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REVIEW PAPER

Journal of Clinical Monitoring and Computing 2016 end of year summary: cardiovascular and hemodynamic monitoring

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Abstract The assessment and optimization of cardiovascular and hemodynamic variables is a mainstay of patient management in the care for critically ill patients in the intensive care unit (ICU) or the operating room (OR). It is, therefore, of outstanding importance to meticulously validate technologies for hemodynamic monitoring and to study their applicability in clinical practice and, finally, their impact on treatment decisions and on patient outcome. In this regard, the Journal of Clinical Monitoring and Computing (JCMC) is an ideal platform for publishing research in the field of cardiovascular and hemodynamic monitoring. In this review, we highlight papers published last year in the JCMC in order to summarize and discuss recent developments in this research area.

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1 Introduction

The assessment and optimization of cardiovascular and hemodynamic variables is a mainstay of patient management in the care for critically ill patients in the intensive care unit (ICU) or the operating room (OR). It is, therefore, of outstanding importance to meticulously validate technologies for hemodynamic monitoring and to study their applicability in clinical practice and, finally, their impact on treatment decisions and patient outcome. In this regard, the Journal of Clinical Monitoring and Computing (JCMC) is an ideal platform for publishing research in the field of cardiovascular and hemodynamic monitoring. In this review, we highlight papers published last year in the JCMC in order to summarize and discuss recent developments in this research area.

2 Cardiac output monitoring

In 2016, various cardiac output (CO) monitoring technologies and ways to evaluate them were featured in the JCMC. The emphasis in CO monitoring has shifted in recent times from invasive methods to less-invasive and totally noninvasive technologies [1]. This shift has been fueled by greater public awareness of patient safety, need for simpler to apply technologies, and goal-directed therapies that require continuous CO readings.

2.1 Cardiac output monitoring: pulse contour analysis

The analysis of the pulse contour of an arterial pressure waveform allows the estimation of CO. The arterial pressure waveform signal can either be recorded invasively (using an arterial catheter) or noninvasively (using innovative technologies) [2, 3]. Pulse contour analysis-derived CO values can be used "uncalibrated" (i.e., calibrated to biometric and physiological data) or calibrated to an external CO measurement (e.g., transpulmonary thermodilution (TPTD), lithium dilution).

In the February issue, Ganter et al. [4] assessed the accuracy of continuous CO monitoring derived from uncalibrated pulse contour analysis (FloTrac sensor; Edwards Lifesciences, Irvine, CA, USA) and of continuous thermodilution obtained with a pulmonary artery catheter (PAC) (Edwards Lifesciences) in 51 adult patients suffering from septic shock. Intermittent pulmonary artery thermodilution (PATD) with bolus injections of cold saline served as the reference technique. In this study, neither uncalibrated pulse contour analysis nor the continuous PAC measurements met the 30% percentage error cut-off compared with PATD. Likewise, both continuous techniques failed to adequately reflect trends in the time course of CO. This study adds further evidence to the fact that the FloTrac-technique may lack accuracy in patients suffering from vasoplegia. It has to be acknowledged though that the authors did not use the most recent software version with the FloTrac sensor in their study. It, therefore, remains unknown whether the newest software generation would have performed better. With regard to the continuous PAC-measurements, the study remembers the clinician of an important drawback of the continuous CO assessment with the PAC: the slow response times of several minutes that clearly impair accuracy in situations in which rapid and dynamic hemodynamic changes are typically occurring. As a consequence, clinicians should always opt for bolus thermodilution, whenever in doubt about the reliability of a particular measurement.

In the October issue, Scully et al. [5] report the effect of recalibration times on the accuracy of CO measurements derived from arterial pulse contour analysis. Using an impressive database of a huge ICU patient population, the authors found that the error between pulse contour analysis and PATD increased with longer (8 and 24 h) versus shorter recalibration intervals (1 and 2 h). Comparable findings were observed for the concordance analysis, i.e., when evaluating the capability of tracking changes in CO. It is well known that CO measurements derived from pulse contour analysis are inaccurate in situations of hemodynamic instability when acute and rapid changes of vascular tone occur unless short recalibration intervals down to 1 h are used [6]. In contrast, recalibration intervals of up to 24 h were not associated with a significant loss of accuracy when hemodynamic conditions were stable [7]. As a conclusion, fixed intervals for recalibration should no longer be considered appropriate for pulse contour analysis-based CO monitoring. Rather, recalibration should be individually prompted by alterations in patient treatment or whenever a change in the hemodynamic condition of the patient is suspected. Such recalibration strategies should be addressed in prospective studies.

