

Recent advance in patient monitoring

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Recent advance in technology has developed a lot of new aspects of clinical monitoring. We can monitor sedation levels during anesthesia using various electroencephalographic (EEG) indices, while it is still not useful for anesthesia depth monitoring. Some attempts are made to monitor the changes in sympathetic nerve activity as one of the indicators of stress, pain/analgesia, or anesthesia. To know the balance of sympathetic and parasympathetic activity, heart rate or blood pressure variability is investigated. For trend of cardiac output, low invasive monitors have been investigated. Improvement of ultrasound enables us to see cardiac structure and function continuously and clearer, increases success rate and decreases complication of central venous puncture and various kinds of nerve blocks. Without inserting an arterial catheter, trends of arterial oxygen tension or carbon dioxide tension can be monitored. Indirect visualization of the airway decreases difficult intubation and makes it easier to teach tracheal intubation. The changes in blood volume can be speculated non-invasively. Cerebral perfusion and metabolism are not ordinary monitored yet, but some studies show their usefulness in management of critically ill. This review introduces recent advances in various monitors used in anesthesia and critical care including some studies of the author, especially focused on EEG and cardiac output. However, the most important is that these new monitors are not almighty but should be used adequately in a limited situation where their meaning is confirmed. (Korean J Anesthesiol 2010; 59: 144-159)

Key Words: Cardiac output, Electroencephalogram, Heart rate variability, Percutaneous carbon dioxide tension, Pulse oximeter, Ultrasound.

Anesthesiologists had used only blood pressure, heart rate, respiratory rate, body temperature, urine volume, and body movement to monitor patients during anesthesia. However, recently, percutaneous oxygen saturation, and end-tidal concentrations of oxygen, carbon dioxide, and inhalation anesthetics have been routine monitors. The most prominent

development is seen in the monitor of hypnosis or depth of anesthesia using electroencephalogram (EEG) and then low- or non-invasive cardiac output measurement. Some recent information of these new monitors including the author's experience are shown in this article, especially focused on EEG and cardiac output.

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EEG

Monitoring of hypnosis has been enthusiastically investigated using EEG and this is the most prominent progress in clinical monitoring. Spectral edge frequency (SEF)95 or SEF90 is one of the first developed indicators of hypnosis using EEG shown by a simple number. SEF is calculated from the area under the power of frequency obtained by Fourier transformation. The frequency at 95% from the lower frequency is SEF95. This is quite simple calculation, not complicated as other indices developed later.

The most popular EEG monitor used during anesthesia is the bispectral index (BIS, Aspect Medical, Newton, MA, USA). The BIS is a number from 0 to 100, 0 means an isoelectric EEG and 100 means complete awake. While the exact algorithm of BIS has not yet been published, the BIS integrates 4 EEG parameters, relative beta ratio, SynchFastSlow, QUAZI, and burst suppression ratio into a single variable. At a BIS range of 30 to 80, changes in BIS correlate well with SynchFastSlow. A burst suppression ratio of more than 40 was linearly correlated with BIS in the range of 30 to 0.

Although BIS is developed to show hypnotic levels during anesthesia, the effects of anesthetics on the EEG differ among various anesthetic drugs. Gamma amino-butyric acid (GABA)_A receptor agonist induces high amplitude and slow wave in EEG, but N-methyl-D-aspartate (NMDA) receptor antagonist usually shows various patterns in EEG [1]. Fentanyl does not have any effects on EEG with the doses usually used, while high dose fentanyl induces slow wave in the EEG [2]. Remifentanyl 0.5 µg/kg/min decreased EEG frequency and BIS [3]. Messner et al. reported that the BIS decreased to 33, 57, and 64 by muscle relaxant only [4]. Therefore, even at the same BIS level, hypnotic level might be different depending on the anesthetics used.

Noxious stimulation can change the EEG to fast wave, and the BIS value will then increase, while BIS does not change at insertion of laryngeal mask airway and surgical incision during general anesthesia in our study [5]. In addition, strong noxious stimulation sometimes induces a large delta wave and induces a very low BIS value. This phenomenon is called paradoxical arousal. Therefore, BIS cannot indicate the response to stimuli.

Severe hypercapnia was shown to be accompanied by a decrease in the BIS. During cardiopulmonary bypass, BIS decreased significantly following cooling [6], a decrease of 1.1 BIS per 1°C has been reported during temperature changes in hypothermic cardiopulmonary bypass [7]. Whether this shows hypnotic effect of cooling or dissociation between hypnosis and EEG changes is not known.

Two BIS electrodes that were placed in the same patient simultaneously did not always show the same number [8], thus emphasizing the potential influence of electrode placement on intra-individual variability.

Recently many other indices and their devices have been developed.

Entropy (GE Healthcare, Helsinki, Finland) calculates two parameters, State entropy (SE, range 0–91) and Response entropy (RE, range 0–100). SE uses the frequency range 0.8–32 Hz, representing predominantly the EEG activity, RE is calculated at 0.8–47 Hz, consisting of both EEG and facial electromyogram (EMG). The difference of RE-SE can indicate EMG, reflecting nociceptive response [9]. Increased RE is followed by increased SE at nociceptive stimuli in patients not receiving muscle relaxants. Due to their overlapping power spectra, the contribution of EMG and EEG cannot be accurately separated [10]. RE and SE are considered to be interchangeable with BIS during general anesthesia, but during cardiopulmonary bypass in hypothermia, the decrease of SE and RE was more significant than the BIS [6], therefore, in hypothermia, RE and SE are not interchangeable with BIS.

The cerebral state index (CSI) is measured by the Cerebral State Monitor (CSM, Danmeter, Odense, Denmark), a small handy-held apparatus. The CSI is also shown as a number from 0 to 100 and adequate range for general anesthesia is 40 to 60 as the BIS. During sevoflurane-nitrous oxide anesthesia, BIS and CSI showed good agreement by the Bland-Altman plot and correlated well [11]. The CSI tended to stabilize in values of 40–60 at intermediate levels of hypnosis, whereas BIS stabilized in values of 20–40 at deeper anesthetic levels [12]. In addition, the CSI better responds to stimuli than the BIS, and recovers faster than the BIS from the noise of electric cautery [11]. Therefore, as a monitor during general anesthesia the CSI might be better than the BIS.

