echocardiography prior to heart valve surgery. In its original definition, left ventricular longitudinal strain has a negative value; however, in this study, we converted the left ventricular longitudinal strain to an absolute value for a more straightforward interpretation.

In the primary analysis, the outcome was all-cause mortality after surgery. The mortality data were obtained from our medical record and the National Health Insurance status. The data on the
survival status were collected until July 31, 2020. Patients who survived over five years were censored at five years, and those who underwent redo-cardiac surgery were censored at the time of redo-surgery. The secondary outcome was operative morbidity defined by the Society of Thoracic Surgeons risk calculator (i.e., composite of operative mortality, stroke, renal failure, prolonged ventilation, mediastinitis/ deep sternal wound infection, and reoperation). The detailed definitions of the secondary outcomes are provided in Supplementary Table 1.

**Statistical analysis**

Sample size was driven by all eligible patients from 2014 to 2018. Missing values were replaced with mode or median. Categorical variables are presented as frequency (proportion), and continuous variables are presented as mean ± SD or median (Q1, Q3). Comparison of descriptive statistics between groups was performed with chi-square test for categorical variables and Student’s t-test or Mann–Whitney U test for continuous variables according to the normality of the data. Correlation between continuous variables was assessed with Pearson’s or Spearman’s correlation test depending on the normality of the variables.

In order to determine the association between predictors and outcomes, univariate Cox proportional hazard regression analysis and univariate logistic regression were performed for the primary outcome and the secondary outcome, respectively. For continuous variables, the univariate association with outcomes was explored using the restricted cubic spline. If there were significant non-linear relationships between continuous variables and the study outcomes, the variables were transformed or categorized as appropriate.

To examine the independent associations between left ventricular longitudinal strain and outcomes, multivariable regression analyses were performed. Multivariable Cox proportional models for the primary outcome were adjusted for LVEF, age, sex, Charlson Comorbidity Index (CCI), pulmonary hypertension, mitral stenosis (MS), MR, aortic stenosis (AS), aortic regurgitation (AR), tricuspid regurgitation (TR), New York Heart Association (NYHA) classification, and atrial fibrillation. Multivariable logistic regression for the secondary outcome was adjusted for LVEF, age, sex, CCI, redo-surgery, pulmonary hypertension, body mass index, hematocrit, hypertension, MS, MR, AS, AR, TR, smoking, combined surgery, NYHA classification, and atrial fibrillation. Possible confounders from background knowledge were selected as adjusted variables.

To assess the incremental value of left ventricular longitudinal strain as a prognostic factor, the likelihood test was used to compare the prediction performance between models with and without left ventricular longitudinal strain. Additional interaction analyses were performed to evaluate the effect-modification of left ventricular longitudinal strain according to prespecified subgroups (LVEF ≥ 50% or < 50%; patients with or without MR). Two sensitivity analyses—multivariable Cox regression including other echocardiographic parameters as potential confounders and multivariable logistic regression with different outcome definitions—were performed, and their details are provided in Supplementary Table 2.

We also performed post-hoc analyses to obtain more straightforward interpretations of our results. These post-hoc analyses categorized preoperative left ventricular function according to left ventricular longitudinal strain and LVEF (LVEF ≥ 50% and left ventricular longitudinal strain ≥ 16.3% vs. LVEF ≥ 50% and left ventricular longitudinal strain < 16.3% vs. LVEF < 50%). For the comparison of patients with preserved and reduced LVEF, a cut-off value of 50% was used [15]. A cut-off value for the left ventricular longitudinal strain was based on the median value of the population (16.3%). Multivariable Cox regression, logistic regression, and Kaplan–Meier survival curve analyses were used as appropriate.

All statistical analyses were two-tailed with a significance level of 0.05. Statistical analysis was performed with R version 4.0.3 (R Foundation for Statistical Computing, Austria).

**Results**

**Patient population and characteristics**

A total of 3,666 patients underwent heart valve surgery at our institution during the study period. Of them, 1,773 were included in the final analysis (Supplementary Fig. 1A). The leading cause of exclusion was the absence of strain analysis, which was primarily due to the low availability of strain during the early study period. The proportion of strain reporting has gradually increased, with 92% of patients in 2018 having strain results [15].

The baseline characteristics of the study patients are shown in Table 1. The median age was 63 years (interquartile range [IQR], 54–70), and 45.9% were female. The median LVEF was 61% (IQR, 56%-65%), and the median left ventricular longitudinal strain was 16.3% (IQR, 13.2%–19.0%). Left ventricular longitudinal strain and LVEF had a moderate degree of positive correlation (Spearman’s ρ = 0.56, P < 0.001). At each level of the LVEF, the left ventricular longitudinal strain had a broad distribution, especially in higher LVEF levels (Fig. 1). The majority (92.4%) of left

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ventricular longitudinal strain data were analyzed with Image-Arena™ (TomTec). The median (Q1, Q3) time interval between preoperative transthoracic echocardiography and surgery was 23 (7, 56) days.

**Primary analysis: postoperative all-cause mortality**

During a median follow-up of 27.2 months (19.1, 38.9), 132 (7.4%) patients died. Patients who survived had higher preoperative left ventricular longitudinal strain values than did non-survivors (16.4 [13.4, 19.2] vs. 14.9 [11.5, 17.2], P < 0.001; Table 1); in contrast, the preoperative LVEF was not significantly different between the survivors and non-survivors (61.0 [56.0, 66.0] vs. 61.0 [52.0, 65.0], P = 0.071). Univariate associations between left ventricular longitudinal strain, LVEF, and all-cause mortality are

![Fig. 1. Relationship between left ventricular longitudinal strain and ejection fraction. A scatter plot showing the relationship between left ventricular longitudinal strain and ejection fraction. Spearman’s coefficient indicated a moderate correlation between left ventricular longitudinal strain and ejection fraction.](https://doi.org/10.4097/kja.22201)

**Table 1. Baseline Characteristics of the Study Patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total population (n = 1,773)</th>
<th>Survivors (n = 1,641)</th>
<th>Non-survivors (n = 132)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.0 [54.0, 70.0]</td>
<td>62.0 [53.0, 70.0]</td>
<td>69.0 [60.5, 75.0]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex (F)</td>
<td>814 (45.9)</td>
<td>756 (46.1)</td>
<td>58 (43.9)</td>
<td>0.703</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.0 [21.9, 26.2]</td>
<td>24.1 [22.0, 26.3]</td>
<td>22.5 [20.2, 25.2]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current smoker*</td>
<td>181 (10.2)</td>
<td>166 (10.1)</td>
<td>15 (11.4)</td>
<td>0.759</td>
</tr>
<tr>
<td>CCI</td>
<td>3.0 [1.0, 4.0]</td>
<td>3.0 [1.0, 4.0]</td>
<td>4.0 [3.0, 6.0]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>750 (42.3)</td>
<td>684 (41.7)</td>
<td>66 (50.0)</td>
<td>0.077</td>
</tr>
<tr>
<td>Pulmonary hypertension†‡</td>
<td>722 (41.0)</td>
<td>649 (39.8)</td>
<td>73 (55.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation†</td>
<td>640 (36.1)</td>
<td>578 (35.2)</td>
<td>62 (47.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>NYHA class ≥ 2†</td>
<td>1263 (73.7)</td>
<td>1157 (72.9)</td>
<td>106 (83.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39.0 [35.5, 42.2]</td>
<td>39.1 [35.8, 42.5]</td>
<td>35.0 [30.4, 39.8]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Redo-surgery</td>
<td>216 (12.2)</td>
<td>189 (11.5)</td>
<td>27 (20.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Combined surgery</td>
<td>262 (14.8)</td>
<td>233 (14.2)</td>
<td>29 (22.0)</td>
<td>0.222</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61.0 [56.0, 65.0]</td>
<td>61.0 [56.0, 66.0]</td>
<td>61.0 [52.0, 65.0]</td>
<td>0.071</td>
</tr>
<tr>
<td>MS§</td>
<td>276 (15.6)</td>
<td>256 (15.6)</td>
<td>20 (15.2)</td>
<td>0.990</td>
</tr>
<tr>
<td>MR§</td>
<td>608 (34.3)</td>
<td>564 (34.4)</td>
<td>44 (33.3)</td>
<td>0.884</td>
</tr>
<tr>
<td>AS§</td>
<td>693 (39.1)</td>
<td>641 (39.1)</td>
<td>52 (39.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>AR§</td>
<td>497 (28.0)</td>
<td>458 (27.9)</td>
<td>39 (29.5)</td>
<td>0.763</td>
</tr>
<tr>
<td>TR§</td>
<td>369 (20.8)</td>
<td>323 (19.7)</td>
<td>46 (34.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>54.0 [48.0, 61.0]</td>
<td>54.0 [48.0, 61.0]</td>
<td>53.0 [47.5, 59.0]</td>
<td>0.284</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>35.0 [29.0, 42.0]</td>
<td>35.0 [29.0, 42.0]</td>
<td>35.0 [30.0, 42.0]</td>
<td>0.869</td>
</tr>
<tr>
<td>LAD† (mm)</td>
<td>47.0 [40.0, 54.0]</td>
<td>47.0 [40.0, 54.0]</td>
<td>48.0 [42.5, 58.0]</td>
<td>0.017</td>
</tr>
</tbody>
</table>

**Strain software vendor**

- TomTec (ARENA) 1638 (92.4) 39 (2.4) 3 (2.3)
- Philips (Qlab) 93 (5.2) 85 (5.2) 8 (6.1)
- General Electric (EchoPAC) 42 (2.4) 1517 (92.4) 121 (91.7)

Values are presented as the number of patients (%) or median (Q1, Q3). CCI: Charlson Comorbidity Index, NYHA class: New York Heart Association Functional Classification, LVEF: left ventricular ejection fraction, MS: mitral stenosis, MR: mitral regurgitation, AS: aortic stenosis, AR: aortic regurgitation, TR: tricuspid regurgitation, LVEDD: left ventricular end-diastolic dimension, LVESD: left ventricular endsystolic dimension, LAD: left atrial dimension. *Smoking history within eight weeks before surgery. Variables with missing values: pulmonary hypertension (10/1773; 0.6%), atrial fibrillation (1/1773; 0.1%), NYHA class (59/1773; 3.3%), LAD (3/1773; 0.2%). Mean pulmonary artery pressure ≥ 25 mmHg assessed by right heart catheterization, peak TR velocity ≥ 2.9 m/s, or early diastolic pulmonary regurgitation velocity > 2.2 m/s on preoperative echocardiography. More than or equal to the moderate grade.

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shown in Supplementary Fig. 2. While left ventricular longitudinal strain had a statistically significant linear negative relationship with all-cause mortality (P value for univariate Cox regression with restricted cubic spline = 0.005, P value for non-linearity = 0.062), LVEF did not show a significant relationship with all-cause mortality (P value for univariate Cox regression with restricted cubic spline = 0.17).

The negative relationship between left ventricular longitudinal strain and all-cause mortality remained statistically significant in a multivariable-adjusted Cox proportional hazard model (Fig. 2A, Table 2). On the contrary, LVEF did not have a statistically significant relationship with all-cause mortality (Fig. 2B, Supplementary Table 3). Combining left ventricular longitudinal strain to the conventional prognostic factors (i.e., age, sex, CCI, PHTN, MS, MR, AS, AR, TR, NYHA class, atrial fibrillation) and LVEF significantly enhanced the prognostic model for all-cause mortality (P = 0.022; Fig. 2C).

**Secondary analysis: operative morbidity**

During index hospitalization or within 30 days postoperatively, 251 (14.2%) had operative morbidity; of them, 40 (2.3%) patients died, 175 (9.9%) had prolonged mechanical ventilation or reintubation, 81 (4.6%) underwent reoperation, 60 (3.5%) had renal failure, 40 (2.3%) had a stroke, and 11 (0.6%) had mediastinitis or deep sternal wound infection.

Descriptive statistics according to the occurrence of morbidity are presented in Supplementary Table 4. Patients with operative morbidity had a lower value of left ventricular longitudinal strain than those without morbidity (15.1 [12.8, 18.0] vs. 16.5 [13.4, 19.1], P < 0.001). LVEF was also lower in patients with morbidity than those without (60.0 [52.5, 64.0] vs. 62.0 [56.0, 66.0], P < 0.001).

Univariate analysis showed that both left ventricular longitudinal strain and LVEF had negative linear relationships with operative morbidity (Supplementary Fig. 3, P values for univariate logistic regression with restricted cubic spline < 0.05). After adjusting for potential confounders, the negative relationship between LVEF and operative morbidity remained statistically sig-

| Table 2. Relationship between Left Ventricular Longitudinal Strain and Clinical Outcomes |
|---------------------------------|-----------------|-----------------|
|                                | All-cause mortality | Operative morbidity |
|                                | Hazard ratio (95% CI) | Odds ratio (95% CI) |
| Adjusted                        | 0.94 (0.90, 0.99) | 0.97 (0.93, 1.01) |
| Subgroup                        |                 |                 |
| LVEF < 50%                      | 1.04 (0.93, 1.16) | 0.98 (0.90, 1.08) |
| LVEF ≥ 50%                      | 0.94 (0.89, 0.99) | 0.96 (0.92, 1.01) |
| Moderate/severe MR              | 0.93 (0.87, 1.00) | 0.93 (0.88, 0.99) |
| No moderate/severe MR           | 0.95 (0.90, 1.01) | 1.00 (0.95, 1.05) |

LVEF: left ventricular ejection fraction, MR: mitral regurgitation.
nificant (odds ratio [OR]: 0.99, 95% CI: 0.97, 1.00, P = 0.049; Supplementary Table 5); however, after further adjustment with left ventricular longitudinal strain, the association between LVEF and operative morbidity was no longer statistically significant (OR: 0.99, 95% CI: 0.98, 1.01, P = 0.543; Fig. 3B). Likewise, left ventricular longitudinal strain did not have a statistically significant relationship with operative morbidity in this final model (OR: 0.99, 95% CI: 0.98, 1.01, P = 0.543; Fig. 3B). Furthermore, combining left ventricular longitudinal strain to the LVEF and conventional risk factors did not show a significant incremental prognostic value for predicting operative morbidity (Fig. 3C).