As a consequence of marked increases in right ventricular afterload, underlying right ventricular dysfunction, or hypovolemia, patients undergoing lung transplantation are at a particularly high risk for intraoperative hemodynamic instability. This makes the use of advanced hemodynamic monitoring mandatory. Tomasi et al. [8] tested the accuracy of the Flotrac sensor in 13 patients undergoing single or double lung transplantations at their institution. In this study, the percentage error of the Flotrac sensor was high (up to 86%), suggesting that uncalibrated arterial waveform analysis is an inappropriate technique for CO monitoring during lung transplantation. Unfortunately, the authors used continuous thermodilution measurements obtained from a PAC as the reference technique, the accuracy/reliability of which has frequently been criticized [4]. It can be presumed that rapid changes in vasomotor tone, the use of vasopressors, and vasoplegia may all have reduced the accuracy of the Flotrac technique. Despite the above-mentioned limitations, the study clearly indicates that uncalibrated arterial pulse contour analysis should not be used as sole CO monitoring technique in lung transplantation. It has to be acknowledged anyway that lung transplantation is one of the very few operations in which the PAC remains indispensable for its ability to continuously monitor right ventricular afterload.

Wagner et al. [9] tested a new algorithm that computes CO by applying pulse contour analysis to arterial pressure waveform data derived from the completely noninvasive volume clamp method using the CNAP system (CNSystems Medizintechnik AG, Graz, Austria). The newly released CO algorithm was applied in a retrospective manner to previously obtained arterial pressure data. Wagner et al. found that the CO algorithm showed an acceptable percentage error (25%) with the reference technique, TPTD, when pulse contour analysis had been calibrated with the first TPTD measurement, but not when using an autocalibration procedure (based on biometric patient data). While this study represents an important step in the development of another noninvasive CO monitor, the interpretation and generalizability of the results were impaired by the fact that a substantial number of patients were in a hyperdynamic circulatory state and that a trending analysis was impossible due to the fact that the patients were hemodynamically relatively stable during the study period.

2.2 Cardiac output monitoring: transpulmonary thermodilution

TPTD is a well-validated and established method to assess CO using a central venous catheter (for cold indicator bolus injection in the central venous circulation) and a dedicated arterial catheter with a thermistor at the tip of the catheter (usually placed in the abdominal aorta through the femoral vein). TPTD has been suggested for hemodynamic monitoring in patients with complex circulatory shock (i.e., shock not responding to initial therapy or complicated by ARDS) [10].

In the December issue, Schmid et al. [11] evaluated the measurement performance of TPTD in comparison with PATD in 11 patients with cardiogenic shock treated in a medical ICU. The authors observed good agreement between TPTD-derived cardiac index (CI) and PATD-derived CI with a mean of the differences of 0.04 ± 0.35 L/min/m^2. Even during intra-aortic balloon pump (IABP) counterpulsation and during therapeutic hypothermia as well as in patients with mitral or tricuspid regurgitation, the agreement between these measurement techniques was good as illustrated by low mean differences and narrow limits of agreement. Based on their findings, the authors conclude that CI measurements by TPTD and PATD are interchangeable in patients with cardiogenic shock and even in patients with IABP, therapeutic hypothermia, and mitral or tricuspid regurgitation.

In a similar study also published in the December issue, Cho et al. [12] compared TPTD-CO with PATD-CO (and with CO estimated using uncalibrated pulse contour analysis) in 20 patients undergoing off-pump coronary artery bypass surgery. The mean difference between TPTD- and PATD-derived CO was −0.12 L/min (with 95% limits of agreement of −0.64 to 0.41 L/min) with a low percentage error of about 13%. Expectedly, the mean differences (95% limits of agreement) and percentage errors were higher when PATD was compared with calibrated and uncalibrated pulse contour analysis (−0.08 (−1.32 to 1.15) L/min; 29%) and (−0.05 (−1.47 to 1.37) L/min; 34%, respectively). In addition, TPTD showed good trending abilities (high concordance rate) for following changes in CO compared with intermittent PATD.

Despite the relatively small sample sizes these studies are valuable validation studies adding to the body of evidence that TPTD-based CO measurements show good agreement with PATD (which is still the clinical gold standard method).

In certain clinical situations, placement of a central venous catheter in the vena cava superior through the internal jugular or subclavian vein is not possible. In these cases, the central venous catheter is usually placed in the vena cava inferior through the femoral vein. As reported in the October issue, Kellner et al. [13] evaluated the impact of the insertion site of the central venous catheter (vena cava superior vs. vena cava inferior) on TPTD measurements in 28 surgical ICU patients. Based on Bland–Altman analysis, the authors found that TPTD using the femoral site for indicator injection (inferior vena cava) provided CI with high accuracy and precision compared with TPTD using indicator injection in the superior vena cava. The results of this study are in line with previous studies also describing that CO monitoring is possible with TPTP using a central venous catheter placed in the inferior vena cava [14, 15].

2.3 Cardiac output monitoring: innovative technologies (other than pulse contour analysis)

Besides pulse contour analysis, several other technologies for the noninvasive assessment of CO are available [3].