The first version of Narcotrend (Schiller AG, Baar, Switzerland) was complicated. Its algorithm classifies the EEG traces into different stages from A (awake) to F (general anesthesia with increasing burst suppression) [13]. The newest Narcotrend software version includes a dimensionless Narcotrend index from 100 (awake) to 0 (electrical silence). Patient State Index (PSI, Hospirqa, IL, USA) uses neurometrics, which takes into account differences in individual background EEG as well as individual variability of the brain's response to anesthetic agents [14], thereby reducing variance within each individual patient. Index of consciousness (IoC, Morpheus Medical, Barcelona, Spain) is based on the symbolic dynamics. The symbolic dynamics detect the complexity of the EEG that makes it correlate to the depth of anesthesia. The IoC also integrates the beta ratio in light anesthesia and EEG suppression ratio in deep anesthesia [15]. Revuelta et al. [15] showed that during induction of anesthesia, the IoC, BIS and CSI showed the equal Pk values, while in maintenance of anesthesia, the IoC and BIS showed good agreement with clinical signs, but the CSI was significantly influenced by muscle relaxant. In our experience,

the BIS and CSI are not influenced by muscle relaxant when anesthesia is deep enough to prevent movement of the patient.

The middle-latency auditory evoked potential (MLAEP), extracted from the EEG 10–100 ms after an auditory signal, represents the earliest cortical response to the acoustic stimulus. Amplitudes and latencies of the MLAEP are influenced by anesthetics and surgical stimuli and are therefore believed to be useful for measuring depth of anesthesia [16,17]. This is the only one EEG index developed to show the depth of anesthesia using the evoked potentials. There are two different methods to show the EEG response to auditory stimulation, the A-line AEP index (AAI) extracted by advanced signal processing using an average of 15 sweeps measured by the A-line AEP (Danmeter, Odense, Denmark), and the AEP index extracted by a moving time average of 256 sweeps measured by the aepEX (Audiomex, Glasgow, Scotland). Therefore, the AAI changed faster than the AEP index by the aepEX [18]. The AAI might be better to detect response to painful stimuli than the AEP index by the aepEX. The AEP index by the aepEX was larger than the AAI at the same anesthesia level, while both manufacturers suggest the same range of the number for adequate anesthesia [19].

The AAI might be a more sensitive indicator of anesthetic depth (i.e. response to stimuli) than the BIS because the AAI increased at insertion of laryngeal mask airway and surgical incision [5]. BIS, SEF, and AAI could not differentiate anesthesia level between isoflurane 0.5% and 1.5% in nitrous oxide anesthesia, and only AAI could detect emergence from anesthesia [20]. The AAI but not the BIS could discriminate slight changes of consciousness during light sedation with propofol infusion in spinal anesthesia [21]. These differences might partly come from the fact that the AAI had smaller variation than the BIS. In addition, the AAI recovered faster from the disturbance by electric cautery than the BIS [22].

When the ranges for adequate hypnosis in general anesthesia recommended by the manufacturers are used, the AAI showed more appropriate numbers, and larger response to stimuli than the BIS and SEF [23]. Thus the AAI might be more reliable monitor of hypnosis in general anesthesia.

The effects of induction doses of intravenous anesthetics on the AAI were studied. The AAI decreased to less than 30 with thiopental and propofol in one minutes, but it increased again in 3 minutes with only thiopental. This means that induction dose of thiopental has significantly shorter duration of hypnosis than propofol. Midazolam decreased AAI slowly to the levels around 30 in 5 minutes, but ketamine increased AAI, although all patients were sedated similarly [24]. Therefore, as same as the BIS, interpretation of the AAI as an indicator of hypnosis depends on the drugs used.

One of the problems of the AAI is that in deep anesthesia as the AAI less than 30, the AEP wave becomes almost flat. To

resolve this problem, a composite A-line autoregressive index (composite AAI) is developed. The A-line AEP/2 (Danmeter) monitor calculates composite AAI. This uses the MLAEP for measuring the lighter depths of anesthesia while using spontaneous cortical EEG to measure the deeper levels. During induction of anesthesia, BIS is reported to perform better than composite AAI, while composite AAI is statistically a better discriminator for the level of consciousness during the wake-up test and emergence [25]. The author compared the composite AAI and original AAI. When propofol doses or sevoflurane concentration were the same, composite AAI was larger than the original AAI, while the range for adequate hypnosis recommended by a manufacturer is the same for both indices (Ex. Composite AAI was 60 when original AAI was 40.). When anesthetic level is adequate, original AAI might be better than composite AAI, while we have no comparative experience in deeper anesthesia levels.

Many comparative studies put AEP monitor and other EEG monitor together on the same patients and simultaneously monitored. However, the click sounds of the AEP monitor transiently increased simultaneously measured BIS, SE and RE during sedation with propofol [26], therefore, for study purpose, they should be careful to monitor the EEG and AEP simultaneously in the same patients.

In summary, there are many indices to monitor hypnotic levels during anesthesia, but every time we need to check raw EEG waves besides the index because of some discrepancies between the EEG wave and index and because of the effects of EMG on the index. The EEG effects of anesthetic drugs are not good predictors of movement in response to a surgical stimulus because the main site of action for anesthetic drugs to prevent movement is the spinal cord [27]. The use of these monitors in children is not as well understood as in adults. [27].

Skin Conductance

As shown in the previous section, EEG changes cannot indicate level of analgesia. Increased activity in cortical and subcortical regions of the brain as a result of arousal or noxious stimuli leads to a higher rate of firing in sympathetic, post-ganglionic cholinergic neurons [28-30]. This results in filling of sweat glands, which is measured by skin conductance [31]. Skin conductance is measured by the MEDSTORM AS 2005 (Medstorm Innovations, Oslo, Norway). The number of fluctuations within the mean skin conductance (NFSC) was reported to perform similarly to BIS during sevoflurane-remifentanyl anesthesia [34]. This suggests that the NFSC is an indicator of hypnosis not analgesia. However, NFSC showed a significant correlation with level of noxious stimuli during anesthesia [32]. In addition, the severity of postoperative

pain significantly influences skin conductance. NFSC was significantly different between patients with different numeric rating scale of pain [33]. The derivative of the mean skin conductance level, another index of skin conductance showed a similar discrimination with RE and SE in entropy between sound responses at the different sedation levels [35]. However, NFSC was better than RE-SE for the measurement of clinical stress during intubation, and was sensitive to tetanic stimuli at different opioid analgesic levels as contrast with RE-SE [36]. Therefore, NFSC might be able to detect pain, while further studies are necessary to confirm it.