**Subgroup and sensitivity analysis**

In the subgroup analysis, the association between left ventricular longitudinal strain and all-cause mortality was different across different levels of LVEF, albeit without statistical significance (P value for interaction = 0.086; Fig. 4A, Table 2). The presence of moderate/severe MR did not significantly alter the relationship between left ventricular longitudinal strain and all-cause mortality as well (P value for interaction = 0.613). On the contrary, there was a significant interaction between left ventricular longitudinal strain and the presence of moderate/severe MR in terms of operative morbidity (P value for interaction = 0.047), as a conditional negative relationship between left ventricular longitudinal strain and operative morbidity was shown in the moderate/severe MR group (Fig. 4B, Table 2).

Sensitivity analyses showed similar results to the main analyses in terms of the relationships of left ventricular longitudinal strain and LVEF with all-cause mortality and operative morbidity. The results are shown in Supplementary Tables 6–9.

**Post-hoc survival analysis according to the left ventricular longitudinal strain and LVEF strata**

All-cause mortality according to the left ventricular longitudinal strain and LVEF strata (LVEF ≥ 50% and left ventricular longitudinal strain ≥ 16.3% vs. LVEF ≥ 50% and left ventricular longitudinal strain < 16.3% vs. LVEF < 50%) is shown in Fig. 5. Patients with preserved LVEF (≥ 50%) and normal left ventricular longitudinal strain (≥ 16.3%) had the lowest risk of death. Moreover, patients with preserved LVEF and low left ventricular longitudinal strain (< 16.3%) had a significantly high mortality rate was comparable to that of patients with low LVEF. Patients with preserved LVEF and normal left ventricular longitudinal strain also had the lowest risk of operative morbidity. Patients

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**Fig. 3.** Adjusted relationship between (A) left ventricular longitudinal strain, (B) LVEF with operative morbidity, and (C) incremental value of left ventricular longitudinal strain for predicting operative morbidity. (A, B) Solid lines represent the adjusted odds ratios, and the shaded areas indicate the 95% CIs. Left ventricular longitudinal strain of 16.3% and LVEF of 50% were used as references. The odds ratios were estimated per 1% increase in left ventricular longitudinal strain or LVEF. (C) Bar plots represent the Chi-Square statistics of each model. P values are from the likelihood ratio test to compare the nested models (including conventional risk factors with or without left ventricular longitudinal strain). BMI: body mass index, CCI: Charlson Comorbidity Index, PHTN: pulmonary hypertension, Hct: hematocrit, HTN: hypertension, MS: mitral stenosis, MR: mitral regurgitation, AS: aortic stenosis, AR: aortic regurgitation, TR: tricuspid regurgitation, NYHA class: New York Heart Association Functional Classification, LVEF: left ventricular ejection fraction.
had significantly higher risks of operative morbidity.

**Discussion**

In this observational study of 1,773 patients who underwent heart valve surgery, we showed that left ventricular longitudinal strain was significantly associated with all-cause mortality after surgery. Furthermore, left ventricular longitudinal strain had incremental value for predicting all-cause mortality beyond previously known risk factors including LVEF. However, left ventricular longitudinal strain did not provide a significant benefit over LVEF in predicting operative morbidity.

Left ventricular longitudinal strain is an emerging parameter of systolic function. Previous studies constantly reported that left ventricular longitudinal strain was a valuable predictor of long-term mortality in a variety of cardiac diseases. In terms of valvular surgery, left ventricular longitudinal strain was also independently associated with long-term survival and had incremental prognostic value beyond LVEF [9,10]. However, most of the existing studies only included patients who underwent surgery to correct MR. In patients with significant MR, the LVEF is a limited parameter of the systolic function because LVEF is overestimated due to the regurgitant fraction. Therefore, the impaired systolic function
may be masked in the preoperative LVEF, and become overt after mitral valve surgery. In contrast, left ventricular longitudinal strain directly reflects the myocardial shortening and is less dependent on loading conditions than LVEF [16]. In this respect, left ventricular longitudinal strain may be a superior parameter of systolic function to LVEF in patients with MR. Indeed, the correlation between preoperative left ventricular longitudinal strain and immediate postoperative LVEF was stronger than that between preoperative LVEF and immediate postoperative LVEF [17,18]. The pronounced association between left ventricular longitudinal strain and operative morbidity in patients with MR in our study further supports the prognostic value of left ventricular longitudinal strain in patients with MR.

Notably, the significant relationship between left ventricular longitudinal strain and long-term mortality shown in this study was not limited to patients with MR. Left ventricular longitudinal strain is regarded to detect subtle left ventricular dysfunction, which LVEF cannot detect. Longitudinal myocardial fibers, which are predominantly presented in the subendocardial layer, are more vulnerable to injury than oblique and circumferential fibers [19–21]. Thus, longitudinal shortening can deteriorate in the early stage of valve disease. In contrast, compensatory ventricular remodeling can lead to preserved LVEF until the manifestation of overt myocardial damage [22–24]. Accordingly, our results also showed that a substantial proportion of patients had impaired left ventricular longitudinal strain while having an LVEF of above 50%. Furthermore, we showed that left ventricular longitudinal strain can differentiate long-term survival among patients with preserved LVEF. Thus, our results also support the current concept that left ventricular longitudinal strain can detect subtle myocardial dysfunction, which can impact the clinical outcomes.

In patients undergoing valve surgery, it should also be considered that left ventricular longitudinal strain may reflect not only the negative myocardial impact of valve diseases but also the reversibility of myocardial damage. For example, Kim et al. [10] reported that patients with preserved left ventricular longitudinal strain had a more significant reduction of left ventricular end-diastolic diameter after mitral valve surgery. Another study also showed that preoperative left ventricular longitudinal strain was associated with remodeling status three months after mitral valve replacement [25]. Thus, impairments in left ventricular longitudinal strain may imply a low likelihood of reverse remodeling after surgery. This is especially important considering that early intervention before the occurrence of irreversible myocardial damage may lead to better survival outcomes. As the aforementioned studies have been conducted in patients with MR, it is unknown whether reverse remodeling can differ according to preoperative left ventricular longitudinal strain in other valve diseases. Our results also do not provide direct evidence on this topic, and further studies are needed to test this hypothesis.

In contrast to long-term survival, left ventricular longitudinal strain did not have a significant incremental predictive value above LVEF regarding operative morbidity. Instead, the statistical significance of LVEF disappeared after left ventricular longitudinal strain was incorporated into the multivariable model. Thus, our results did not support incorporating left ventricular longitudinal strain as a predictor of operative morbidity. Left ventricular longitudinal strain may have limited role in specific situations such as the presence of significant MR.

Our study has several limitations. First, this study is from a single tertiary referral center and the study population exclusively consisted of Asian patients. Thus, our findings should be validated in different clinical settings. Second, more than one-third of the eligible patients did not have strain measurements. This is presumed to be largely due to the limited availability of strain analysis in the initial phase of the introduction of the strain measurement, but we cannot preclude the possibility of other patient-specific reasons, such as suboptimal endocardial tracing, atrial fibrillation, and tachycardia. Finally, the strain analysis in our study had a few practical limitations. All values were from the strain adaptation period in clinical practice; accordingly, a tradeoff between clinical feasibility and measurement precision was inevitable. There were heterogeneities in the vendors and versions of the strain softwares used. Also, the experience levels of the sonographers might have been different and interobserver variability also existed. However, in the mid-2010s, inter-vendor variability decreased to a level similar to conventional echocardiogram parameters [26,27]. Also, the reproducibility of left ventricular longitudinal strain was better than that of LVEF, and competency could be achieved with a short learning curve [26,28,29].

Nevertheless, the most critical limitation of our strain measurement was that left ventricular longitudinal strain values were not a global one and obtained from apical four-chamber view. Left ventricular global longitudinal strain is the standard method that averages four, two, and three-chamber longitudinal strain. Thus, some valuable prognostic information from other views might have been ignored in the apical four-chamber longitudinal strain. Nevertheless, a few studies advocated the apical four-chamber longitudinal strain. For example, Alenezi et al. [12] reported that there was little difference between apical four-chamber longitudinal strain with global longitudinal strain in patients with heart failure without regional wall motion abnormality (median difference, −0.03%; interquartile range, −0.3% to 0.27%; 95% pairwise difference < 2% in absolute magnitude). Similarly, a study of pa-
tients with moderate to severe AS showed that apical four-chamber longitudinal strain was in good agreement with global longitudinal strain (mean bias: –0.09%, 95% limits: –3.6 to 3.4%) [11]. Moreover, apical four-chamber longitudinal strain was independently associated with mortality, suggesting it may serve as a new prognostic factor for patients with AS [11]. Considering the above-mentioned studies and our findings, the apical four-chamber longitudinal strain measurement could be a useful alternative. As an example, apical four-chamber longitudinal strain could be implemented more easily in routine clinical practice, as we have experienced. It may be also useful as a substitute for global longitudinal strain when the imaging quality from apical two or three-chamber view is poor. Nevertheless, it should be noted that studies investigating apical four-chamber longitudinal strain excluded patients with regional wall motion abnormality or significant coronary artery disease. Also, the apical four-chamber longitudinal strain needs to be validated in other cardiac diseases, such as amyloidosis, congenital heart disease, etc.

Although the value of left ventricular longitudinal strain for risk prediction in a broad spectrum of cardiac diseases has been repeatedly studied, the widespread clinical implementation of left ventricular longitudinal strain has been slow [20]. This may be due to the lack of availability and concern about standardization [21,22]. However, our study showed that the gradual implementation of left ventricular longitudinal strain may be feasible. Moreover, even in its limited form, left ventricular longitudinal strain provided additional prognostic information in the actual clinical setting. Although further validation is needed, our results suggest that it may be worthwhile to implement strain analysis according to the availability of each institution while considering the current limitation of strain measurement described above. Newer systems that allow fully automated analysis may facilitate the clinical implementation of left ventricular longitudinal strain in the future. Along with the widespread clinical implementation of left ventricular longitudinal strain, a future pragmatic trial can answer whether strain-based surgical decisions can improve the clinical outcomes in patients with valve disease.

In patients undergoing heart valve surgery without coronary artery disease, apical four-chamber left ventricular longitudinal strain measured in a real-world clinical practice was independently associated with postoperative survival. Left ventricular longitudinal strain may be successfully implemented in clinical practice and aid the outcome prediction after valve surgery.

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Conflicts of Interest

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

Author Contributions

Jae-Sik Nam (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft)
Ji-Hyun Chin (Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing)
Hyun-Uk Kang (Investigation)
Juyoun Kim (Data curation)
Kyoung-Woon Joung (Data curation)
In-Cheol Choi (Conceptualization; Supervision)

Supplementary Materials

Supplementary Fig. 1. (A) Flow diagram of the study and (B) surgery case volume with or without preoperative strain analysis.
Supplementary Fig. 2. Unadjusted relationship between longitudinal strain, ejection fraction, and all-cause mortality using restricted cubic spline.
Supplementary Fig. 3. Unadjusted relationship between longitudinal strain, ejection fraction, and operative morbidity using restricted cubic spline.
Supplementary Table 1. Definitions of outcomes
Supplementary Table 2. Sensitivity analyses
Supplementary Table 3. Multivariate Cox regression analyses for all-cause mortality
Supplementary Table 4. Descriptive statistics according to the occurrence of the operative morbidity
Supplementary Table 5. Multivariate logistic regression analyses for all-cause mortality
Supplementary Table 6. Sensitivity analyses for all-cause mortality
Supplementary Table 7. Sensitivity analyses for MACCE
Supplementary Table 8. Sensitivity analyses for all-cause mortality

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Supplementary Table 9. Sensitivity analyses for operative morbidity

**ORCID**

Jae-Sik Nam, https://orcid.org/0000-0002-9378-2720

Ji-Hyun Chin, https://orcid.org/0000-0001-9312-1685

Hyun-Uk Kang, https://orcid.org/0000-0002-9486-7021

Juyoun Kim, https://orcid.org/0000-0002-1991-2275

Kyoung-Woon Joung, https://orcid.org/0000-0002-0626-4424

In-Cheol Choi, https://orcid.org/0000-0002-7386-5043

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The state of anesthesia in South Korea: a national survey of the status of anesthetic service activity in 2014–2016

Eun-Su Choi, Hee-Won Jung, Woon Young Kim, Jae Hwan Kim, Yoon-Sook Lee

Department of Anesthesiology and Pain Medicine, Korea University Ansan Hospital, Ansan, Korea

Background: Because the quality of anesthesia affects the surgical outcome, the aim of this study was to investigate the current status of anesthetic services performed by anesthesiologists and non-anesthesiologists in South Korea from 2014 to 2016 and to compare the results with data from 2011 to 2013.