One of the newer CO technologies being introduced is modified pulse wave transit time (mPWTT) and the Japanese manufacturer of medical electronic equipment Nihon Kohden (Tokyo, Japan) produces a system that uses data from the electrocardiogram and pulse oximeter on the finger to produce a technology called estimated continuous cardiac output (esCCO). Terada et al. [16] report a study that compared esCCO to arterial pulse contour analysis CO (FloTrac sensor used with software version 3) using single bolus PATD CO as their reference method, subjects being 15 renal transplant patients with severe cardiac disease. The study shows esCCO to be marginally better when compared to pulse contour analysis in respect to accuracy, with percentage errors of 36% compared to 43%, and better ability to follow changes in CO or trending, with concordance rates on the four quadrant plot of 93% compared to 90% and better polar plot statistics. However, one is still left wondering whether esCCO is sufficiently reliable to be used routinely in clinical practice and whether one can base management decisions regarding giving IV fluid boluses and cardiovascular drug infusions intraoperatively on esCCO monitoring.

Impedance cardiography and electrical velocimetry, a newer impedance technology, featured in two papers [17, 18]. Osypka Medical (Berlin, Germany) produce a device called the AESCULON and its portable transport version called the ICON. It uses a four skin electrode montage and incorporates a modified impedance equation to determine stroke volume and CO. Trinkmann et al. [17] report a study that compared AESCULON CO readings with cardiac magnetic resonance (CMR) imaging-derived CO in 134 adult heart disease patients. CMR measurements have to be performed in the radiology department, time is spent analyzing the gated images to outline systolic and diastolic regions of interest, and simultaneous measurements using a test method are impossible. Their

results showed large discrepancies between AESCULON and CMR readings with a percentage error of 51%, but this result may reflect the heterogeneous nature of the study groups that included patients with a wide variety of heart and cardiovascular disease which may not be ideal for accurate calibration of the AESCULON which relies partly on input of patient demographic data such as height, body mass index, etc. The study provides no information on whether the AESCULON can be used reliably for tracking changes in CO in the hemodynamically unstable patient. The discussion provides a lot of information on impedance cardiography regarding poor study outcomes and its limitations in certain patient groups.

Suehiro et al. [18] published a systematic review and meta-analysis of minimally-invasive CO monitoring in children. Twenty papers were included. The review was based on the results from Bland–Altman style comparison studies. Suehiro et al. found in their meta-analysis an overall percentage error for electrical velocimetry of 24% from 8 studies, which was well below the benchmark of <30% set by Critchley and Critchley [19]. So, electrical velocimetry may be useful for monitoring CO in pediatric anesthesia and the critical care unit. Also, their meta-analysis found that 2D echo Doppler which was used in 9 studies to be the most reliable noninvasive reference method in children. The paper of Suehiro et al. provides an excellent example of how to perform a modern day meta-analysis using Bland–Altman statistics. With the recent publication in the literature of high quality meta-analyses the need for and calls to produce standards on how the results of such CO validation studies should be reported have emerged, so that study outcomes can be easily understood and incorporated into future reviews [20].

The noninvasive transthoracic Doppler method of measuring CO featured in three papers, the monitoring device being the UltraSound Cardiac Output Monitor (USCOM) (Uscom; Sydney, Australia). Gregory et al. [21] describe an in-vitro Mock Circulation Loop (MCL) test rig that generates pulsatile blood flows that can mimic a range of circulatory conditions and can be used to test circulatory implants such as heart valves. A mock aorta within the test rig set up was used to test the ability of USCOM users to insonate flow across the aortic valve and perform USCOM scans. Data assessing the abilities of three users to perform USCOM scans was presented. There is a good discussion section on user variability and learning curves when performing USCOM scans. However, there was no mention of the problems of aging and morphological changes within upper thorax which Huang et al. have shown recently affect the ability to perform reliable USCOM scans [22, 23]. The MCL test rig is potentially a useful teaching aid and research tool.

Zhang et al. [24] compared USCOM readings with those of a bioimpedance device, the NICOM (Cheetah; Tel Aviv, Israel), in healthy volunteer athletes (n = 14) being tilted head up. The NICOM uses an advanced method of analyzing the impedance signal called bioreactance which measures phase-shift rather amplitude change of the transthoracic impedance signal. Tilting causes postural and adaptive changes in the circulation including decreases in stroke volume that are related to the angle of head up tilt [25]. There were significant differences in the stroke volume measurements between the two methods with USCOM following the well described and expected gravitational induced changes, while the NICOM appeared to under read the stroke volume changes and overestimated the pre-tilt baseline readings when compared to USCOM. Tilting causes significant increases in the peripheral vascular tone which appeared to affect the NICOM's measurements.

Another paper by the same group authored by Huang et al. [26] provides an analysis of the combined data from three trend analysis studies (n = 53 patients) in which the authors used minimally invasive Doppler CO methods, USCOM and oesophageal Doppler, to produce an intraoperative model of reliable CO trends against which other minimally invasive CO monitoring devices can be assessed, most notably the NICOM [27, 28]. Their dual Doppler method used the combination of two Doppler methods to determine the most reliable CO reading at each of the time points, which were then used to generate a reference trend-line for making comparisons. After normalization of data from each subject (7–21 readings per case) in order to eliminate systematic errors due to variations in calibration the percentage error between data pooled from the two Doppler methods was reduced from 38 to 14%. The concordance rate between the two Doppler methods was 97% with polar plot data confirming reliable trending ability. In 83% of included cases the correlation between the two methods was excellent ($R^2 > 0.80$) and in 96% it was good ($R^2 > 0.60$). The dual Doppler intraoperative model has the potential to evaluate the trending ability of other continuous minimally invasive CO technologies.