The similar parameter is a skin impedance measured by an electro-sympathicograph (ESG 1001 Monitor-System, Dr. Janitzki Consulting Engineers, Altenbeken, Germany). The changes in the impedance correlated well with the changes in the BIS during target control infusion of propofol [37]. Only one study is found to investigate a skin impedance, therefore, whether this is used as a monitor of analgesia (anesthesia) or hypnosis is not known.

In summary, skin conductance or impedance has been investigated for many years, but only recently it can be studied in clinical practice. However, still it is complicated for setting up to use as a routine monitor and only a few data are available. Further improvement and studies are necessary.

Other Indices Targeting for Depth of Anesthesia

Surgical stress index (SSI) is based on the normalized pulse beat interval and photoplethysmographic pulse wave amplitude and it is developed to assess surgical stress and analgesia. In the study for postoperative pain, the difference between different pain score might be larger in the SSI than that in the skin conductance [38]. When SSI was used to control remifentanyl administration, it decreased remifentanyl consumption, and gave more stable hemodynamics and lower incidence of unwanted events than without SSI [39].

The noxious stimulation response index (NSRI) is calculated from the weighted propofol and remifentanyl concentrations corrected for interaction and normalized to a range between 0 and 100, where 100 reflects 100% probability and values approaching 0 reflect close to 0% probability of responding to laryngoscopy. The NSRI better predicted the response to noxious stimulation of the forearm than the BIS, although the BIS better predicted measure of hypnosis [40]. However, this is available only for propofol-remifentanyl anesthesia.

The RIII reflex as a component of the nociceptive flexion reflex is a polysynaptic spinal withdrawal reflex that is elicited by stimulation of nociceptive nerve afferents. The RIII reflex threshold correlates with non-responsiveness better than the

BIS in propofol-remifentanyl anesthesia [41]. To assess the RIII reflex, biceps femoris muscle activity is monitored using an electromyogram during the application of electrocutaneous stimuli to the ipsilateral sural nerve. The procedure of setting up to record the reflex is much more complex than simply applying EEG and takes more time. This is a disadvantage of the RIII reflex as a monitor. In addition, normalization of the RIII reflex threshold is necessary for inter-individual compatibility. Therefore, RIII reflex cannot be applied when anesthesia has already been started.

In summary, these new concepts are more complicated than EEG and skin conductance. We need much more studies to apply these new monitors to show anesthesia depth in clinical practice.

Heart Rate or Blood Pressure Variability

To know stress response during anesthesia, plasma catecholamine concentrations have been measured. However, this is not continuous monitoring and we cannot get the results on time. Beat-to-beat variations in heart rate largely reflects fluctuations in sympathetic and parasympathetic activity at the sino-atrial node. Several linear and non-linear methods have been used to assess heart rate variability (HRV). The most frequently used linear method is the power spectral analysis of R-R interval defining low frequency component (LF) and high frequency component (HF) [42]. LF (0.04–0.15 Hz) reflects cardiac sympathetic and parasympathetic nerve activity, HF (0.15–0.4 Hz) represents cardiac parasympathetic nerve activity, and LF/HF ratio represents the balance between sympathetic and parasympathetic activities. The HF is significantly dependent on the respiratory rate and not on the tidal volume [43]. If the respiratory rate is less than 8 breaths per minute, it is difficult to separate the high-frequency peak in the power spectrum from the low-frequency peak. In addition, changes in carbon dioxide affect HRV. High carbon dioxide concentration increases HF and LF, but this reactivity is abolished during general anesthesia [44]. Another linear method calculates standard deviation of R-R interval and root of mean squared difference between successive R-R interval (RMSSD). Non-linear method such as spectral entropy is better suited for non-stationary signals as may occur in patients under noxious stimulation [45]. Entropy quantifies the repetition of patterns in the signal. Larger values of entropy correspond to greater apparent randomness or irregularity, whereas smaller values correspond to more instances of recognizable patterns in the data [46]. The entropy is reported to reflect parasympathetic modulation of heart rate under varying physiologic conditions and in response to pharmacological denervation [47]. Entropy increased by laryngeal mask airway insertion, while LF and

LF/HF increased by surgical stimuli [48]. Thus, the response to different stimuli might be different between entropy and LF, LF/HF.

For analysis of HRV, recordings of 5 minutes should be made under physiologically stable conditions processed by the frequency domain method [49]. Spectral analysis of HRV is not appropriate for the assessment of autonomic nervous activities when heart rate is unstable or changing progressively. Although the time course of total power and LF/HF seems to follow the BIS and the plasma levels of stress hormones, there were only weak correlations between the LF/HF ratio and the level of norepinephrine [50].

The variability of blood pressure is also investigated. The LF of blood pressure variability (LFBP) is considered to be indicative of peripheral vasomotor sympathetic activity and modulation [51]. The HF of blood pressure variability (HFBP) is reported to be mediated largely by the mechanical effect of respiration on intrathoracic pressure and/or cardiac filling [51,52].

There are many studies of HRV in anesthesia, but some discrepancies exist among the studies. Barbiturate decreased both LF and HF [53,54]. Thiopental and fentanyl could not inhibit the increases in HF and LF/HF at tracheal intubation [55]. Propofol decreased HF and entropy without significant changes in LF, suggesting sympathetic dominance [53], while Win et al. [56] reported that total power, LF, HF, LF/HF, and entropy were significantly decreased in propofol sedated patients compared with awake patients. Kanaya et al. showed no change in LF/HF by induction with propofol [57]. Etomidate showed no effects on LF and HF [53], while Zickmann et al. [54] reported that etomidate decreased both LF and HF. Midazolam was reported to decrease HF and LF but did not change LF/HF [56]. However, Komatsu et al. showed that midazolam increased HF and decreased LF [58]. Midazolam and fentanyl decreased LF [54], did not change HF and LF/HF and inhibited these increases by tracheal intubation [55]. From these different results in different studies, it is suggested that HRV is quite variable depending on the situation tested, which means it is not useful to measure sympathetic and parasympathetic activity in anesthesia.