Methods: The claimed anesthesia services at medical institutions with employed anesthesiologists and the claims for an invitation fee for an anesthesiologist at medical institutions without employed anesthesiologists were regarded as anesthetic services performed by an anesthesiologist. From 2014 to 2016, the employment of anesthesiologists according to the type of medical institution, the status of anesthetic services according to the presence or absence of employed anesthesiologists, and status of anesthetic services at medical institutions without employed anesthesiologists were analyzed.

Results: The proportion of medical institutions that employed anesthesiologists slightly increased from 27.8% in 2014 to 28.8% in 2016. General anesthesia was more concentrated at higher medical institutions, and most anesthesias were performed by an anesthesiologist. The proportion of spinal anesthesia, epidural anesthesia, and brachial plexus performed by non-anesthesiologists was 11%, 15%, and 16.5%, respectively. Intravenous anesthesia performed by non-anesthesiologists was 58% and has increased compared to the past.

Conclusions: The employment of anesthesiologists has increased with time, and general anesthesia was mostly performed by anesthesiologists. However, since the proportion of anesthetic services performed by non-anesthesiologists in regional anesthesia and intravenous anesthesia was maintained high, it is necessary to find ways to expand the safety of anesthetic services.

Keywords: Anesthesia; Anesthesiologist; Health; Insurance; Non-anesthesiologists; Patient safety; Risk; Surgeons.

Introduction

South Korea’s health insurance system has been considered to be an unprecedented social insurance program worldwide, as it has achieved health insurance coverage for the entire population in a short period of time [1]. In addition, to reduce the burden on the people while guaranteeing the benefits to many people, the national insurance system is aiming to establish a low-guarantee, low-cost system. Nevertheless, the quality of national healthcare systems and medical technology in South Korea are very high, and the medical staff tends to accept advanced medical technologies and apply them to patient care relatively quickly [2]. In addition, because it is easy to search for medical knowledge
through the Internet, the demand for high-quality medical services is increasing.

Since anesthesia has a significant impact on patient outcomes, it is very important to ensure high-quality anesthesia management during the perioperative period. However, anesthesiologists usually anesthetize patients in the operating room as a support procedure, and they do not usually meet patients at outpatient clinics before anesthesia. In addition, although patients undergoing surgery pay a lot of attention to the surgeon, they often do not have much interest in their anesthesiologists. Moreover, it is difficult to determine who performed anesthesia in the operating room without closely checking the medical records. Furthermore, the number of anesthetic procedures at medical institutions in South Korea is increasing every year, as it is legally acceptable for other medical specialists or general doctors to perform anesthetic procedures.

To ensure the provision of high-quality anesthetic services to patients, the Korean anesthesiologists and Korean Society of Anesthesiologists (KSA) make efforts to establish support and quality-check systems. The KSA has attempted to improve the quality of anesthetic procedures by investigating the current status of anesthetic services and identifying and solving problems. The KSA first investigated the status of anesthetic services performed by anesthesiologists and non-anesthesiologists in South Korea from 2011 to 2013 [3]. And as a second effort, the state of anesthetic service performed by anesthesiologists and non-anesthesiologists was investigated from 2014 to 2016 in this study.

In order to establish a system for improving the safety and quality of anesthetic services and to generate basic data for future research, the aim of this study was to identify the current status of anesthetic services performed by anesthesiologists and non-anesthesiologists in South Korea using the insurance claims data of the National Health Insurance (NHI) from 2014 to 2016. In addition, we analyzed changes in the status of anesthetic services between our findings from 2014 to 2016 and the previous investigation from 2011 to 2013.

Materials and Methods

This study was based on NHI claims data recorded from medical institutions nationwide from January 1, 2014, to December 31, 2016, extracted through the NHI Review and Assessment Service. These data are released by the NHI Data Sharing Service of South Korea for public research. Informed consent was obtained from all the participants or their legal guardians in advance. The study protocol was approved by the Institutional Review Board of Korea University Ansan Hospital (IRB no. 2020AS0156, Approval on May 25, 2020) and conducted at Korea University Ansan Hospital (Gyeyong-gi-do, Korea). The following data were collected from the claims: anesthesia service–related claims for all age groups, such as anesthesia procedure fees, anesthesia fees, and invitation fees for anesthesiologists but not government grants and veterans’ subsidies. In addition, the medical treatment history, patient’s disease diagnosis history, and prescription details were reviewed, and the current status of the medical institution was recorded.

The medical institutions were classified according to Korean medical law, and the following definitions were used: clinics having less than 30 beds, hospitals having 30 to 100 beds, general hospitals with more than 100 beds, and tertiary referral hospitals designated by the government as specialized hospitals for treating serious diseases. Clinics and hospitals with less than 100 beds were further classified as primary medical institutions and general hospitals with less than 100 beds as secondary medical institutions. Dental hospitals were classified separately. An anesthetic procedure was classified as an anesthetic service performed by an anesthesiologist when it was performed at a medical institution with an employed anesthesiologist or when the anesthesia procedure fees were claimed together with the invitation fee of an anesthesiologist at medical institutions without an employed anesthesiologist. As for the type of anesthesia, all anesthetic procedures, except for local anesthetic infiltration, were classified as general, regional, and intravenous anesthesia. General anesthesia was subdivided into endotracheal intubation and mask ventilation. Regional anesthesia was subdivided into spinal, epidural, and brachial plexus block. Intravenous anesthesia was defined as anesthesia that anesthetizes the patient using intravenous anesthetics while maintaining spontaneous breathing, as specified by the NHI.

Based on the data collected from 2014 to 2016, the employment status of anesthesiologists according to the type of medical institution, the status of anesthetic services according to the presence or absence of an employed anesthesiologist, and the status of anesthetic services at a medical institution without an employed anesthesiologist were analyzed. The data were expressed as numbers (percentages). In order to compare our data with the data from 2011 to 2013, we used the data that the KSA investigated [3], and the data were compared with a χ² (chi-squared) test (SPSS ver. 22, IBM Corp., USA). P < 0.05 was considered statistically significant.

Results

Employment status of anesthesiologists by type of medical institution and overall status of anesthetic service performed by anesthesiologist or non-anesthesiologist

The proportion of medical institutions with employed anesthe-
siologists slightly increased in all medical institutions (Table 1). Approximately 63% of the hospitals employed their own anesthesiologists, but 92% of clinics did not. The rate of dental hospitals with employed anesthesiologists showed an increasing trend.

The total number of anesthesia cases was about 2 million in 2014–2016 (Tables 2–7). The average proportions of general, regional, and intravenous anesthesia for three years were approximately 53.4%, 37.8%, and 8.8%, respectively (Fig. 1). During 2014–2016, the annual proportion of total anesthesia performed at primary and dental hospitals without employed anesthesiologists was about 14% (Table 2). During 2014–2016, the annual proportion of total anesthetic procedures performed by non-anesthesiologist clinicians at primary hospitals and dental hospitals without employed anesthesiologists was about 10% (Table 2).

The proportion of hospitals with employed anesthesiologists had increased from 50% in the 2011–2013 analysis to 63% in 2014 (P < 0.001). The proportion of anesthetic procedures performed by non-anesthesiologists decreased slightly from 13–17% in 2011–2013 to 10.0% in 2016 (P < 0.001). In addition, the proportion of anesthetic procedures performed by non-anesthesiologists at medical institutions without employed anesthesiologists showed a decreasing trend from 76–78% in 2011–2013 to 71% in 2016 (P < 0.001).

The status of general anesthesia with endotracheal intubation by an anesthesiologist or non-anesthesiologist

During 2014–2016, approximately one million cases of general anesthesia with endotracheal intubation were performed (Table 3). The proportion of general anesthesia performed by non-anesthesiologists decreased slightly from 9.7% in 2011–2013 to 8.1% in 2016 (P < 0.001).

Table 1. The Number of Institutions with Directly Employed Anesthesiologists (Sorted by Class of Institutions and Included All Kind of Anesthetic Procedure)

<table>
<thead>
<tr>
<th>Class of institutions</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NEA (%)</td>
<td>EA (%)</td>
<td>Total</td>
</tr>
<tr>
<td>Tertiary referral hospital</td>
<td>43 (100.0)</td>
<td>43</td>
<td>43 (100.0)</td>
</tr>
<tr>
<td>General hospital</td>
<td>288 (100.0)</td>
<td>288</td>
<td>337 (37.0)</td>
</tr>
<tr>
<td>Hospital</td>
<td>363 (36.6)</td>
<td>630 (63.4)</td>
<td>529 (92.4)</td>
</tr>
<tr>
<td>Clinic</td>
<td>2780 (92.1)</td>
<td>237 (7.9)</td>
<td>3017</td>
</tr>
<tr>
<td>Dental hospital</td>
<td>4 (26.7)</td>
<td>11 (73.3)</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>3147 (72.2)</td>
<td>1209 (27.8)</td>
<td>4356</td>
</tr>
</tbody>
</table>

NEA: non-employed anesthesiologist, EA: employed anesthesiologist.

Table 2. The Number of Anesthesia Performed in Primary Institutions without Employed Anesthesiologists

<table>
<thead>
<tr>
<th>Type of anesthesia</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA (%)</td>
<td>AA (%)</td>
<td>NA (%)</td>
</tr>
<tr>
<td>Endotracheal</td>
<td>11,080 (37.0)</td>
<td>18,901 (63.0)</td>
<td>9,722 (32.7)</td>
</tr>
<tr>
<td>Mask</td>
<td>5,817 (62.9)</td>
<td>3,424 (37.1)</td>
<td>5,940 (60.9)</td>
</tr>
<tr>
<td>Spinal</td>
<td>48,784 (66.7)</td>
<td>24,369 (33.3)</td>
<td>52,809 (67.4)</td>
</tr>
<tr>
<td>Epidural</td>
<td>27,476 (50.6)</td>
<td>26,819 (49.4)</td>
<td>28,583 (49.3)</td>
</tr>
<tr>
<td>Brachial block</td>
<td>27,972 (68.8)</td>
<td>12,700 (31.2)</td>
<td>26,067 (63.5)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>91,999 (99.8)</td>
<td>203 (0.2)</td>
<td>91,230 (99.8)</td>
</tr>
<tr>
<td>Total</td>
<td>213,128</td>
<td>86,416</td>
<td>214,351</td>
</tr>
</tbody>
</table>

NA: number of anesthesia performed by non-anesthesiologists, AA: number of anesthesia performed by anesthesiologists.

Table 3. The Number of General Anesthesia with Endotracheal Intubation Performed by Anesthesiologists (Sorted by Class of Institutions)

<table>
<thead>
<tr>
<th>Class of institutions</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA (%)</td>
<td>AA (%)</td>
<td>NA (%)</td>
</tr>
<tr>
<td>Tertiary referral hospital</td>
<td>431,088 (100.0)</td>
<td>439,579 (100.0)</td>
<td>479,677 (100.0)</td>
</tr>
<tr>
<td>General hospital</td>
<td>340,451 (100.0)</td>
<td>328,538 (100.0)</td>
<td>437,012 (100.0)</td>
</tr>
<tr>
<td>Hospital</td>
<td>5,742 (3.4)</td>
<td>164,285 (96.6)</td>
<td>4,902 (2.8)</td>
</tr>
<tr>
<td>Clinic</td>
<td>4,947 (18.2)</td>
<td>22,163 (81.8)</td>
<td>4,902 (18.5)</td>
</tr>
<tr>
<td>Dental hospital</td>
<td>391 (9.7)</td>
<td>3,643 (85.6)</td>
<td>323 (7.8)</td>
</tr>
<tr>
<td>Total</td>
<td>11,080 (1.1)</td>
<td>961,630 (98.9)</td>
<td>9,722 (1.0)</td>
</tr>
</tbody>
</table>

NA: number of anesthesia performed by non-anesthesiologists, AA: number of anesthesia performed by anesthesiologists.

https://doi.org/10.4097/kja.22286
Table 4. The Number of General Anesthesia with Mask Ventilation Performed by Anesthesiologists (Sorted by Class of Institutions)

<table>
<thead>
<tr>
<th>Class of institutions</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA (%)</td>
<td>AA (%)</td>
<td>NA (%)</td>
</tr>
<tr>
<td>Tertiary referral hospital</td>
<td>17,235</td>
<td>(100.0)</td>
<td>20,586</td>
</tr>
<tr>
<td>General hospital</td>
<td>32,698</td>
<td>(100.0)</td>
<td>33,657</td>
</tr>
<tr>
<td>Hospital</td>
<td>4,357</td>
<td>(7.2)</td>
<td>4,240</td>
</tr>
<tr>
<td>Clinic</td>
<td>1,460</td>
<td>(20.0)</td>
<td>1,700</td>
</tr>
<tr>
<td>Dental hospital</td>
<td>452</td>
<td>(100.0)</td>
<td>281</td>
</tr>
<tr>
<td>Total</td>
<td>5,817</td>
<td>(4.9)</td>
<td>5,940</td>
</tr>
</tbody>
</table>

NA: number of anesthesia performed by non-anesthesiologists, AA: number of anesthesia performed by anesthesiologists.