3 Hemodynamic monitoring using dynamic cardiac preload parameters

Dynamic preload indices such as stroke volume variation (SVV) and pulse pressure variation (PPV) have gained increasing popularity for fluid management based on the assessment of fluid responsiveness.

The diagnostic accuracy of SVV for the prediction of fluid responsiveness has not yet been thoroughly tested in patients with impaired left ventricular (LV) function. Montenij et al. [29] investigated the validity of

SVV derived from uncalibrated pulse contour analysis (FloTrac sensor) in 22 patients with a LV ejection fraction <40% undergoing coronary artery bypass grafting. Prior to sternotomy (i.e., under closed-chest conditions), the patients received a standardized fluid bolus, and the diagnostic performance of SVV for the prediction of a 15% increase in CO was analyzed using common test statistics. Notably, the diagnostic performance of SVV derived from uncalibrated waveform analysis was disappointing, with a positive predictive value and an overall accuracy as low as 56 and 64%, respectively. This study highlights another potential and important caveat for functional hemodynamic monitoring, i.e., limited accuracy in patients with impaired LV function (and hence unfortunately in a patient population that probably is in most need for a reliable assessment of preload and preload reserve). Further trials are warranted to test whether these results can be confirmed in larger patient populations.

In the February issue, Kong et al. [30] tested the hypothesis that different vasopressors would affect SVV and PPV to a different extent. In hemodynamically stable patients under general anesthesia, Kong et al. infused different doses of phenylephrine, dopamine, or ephedrine titrated to reach predefined increases in arterial pressure. They found the dynamic preload indicators to be significantly decreased by (in descending order) phenylephrine, dopamine, and ephedrine. The investigators attribute their findings to the different effects of these various substances on venous tone (venoconstriction leads to an increase in stressed volume and hence preload) and on heart rate (with tachycardia decreasing cardiac filling times). Unfortunately, changes in preload were not measured in this study. Moreover, the authors did not elaborate the possibility that increases in afterload per se could have an effect on the magnitude of SVV and PPV. Last, the authors did not test whether SVV or PPV are still valuable predictors of fluid responsiveness when vasopressors are infused.

Stens et al. [31] studied the accuracy of SVV and PPV that were obtained with the Nexfin monitor (now called Clearsight; Edwards Lifesciences) in mechanically ventilated patients during general anesthesia. The Trendelenburg position was used as a fluid challenge. Both SVV and PPV predicted a 10% increase in stroke volume with a fair accuracy (area under the curve in the receiver operating characteristic curve 0.73 and 0.64, respectively). Interestingly, the investigators found a significant bias between SVV and PPV which was clearly dependent on age. Further studies must test whether this bias is inherent to the CO measurement algorithm or reflective for an altered vascular compliance in older patients.

4 Hemodynamic monitoring using photo-plethysmographic signals

This section will focus on hemodynamic monitoring using photo-plethysmographic (PPG) signals usually measured non-invasively at peripheral sites such as the finger or the earlobe. In recent years, photo-plethysmography, i.e. the optical detection of a pulse signal, has gained widespread applications going far beyond its use for pulse oximetry. In theory, the PPG signals contain as much information as the arterial pressure waveform, including ventricular contractility, pulse rate variability, arterial elastance or stiffness, pulse wave velocity etc., and should be influenced in a similar manner by vascular reactions such as vasoconstriction.

In the April issue of the journal, Hemon and Phillips [32] tried to find the foot point of a pulse wave measured by earlobe plethysmography in healthy volunteers. The correct identification of the foot point is essential when the PPG waveform is used to determine pulse arrival time at the periphery, such as applied for continuously measuring trends in CO by pulse wave transit time [16]. The authors used six methods of deriving the pulse period, each based on a different method of finding specific landmark points on the complex PPG waveform, and compared these to RR-intervals simultaneously derived from the electrocardiogram as the reference. They choose the foot point of the PPG waveform, reflecting the arrival of the pulse, over other waveform characteristics like the peak of the waveform, since the foot point is less sensitive to wave reflections from distal sites. Although the mean pulse periods agreed closely with the mean cardiac period over the 15-min measurement period, the instantaneous pulse period showed noticeable variation with instantaneous cardiac period depending on the pulse period derivation method. The best correlation with cardiac period was found for pulse period derived with the intersecting tangents method, i.e. the intersection point of the tangent to the maximum gradient and tangent of the minimum value, the latter being horizontal by definition. These results suggest that the 'foot' of the PPG wave gives a more reliable indication of the timing of the pulse than the peak, confirming the expected sensitivity of the peak position to wave reflections from the periphery. The authors speculate that with such an accurate determination of pulse period, pulse rate variability as determined non-invasively with PPG might replace heart rate variability, which requires electrocardiogram recording.