In sevoflurane anesthesia, LF decreased with a reduction in the BIS. Entropy and HF decreased after induction of anesthesia, but no further decrease was observed in spite of a reduction in the BIS [57]. Sevoflurane-nitrous oxide decreased HF and inhibited the increase in HF and LF/HF by tracheal intubation [55]. In sevoflurane-nitrous oxide anesthesia, LFBP, LF and HF decreased significantly. In propofol-fentanyl anesthesia, LFBP and LF decreased significantly. The degree of reduction in LFBP was greater in sevoflurane-nitrous oxide anesthesia than in propofol-fentanyl anesthesia [59]. These results suggest that reduction in autonomic nervous modulation to the heart might not be different between sevoflurane-nitrous oxide

anesthesia and propofol-fentanyl anesthesia, while reduction in sympathetic nervous modulation to peripheral vasculature is greater in sevoflurane-nitrous oxide anesthesia than in propofol-fentanyl anesthesia. During light anesthesia, LF was more suppressed by sevoflurane than by propofol, and propofol markedly increased LF/HF [60].

In spinal anesthesia, some patients with a low block level developed a marked increase in LF/HF, which was abolished by supplementation with intrathecal fentanyl, but not intravenous fentanyl [61]. Activation of the sympathetic nervous system in the upper body may be elicited as a compensatory mechanism for vasodilation in the lower body caused by spinal anesthesia when anesthesia level is low.

In summary, considering of these various results and author's experience that the absolute value of HRV parameter has large variations, further improvement is necessary to use HRV as an ordinal monitor of cardiac sympathetic and parasympathetic activities, and blood pressure variability may be the same.

Low-or Non-invasive Cardiac Output Monitoring

Cardiac output has been measured intermittently by transpulmonary thermodilution methods using a Swan-Ganz catheter. Vigilance™ (Edwards LifeSciences, Irvine, CA, USA) enables continuous monitoring of cardiac output using a Swan-Ganz catheter, while we well know that continuous measurements do not agree with intermittent bolus thermodilution measurements.

Recently, many kinds of low-or non-invasive cardiac output monitoring have been developed without a pulmonary thermodilution catheter. Pulse contour analysis is the most ordinal method to measure cardiac output in less invasive monitoring.

FloTrac™ and Vigileo™ system (Edwards LifeSciences, Irvine, CA, USA) uses arterial pulse waveform analysis of radial artery to measure cardiac output. FloTrac™ and Vigileo™ system do not need manual calibration. It calibrates itself on the basis of patient's characteristic data in conjunction with internal correction variables.

Cardiac output measured by FloTrac™ and Vigileo™ correlated well with cardiac output measured by transpulmonary thermodilution for patients being paced or in sinus rhythm and poor for patients in atrial fibrillation [62]. Lorsomradee et al. reported that cardiac output measured by FloTrac™ and Vigileo™ and that by Vigilance™ yield comparable results during cardiac surgery with cardiopulmonary bypass [63]. However, phenylephrine administration decreased cardiac output by Vigilance™ and increased that by FloTrac™ and Vigileo™ [63]. The repeatability of cardiac output measured by transpulmonary thermodilution, as well as of cardiac output

measured by FloTrac™ and Vigileo™ is reduced in patients with aortic stenosis. The repeatability of both methods, as well as the agreement between methods, decreased significantly immediately after termination of cardiopulmonary bypass [64]. In mechanically ventilated patients with circulatory failure after liver transplantation, stroke volume variation by FloTrac™ and Vigileo™ is a useful predictor of increased cardiac output in response to volume expansion and cardiac output measured by FloTrac™ and Vigileo™ is able to track changes in cardiac output induced by volume expansion [65]. In contrast, Matthieu et al. reported that cardiac output obtained with FloTrac™ and Vigileo™ in patients undergoing liver transplantation do not agree with thermodilution measurements, particularly in patients with low systemic vascular resistance as attested by Child-Pugh grade B and C [66]. Stroke volume variation obtained by FloTrac™ and Vigileo™ predicts fluid responsiveness with an acceptable sensitivity and specificity and is also a potential surrogate for continuous monitoring of the respiratory variation in arterial pulse pressure in mechanically ventilated patients [67]. However, interpretation of stroke volume variation should be cautious in patients with spontaneous breathing, arrhythmia, open chest condition, and ventricular dysfunction. Stroke volume variation obtained by FloTrac™ and Vigileo™ is reported not to be a reliable predictor of fluid responsiveness in major abdominal surgery [68]. Prone position induced a significant increase in pulse pressure variation and stroke volume variation measured by FloTrac™ and Vigileo™, but did not alter their abilities to predict fluid responsiveness [69].

PulseCO™ (LiDCO, London, UK) relies on a pulse power analysis, which is based on the principle of mass/power conservation in a system and the assumption that following the correction for compliance and calibration. PulseCO™ provides stroke volume from the arterial pressure waveform of radial artery using an autocorrelation algorithm. The algorithm calculates nominal stroke volume after a pressure to volume transformation and it is converted to actual stroke volume by calibration using lithium dilution measurement (LiDCO™ system). Lithium is rapidly redistributed and has no first pass loss from the circulation. Lithium calibration cannot be used in patients who have recently (in 15 to 30 min) received neuromuscular blockers because these drugs react with the lithium sensor.

Cardiac output measured by PulseCO™ calibrated with thermodilution performs well as a continuous cardiac output monitor and shows acceptable agreement with pulmonary thermodilution in off-pump coronary artery bypass surgery [70]. However, our study showed that cardiac output measured by PulseCO™ was not interchangeable with that measured by Vigilance™ even when PulseCO™ is calibrated with the data of

Vigilance™ at first in off-pump coronary artery bypass surgery [71]. Agreement between intermittent and continuous cardiac output values obtained with the LiDCO™ and Vigilance™ was found to be clinically acceptable in patients with hyperdynamic circulation [72], while PulseCO™ might underestimate cardiac output compared to that by bolus transpulmonary thermodilution when simply decreasing systemic vascular resistance by infusion of prostaglandin E1 in cardiac surgery [73]. Pulse pressure variation and systolic volume variation measured by LiDCO™ can predict fluid responsiveness in mechanically ventilated patients during general anesthesia [74].