Table 5. The Number of Spinal Anesthesia Performed by Anesthesiologists (Sorted by Class of Institutions)

<table>
<thead>
<tr>
<th>Class of institutions</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA (%)</td>
<td>AA (%)</td>
<td>NA (%)</td>
</tr>
<tr>
<td>Tertiary referral hospital</td>
<td>42,907</td>
<td>(100.0)</td>
<td>39,163</td>
</tr>
<tr>
<td>General hospital</td>
<td>125,892</td>
<td>(100.0)</td>
<td>130,278</td>
</tr>
<tr>
<td>Hospital</td>
<td>16,405</td>
<td>(7.9)</td>
<td>20,096</td>
</tr>
<tr>
<td>Clinic</td>
<td>32,379</td>
<td>(64.1)</td>
<td>18,096</td>
</tr>
<tr>
<td>Dental hospital</td>
<td>1</td>
<td>(100.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>48,784</td>
<td>(11.5)</td>
<td>377,250</td>
</tr>
</tbody>
</table>

NA: number of anesthesia performed by non-anesthesiologists, AA: number of anesthesia performed by anesthesiologists.

Table 6. The Number of Epidural Anesthesia Performed by Anesthesiologists (Sorted by Class of Institutions)

<table>
<thead>
<tr>
<th>Class of institutions</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA (%)</td>
<td>AA (%)</td>
<td>NA (%)</td>
</tr>
<tr>
<td>Tertiary referral hospital</td>
<td>5,292</td>
<td>(100.0)</td>
<td>4,977</td>
</tr>
<tr>
<td>General hospital</td>
<td>16,892</td>
<td>(100.0)</td>
<td>16,719</td>
</tr>
<tr>
<td>Hospital</td>
<td>14,515</td>
<td>(14.2)</td>
<td>14,000</td>
</tr>
<tr>
<td>Clinic</td>
<td>12,961</td>
<td>(24.9)</td>
<td>39,192</td>
</tr>
<tr>
<td>Dental hospital</td>
<td></td>
<td></td>
<td>5,424</td>
</tr>
<tr>
<td>Total</td>
<td>27,972</td>
<td>(15.5)</td>
<td>149,234</td>
</tr>
</tbody>
</table>

NA: number of anesthesia performed by non-anesthesiologists, AA: number of anesthesia performed by anesthesiologists.

Table 7. The Number of Brachial Plexus Block Performed by Anesthesiologists (Sorted by Class of Institutions)

<table>
<thead>
<tr>
<th>Class of institutions</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA (%)</td>
<td>AA (%)</td>
<td>NA (%)</td>
</tr>
<tr>
<td>Tertiary referral hospital</td>
<td>4,369</td>
<td>(100.0)</td>
<td>4,251</td>
</tr>
<tr>
<td>General hospital</td>
<td>34,338</td>
<td>(100.0)</td>
<td>36,246</td>
</tr>
<tr>
<td>Hospital</td>
<td>15,014</td>
<td>(15.9)</td>
<td>14,478</td>
</tr>
<tr>
<td>Clinic</td>
<td>12,958</td>
<td>(65.4)</td>
<td>8,016</td>
</tr>
<tr>
<td>Dental hospital</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>27,972</td>
<td>(18.3)</td>
<td>26,067</td>
</tr>
</tbody>
</table>

NA: number of anesthesia performed by non-anesthesiologists, AA: number of anesthesia performed by anesthesiologists.

anesthesia with endotracheal intubation were performed annually at all medical institutions, and 1% of them were performed by non-anesthesiologists (Table 3). The annual proportions of anesthesia performed in primary and dental hospitals were 20.7% in 2014, 20.2% in 2015, and 18.9% in 2016. During 2014–2016, the annual proportion of anesthesia performed at medical institutions
without employed anesthesiologists was about 3% (Tables 2 and 3). Among them, over 30% were performed by non-anesthesiologists (Table 2).

In 2014–2016, most of the anesthesia was performed more prominently in higher ranking medical institutions than clinics (P < 0.001). The rate of anesthesia performed at medical institutions without employed anesthesiologists was 5–9% in 2011–2013 and only 3% in 2014–2016 (P < 0.001). In addition, the proportion of anesthesia performed by non-anesthesiologists in medical institutions without employed anesthesiologists also decreased to approximately 30% in 2014–2016 from 57–63% in 2011–2013 (P < 0.001).

The status of general anesthesia with mask ventilation by an anesthesiologist or non-anesthesiologist

A total of 110,000–130,000 procedures of general anesthesia with mask ventilation were performed annually; among them, 4.3–4.9% were performed by a non-anesthesiologist (Table 4). The annual proportions of anesthesia performed in primary and dental hospitals were 57.6% in 2014, 56.8% in 2015, and 59.6% in 2016. During 2014–2016, the annual proportion of anesthesia performed at medical institutions without employed anesthesiologists was about 7.8% (Tables 2 and 4), and among them, 62.9%, 60.9%, and 55.7%, in 2014, 2015, and 2016, respectively, were performed by non-anesthesiologists (Table 2).

The overall proportion of anesthesia performed by non-anesthesiologists decreased from 9–14% in 2011–2013 to 4% in 2014–2016 (P < 0.001). The proportion of anesthesia performed at primary medical institutions decreased from 60.8% in 2012 to 56.8% in 2015, but increased from 56.8% in 2015 to 59.6% in 2016 (P < 0.001). The rates of anesthesia performed at medical institutions without employed anesthesiologists were 12–18% in 2011–2013 and only 7% in 2014–2016 (P < 0.001). In addition, the proportion of anesthesia performed by non-anesthesiologists at medical institutions without employed anesthesiologists decreased to approximately 55–62% in 2014–2016 from 75–80% in 2011–2013 (P < 0.001).

The status of regional anesthesia by an anesthesiologist or non-anesthesiologist

Spinal anesthesia

Annually, 380,000–450,000 spinal anesthesia procedures were performed in 2014–2016, and approximately 11% were performed by a non-anesthesiologist (Table 5). During 2014–2016, the annual proportion of anesthesia performed at primary medical institutions and dental hospitals was about 60%. During 2014–2016, the annual proportion of anesthesia performed at medical institutions without employed anesthesiologists was about 17%. Among them, about 66% was performed by non-anesthesiologists (Table 2).

The overall proportion of anesthesia performed by non-anesthesiologists decreased from 16–22% in 2011–2013 to 11% in 2014–2016 (P < 0.001). The proportion of anesthesia performed in primary medical institutions was 60.1% in 2014, 61.6% in 2015, and 61.2% in 2016 and rather increased in 2015 and 2016 from the average 60.1% in 2011–2013 (P = 1.00 in 2014, and P < 0.001 in 2016).

**Table 8. The Number of Intravenous Anesthesia Performed by Anesthesiologists (Sorted by Class of Institutions)**

<table>
<thead>
<tr>
<th>Class of institutions</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA (%)</td>
<td>AA (%)</td>
<td>NA (%)</td>
</tr>
<tr>
<td>Tertiary referral hospital</td>
<td>19,560 (100.0)</td>
<td>15,472 (100.0)</td>
<td>8,532 (100.0)</td>
</tr>
<tr>
<td>General hospital</td>
<td>52,152 (36.9)</td>
<td>73,180 (38.3)</td>
<td>804,528 (38.5)</td>
</tr>
<tr>
<td>Hospital</td>
<td>75,529 (52.1%)</td>
<td>79,120 (52.6%)</td>
<td>112,588 (54.0%)</td>
</tr>
<tr>
<td>Clinic</td>
<td>1,080,625 (84.0%)</td>
<td>1,087,625 (84.4%)</td>
<td>1,128,588 (54.0%)</td>
</tr>
<tr>
<td>Dental hospital</td>
<td>1,128,588 (84.0%)</td>
<td>1,128,588 (84.0%)</td>
<td>1,128,588 (84.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>91,999 (45.1%)</td>
<td>112,091 (54.9%)</td>
<td>91,230 (48.6%)</td>
</tr>
</tbody>
</table>

NA: number of anesthesia performed by non-anesthesiologists, AA: number of anesthesia performed by anesthesiologists.
2015 and 2016). The proportion of anesthesia performed by anesthesiologists at medical institutions without employed anesthesiologists and the proportion of anesthesia performed by anesthesiologists at these hospitals decreased from 20–30% to 17% in 2014–2016 and from 74% to 65% in 2011–2013, respectively (P < 0.001).

**Epidural anesthesia**

Annually, 176,000–186,000 epidural anesthesias were performed, and approximately 15% of them were performed by non-anesthesiologists (Table 6). During 2014–2016, the annual proportion of anesthesia performed at primary medical institutions was about 88%. During 2014–2016, the annual proportion of anesthesia performed at medical institutions without employed anesthesiologists was about 31%. Among them, about 50% was performed by a non-anesthesiologist (Table 2).

The overall proportions of anesthesia performed by non-anesthesiologists decreased from 29% in 2011–2013 to 15% in 2014–2016 (P < 0.001). The proportion of anesthesia performed at primary medical institutions increased from 86% in 2011–2013 to 88% in 2014–2016 (P < 0.001). The proportion of anesthesia performed at medical institutions without employed anesthesiologists increased from 37–46% in 2011–2013 to 30% in 2014–2016 (P < 0.001). In addition, the proportion of anesthesia performed by non-anesthesiologists at these hospitals also decreased to approximately 50% in 2014–2016 from approximately 70% in 2011–2013 (P < 0.001).

**Brachial plexus block**

Annually, 150,000–170,000 brachial plexus blocks were performed, and approximately 16.5% of them were performed by non-anesthesiologists (Table 7). The annual proportion of anesthesia performed at primary medical institutions and dental hospitals was about 75%. During 2014–2016, the annual proportions of anesthesia performed at medical institutions without an employed anesthesiologist was about 26%. Among them, 68.8% in 2014, 63.5% in 2015, and 60.2% in 2016 were performed by non-anesthesiologists (Table 2).

The annual number of cases increased from 100,000–150,000 in 2011–2013 to 150,000–170,000 in 2014–2016, and the overall proportions of anesthesia performed by non-anesthesiologists decreased from 26% in 2011–2013 to 16.5% in 2014–2016 (P < 0.001). The proportion of anesthesia performed at primary medical institutions increased from an average of 72.7% in 2011–2013 to an average of 74.4% in 2014–2016 (P < 0.001). The proportion of anesthesia performed at medical institutions without employed anesthesiologists decreased from 35% in 2011–2013 to 25% in 2014–2016 (P < 0.001). In addition, the proportion of anesthesia performed by non-anesthesiologists at these hospitals also decreased to approximately 65% in 2014–2016 from approximately 75% in 2011–2013 (P < 0.001).

**The status of intravenous anesthesia by anesthesiologist or non-anesthesiologist**

The annual number of anesthesia decreased from 200,000 to 150,000 from 2014 to 2016; however, the proportions of anesthesia performed by non-anesthesiologists increased from 45% to 58% (Table 8). In addition, the proportion of anesthesia performed at primary institutions and dental hospitals increased over 76.6% in 2014 and 78.9% in 2015 to 85.8% in 2016. Moreover, the proportions of anesthesia performed at medical institutions without employed anesthesiologists increased from 45.2% in 2014 and 48.7% in 2015 to 58.3% in 2016, and most of them were performed by non-anesthesiologists (Table 2).

The overall proportions of anesthesia performed by non-anesthesiologists decreased from 54% in 2011 to 45.1% in 2014, but increased from 45.1% in 2014 to 58.1% in 2016, and in particular, in 2016, it increased significantly compared to 2011 (P < 0.001). The proportion of anesthesia performed at primary medical institutions increased from an average of 76.0% in 2011–2013 to an average of 80.7% in 2014–2016 (P < 0.001). The proportion of anesthesia performed at medical institutions without employed anesthesiologists decreased from 54% in 2011 to 45.2% in 2014, but increased from 45.2% in 2014 to 58.3% in 2016 (P < 0.001). In addition, the proportion of anesthesia performed by non-anesthesiologists at these hospitals also decreased to approximately 99.5% in 2014–2016 from 100% in 2011–2013 (P < 0.001).

**Discussion**

The practice of general anesthesia was more prominent at higher medical institutions than at institutions at the clinic level and below, and most anesthesias were performed by anesthesiologists. Even at medical institutions without employed anesthesiologists, the proportion of anesthesia performed by non-anesthesiologists in 2014–2016 was less than that in 2011–2013 by 50%. In the case of regional anesthesia, the proportion of anesthesia performed by non-anesthesiologists decreased, but the proportion of anesthesia performed in primary medical institutions increased. Fortunately, both the proportion of anesthesia performed at medical institutions without employed anesthesiologists and the proportion of anesthesia performed by non-anesthesiologists there decreased. The problem is that although the annual number of intravenous anesthesia has been reduced, the overall proportions of anesthesia...
performed by non-anesthesiologists decreased from 2011 to 2014 but increased from 2014 to 2016. The proportions of anesthesia performed in primary medical institutions increased, and the proportion of anesthesia performed at medical institutions without employed anesthesiologists decreased from 2011 to 2014 but increased from 2014 to 2016. Moreover, although the proportions of intravenous anesthesia performed by non-anesthesiologists at medical institutions without employed anesthesiologists statistically decreased compared to the past, most of them are still performed by non-anesthesiologists.

Endotracheal intubation is a procedure that requires special expertise in anesthesiology. If it fails, serious complications can arise, such as hypoxia and respiratory arrest; therefore, it is mostly performed by specialists. According to our study, the proportion of general anesthesia performed by anesthesiologists at upper-level medical institutions increased from 2014 to 2016. This change occurred when both medical staff and patients recognized the importance of general anesthesia being performed by anesthesiologists. In addition, general anesthesia with mask ventilation has a lower failure rate and is easier to perform than endotracheal intubation; non-anesthesiologist can be trained to carry out this procedure in a short period of time [4]. Therefore, the proportions of general anesthesia with mask ventilation performed by non-anesthesiologists at primary medical institutions and medical institutions without employed anesthesiologists were higher than the proportions of general anesthesia with endotracheal intubation.