Another investigation on the PPG waveform morphology was published in the October issue of the journal by Hickey et al. [33]. They performed a hand elevation study in 20 healthy volunteers who were bilaterally equipped with PPG sensors on both index fingers in order to better understand the complex pulsatile PPG signal. Changes in

multiple PPG waveform features including amplitude, pulse width, and crest time were compared between both hands, one of which was raised and lowered relative to heart level with the other remaining static. In general, PPG features were found to change with hand elevation. For instance, PPG amplitude increased with hand raising and decreased with hand lowering, while the dicrotic peak diminished in all subjects on hand elevation. The authors speculate that these morphologic changes in PPG waveform were caused by a combination of physical (hydrostatic) effects and physiological responses of vascular resistance. In particular, they hypothesize that changes in downstream (venous) resistance rather than in arterial inflow or arteriolar resistance are responsible for the observed effects. The study results imply that, like the arterial pressure waveform, the PPG waveform is affected by similar vascular mechanisms, although it primarily represents changes in vascular volume rather than pressure. Furthermore, the height of the measurement site relative to the heart level should be taken into account when interpreting the PPG morphology.

In the June issue of the journal, Høiseth et al. [34] looked at the respiratory variations in PPG waveforms, which are often used to predict fluid responsiveness non-invasively in patients not equipped with arterial lines [35]. The authors investigated whether the type of device used to measure the PPG waveforms matters, since processing of the PPG signal may vary between different devices. In 43 patients undergoing cardiac surgery they simultaneously measured PPG waveforms with two different pulse oximeters (Nellcor OxiMax; Covidien, Mansfield, MASS, USA and Masimo Radical 7; Masimo, Irvine, CA, USA) placed on two fingers of the same hand. From these, the respiratory variations of the PPG waveform amplitude (ΔPOP) were calculated over ten respiratory cycles as the difference between the maximal and minimal amplitudes (peak to trough) divided by the mean amplitude. These ΔPOP values were compared to PPV obtained invasively from the arterial waveform. Furthermore, the pleth variability index (PVI), a commercially available feature of the Masimo device calculated as the difference between the maximal and minimal perfusion index (PI)-values, was recorded. Fluid responsiveness was defined as an increase in stroke volume by >15% as obtained by esophageal Doppler. Comparing ΔPOP values between both pulse oximeters revealed a bias of 7% with wide limits of agreement (23%) and a percentage error of 164%. The Masimo specific variable PVI agreed more with the comparator (gold standard) PPV than the Nellcor ΔPOP. Both devices predicted fluid responsiveness moderately with similar areas under the ROC curves. The poor agreement between both devices raises questions about the validation of such monitors and their proprietary signal processing algorithms of the complex PPG waveforms for relevant endpoints before their clinical implementation. Separating cardiac from respiratory influences on PPG waveform variations might be needed, since the latter can affect the calculation of ΔPOP even in the absence of changes in the cardiac component, as nicely demonstrated by the authors using sine wave simulations. Nevertheless, the study shows that ΔPOP values obtained from different pulse oximeters are not interchangeable, and that the device used should be taken into consideration when interpreting data based on the PPG waveform.

Also in the June issue, Chu et al. [36] present a systematic review and meta-analysis of 18 studies including 665 patients on the question how accurate the PPG-derived PVI can predict fluid responsiveness in mechanically ventilated patients. This is based on the fact that fluid responsiveness cannot only be predicted by dynamic variables derived from the arterial waveform analysis, such as PPV or SVV, but also non-invasively from the PPG waveform. After pooling and analyzing the data from the 18 studies included from the literature, the authors found a sensitivity of 0.73 (95% CI 0.68–0.78) and a specificity of 0.82 (95% CI 0.77–0.86), respectively, for PVI to predict fluid responsiveness, with an area under the ROC curve (AUC) of 0.88 (95% CI 0.84–0.91). Subgroup analysis revealed no differences between OR (13 studies) and ICU settings (5 studies) with AUCs of 0.89 (95% CI 0.85–0.92) versus 0.90 (95% CI 0.82–0.94), respectively ($P = 0.97$). However, sensitivity was higher in the OR subgroup than in the ICU subgroup (0.84 (95% CI 0.78–0.88) vs. 0.56 (95% CI 0.47–0.64); $P < 0.01$). A possible reason for this could be a lower perfusion index in ICU patients due to peripheral hypoperfusion or vasopressor use, reducing the accuracy of PVI to predict fluid responsiveness. Changing the measurement site from digital (the finger) to cephalic sites (i.e. earlobe or forehead) might circumvent this problem [37]. The authors conclude that the ability of the PVI to predict fluid responsiveness is reasonable. It has to be noted that this statement applies to mechanically ventilated patients with a regular heart rhythm and cannot be extrapolated to patients breathing spontaneously or having arrhythmias, since heart–lung interaction due to positive pressure ventilation and regular heart rhythm are required. Furthermore, the amount of fluid needed for determining fluid responsiveness was not studied.