PiCCO™ (Pulsion, Munich, Germany) uses a thermister-tipped catheter usually introduced into the femoral artery that is used to track stroke volume on a beat-by-beat basis after calibration by transpulmonary thermodilution. The measurement with a radial artery catheter (50 cm, Pulsion) is interchangeable with that derived from a pulmonary catheter in patients with coronary artery bypass surgery, and that a centrally inserted arterial catheter is required for accurate determination of cardiac output by PiCCO™ [64]. Cardiac output measured by PiCCO™ is most often found to be higher than the corresponding cardiac output measured by transpulmonary thermodilution, and this is considered to be caused by the cold-induced reduction in heart rate [76] and the loss of indicator [77]. Continuous cardiac output determination using PiCCO™ is a reliable method of assessing cardiac output up to 5 hour without recalibration in porcine septic shock model [78]. When systemic vascular resistance decreased by prostaglandin E1, PiCCO™ underestimate cardiac output up to 40% compared with that by thermodilution method [79].

Intrathoracic blood volume calculated by PiCCO™ shows cardiac preload [80] and extravascular lung water is an indicator of acute pulmonary edema [81]. Stroke volume variation calculated by PiCCO™ is affected by the depth of tidal volume under mechanical ventilation [82]. However, the presence of severe arrhythmias, valvular regurgitation, or intra- or extra cardiac shunts gives inaccurate results [78]. The pulse pressure variation and stroke volume variation are only reliable in fully sedated, mechanically ventilated patients with a relatively high tidal volume.

Non-invasive cardiac output measurement is performed with the HDI/Pulse Wave CR-2000 Cardiovascular Profiling Instrument™ (Hypertension Diagnostics, Inc., Eagan, MN, USA). With this, radial artery pressure waveforms are obtained non-invasively using a tonometer applied to the skin of the distal forearm overlying the radial artery. The arterial pressure waveforms are calibrated with a blood pressure cuff. In critically ill hemodynamically unstable patients, cardiac output measured by the HDI/Pulse Wave CR-2000 Cardiovascular Profiling Instrument™ was significantly lower than those

measured by trans pulmonary thermodilution or PiCCO™ [83]. A significant increase in the invasively determined cardiac output (by thermodilution or PiCCO™) was observed when a fluid bolus was administered, though these changes were not reflected by the non-invasive method by the HDI/Pulse Wave CR-2000 Cardiovascular Profiling Instrument™ [83].

Wesseling's cZ method (BMEYE, Academic Medical Center, Amsterdam, the Netherlands) relates cardiac output to the area under the systolic portion of the arterial pressure wave. Dividing area under the systolic portion of the arterial pressure wave by aortic impedance provides a measure of stroke volume. The Modelflow method (BMEYE) simulates the classical three-element Windkessel model; characteristic impedance, Windkessel compliance, and peripheral resistance to estimate cardiac output. The Hemac pulse contour method is based on a three-element Windkessel model similar to the Modelflow method. The Modelflow method uses in vitro non-linear relations between cross-sectional area of the aorta and arterial pressure described by Langewouters [84], while the Hemac method uses in vivo measurements of patients to correct the Langewouters relations. Among the PiCCO™, LiDCO™, Modelflow method, Wesseling's cZ method, and Hemac method, Modelflow and Hemac methods showed the best results in absolute values and in tracking changes in cardiac output in patients without congestive heart failure, with normal heart rhythm and reasonable peripheral circulation [85].

The partial CO₂ rebreathing method (NICO™, Novamatrix Medical Systems, Wallingford, CT, USA) uses changes in CO₂ elimination and end-tidal CO₂ measured in response to a brief rebreathing period to calculate pulmonary blood flow. NICO™ provides an accurate estimate of cardiac output after induction of anesthesia, but underestimates cardiac output after aortic cross clamping and declamping in abdominal aortic aneurysm surgery [86]. Continuous cardiac output measured by Vigilance™ shows a relatively smaller degree of bias than NICO™ but overestimates cardiac output at the end of the surgery [86]. In the author's experience, NICO™ is quite unstable to have large variations in a stable hemodynamic state during general anesthesia.

Thoracic electrical bioimpedance is based on the theory that the thorax is a cylinder that is perfused with a fluid (blood) of a specific resistivity. Thoracic bioimpedance is the electrical resistance to high frequency low amplitude current that is transmitted from electrodes placed on the upper and lower thorax. Thoracic bioimpedance is affected by tissue fluid volume and changes in the volume of pulmonary and venous blood induced by respiration. Intraoperative environment is not conducive to thoracic electrical bioimpedance measurements of cardiac output due to interference by noise from electric cautery, mechanical ventilation and surgical

manipulation. Thoracic electrical impedance method (BioZ.com™; Cardiodynamics International, Now SonoSite, Seattle, WA, USA) does not correlate with continuous measurement by Vigilance™ in cardiac surgery [87]. Cardiac output measurements by thoracic electrical bioimpedance/electrical velocimetry (Aesculon, Osypka Medical, Berlin, Germany) and that measured by PiCCO™ were not interchangeable in septic patients [88].

Flow measurement by pulse-wave Doppler across a cardiac valve or in the left ventricular outflow tract and the assessment of the cross-sectional area at the site of the flow quantification (aortic valve) allow cardiac output measurement by transesophageal echocardiography. A Doppler beam orientation strictly parallel to the blood flow and an unchanged cross-sectional area over time are needed for optimal measurement. Esophageal Doppler only measures descending aortic blood flow, and excludes flow to the aortic arch vessels. This method is highly operator dependent. Both esophageal Doppler and pulse contour analysis by PiCCO™ lack sufficient accuracy to measure rapidly changing beat-to-beat stroke volume over a short time period under a wide range of conditions [89]. The real benefit of echocardiography is the visualization of ventricular function, wall motion abnormalities and cardiac filling as well as the real time guidance of fluid therapy in acute, critical hemodynamic situations.

In summary, many low- or non-invasive measurements of cardiac output have been developed, but all of these can be used to observe the changes of cardiac output only in almost normal heart, not in low or high cardiac output, valvular diseases, or arrhythmias.