However, at medical institutions without employed anesthesiologists, regular education and continued training will be needed in the future to prevent medical accidents and reduce the risk of complications. Paramedics such as emergency medical technicians usually have many opportunities to intubate, but studies have shown that emergency medical technicians usually attempt intubation 1.3 times and have a success rate of 80.6%. One study showed that the higher the intubation experience, the higher the success rate of intubation [5]. In a study involving interns, the success rate of mask ventilation was 85%, while the success rate of endotracheal intubation was 78%; the success rates increased to 94% and 90%, respectively, after some training [4]. In addition, the recently popular video laryngoscope can increase the intubation success rate of interns who have experienced lesser than 10 cases; therefore, in order to minimize the risk of failed intubation, we recommend the use of appropriate assistive devices and continued training of personnel [6,7].

The overall proportion of regional anesthesia performed by non-anesthesiologists decreased. The proportion of regional anesthesia performed by anesthesiologists at medical institutions without employed anesthesiologists and the proportion of anesthesia performed by anesthesiologists at these hospitals decreased. However, the proportion of anesthesia performed at primary medical institutions rather increased. The overall proportion of regional anesthesia performed by non-anesthesiologists and the proportion performed by non-anesthesiologists at medical institutions without employed anesthesiologists were higher than those of general anesthesia. A large percentage of spinal anesthesia is performed for orthopedic and general surgery. Since most of the surgeries are short, an anesthesiologist invited to medical institutions without employed anesthesiologists performs several spinal anesthesias during a single visit. In hospitals with branch offices, a small number of employed anesthesiologists are dispatched to other offices to perform procedures. In these cases, even though the procedure was performed by an anesthesiologist, the number of claims for the invitation fee of an anesthesiologist was less than the number of claims for anesthetic procedures, so the proportion of anesthesia performed by non-anesthesiologists may be overestimated. Epidural catheters inserted by anesthesiologists for labor analgesia can be used for cesarean section. In this case, an invitation fee of an anesthesiologist for cesarean section may not be additionally claimed and it may have been considered as performed by non-anesthesiologists in our study. In addition, spinal and epidural anesthesia for cesarean sections have been categorized in the Diagnosis-Related Group (DRG) since July 2013. As a result, anesthesia fee cannot be claimed separately, so it is possible that the proportion of anesthetic procedures performed by non-anesthesiologists was overestimated relatively as it was excluded from the analysis or classified as performed by non-anesthesiologists.

Brachial plexus block is being performed more frequently than in the past, but the proportion performed in medical institutions without employed anesthesiologists decreased slightly. However, the proportion performed by non-anesthesiologists was still higher than that of other types of anesthesia. The reason is thought to be that as the number of brachial plexus blocks guided by ultrasound increased, the proportion performed by non-anesthesiologists increased. Some studies on brachial plexus block reveal that it was performed by orthopedic surgeons [8,9], and globally, there is an increasing trend of regional anesthesia performed by non-anesthesiologists, nurse practitioners, or physician assistants [10]. In addition, the spread of ultrasound and the diversification of the practitioner [11,12] will lead to an increase in brachial plexus blocks for ambulatory surgery in primary medical institutions without employed anesthesiologists.

However, in addition to puncturing a needle in the target structure, regional anesthesia involves many other aspects, for example, interpreting readings from monitoring devices to check for ad-
verse effects/complications, converting to general anesthesia if required, identifying signs/symptoms of local anesthetic systemic toxicity, and administering inotropes [10]. Very few studies have compared the rates of complications between anesthesiologists and non-anesthesiologists in regional anesthesia. In one study, for non-anesthesiologists to have a success rate of 90% or higher, experience of at least 45 cases of spinal anesthesia and 60 cases of epidural anesthesia was required [13]. However, experience of 27 cases of endotracheal intubation and 112 cases of spinal anesthesia was required for a high success rate of over 88%, suggesting that spinal anesthesia requires more training than the former [14]. Therefore, when regional anesthesia is performed by a non-anesthesiologist, caution must be needed and sufficient education and guidelines by anesthesiologists should be provided.

In this study, intravenous anesthesia was the most common anesthetic service performed by non-anesthesiologists, and more than half of the anesthesia was performed at primary medical institutions. In addition, when intravenous anesthesia was performed at medical institutions without employed anesthesiologists, most anesthesias were performed by non-anesthesiologists. There have been many studies on the risks of intravenous anesthesia by a non-anesthesiologist. In studies of the American Society of Anesthesiologists physical status (ASA-PS) class I and II patients, the incidence of complications was similar between intravenous anesthesia performed by an anesthesiologist and that performed by a non-anesthesiologist, and most of them were found to be safe [15–17]. However, according to a meta-analysis [18], the risk of cardiopulmonary events was significantly higher for anesthesia performed by a non-anesthesiologist. Also, among the anesthesia-related medical disputes that occurred in Korea between 2009 and 2014 [19], the proportion of patients under the age of 60 was 82.9%, and the ASA-PS class I and II was 90.5%. Among them, about 33% of all medical accidents were due to intravenous anesthesia, and 92.3% of them were performed by a non-anesthesiologist, so the risk of anesthesia performed by a non-anesthesiologist in young and healthy patients cannot be overlooked. In the case of patients with ASA class 3 and 4, there is a study reporting that anesthesia by an anesthesiologist is desirable [20], and previous studies have mentioned that intravenous anesthesia should be performed by an anesthesiologist for patients in high-risk groups [21,22]. The reason is that, first, intravenous anesthesia is mostly performed at primary medical institutions, and the patient must cooperate with the treatment by providing information on smoking cessation, abstinence, drugs, and underlying diseases; however, these aspects are difficult to confirm in advance before surgery. In addition, because each patient has a different response to anesthetic drugs, emergency airway management may be required if the patient is deeply sedated, even if the correct dose is administered to the patient according to his/her weight. In order to respond competently to emergency situations, education on airway management such as knowledge of sedation drugs and airway intubation is required. However, in a study of Korean endoscopists, 27.3% of the respondents were not appropriately trained in sedation procedures and did not follow a specific sedation protocol [23].

Severe incidents may occur if accurate procedures are not performed by anesthesiologists. According to a study that analyzed the status of medical incidents that occurred at clinic-level hospitals in South Korea from 2010 to 2012, anesthesia was the cause of medical malpractice in approximately 0.3% of cases [24]. However, according to previous studies, when complications occurred, the period required for resolution was 28.1 weeks, which is quite a long time [24–26]. Moreover, in a study that analyzed 105 cases of anesthesia-related medical disputes in South Korea from 2009 to 2014, 35 of 39 cases of intravenous anesthesia were cases of propofol use. Among intravenous anesthesia disputes, 30 disputes were related to fatal severity, and six disputes were related to permanent and severe sequelae [19]. Just as the hiring of non-physician providers such as nurse anesthetists and anesthesiology assistants in the United States has led to cost savings [27], the surgeons or non-anesthesiologists performing anesthetic services may have a cost-saving effect in South Korea. However, depending on the clinician who performs the anesthetic procedure, the patient’s postoperative outcome or length may be affected [28]. Anesthesia plays a crucial role in medical procedures, and it has a major influence on postoperative complications and surgical outcomes. Therefore, efforts to prevent side effects are required. In order to increase the employment and performance rate of anesthesiologists, efforts should be made to improve the safety of anesthetic procedures, such as introducing a real-name anesthesia system and expanding the evaluation of anesthesia adequacy to hospitals and clinic-level medical institutions. Also, enhanced anesthesia training and education for non-anesthesiologists and regular anesthesia-related patient safety identification should be implemented.

Our study has several limitations. First, some surgeries were categorized under the DRG, and this non-insured group was excluded from our status analysis. Since July 2013, South Korea implemented a DRG system for seven surgeries that are widely performed in all hospitals. In the fee-for-service system, anesthesia is charged separately, and it is possible to determine whether anesthesia was performed by an anesthesiologist. However, because anesthesia is not charged separately in the DRG system, it is not possible to determine whether anesthesia is performed by an anesthesiologist in the DRG surgeries. According to our analysis, the
annual number of surgeries categorized as DRG increased rapidly from 766,223 in 2011 and 805,364 in 2012 to 964,012 in 2013 and from 1,098,517 in 2014 and 1,110,401 in 2015 to 1,153,465 in 2016. Considering that a large number of surgeries were classified as DRG surgeries, omitting them from the analysis may have led to biased results. In addition, in the case of non-insured surgeries, for which the patients pay the full costs, the Health Insurance Review and Assessment Service does not claim medical care benefits, so they were excluded from this analysis, and this may have limited the accuracy of our analysis. Second, under the Korean medical law, anesthetic procedures can be performed by a non-anesthesiologist. Therefore, it is difficult to say that all anesthetic procedures were performed by an anesthesiologist even at hospitals with employed anesthesiologists, so the numbers of anesthesia performed by anesthesiologists could have been overestimated, resulting in a fundamental bias.

In South Korea, given the pursuit of advanced medical care and increased public awareness of the needs of specialists, most general anesthesia requiring airway management is performed by anesthesiologists. The numbers of regional anesthesia and intravenous anesthesia performed by anesthesiologists are gradually increasing, but the rates of anesthesia performed by non-anesthesiologists are still high. In the event of a medical incident or complications caused by anesthesia, if an appropriate response is not provided, the consequences could be fatal. To promote anesthesia services that prioritize patient safety, it is necessary to improve public awareness of the importance of specialists, regularly investigate patient safety related to anesthesia, and implement legal and medical fee systems. Finally, it is important to establish a healthcare system that can provide safe and satisfactory anesthesia to patients.

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**Author Contributions**

Eun-Su Choi (Conceptualization; Data curation; Formal analysis; Writing – original draft)
Hee-Won Jung (Formal analysis)
Woon Young Kim (Formal analysis; Writing – review & editing)

Jae Hwan Kim (Conceptualization; Writing – review & editing)
Yoon-Sook Lee (Conceptualization; Data curation; Formal analysis; Writing – review & editing)

**ORCID**

Eun-Su Choi, https://orcid.org/0000-0002-2738-8573
Hee-Won Jung, https://orcid.org/0000-0001-6647-7993
Woon Young Kim, https://orcid.org/0000-0002-3128-7142
Jae Hwan Kim, https://orcid.org/0000-0002-1360-1708
Yoon-Sook Lee, https://orcid.org/0000-0002-6455-0680

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Corresponding author:
Mridul Dhar, M.D.
Department of Anesthesiology and Critical Care, All India Institute of Medical Sciences, Veerbhadra Road, Rishikesh 249203, India
Tel: +91-9717778374
Email: mridul.anaes@aiimsrishikesh.edu.in
ORCID: https://orcid.org/0000-0002-1913-2586

Previous presentation in conferences:

Use of a human patient simulator for apnea studies: a preliminary in vitro trial

Debendra Kumar Tripathy¹, Mridul Dhar¹, Bharat Bhushan Bhardwaj², K Hemanthkumar³, Praveen Talawar¹, Shalinee Rao³,⁴
¹Department of Anesthesiology and Critical Care, ²Department of Emergency Medicine, ³Advanced Center for Simulation and Skills, ⁴Department of Pathology, All India Institute of Medical Sciences, Rishikesh, India

Background: Modern human patient simulators (HPSs) could be used for researching critical scenarios such as apnea oxygenation. We aimed to study the use of a high-fidelity HPS to assess prolonged apnea using various oxygenation strategies with a simple high-flow nasal cannula (15 L/min).

Methods: An experimental simulation study using an HPS (CAE Healthcare™) was conducted after obtaining approval from the Institutional Review Board. The HPS responded according to real-time physiologically modeled responses to external gases, such as oxygen (O₂). Apnea experiments were performed with different physiological settings, such as shunt fraction (5%) and O₂ consumption (250, 500, and 750 ml/min). The following four apnea experiments were conducted: no oxygenation (NO), apnea oxygenation alone (AO), preoxygenation alone (PO), and para-oxygenation (PAO). The time to 92%, 75%, and 50% saturation was recorded. Alveolar and arterial gas levels were recorded till 50% saturation.

Results: At 250 ml/min, PO (1121 s) and PAO (1274.5 s) had a significantly longer time to 50% saturation (400% increase) compared to NO (222.5 s) and AO (239 s). A similar trend was observed for the time to 92% and 75% saturation. At higher O₂ consumption rates, a shorter time to desaturation was observed.

Conclusions: Apnea trends in the HPS correlated with similar prior human experiments. AO without preoxygenation was found to provide no additional benefit. Preoxygenation with high-flow O₂ via nasal cannula prolonged the time to desaturation in the PAO more than PO scenario. Therefore, HPSs can be used in future studies where patient safety is a concern.

Keywords: Apnea; Hypoxia; Nasal cannula; Oxygen inhalation therapy; Oxygen saturation; Patient simulation.

Introduction

The use of simulations in medical practice is an exciting new sub-specialty that is being widely used for teaching, especially to simulate rare events and prepare students for real-life emergency scenarios. Simulations have been used effectively for procedural training, with mannequins replacing real patients, to avoid exposing novice students to patients for learning [1,2]. The use of simulations in research is still limited to statistical models and a few experimental studies, although there are many unexplored potential applications [2,3].
With the availability of human patient simulator (HPS) machines that can precisely simulate various physiological and pathological conditions through input from computer-based software, the role of simulators in anesthesia has expanded to an advanced level [4]. Newer types of HPSs are based on physio-pharmacological models, which include real-time monitoring and feedback while interventions are performed on the simulator. HPSs are therefore ideal for complex critical scenarios and, thus, an appropriate tool for clinical research based on such scenarios.