In the October issue, Zahari et al. [38] present an interesting re-analysis of data and developed adjustment algorithms to correct for offset and artefacts of previously published studies. To understand the history behind this study one has to discuss the Oxygen Saturation Targeting-New Zealand (BOOST-NZ) trial, which was aimed at assessing whether targeting an oxygen saturation of 85–89% compared with 91–95% increased or decreased the risk of death or neuro-disability at 18–24 months of age [39]. For this

purpose, an offset in the oxygen saturation readings of the 50 monitors used in the trial was introduced, displaying 3% higher oxygen saturation values in the lower oxygen saturation target group and vice versa, in order to mask the study intervention and separate the two saturation target groups. As a result, the BOOST-NZ trial oximeters revealed fewer oxygen saturation readings in the range of 87–90%, which was attributable to the calibration software. While this study demonstrated no outcome differences between groups, the software of the oximeter used (Masimo) was revised due to a OS calibration artefact after the study, which led to an increase in mortality in the lower oxygen saturation target group at hospital discharge in similar follow-up studies [40]. The aim of the current study [38] was therefore to smooth out the calibration artefacts in Masimo oximeters from the original calibration software in order to facilitate further analysis of the follow-up data. Oxygen saturation data from 257 of the 340 babies of the original BOOST-NZ trial who had at least 2 weeks (!) of data available were re-analyzed. The authors identified distinct patterns of oxygen saturation frequency distributions for the two oxygen saturation target oximeters, and adjusted the frequency distributions for the artefactual offsets by recovering the missing values eliminated by the offset. Consequently, the authors developed two three-step algorithms that can be used to adjust the readings of the higher and the lower oxygen saturation target oximeter readings, respectively. These algorithms were then validated using oxygen saturation data from another baby that had been obtained using a different type of oximeter (Siemens, Munich, Germany), confirming that the adjustment process was successful. These findings represent an important contribution to yield the actually achieved saturation values in both arms of the abovementioned randomized controlled trials and thus help with the interpretation of the associated outcomes of oxygen therapy in preterm infants.

A special application of dynamic preload indices to predict fluid responsiveness was published in the December issue by Lee et al. [41]. They investigated 42 ventilated patients in the beach chair position and compared the ability of the plethysmographic PVI to predict an increase in stroke volume index by 15% after a 6 ml/kg colloid bolus applied over 10 min with that of the arterial pressure waveform derived SVV and PPV. While providing some advantages concerning the surgical field, the beach chair position may compromise cerebral perfusion by reducing mean arterial pressure and thus cerebral perfusion pressure, as well as by decreasing venous return, intrathoracic blood volume, and thus CO. A prerequisite for maintaining cerebral perfusion is an adequate filling of the patients' vascular bed, and dynamic preload variables are generally used to predict fluid responsiveness. However, since different surgical positions may compromise the diagnostic accuracy of dynamic preload variables, the current study was undertaken. In the beach chair position before fluid loading, all dynamic preload variables were higher in fluid responders (n = 26) than in non-responders (n = 14). Interestingly, while all dynamic preload variables decreased after volume expansion in responders, the non-responders showed significant decreases only in SVV and PPV but not in PVI. The AUCs of the ROC curves for predicting an increase in stroke volume index of >15% were comparable with 0.83 for SVV, 0.81 for PPV, and 0.79 for PVI, the threshold values to discriminate responders from non-responders being 12, 15 and 10%, respectively. The authors conclude that the dynamic preload variables studied were reliable predictors of fluid responsiveness in ventilated patients in the BCP and may be used to guide fluid therapy also in this particular surgical position.

5 Hemodynamic monitoring and cardiovascular physiology

In the August issue, Pham et al. [42] investigated prospectively 281 patients admitted to the surgical ICU to determine the prevalence of prolonged QT intervals (QTc). The authors' hypothesis was that more than 50% of patients post-operatively admitted to the surgical ICU would have prolonged QTc [42]. In a cross-sectional study over a 15-month period, the authors found a high prevalence (67%) of long QTc among patients undergoing non cardiac surgery [42]. The present study was well designed as the authors performed electrocardiograms before and after ICU admission and the QT intervals were obtained from the computer measurement of the 12-lead electrocardiograms [42]. They averaged QT interval over the 12 leads of the electrocardiogram and corrected QT intervals (Bazett's equation) with QTc defined as prolonged when the value was higher than 440 ms. Not surprisingly, patients who had pre-admission long QTc (32% of patients) were more likely to have post-admission long QTc [42]. The authors also found that both pre- and intra-operative treatments with magnesium and beta-blockers reduced the likelihood of having post-admission long QTc. This finding is surprising, as antiarrhythmic drugs are well known to increase QT interval instead of decreasing it [43]. We may, also, regret that authors used single automatic electrocardiogram measurement software with a pre-processing tool to diminish electrocardiogram noise as some real signals could be considered as artefacts and removed by the automatic reading software. Moreover, the huge limitation of the present study is that, besides beta-blockers, the authors did not collect information about other pre-operative medications and the type of anesthesia.