Ultrasound

As shown in the previous section, transesophageal echocardiography is useful for the visualization of ventricular function, wall motion abnormalities, embolic and thrombotic structures, and cardiac filling as well as the real time guidance of fluid therapy in acute, critical hemodynamic situations. Practice guidelines for perioperative transesophageal echocardiography is published in Anesthesiology [90]. For adult patients in open heart surgery, transesophageal echocardiography should be used to confirm preoperative diagnosis, detect unsuspected pathology, adjust intraoperative management, and assess the results of surgery. In non-cardiac surgery, for patients with suspected hemodynamic, pulmonary, or neurologic compromise, transesophageal echocardiography may be useful. However, this is one of the invasive monitors to have potential complications such as esophageal perforation, esophageal injury, hematoma, laryngeal palsy, dysphagia, and dental injury. Therefore, this should be used only for the patients who

really can get benefit from echocardiography.

Ultrasound is also quite useful for vascular access such as central venous cannulation [91] and arterial cannulation [92] decreasing neurological complications and pneumothorax. It is well known that ultrasound-guided cannulation of internal jugular vein decreases arterial puncture and multiple attempts, and decreases the time for cannulation [91]. In contrast to the internal jugular vein, ultrasound guided access to the subclavian or axillary vein is sometimes difficult in central part of subclavian vein due to the sound barrier generated by the clavicle bone, while lateral approach can visualize the vein [93].

Recent most prominent advance in ultrasound is its use in peripheral nerve block. Using the ultrasound to depict the nerve and surround structures can make the needle direction to reduce unintended violation of vessels and organs [94]. To improve the discrimination of the needle, some modifications of needles are performed [95,96]. Thus, ultrasound guidance shortens the block performance time and reduces the number of needle passes [97]. The visually controlled injection of the local anesthetic ideally results in a circumferential spread around the targeted nerve [98], reduction of the volume of local anesthetic [99], and decrease in the onset time of the block [100]. For a catheter insertion in peripheral nerve, ultrasound guide is also useful to improve effectiveness and decreases the number of needling and procedural pain [101]. Epidural puncture is sometimes difficult by blind loss of resistance method, especially in obese patients. The potential of ultrasound-guided epidural puncture is somewhat limited by the interfering bone structure and the relatively deep position of the epidural space, which detracts from the quality of the images [102]. In children, usually regional anesthesia is performed under general anesthesia. Therefore, ultrasound-guided block is useful to decrease complications [103].

Most recent advances are using three- or four-dimensional ultrasound imaging [104,105] and changing the ultrasound beam insertion angle to detect the insertion needle better. However, most important in using ultrasound is to learn anatomy specified for ultrasound.

In summary, now ultrasound is quite useful to monitor cardiac performance, to insert some kinds of catheters, to perform various kinds of nerve block. We need to learn anatomy for ultrasound.

Percutaneous Oxygen and Carbon Dioxide Tension

Percutaneous oxygen saturation (SaO_2) measured by pulse oximetry is now a routine monitor of oxygenation. However, SaO_2 shows oxygen binding to hemoglobin, not dissolved oxygen measured as an arterial oxygen tension (PaO_2). The

arterial carbon dioxide tension ($PaCO_2$) is an important indicator of respiratory function and ventilation during anesthesia, sedation, and in the intensive care unit. To measure PaO_2 and/or $PaCO_2$, arterial puncture or cannulation and withdrawal of blood are necessary. End-tidal carbon dioxide tension ($EtCO_2$) monitoring is non-invasive and continuous monitoring in intubated patients, but it is not accurate in non-intubated patients and underestimates $PaCO_2$ [106].

Percutaneous measurements of oxygen tension ($tcPO_2$) and carbon dioxide tension ($tcPCO_2$) are non-invasive and are investigated much in infants [107] because it is difficult to insert arterial catheter and not so much blood can be withdrawn in infants. Several monitors to measure $tcPO_2$ and/or $tcPCO_2$ and/or $tcPO_2$ have been developed. TCM 400TM (Radiometer, Copenhagen, Denmark) can measure $tcPO_2$ simultaneously at 6 locations. TCM3TM and TCM4TM (Radiometer) can measure $tcPO_2$ and $tcPCO_2$ with one electrode. SenTec Digital MonitorTM (Sentec AG, Therwil, Switzerland) and TOSCATM (Linda Medical Sensors, Basel, Switzerland) use ear sensor to measure $tcPCO_2$ and SpO_2 . All the monitors use the electrode as same as that used in blood gas analyzer; the Clark type electrode for $tcPO_2$ and glass pH electrode for $tcPCO_2$ with chloride silver electrode as a reference [108].

The electrodes of the TCM3TM and TCM4TM can be put anywhere. In our study, $tcPO_2$ and PaO_2 , $tcPCO_2$ and $PaCO_2$ or $EtCO_2$ correlated well when the electrode of TCM4TM was put on the chest, but not on the upper arm or forearm during general anesthesia for abdominal surgery [109]. However, limits of agreement were too large to use $tcPO_2$ and $tcPCO_2$ as surrogate measures of PaO_2 and $PaCO_2$ wherever the electrode was put on during general anesthesia in adult [109]. In patients after elective cardiac surgery, the best agreement between $tcPCO_2$ measured by TOSCATM and $PaCO_2$ was found during normo- and hypoventilation [110]. In this study, Baulig et al. [110] suggested that the location of the sensor at the ear lobe might not be the optimal place for transcutaneous detection of oxygen saturation and pulse rate in patients early after cardiac surgery.

To arterialize capillary, skin under the electrode should be heated, but high temperature causes burn injury. The electrode of the TCM4TM should be heated to at least 43°C to have good correlation of $tcPO_2$ and $tcPCO_2$ with PaO_2 and $PaCO_2$ [111]. Less than 2 hours continuous monitoring induced no burn injury [111]. In the majority of patients, an initial overshoot and/or a drift to lower $tcPCO_2$ was observed with SenTec Digital MonitorTM [110]. An initial heating of the ear sensor to 45°C for the first 15 min. and then a decrease to 42°C prevented the overshoot and provided valid $tcPCO_2$ [112].

$TcPCO_2$ and $EtCO_2$ correlated well with $PaCO_2$ during general anesthesia, while the difference between $EtCO_2$ and $PaCO_2$ was greater than that between $tcPCO_2$ and $PaCO_2$ [113].