Preoxygenation and apnea oxygenation are established techniques for prolonging the duration of apnea during intubation attempts in operation rooms and intensive care units [5–8], but most studies have been performed only on certain oxygen (O₂) saturation levels because of ethical issues related to exposing patients to apnea and potential hypoxia [9–11]. Recent literature has documented the efficacy of high-flow O₂ administered through a nasal cannula to provide longer periods of apnea in operation rooms and to maintain oxygenation in patients with pulmonary pathologies [12–17].

Through this experimental study, we aimed to investigate the effect of O₂ therapy on prolonged apnea using a high-fidelity HPS. This allowed for longer periods of apnea to be studied and analyzed without risking patient safety. The primary objective of our study was to assess the utility of an HPS for apnea simulation and O₂ therapy research, and the validity of extrapolating the data to human patients. The secondary objective was to compare the efficacy of different oxygenation strategies using a simple nasal cannula during apnea in terms of the time to desaturation.

Materials and Methods

Setup

After approval from the Institutional Review Board (IRB no. 261/IEC/IM/NF/2019), an experimental simulation study using an HPS was planned over four months. The HPS (CAE Healthcare™, USA) is equipped to detect delivered O₂ and is used along with an anesthesia workstation and monitor with hemodynamic and oxygenation parameters.

Functioning of the HPS

The study object was a high-fidelity HPS. The basic components of this HPS are a mannequin attached to a central control unit or lab rack (Fig. 1A) through an umbilical assembly (Fig. 1B). The lab rack is driven by various gases, such as O₂, nitrogen (N₂), carbon dioxide (CO₂), and compressed air. A specific software (Müse, CAE Healthcare™, USA) is used to control the functioning of the HPS (Fig. 1C). Circulation and respiration are simulated through the lab rack. Two bellows inside the lab rack serve the function of the lungs (Fig. 1A). Gas monitoring sensors are present at the level of the lab rack even though sampling is performed on the mannequin (Fig. 1D). Simulated hemodynamic measurements, such as non-invasive blood pressure, pulse oximetry for O₂ saturation (SpO₂), and electrocardiography, can also be obtained from the mannequin using actual monitors.

Software

The HPS software, allows for two modes of functioning (Fig. 1C). In the first mode, the HPS response is controlled by an operator at the computer interface, whereas with the second mode, responses are modeled based on normal adult physiology. Several parameters are set for normal adult physiology, such as the shunt fraction (set at 5% for this study), O₂ consumption, lung volume, and respiratory quotient, among others. Table 1 shows a list of all the parameters that were set using the default values [4]. The clinical hemodynamic and blood gas parameters, such as partial pressure of alveolar (PA), arterial (Pa), and venous (Pv) O₂ and CO₂, are visible on a separate screen, which can either be a fixed expected response based on the experiment, a setting that is applied in the software, or a modeled response after synchronizing the monitors with the HPS mannequin. Once in the modeled mode,
Table 1. List of Respiratory Parameters That Can Be Adjusted in the Software

<table>
<thead>
<tr>
<th>Basic parameters</th>
<th>Additional parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen tongue</td>
<td>Shunt fraction</td>
</tr>
<tr>
<td>Airway occluder</td>
<td>SpO₂</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>NMB</td>
</tr>
<tr>
<td>Needle decompression</td>
<td>Tidal volume</td>
</tr>
<tr>
<td>Bronchial occlusion (left and right)</td>
<td>Intrapleural volume: left</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Intrapleural volume: right</td>
</tr>
<tr>
<td>Respiratory rate factor</td>
<td>Fraction of inspired O₂</td>
</tr>
<tr>
<td>ETCO₂</td>
<td>Chest tube flow</td>
</tr>
<tr>
<td>Tidal volume factor</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>pH shift</td>
<td>Lung compliance factor: left</td>
</tr>
<tr>
<td>PEEP</td>
<td>Lung compliance factor: right</td>
</tr>
<tr>
<td>Chest tube</td>
<td>Venous CO₂ shift</td>
</tr>
<tr>
<td>Chest tube flow</td>
<td>Bronchial resistance factor: left</td>
</tr>
<tr>
<td>Chest tube air leak</td>
<td>Bronchial resistance factor: right</td>
</tr>
<tr>
<td>O₂ consumption</td>
<td>Alveolar enflurane</td>
</tr>
<tr>
<td>CO₂ production factor</td>
<td>Fraction of inspired enflurane</td>
</tr>
<tr>
<td>PaCO₂ set-point</td>
<td>Alveolar halothane</td>
</tr>
<tr>
<td>PaO₂ set-point</td>
<td>Fraction of inspired halothane</td>
</tr>
<tr>
<td>I to E ratio (1:X)</td>
<td>Alveolar isoflurane</td>
</tr>
<tr>
<td>PetCO₂-PaCO₂ factor</td>
<td>Fraction of inspired isoflurane</td>
</tr>
<tr>
<td>Respiratory gain factor</td>
<td>Alveolar nitrous oxide</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>Fraction of inspired nitrous oxide</td>
</tr>
<tr>
<td>Volume/rate control factor</td>
<td>Alveolar sevoflurane</td>
</tr>
<tr>
<td>Chest wall capacity</td>
<td>Fraction of inspired sevoflurane</td>
</tr>
</tbody>
</table>


in hemodynamic and blood gas parameters (PAO₂, PaO₂, PACO₂, PaCO₂, SpO₂, pH) were recorded until the end of the experiment, which was defined as the attainment of 50% SpO₂. The following four experiments were conducted with apnea: 1) no oxygenation (NO): only apnea was applied, 2) only apnea oxygenation (AO): 15 L/min O₂ was provided via simple nasal cannula after apnea was applied, 3) only preoxygenation (PO): O₂ was provided until the PAO₂ reached 400 mmHg, at which time apnea was applied with no O₂ during apnea; and 4) para-oxygenation (PAO): preoxygenation was provided until the PAO₂ reached 400 mmHg, at which time apnea was applied and 15 L/min O₂ was administered via simple nasal cannula during apnea. Alveolar and arterial gas levels were noted every 1 min from the beginning of the apnea period till 50% SpO₂ was reached. Time to desaturation was noted for 92%, 75%, and 50% SpO₂.

**Settings and analysis**

Initial O₂ consumption was set at 250 ml/min. Each apnea experiment was repeated three times (at different sittings), and the mean values of the three recordings were used for the comparative analysis. Each set of four experiments was performed on different days to allow the machine to restart and equilibrate to baseline physiological values. This allowed us to maintain a quality check on the data and avoid erroneous readings. All experiments were then performed again at O₂ consumption rates of 500 and 750 ml/ min. The apnea trends were compared among all four experiments (NO, AO, PO, and PAO). The time to desaturation was compared between the experiments and between the different O₂ consumption rates.

**Results**

Fig. 2 shows a comparison of the desaturation time to 50%, 75%, and 92% SpO₂ among the four experimental settings at O₂ consumptions of 250, 500, and 750 ml/min. At 250 ml/min, NO (222.5 s) and AO (239 s) had a similar desaturation time to 50% SpO₂. PAO (1274.5 s) had a longer desaturation time to 50% SpO₂ than PO (1121 s), which was a 400% increase compared to NO. At higher O₂ consumption rates, the desaturation times were shorter. At 500 ml/min, the desaturation time to 50% SpO₂ for NO and AO was 97 s and 98 s, respectively. Compared with NO, the desaturation time to 50% SpO₂ for PO and PAO was 300 s and 316 s, respectively, which was an increase of approximately 200%. Similar comparative trends were observed for the desaturation time to 92% and 75% SpO₂ (Fig. 2).

Fig. 3 shows a graphical trend of the partial pressure of O₂ in the HPS behaves like an independent unit from the fixed software and responds physiologically to real-time interventions, such as external O₂ or anesthetic agents. For this particular study, we were specifically interested in the functioning of the respiratory system, simulation of lung function, and gas-sensing mechanisms. For gas monitoring, alveolar O₂ and CO₂ values were sensed at the level of the lab rack, and for all other arterial parameters, including pulse oximetry, the values were determined based on set physiological parameters. Fig. 1 shows a schematic of the components and functions of the HPS system.

**Experiments**

Apnea settings were applied from baseline values, and changes...
Time to 50%, 75%, and 92% saturation among all four experimental settings at oxygen consumptions of 250, 500, and 750 ml/min. NO: no oxygenation, AO: apnea oxygenation alone, PO: pre-oxygenation alone, PAO: para-oxygenation.

Fig. 2. Time to 50%, 75%, and 92% saturation among all four experimental settings at oxygen consumptions of 250, 500, and 750 ml/min. NO: no oxygenation, AO: apnea oxygenation alone, PO: pre-oxygenation alone, PAO: para-oxygenation.

Table 2 shows the “end of experiment” values of PaCO₂ and pH for all four experiments and different O₂ consumption rates. Because of the shorter time to 50% SpO₂ at 250 ml/min O₂ consumption, the maximum PaCO₂ achieved was lower with NO (52.13 mmHg) and AO (52.9 mmHg) than with PO (72.5 mmHg) and PAO (75.1 mmHg), which allowed for longer apnea times and higher PaCO₂ values (Table 2). Thus, lower pH values were observed with PO (7.2) and PAO (7.18), primarily due to respiratory acidosis. Similarly, experiments at higher O₂ consumption rates also had lower PaCO₂ and higher pH values than the 250 ml/min experiments due to the shorter times to desaturation (Table 2).

Discussion

Recently, there has been growing interest in simulation/mannequin-related research. One advantage of such in vitro studies includes being able to perform research on complex clinical scenarios that are rarely encountered in practice or that would be a potential health risk to the patient [2,3]. One such scenario is apnea oxygenation. Also described as “apneic diffusion oxygenation,” this technique primarily involves drawing ambient O₂ “en masse” into the lungs by providing continuous flow through the airways [18]. Devices such as nasal cannula have conventionally been used, though higher flow devices such as transnasal humidified rapid-insufflation ventilatory exchange (THRIVE), which allow for the toleration of longer apnea times in clinical situations, have been developed [16].

Apnea oxygenation has been studied in humans since 1959. In one of the first studies, conducted by Frumin et al. [18], patients undergoing elective surgeries under general anesthesia with neuromuscular blockades were subjected to prolonged apnea following a period of preoxygenation and de-nitrogenation. Although the apnea termination point was not fixed, periods of apnea ranged from 15 to 55 min, during which arterial samples were monitored for blood gas analysis and catecholamine levels. The lowest SpO₂ level reached was 98%, the lowest pH was 6.88, and the highest PaCO₂ was 250 mmHg. A similar study would be very difficult to perform in modern research settings due to the ethical issues of subjecting patients to such high levels of respiratory acidosis and CO₂. In the current study, a normal physiologically modeled HPS was used to study various oxygenation strategies during apnea to an extent that would not be feasible for real subjects (50% SpO₂). The lowest pH reached was 7.18 and the highest PaCO₂ value was 75 mmHg (250 ml/min O₂ consumption) at 50% SpO₂.

Another in vitro study conducted by Struys et al. [3] compared the time course of inhaled anesthetic drug delivery between two types of anesthesia machine circuits using test lungs. Different combinations of settings (e.g., flow) were applied to observe various patterns of anesthetic delivery and end-tidal concentrations. Such studies can also be performed using an HPS and would even be more accurate than a test lung due to its more advanced real-time gas-sensing mechanisms once synchronized to the modeled mode. A substantial amount of anesthesia-related simulation research has been conducted in the field of airway management, with various studies involving airway techniques and devices [2]. Although such studies are criticized for seldom following up with
Fig. 3. Graphical trend of partial pressure of oxygen in the alveoli and arterial blood among all four experiments across time until 50% SpO$_2$, at oxygen consumption rates of 250, 500, and 750 ml/min. NO: no oxygenation, AO: apnea oxygenation alone, PO: pre-oxygenation alone, PAO: para-oxygenation, alv: alveolar, art: arterial.
In the present study, we compared different nasal oxygenation strategies on an HPS mannequin that varied from no oxygenation to apnea oxygenation alone to para-oxygenation, to assess the time to 92%, 75%, and 50% SpO2. Across all settings, no oxygenation and oxygenation only during apnea showed similar times to desaturation, and para-oxygenation produced marginally longer times to desaturation compared to preoxygenation alone, both of which were significantly longer than those in the earlier two settings. The above findings highlight that, without preoxygenation, apnea oxygenation alone does not provide any additional benefit, and that para-oxygenation can be used to maximize the duration of safe apnea.

The four experimental settings were also applied at O2 consumption rates of 250, 500, and 750 ml/min to evaluate the performance of the HPS at different O2 settings, which can be further extrapolated to varied O2 demand situations. The comparative findings were similar across all consumption rates. In the current study, only the shunt fraction and O2 consumption rate were manipulated; however, complex pulmonary pathologies may be simulated by adjusting various physiological parameters to estimate how an actual patient might behave under various conditions, such as anesthesia and surgery [4]. For example, chest wall compliance and bronchial resistance factors can be used to simulate restrictive and obstructive lung pathologies, respectively. Different flow rates of nasal oxygenation could also be compared on the HPS, similar to the protocol proposed by Theiler et al. [22].

The major and obvious limitation of the study is that the results obtained with any simulator experiment cannot with absolute certainty be compared to human data. Only its proximity to reality, as much as possible, can be ascertained, as was done in the present study. Another limitation is that the full spectrum of the software modifiable physiological factors could not be explored in the present study. This can be planned in future projects.