In the October issue, Lu et al. [44] investigated the residual heart rate variability (HRV) measurement in patients following orthotopic heart transplantation (OHT). The aim of their study was to examine if HRV measures can be used as the indices of the presence of autonomic nervous modulation and thus as a demonstration of heart re-innervation 2 years after transplantation [44]. The authors studied 13 patients after OHT surgery receiving immunosuppressive therapy, and 14 patients 1–2 years after coronary artery bypass graft (CABG) surgery recruited as a control group [44]. The result was that the patients after OHT had smaller time and frequency domain HRV measures than patients after CABG, except that the heart rate and normalized high-frequency power (nHFP) of the OHT patients were greater than those of CABG patients [44]. This principal finding highlights that the use of nHFP as an index of vagal modulation might be doubtful in patients after OHT, as a high HR is supposed to be associated with a low vagal modulation (low nHFP). In this regard, even if OHT patients have residual HRV, its use for vagal modulation evaluation must be cautious.

With another report on HRV in adult patients undergoing elective surgery, Mandel-Portnoy et al. [45] in the issue of December reported a very nice study investigating the relationship between perioperative HRV and early postoperative mortality. In this retrospective case-control study they found that reduced intra-operative HRV was associated with increased mortality within 48 h postoperatively and this effect was seen in both the univariate and the multivariate analysis [45]. The authors studied 283 patients who died in comparison to 566 patients classified as control [45]. The median procedure duration for various ASA physical status was 150 min with patients who died having a median of 10 min with low HRV while patients who survived beyond 48 h postoperatively had a median of 5 min with low HRV [45]. These results add a new temporal dimension (the intraoperative period) to the previously published data indicating that markers of autonomic dysfunction may serve as clinically useful tools in the evaluation and management of critically ill patients [46]. There is, however, an important limitation in the present study, as most patients of the cohort received inhaled anesthetic agents, which are well known to be huge depressor of the autonomic nervous system.

Also in the December issue, Shin reported a very interesting study investigating if pulse rate variability (PRV) could be used as a substitute for HRV at various ambient temperatures [47]. The purpose of the study was to better understand the behavior of PRV assessed using the PPG technique when an external parameter like temperature changes [47]. The author used three rooms set to different ambient temperatures [47]. The room temperature was controlled to a relatively low (17 °C), moderate (25 °C), or a high temperature (38 °C) by air conditioning systems and heating devices [47]. Twenty-eight healthy young subjects (11 women, 17 men) participated in this study and the authors demonstrated that ambient temperature induces discrepancies between PRV and HRV with deviations increased at a higher ambient temperature [47]. The author explained his finding by the fact that high temperature induces vasodilatation, which may affect blood flow of small arteries [47]. Moreover, we may also speculate that temperature environment impacts respiratory activity and baroreflex, as the discrepancies were found in the short-term variables that reflect the parasympathetic activity. The present work is of importance as it highlights all ambiguities on how ambient temperature could affect PPG [48].

Morel and collaborators [49] retrospectively analyzed 220 patients admitted to the ICU after elective cardiac surgery (December issue). In this study, the aim of the authors was to demonstrate that central venous-arterial difference in CO_2 tension (ΔCO_2) was a good global marker to assess postoperative organ failure [49]. Surprisingly, the authors showed that a high ΔCO_2 did not predict post-operative organ dysfunctions, since these patients experienced, after cardiac surgery, a lower SOFA score, and lower hospital mortality [49]. The authors concluded that in this clinical setting, the venous-arterial CO_2 gradient is not predictive of poor outcome [50]. However, these apparently paradoxical results should be understood cautiously as the setting of post cardiopulmonary bypass (CPB) is specific for hemodynamic monitoring [51]. Indeed, several studies demonstrated that the lungs produce lactate after CPB [52], with pulmonary lactate flux being correlated to ΔCO_2 [53]. We may, thus, regret the fact that the present lung hypothesis was not studied in the Morel et al. study.

6 Technical aspects and technical developments in the field of hemodynamic monitoring

Topics related to technological principles of monitoring technologies in the field of anesthesia and intensive care are one of the primary scopes of the JCMC. In this field, a variety of papers of high interest have been published last year.

With regard to continuous arterial blood pressure measurement, the direct invasive measurement with an arterial catheter, a fluid-filled tubing system, and a pressure transducer is still the clinical reference standard.