TcPCO₂ by TCM3™ was more accurate than EtCO₂ in patients receiving artificial ventilation via an endotracheal tube and it was also more accurate than the nasal EtCO₂ in patients breathing spontaneously [114]. TcPCO₂ measured by TOSCA™ demonstrated better agreement with PaCO₂ than nasal EtCO₂ for patients under monitored anesthesia care with deep sedation.

TcPCO₂ was reported to be more sensitive for detection of hypoventilation than EtCO₂ [115]. Kopka et al. [116] and McCormack et al. [117] showed that tcPCO₂ was useful to detect hypoventilation by analgesia after surgery. However, they had no any other monitors, as a control to compare with tcPCO₂, therefore, its usefulness is questionable. Nasal EtCO₂ is inaccurate because patients breathe through both nose and mouth.

There was insufficient agreement between tcPCO₂ derived from SenTec Digital Monitor™ or TOSCA™ and PaCO₂ for both the absolute values and trends [118]. During general anesthesia, ear and face become cold. Therefore, even if ear sensor is heated, the difference between tcPCO₂ and PaCO₂ might be larger than that sensor is put on the trunks considered from the author's experience.

It is well recognized that the absolute value of tcPO₂ is far from PaO₂. However, as shown above, tcPO₂ and PaO₂ correlated well when the electrode of TCM4™ was put on the chest [109]. Therefore, only the trend is useful to use tcPO₂ as surrogate of PaO₂.

In spinal anesthesia, vasodilation occurs in anesthetized area by sympathetic block. The author investigated the changes in tcPO₂ in spinal anesthesia whether we can detect sympathetic block by changes in tcPO₂. TcPO₂ increased in the anesthetized area by spinal anesthesia. After oxygen administration, the increase in tcPO₂ was larger in the non-anesthetized area, although the absolute values were not different between anesthetized and non-anesthetized areas [119]. Therefore, measurement of tcPO₂ may have a role to check anesthesia level of spinal anesthesia when patient cannot answer to questions and cannot respond to stimuli.

In summary, tcPCO₂ can be used to know the changes of PaCO₂ when the electrode is put on the trunks at 43°C, while the availability of tcPO₂ is lower than tcPCO₂.

Airway Observing Device

For tracheal intubation, laryngoscopy with Macintosh or Miller blade has been ordinarily used. In recent years, advances in optical technologies have facilitated the development of multiple novel indirect laryngoscopes. There are tremendous publications of airway observing devices. To view the larynx during laryngoscopy, a head-mounted camera (Airway Cam™,

Airway Cam Technologies, Wayne, PA, USA) was first developed for training purpose [120], but the camera interferes with the trainee's line of sight and the view was still limited to the 15° of a standard Macintosh blade. A superior system has been developed in which both a light source and micro camera are at the tip of the laryngoscope, one using a special laryngoscope (GlideScope™; Verathon Medical, Bothell, WA, USA) and the other using a standard Macintosh blade (BERCI DCI™ Video Laryngoscope; Karl Storz, Tuttlingen, Germany). Both have a display monitor mounted on a standing pole or on the table. In the study of teaching laryngoscopy to trainee, BERCI DCI™ Video Laryngoscope showed the benefit to decrease number of attempts and repositioning and teeth trauma [121]. GlideScope™ significantly improved the laryngeal exposure to facilitate tracheal intubation [122].

Some new devices have display monitor on the laryngoscope. The anatomically shaped blades of the Airway Scope™ (Pentax, Tokyo, Japan) and Airtraq™ (Prodol Meditec, Vizcaya, Spain) do not require alignment of the oral, pharyngeal, and tracheal axes to visualize the glottic opening, and, therefore, less force is applied during laryngoscopy. The differences between these two are, Airway Scope™ is designed to use as a Miller blade (with the tip of the blade under the epiglottis), but Airtraq™ is recommended to use as a Macintosh blade (with the tip of the blade in the vallecula), the Airway Scope™ has shorter distance from the tip of the blade to camera or lens than Airtraq™, which gives wider view of the Airtraq™. In our study by expert anesthesiologists, Macintosh laryngoscope was better than the Airway Scope™ and the Airtraq™ in patients with Cormack and Lehane classification 1 or 2, while these two were better than the Macintosh laryngoscope in patients with Cormack and Lehane classification 3 or 4 (personal communication). The time to intubation with Airway Scope™ was significantly shorter than with Airtraq™ and Macintosh laryngoscope for medical students in manikin study [123].

Tracheal intubation with Airway Scope™ but not with the Glidescope™ decreased hemodynamic changes by intubation compared with the Macintosh laryngoscope [124]. Tan et al. [125] also showed that the Airway Scope™ is better to improve tracheal intubation than Glidescope™ in a manikin study. The use of Airway Scope™ may be impaired in patients with difficult mouth opening, because the width of the blade is greater than Macintosh laryngoscope. From this reason, for morbid obese patients, sometimes Macintosh laryngoscope is better than the Airway Scope™ in our experience.

Truview EVO2™ (Truphatek International, Netanya, Israel) laryngoscope blade incorporates an optic side port to its curved blade and provision for O₂ insufflation. In manikin study, in the simulated easy laryngoscopy scenarios, there was no difference among the Airway Scope™, Truview EVO2™, Glidescope™

and Macintosh laryngoscope [126]. In more difficult tracheal intubation scenarios, Glidescope™ and Airway Scope™, and to a lesser extent TruviewEVO2™ demonstrated advantages over the Macintosh laryngoscope including a better view of the glottis, greater success of tracheal intubation, and ease of device use [126]. Airway Scope™ was more successful in achieving tracheal intubation, required less time for intubation, caused less dental trauma.

McGrath™ (Aircraft Medical, Edinburgh, UK) is a self-contained video laryngoscope. For the trainees, duration of intubation was longer with McGrath™ than with Macintosh laryngoscope in uncomplicated tracheal intubation [127]. Ray et al. [128] reported that novices achieved a higher successful tracheal intubation with less dental trauma with the McGrath™ compared with the Macintosh laryngoscope, while intubation time was similar. In the study using manikin to compare Glidescope™, McGrath™, Airtraq™, and Macintosh laryngoscopes, Airtraq™ consistently provided the most rapid intubation. Laryngeal grade views were superior with the Airtraq™ and McGrath™ than with the Glidescope™ [129].