In conclusion, apnea trends in the HPS in the current study correlated well with similar prior human experiments, providing support for the use of HPS in similar future research and extrapolation of data to human patients. Through simulation experiments, we deduced that AO alone without preoxygenation provides no additional benefit to NO. High-flow O2 via nasal cannula prolonged the time to desaturation in the PAO scenario more than in the PO scenario. Complex, rare, and potentially dangerous scenarios, such as apnea oxygenation, can be easily performed using HPS to study the patterns of various new interventions without the ethical concerns of exposing real patients.

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

Debendra Kumar Tripathy (Conceptualization; Formal analysis; Project administration; Resources; Supervision; Validation; Writing – review & editing)
Mridul Dhar (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft; Writing – review & editing)
Bharat Bhushan Bhardwaj (Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Writing – review & editing)
K Hemanthkumar (Data curation; Investigation; Methodology; Resources; Software; Supervision)
Praveen Talawar (Conceptualization; Investigation; Software; Supervision; Writing – review & editing)
Shalinee Rao (Formal analysis; Project administration; Resources; Software; Supervision; Writing – review & editing)

ORCID

Debendra Kumar Tripathy, https://orcid.org/0000-0003-0346-1374
Mridul Dhar, https://orcid.org/0000-0002-1913-2586
Bharat Bhushan Bhardwaj, https://orcid.org/0000-0002-0899-5204
K Hemanthkumar, https://orcid.org/0000-0002-4521-7209
Praveen Talawar, https://orcid.org/0000-0002-9931-2316
Shalinee Rao, https://orcid.org/0000-0002-9833-5305

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Hydrolocation assisted subclavian venous catheterization -two case reports-

Joshua Frohlich, Sushil Sancheti

Department of Anesthesia, Memorial University of Newfoundland, St. John’s, NL, Canada

Background: Of the three common central access sites, subclavian vein catheterization has the lowest risk of infection but the highest risk of pneumothorax. The main disadvantage of the short-axis ultrasound guided approach is difficult needle-tip visualization. We describe use of the hydrolocation technique to improve needle-tip localization.

Case: Two females, an 81-year-old and a 72-year-old, presented for coronary artery bypass grafting requiring central vein cannulation. To confirm that the needle tip was visualized and not the shaft, needle advancement was paused and 1 ml of saline injected. The appearance of a small anechoic pocket superficial to the subclavian vein helped to visualize the needle tip. Negative aspiration was then re-applied and slight advancement resulted in aspiration of blood and successful subclavian vein puncture.

Conclusions: The use of hydrolocation for subclavian vein access was easily implemented, required little modification in setup and technique, and provided improved localization of the needle tip.

Keywords: Anatomic landmarks; Central venous catheterization; Patient safety; Pneumothorax; Subclavian vein; Ultrasonography.
Case Reports

Two female patients, an 81-year-old with body mass index (BMI) 24 kg/m\(^2\) and a 72-year-old with BMI 35 kg/m\(^2\) presented for coronary artery bypass grafting requiring central vein cannulation. Written informed consent for case reports publication was obtained from both patients. Under general anesthetic and positive pressure ventilation, the patients were placed in 20 degrees Trendelenburg and prepped for left subclavian vein access. During tray set-up, the 18 g, 6.35 cm introducer needle was attached to the 5 ml introduction syringe, and 3 ml of sterile normal saline was drawn up through the needle. This ensured the introducer needle was primed with normal saline and not air, which would obscure the ultrasound image during hydrolocation. The linear ultrasound probe (4.2–13.0 MHz) (LOGIQ™ E ultrasound, GE Healthcare, USA) was placed in the lateral sub-clavicular region and the subclavian vein and artery identified in short-axis. The vein was followed medially until the clavicle was just visible at the cephalad edge of the ultrasound image and the vein was immediately caudad to the clavicle. After skin puncture, negative aspiration was applied to the saline loaded syringe/needle as it was advanced into the deeper subcutaneous structures.

Case 1

In the first case, the needle can be seen in Fig. 1A (Supplementary Video 1), superficial to the subclavian vein. To confirm this was indeed the needle tip and not the shaft, needle advancement was paused and 1 ml of saline injected. The appearance of a small anechoic pocket superficial to the subclavian vein helped to confirm needle tip position as seen in Fig. 1B (Supplementary Video 1).

Case 2

In the second case, difficulty was encountered visualizing the needle and the needle tip was approximated using controlled gentle micro movements and observing for corresponding surrounding tissue movement prior to the 1 ml saline injection as seen in Fig. 2A. The appearance of a small anechoic pocket superficial to the subclavian vein helped to better approximate needle tip position as seen in Fig. 2B (Supplementary Video 2). The subclavian vein also becomes more ovoid as the injection compresses it slightly. Negative aspiration was then re-applied and slight advancement resulted in aspiration of blood and successful subclavian vein puncture. The Seldinger technique and a percutaneous sheath introducer kit (ARROW® PSI, Teleflex Medical, USA) was then used to successfully place a side-port with a single lumen introducer catheter.

Discussion

The use of hydrolocation for subclavian venous access was easily implemented, required little modification in setup and technique, and provided improved localization of the needle tip. Kim et al. [5] recently published a randomized non-inferiority trail investigating the incidence of catheterization-related complications.
between supra- and infraclavicular ultrasound-guided subclavian venous catheterization approaches. The reported statistically non-significant but potentially clinically significant difference in pneumothorax cases, two in the infraclavicular and none in the supraclavicular approach, was ‘thought to be due to the difference in ability to view and identify the needle tip despite the use of ultrasound’ [5]. Conceivably, the hydrolocation technique could potentially reduce complications such as pneumothorax, but further research would be required to verify this. We encountered difficulty visualizing the needle in case 2 likely secondary to increased BMI making the ultrasound views more difficult. In this case, the use of hydrolocation was regarded as being even more useful in approximating needle tip position as compared to case 1 where hydrolocation was used more as a confirmation of needle tip location. Without the use of hydrolocation in case 2, the next confirmatory endpoints would be aspiration of blood (indicating arterial or venous puncture) or air (indicating pleural puncture and pneumothorax). The hydrolocation technique provided reassurance that even when the needle is difficult to visualize (case 2) the needle tip is still above the puncture site of interest and not approaching the pleura.

A 1 ml injection was used, representing the upper limit of optimal injection volume (0.5–1 ml), as recommended in the regional literature describing the hydrolocation technique [4]. Though an increased injection volume may help to better visualize the forming anechoic pocket on ultrasound, it has the potential to further distort the anatomy and introduce air bubbles creating a suboptimal ultrasound image. We recognize the possibility that the appearance of the anechoic pocket may be misaligned with the needle tip secondary to fluid tracking proximally or distally to the needle. Nonetheless, the hydrolocation technique provides additional information on approximating the needle tip position allowing for a more confident approach to central access. We stress the importance of introducer needle priming with normal saline to prevent air injection and subsequent ultrasound image artifact. This case series is a preliminary report of a novel approach to central venous catheterization using hydrolocation. However, we are unable to demonstrate that the technique of hydrolocation during ultrasound guided central line placement provides added safety compared to conventional methods given insufficient number of patients, lack of a comparison group, and lack of statistical evidence. Therefore, no definitive recommendations are made. However, the described technique of hydrolocation offers proof of concept and preliminary data for ongoing investigation into this novel technique. Although we describe the approach for subclavian venous access, the hydrolocation technique could easily be applied to alternative central access sites.

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Conflicts of Interest

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Author Contributions

Joshua Frohlich (Investigation; Methodology; Writing – original draft; Writing – review & editing)
Sushil Sancheti (Conceptualization; Investigation; Supervision; Writing – review & editing)

Supplementary Materials

Supplementary Video 1. Hydrolocation to confirm needle tip location.
Supplementary Video 2. Hydrolocation to localize needle tip.

ORCID

Joshua Frohlich, https://orcid.org/0000-0001-7909-3083
Sushil Sancheti, https://orcid.org/0000-0001-7767-7827

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Psychogenic coma after general anesthesia with remimazolam and remifentanil
-a case report-

Song Hyun Kim, Kye Min Kim, Yun-Hee Lim, Byung Hoon Yoo, Joonho Cho, In-Jung Jun

Department of Anesthesiology and Pain Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea

Background: Delayed emergence from general anesthesia is associated with life-threatening conditions with pharmacological, neurological, metabolic, and rarely, psychiatric causes. This case report was presented to report psychogenic coma after recovery from anesthesia with remimazolam and remifentanil.

Case: An elderly woman was unresponsive after recovery from anesthesia with remimazolam and remifentanil. Physical examination, laboratory testing, and radiographic imaging did not reveal any obvious organic causes. Pharmacological or metabolic abnormalities were not found. Absence of those causes strongly suggests that prolonged unconsciousness is related to psychiatric origin. The patient spontaneously regained consciousness after 48 h without any neurological complications.

Conclusions: Anesthesiologists should be aware of the possibility of psychogenic coma for patients with unexplained delay in emergence from anesthesia after the exclusion of other causes.

Keywords: Benzodiazepines; Coma; Delayed emergence from anesthesia; General anesthesia; Postoperative complications; Unconsciousness.

In recent anesthesia, the introduction of short-acting anesthetics has enabled patients to awaken rapidly after general anesthesia. Thus, today it is relatively uncommon for patients to experience delayed emergence from anesthesia or changes in their level of consciousness after general anesthesia. When such events do occur, they are usually associated with serious problems, such as cerebrovascular incidents or drug-related side effects [1]. Psychogenic causes can cause unconsciousness, but only rarely [2].

General anesthesia was induced and maintained in our patient using remimazolam and remifentanil, short-acting benzodiazepine, and opioid. The patient experienced prolonged unconsciousness after waking up from anesthesia. We excluded organic causes through extensive testing and speculated that she experienced psychogenic coma. Psychogenic coma occurs very rarely and seems serious, but it resolves spontaneously without special treatment [2]. Here, we would like to share our experience because psychogenic coma is typically unfamiliar to anesthesiologists and responsible clinicians may experience distress until the patient regains consciousness.
Case Report

A written informed consent was obtained for publication of this case report. A 93-year-old woman was scheduled for bipolar hemiarthroplasty under general anesthesia. She had a medical history of hypertension, hypothyroidism, depression, insomnias, and somatic symptom disorder and was diagnosed as having sick sinus syndrome nine months ago. A cardiologist had recommended that she needed a pacemaker implanted, but she rejected it. She was taking levothyroxine, antihypertensive agent, analgesics with several psychiatric drugs, including benzodiazepine, zolpidem, and pregabalin, and two more unidentified drugs prescribed by a local clinic. Laboratory testing on admission revealed hyponatremia with sodium levels of 124 mEq/L, which was slowly improving. Thyroid function test was within normal range. A preoperative electrocardiogram showed normal sinus rhythms and a heart rate of 78 beats/min. Transthoracic echocardiography showed an ejection fraction of 56%. Her condition was otherwise evaluated as normal.

On arrival in the operating room, standard monitoring, namely by electrocardiogram, non-invasive blood pressure monitoring, and pulse oximetry of the patient was begun. Preoperative vital signs were normal. The radial artery was catherized, and general anesthesia was induced and maintained using remimazolam and remifentanil. Remimazolam was started with a loading dose of 6 mg/kg/h until loss of consciousness and thereafter was maintained at a rate of 1 ml/kg/h. Remifentanil was adjusted to effect site target concentration of 2–10 ng/ml during the operation.

During the operation, mean arterial pressure was maintained above 80 mmHg and there were no episodes of arrhythmia. Adequate depth of anesthesia was maintained with a bispectral index (BIS) of 40–60. The operation proceeded uneventfully, and anesthesia lasted for 155 min. Remimazolam was discontinued when skin suture was commenced 20 min before extubation. At the end of anesthesia, 25 μg of fentanyl was injected intravenously for pain management followed by 200 mg of sugammadex and subsequently the train-of-four ratio showed 98%. Shortly, the patient responded to verbal commands and adequately breathed spontaneously and BIS remained over 95. She was extubated and brought out to the post anesthesia care unit (PACU).

On arrival in the PACU, the patient was fully awake and normothermic. The patient complained of pain with numeric rating scale (NRS) of 8 that we administered 30 μg of fentanyl. After 15 minutes, the patient was fine with NRS of 2. One hour after admission to the PACU, the patient’s vital signs remained stable, so we decided to transfer her to the general ward. Immediately after the patient was prepared for transfer to the general ward, she suddenly became unresponsive to verbal commands and any external stimuli. Her eyes were closed firmly, and her eyes were directed downwards when we opened her eyelids (Fig. 1). She had adequate spontaneous ventilation and was hemodynamically stable. The train-of-four ratio was 98% and her BIS was 77. Arterial blood gas analysis performed in the PACU showed that her blood pH level was 7.414, PaCO₂ level was 33 mmHg, PaO₂ level was 114 mmHg, bicarbonate level was 22 mmol/L and glucose level was 143 mg/dl. Oxygen saturation was 98% with oxygen mask 5 L/min. Serum electrolytes and other serum chemistries were within normal limits. Out of concern for residual effects of remimazolam or opioid overdose, we intravenously administered flumazenil 0.3 mg twice and naloxone 0.04 mg four times intermittently. However, the patient was still comatose with a Glasgow Coma Scale score of 3. We quickly performed brain computed tomography, which showed no evidence of brain hemorrhage or acute ischemic infarction. She was subsequently transferred to the intensive care unit (ICU) for further observation.

A neurologist in the ICU conducted a neurological examination but did not find any abnormal results. The day after the operation, brain magnetic resonance imaging and electroencephalography were conducted, and their results were normal. Thus, intracranial abnormalities, cerebrovascular incidents, and seizure were excluded as potential causes of the coma. A psychiatrist was then consulted, and they recommended to simply wait while providing her with supportive care.

After 36 h of no response, a nurse in the ICU heard the patient suddenly saying ‘I’m cold’ and appearing drowsy. At 48 h of no response, she opened her eyes and followed verbal commands. After recovery, the patient had no memory of the surgery but remembered hearing enough noise that she couldn’t sleep while she was in the ICU. She seemed to remember, at least faintly, of the times that she was unresponsive. She was transferred to the general ward and the remainder of her hospitalization was unremark-

![Fig. 1. Eyeballs directed downwards on opening the patient’s eyelids.](https://doi.org/10.4097/kja.22242)
able. The patient was discharged without any neurological complications.

Discussion

With the use of fast-acting general anesthetic drugs, we expect patients to awake within a few minutes after surgery. Rarely, patients may not regain consciousness quickly after general anesthesia as a result of various causes, including pharmacological, metabolic, and neurological causes [1]. Occasionally, residual anesthetic drugs may delay emergence from anesthesia as a result of overdosing or recurarization [1]. There are also nonpharmacological causes, such as seizure, stroke, and, in rare cases, psychogenic disease [3]. Psychogenic coma can be diagnosed as the cause when all other organic causes have been ruled out [4]. It is difficult for an anesthesiologist to immediately suspect psychogenic coma when the patient fails to regain consciousness after anesthesia, because it occurs rarely and can be diagnosed at the end of the evaluation [5].

The mechanisms and causes of psychogenic coma are poorly understood. Previous cases involved being female, undergoing general anesthesia, undergoing head or neck surgery, having psychiatric disease, and experiencing stress as predisposing factors [2]. Psychogenic coma has several characteristics that differentiate it from true coma. As in our case, patients close their eyes tightly and consistently look either upward or downward [6]. During the hand drop test, patients with psychogenic coma show hand drop avoidance [7]. In addition, often the results of the doll’s eye or caloric examinations are not abnormal, which would be the case if there was a neurological problem [8]. In most cases, self-respiration is sufficiently preserved even in the comatose state [9]. Patients generally regain consciousness spontaneously in 3–48 h without any special treatment [2].

Our patient awakened after general anesthesia but fell into coma shortly thereafter in the PACU. Resedation after remimazolam reversal with flumazenil has been reported to be effective in such situations as the blood concentration of flumazenil decreases [10]. In our case, the patient was awakened without flumazenil administration in the operating room and was alert upon arrival in the PACU. As flumazenil and naloxone administration was ineffective, resedation due to the residual effects of the anesthetic drugs can be excluded as the cause of the coma. As in our case, another patient was reported to have fully woken up immediately after surgery but to have then lost consciousness again several hours later [5]. She experienced psychogenic coma each of the three times she underwent general anesthesia thereafter. Therefore, in patients with a history of psychogenic coma, there is a possibility of repeated episodes following anesthesia.

Decreased levels of consciousness during the perioperative period can be confused with hypoxic delirium, especially in elderly patients. During hypoxic delirium, EEGs slow as the level of consciousness approaches stupor [11,12]. Our patient was determined to be in a psychogenic coma, not experiencing hypoxic delirium, because her EEG was normal while she was comatose. Furthermore, the patient appeared to be experiencing a significant psychogenic burden as indicated by the many psychiatric medications she took for uncontrolled anxiety, insomnia, and somatic symptoms as determined during the preoperative checkup.

Treatment of psychogenic coma is largely limited to relieving the anxiety of the patient and caregivers with supportive care. Clinicians should not repeat stimuli to wake the patient. Anxiety is believed to be a contributing factor to psychogenic coma, so more noxious stimuli may cause greater anxiety in patients and delay recovery even more [13]. Anxiolytics, such as lorazepam, have been suggested for recovery [5]. In this respect, the present case was unique because remimazolam, a short-acting benzodiazepine, was used to maintain anesthesia. Various anesthetics were used in previous cases of psychogenic coma, including sevoflurane, isoflurane, propofol, and thiopental [2]. There seems to be no correlation between anesthetic type and the occurrence of psychogenic coma.

In conclusion, psychogenic coma may be a rare cause of delayed recovery of consciousness after anesthesia. Its poorly understood etiology and low incidence rate make it difficult to diagnose. Anesthesiologists should consider this rare condition for patients with unexplained delay in emergence from anesthesia. Appropriate examinations and treatments can improve patient prognosis.

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Author Contributions

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Kye Min Kim (Supervision)
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Byung Hoon Yoo (Writing – review & editing)
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Corresponding author:
Zhi-Fu Wu, M.D.
Department of Anesthesiology, Kaohsiung Medical University Chung-Ho Memorial Hospital, No.100, Tzyou 1st road, Sanmin Dist., Kaohsiung City 80756, Taiwan
Tel: +886-7-3121101 ext. 7035
Fax: +886-7-3217874
Email: aneswu@kmu.edu.tw
ORCID: https://orcid.org/0000-0001-6376-9085

Reading beyond quantitative electroencephalography-based indices: a case of erroneously high entropy values during ophthalmic surgery

Yuh-Shyan Wu¹, Po-Nien Chen¹, Gwo-Ching Sun¹,²,³, Kuang-I Cheng¹,², Zhi-Fu Wu¹,²,⁴

¹Department of Anesthesiology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, ²Department of Anesthesiology, College of Medicine, Kaohsiung Medical University, Kaohsiung City, ³Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung City, ⁴Department of Anesthesiology, Tri-Service General Hospital and National Defense Medical Center, Taipei City, Taiwan

The maintenance of an adequate depth of anesthesia (DoA) is important for patients undergoing general anesthesia. Quantitative electroencephalography (EEG) - based monitors, such as the bispectral (BIS) index and entropy, have been established to assess DoA. However, these measures can be affected by various factors, and the processed numerical output can often be misleading; therefore, quantitative EEG-based indices should be interpreted with caution. We report a case of a patient with abnormally high entropy values during ophthalmic surgery with no evidence of intraoperative awareness. Written informed consent was obtained.

A 61-year-old woman was scheduled for retinal detachment repair. Monitoring systems included electrocardiography, noninvasive blood pressure testing, pulse oximetry, end-tidal carbon dioxide, entropy (“Entropy™ monitor; GE Healthcare, Finland), and neuromuscular transmission (E-NMT-01; GE Healthcare, Finland). General anesthesia was induced with intravenous injections of fentanyl (75 µg), lidocaine (100 mg), propofol using a target-controlled infusion system (Fresenius Orchestra Primea; Fresenius Kabi AG, Germany) to an effect-site concentration (Ce) of 4.0 µg/ml, and rocuronium (40 mg). General anesthesia was initially maintained with a propofol Ce of 3.0 µg/ml and rocuronium (20 mg/h). However, during the procedure, the entropy values were extremely high (response entropy [RE] > 90, state entropy [SE] between 80 and 90). The train-of-four count of the neuromuscular transmission monitor was 0. Since we assumed there was inadequate DoA, we titrated the propofol Ce to 3.5 µg/ml and administered sevoflurane at a minimal alveolar concentration of 0.5. However, even after titrating the anesthetic doses to deepen the DoA, the entropy values remained abnormally high even though there were no clinical signs of inadequate DoA, such as tachycardia or hypertension.

Additionally, the raw EEG waveform changed from ‘fuzzy’ high frequency beta and gamma waves before anesthetic induction to the slow frequency waves of sleep spindles (Fig. 1) normally present during anesthesia maintenance. Meanwhile, the RE values were still > 90 and the SE values were between 80 and 90, even though the patient was unconscious according to the change in the raw EEG waveform. Since we were certain that the patient was adequately anesthetized, we discontinued the sevoflurane. The operation was completed uneventfully, and the patient recovered well with no memory of intraoperative awareness.
This case study demonstrates the importance of examining raw EEG waves in real time rather than relying solely on quantitative EEG-derived indices. Despite the common use of quantitative EEG-based monitors for assessing DoA, the values shown on the monitors can potentially be misleading. For instance, in circumstances with elevated electrode impedance caused by erroneous placement or reduced adherence, the cause of the low-frequency electromyography signals can be misinterpreted as high-frequency EEG signals, iatrogenic movement of the limbs, interference from strong vibration-producing instruments or electrical equipment (such as electric scalpels, electrocautery, or thermal blankets), or a pathological EEG [1–3]. Hypothermia and hypoglycemia have also been found to alter EEG-based indices [3]. In addition, one EEG-based monitor will not necessarily perform the same as another model, and thus can influence the interpretation of the results [3].

Common causes of erroneously high entropy values during ophthalmic surgery include electrocautery, electro-oculography, and electromyographic activity. Alternatively, the surgeon’s hand on the patient’s frontal region, where the entropy sensing lead is placed, may affect electromyography readings and indirectly affect entropy values. However, throughout the reported operation, both RE and SE values remained > 80 despite temporarily ceasing electrocautery. Additionally, the difference between the RE and SE values remained < 8 and the train-of-four count of the neuromuscular transmission monitor was 0, indicating that neither electro-oculographic nor electromyographic activity was the cause of elevated entropy values in this case. All these measurements suggest that none of the common causes of falsely elevated entropy values during ophthalmic surgery were the culprit in this case. Moreover, the particular entropy monitor that was used was presumed to function normally, as no other patients had erroneous results with the model.

The algorithm used to calculate entropy is the mathematical normalization of the overall frequency range of values between 1 (maximum irregularity) and 0 (complete regularity). The theoretical assumption is that irregularities in the EEG signal decrease under anesthesia [1]. In our case, the EEG signals revealed random wavelengths and amplitudes from general anesthesia induction to emergence, which might have contributed to the erroneously high entropy values. On the other hand, 5–10% of the population has genetically determined EEG variants, meaning their EEG-based indices do not coincide with their clinical state of sedation, and are not associated with any actual cerebral dysfunction [3]. However, we were unable to determine whether our patient had a genetic EEG variant.

Since BIS and entropy values are calculated using different algorithms, BIS and entropy values that are concomitantly recorded may occasionally show discordant trends during general anesthesia. Aho et al. [4] reported that 11% of the concurrent pairs they analyzed had discrepancies between the BIS and entropy values. Pilge et al. [2] also reported more false classifications of the clinical state at transition with SE compared to the BIS index (14% vs. 9%). We do not intend to claim that one index is superior to the other; however, whenever a discrepancy exists between EEG-based indices and the actual clinical condition, the use of two concurrent monitoring devices with different EEG algorithms may allow for a more accurate assessment. In addition, as Akavipat et al. [5] have suggested that for neurosurgery, the postauricular placement of a BIS electrode can be a practical alternative to frontal lobe placement, we support the use of this modality during ophthalmic surgery.

While we are still uncertain of the factors that caused the erroneously high entropy values in this case, we cannot overemphasize the importance of interpreting the raw EEG waveform and considering the patient’s clinical condition rather than relying solely on quantitative EEG-based indices for assuming an inadequate DoA. We suggest that two EEG-based monitors with different algorithms be employed, since this may provide a more accurate assessment when numerical data are inconsistent with the clinical condition. Moreover, we recommend that, as a practical alternative, the EEG sensing electrode be placed at the posterior auricular position during ophthalmic surgery.
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**Conflicts of Interest**

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**Author Contributions**

Yuh-Shyan Wu (Writing – original draft)
Po-Nien Chen (Supervision)
Gwo-Ching Sun (Visualization)
Kuang-I Cheng (Conceptualization)
Zhi-Fu Wu (Writing – review & editing)

**ORCID**

Yuh-Shyan Wu, https://orcid.org/0000-0002-3973-7013
Po-Nien Chen, https://orcid.org/0000-0003-0550-0357
Gwo-Ching Sun, https://orcid.org/0000-0001-7626-8896
Kuang-I Cheng, https://orcid.org/0000-0002-3766-6450

**References**

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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
other published article(s), or are determined to violate our journal publishing ethics guidelines in the view of the editors (such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like), may be “Withdrawn”.

2) Article retraction
Errors serious enough to invalidate a paper’s results and conclusions (Infringements of professional ethical codes, such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like) may require retraction.

3) Article replacement
Replacement (retraction with republication) can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then replacement of the changed paper, with an explanation, allows full correction of the scientific literature.

See also the National Library of Medicine’s policy on retractions and the recommendations of the International Committee of Medical Journal Editors (ICMJE) concerning corrections and retractions, or https://publicationethics.org/resources/guidelines.

9-3. Appeals and complaints
KJA adheres to COPE guidelines regarding appeals to editorial decisions and complaints. For additional information, please visit https://publicationethics.org/core-practices.

Data sharing statement

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 following 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.
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.⁶
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

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/
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 control 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

- Drug Names and Equipment
Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide ® or TM as a superscript and manufacturer’s name, and country.

- Ions
Ex) Na+ [O], Mg2+ [O], Mg3+ [X], Mg2+ [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.

- 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 be 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


B. Monographs
- If reference page is only 1 page, mark ‘p’.
- Mark if it is beyond the 2nd edition.


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.

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
- 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.
- 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.
- 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 play-back 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 registered 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. A figure or a table may be used. A maximum of five authors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.
   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 be 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 meeting dates 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. Letters to the Editor cover individual articles not described by any of the above categories. The short manuscripts with a constructive note on the Journal or the anesthesiology at large are welcome.

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 authors 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 anesthesia 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 February 2021 submissions.