The LMA CTrach™ (SEBAC, Pantin, France) is an intubating laryngeal mask airway with a detachable liquid crystal display. This system enables viewing of the larynx and the process of endotracheal intubation through the laryngeal mask airway. However, the display is too big to attach it to the LMA during insertion. Therefore, the display should be attached after insertion of the device. The mean time to see the glottis and tracheal intubation were shorter with the Airtraq™ than the LMA CTrach™ [130].

StyletScope™ (Nihon Kohden, Tokyo, Japan) uses a plastic fiberoptic imaging system incorporated into an endotracheal tube stylet that can be flexed by the handle. Intubation time was significantly shorter with Airway Scope™ than with StyletScope™ [131]. Many other this kind of devices have been developed, but not so much used.

In summary, Airway Scope™, Airtraq™, and McGrath™ might be better than other devices for difficult intubation, while for patients with Cormack and Lehane classification 1 or 2, these devices are not necessary because Macintosh is better.

Pulse Oximeter

Pulse oximeter is now one of the routine monitors to know oxygen saturation. However, it is well known that skin pigmentation, dye infusion, peripheral hypothermia, etc. interfere the measurement of pulse oximeter. Van Oostrom et al. [132] reported that a flameless stereotactic neurosurgical positioning system reduced the accuracy of pulse oximeter measurement. Infrared pulse waves from neurosurgical navigation system also interfere with pulse oximeter measurement [133]. A single layer

of aluminum may inhibit the interference.

Some new indices using pulse oximeter are developed. Plethysmographic (pulse oximetry) waveform variation and delta pulse oximetry plethysmography increased significantly by hypovolemia [134].

Photoplethysmographic waveform variation is used to detect volume changes in the microvascular bed of tissues [135] and it is also a reliable monitor of changes of sympathetic function [136]. Perfusion index derived from photoplethysmography waveform analysis provides an earlier and a clearer indication of sympathetic block than changes in blood pressure [137].

Pleth variability index is a new algorithm allowing for automated and continuous calculation of respiratory variations in the pulse oximeter plethysmographic waveform amplitude. In patients ventilated with tidal volume over 8 ml/kg under sedation, pleth variability index can detect hemodynamic effects of positive end-expiratory pressure [138].

In summary, similar to arterial waveform analysis, some indices derived from pulse oximeter waveform are developed. However, these might have more variations than arterial waveform analysis in author's experience, which make these difficult to be popular.

Cerebral Monitoring

Intracranial pressure is sometimes monitored postoperatively or in patients with traumatic brain injury. To measure intracranial pressure, we need to insert the catheter. As a non-invasive monitor, transcranial Doppler (TCD) has been used to measure cerebral blood flow of major intracranial artery such as middle cerebral artery, anterior cerebral artery, vertebral artery, etc. It is commonly used to detect vasospasm after subarachnoid hemorrhage. After the experience of brain stem infarction after aortic arch replacement for dissecting aortic arch aneurysm, the author routinely check blood flow of both vertebral artery by TCD before such surgery to determine whether we need to supply every three branches of aortic arch. Engelhardt et al. [139] showed that detection of foramen ovale using TCD and contrast medium before surgery scheduled in sitting position was useful to avoid air embolism. TCD is also used to check autoregulation of cerebral blood flow [140] and cerebral perfusion during carotid endarterectomy [141]. For continuous monitoring, the probe of TCD should be kept in the same position, but it needs high skill, which is the problem to use TCD during general anesthesia.

During carotid endarterectomy, Pugliese et al. [141] said that regional cerebral oxygen saturation (SctO₂) measured by near-infrared spectroscopy (INVOS Cerebral Oximeter™, Somanetics Troy, Michigan, USA) decreased with more relation with neurological symptom than blood flow velocity by TCD. They

concluded that SctO₂ is better than cerebral blood flow velocity to detect cerebral hypoxia. However, when SctO₂ decreases, neurological symptom occurs, which means it is too late when SctO₂ decreases. Therefore, from their results, the author thinks that decrease in cerebral blood flow velocity should be used to avoid hypoxic brain damage. Fischer et al. [142] also reported that decrease in SctO₂ correlated well with decrease in blood pressure and increase in SctO₂ correlated well with increase in EtCO₂ in beach chair position to conclude that SctO₂ was useful. However, if these correlations were well, blood pressure and EtCO₂ are enough to suspect the changes of SctO₂.

SctO₂ shows local oxygen saturation, while jugular venous oxygen saturation (SjO₂) provides global cerebral oxygen consumption. In addition, increase in path length of near-infrared light in pathologic conditions such as brain swelling can affect the accuracy of SctO₂. Therefore, SctO₂ should be interpreted carefully, while SjO₂ may indicate the balance of cerebral blood flow and cerebral metabolic rate of oxygen.

Measurement of brain tissue oxygen partial pressure (PbO₂) is increasingly used in the intensive care unit. For this measurement, insertion of the sensor into brain parenchyma is necessary. PbO₂ less than 8–10 mmHg shows a high risk of ischemia [143], tissue pH less than 7.0 and brain tissue carbon dioxide partial pressure (PbCO₂) greater than 60 mmHg increase the risk of vasospasm [144]. Changes in PbO₂ correlated well with changes in SjO₂, particularly when the sensor was inserted into non-contusional area of brain [145].

Recently, cerebral microdialysis is applied in critically ill patients. This allows on-line monitoring of changes in brain tissue chemistry, achieved by inserting a catheter lined with polyamide dialysis membrane into brain parenchyma, which is perfused with a physiological solution. However, this has disadvantages such as disruption of local tissues, small hemorrhages, astrogliosis and macrophage infiltration [146], while cerebral microdialysis has great potential for exploring the pathophysiology of acute brain injury, pharmacokinetics of drugs within the central nervous system and the response to therapeutic intervention.

In summary, cerebral monitoring is difficult but quite important in the management of critically ill, therefore, further improvement or new development are expected.

Conclusion

Recent advance in clinical monitoring is tremendous. However, each monitor has advantage and disadvantage of its own. We should not completely trust on these monitors, but every time we need to combine some kinds of parameters to confirm patients status including traditional blood pressure, heart arte, etc.

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