In the October issue, He et al. [54] report the results of an interesting and clinically relevant study evaluating the impact of the position of the arterial pressure transducer in relation to the reference level on hemodynamic variables assessed with pulse contour analysis. In 42 critically ill patients, the authors defined the phlebostatic axis as the

zero reference level and then vertically adjusted the arterial pressure transducer to different heights in relation to the zero reference site (+5, +10, +15, +20, −20, −15, −10, −5 cm). An elevation of the pressure transducer caused positive changes in the pulse contour analysis-derived CI (more than 5% at 15 cm and about 10% at 20 cm), stroke volume index, and SVV and negative changes in the systemic vascular resistance index (and vice versa). For every centimeter change of the transducer, there was a corresponding 0.014 L/min/m^2 or 0.36% change in CI. The authors conclude that it is important to be aware of the fact that the variation of the arterial pressure transducer position can result in inaccurate measurements of pulse contour analysis-derived variables. With this simple but elegant study, the authors emphasize the importance of a profound understanding of basic technological principles underlying clinical hemodynamic monitoring.

In the December issue, Fujiwara et al. [55] report a study investigating the impact of a closed port system with a three-way stopcocks on the natural frequency and damping coefficients of commercially available arterial pressure transducer/tubing kits in a laboratory model. Closed injection systems allow drawing blood without the risk of infection or entrance of air in the tubing system. However, these systems have been demonstrated to decrease the natural frequency of arterial transducer/tubing systems. The closed port system with three-way stopcock tested in this study using a model with artificial radial blood pressure waves was the JV-PNSC1R (JMS, Hiroshima, Japan). The authors revealed that including one or two closed port systems with three-way stopcock did not markedly decrease the natural frequency or increase the damping coefficient of the measurement set-up.

Another study published in the October issue by Bocchi et al. [56] investigated resonance artefacts in an arterial pressure monitoring system in a laboratory model. The author's aim was to evaluate in which cases the coupling between the arterial catheter and the device can cause resonances resulting in erroneous arterial pressure recording. Although—as explained by the authors—modern piezoelectric pressure transducer systems should have mechanical properties avoiding resonance artefacts by providing an appropriate resonance frequency and damping factor the authors revealed that the use of different catheters can significantly alter the arterial pressure signal. Catheters with smaller diameters resulted in higher damping coefficients that could help avoiding undesired oscillations. This study shows that it is of crucial importance for the clinician to understand measurement principles of invasive arterial pressure monitoring and to take the possibility of artefacts caused by technical problems into consideration.

In the October issue, Liu et al. [57] report an adaptive method to detect heart beats from continuous blood pressure signals. This is of importance because blood pressure variability (in analogy to HRV assessed using an electrocardiogram) can reflect autonomic control of cardiovascular function. According to the authors, heart beat detection from continuous arterial pressure signals is more challenging than from an electrocardiogram because the arterial waveform shows more variability compared with the QRS-complex. In their work, the authors describe a novel adaptively tuned real-time beat detection method for pressure related signals using a so-called enhanced mean shift (EMS) algorithm consisting of three components: estimates of the heart rate (Welch power spectral density method), enhanced mean shift algorithm, and classification logic (to detect the locations of misdetections and over detections). The authors validated their method using three databases and concluded that it showed a very promising performance in blood pressure detections.

In anesthesiology and intensive care medicine, automatic patient monitoring is of paramount importance for patient safety. Nevertheless, high rates of false alarms can put the patient at risk because they de-sensitize the medical staff and result in less attention for true alarms [58].

In the December issue, Borges et al. [59] report a study aiming to improve heart rate monitoring by avoiding false alarms. The authors propose a set of different algorithms allowing combining the information from the electrocardiogram, arterial blood pressure signal, and the photoplethysmogram. The authors analyzed (and included in the algorithms) HRV, the heart rate difference between sensors, and the spectral analysis of low and high noise of each sensor and validated their algorithms using the MIMIC database (a database including hemodynamic data of ICU patients). The authors report that "neural networks fusion" had the best false alarm reduction (93%), while the "Bayesian technique", "fuzzy logic", "majority voter", and "heart rate variability index" resulted in a reduction of false alarms of 84, 81, 73, and 68%, respectively. The proposed algorithms should be tested in clinical settings to further evaluate their applicability in bedside monitors.

7 Statistics in method comparison studies

Hemodynamic variables assessed during hemodynamic monitoring can have a tremendous impact on the management of critically ill patients. Therefore, technologies suggested for hemodynamic monitoring need to be carefully validated before they can be recommended for clinical use. A crucial part of a careful validation is to correctly apply appropriate statistical methods in method comparison studies testing the measurement performance of a test method in comparison with an established reference method. In these studies, the agreement between

two methods is usually described as accuracy (mean of the differences) and precision (limits of agreement). In CO method comparison studies, the percentage error is frequently reported [19]. It has been stressed before that the percentage error depends on both the precision of the test method and the precision of the reference method [60, 61].

In the April issue, Hapfelmeier et al. [62] explain the importance to understand that in CO method comparison studies, the precision of agreement between two methods (test method and reference method) must not be confused with the precision of each method (that is important in the interpretation of the percentage error). The authors expand on the fact that the "precision of agreement" depends on the "precision of method", i.e., the precision that the test and the reference method are able to achieve. In addition, the authors stress that the agreement between methods does not only depend on the "precision of method" but also "the method's general variability about the true values". Moreover, they state that CO is a rapidly changing variable and serial measurements of this changing CO should not be confused with repeated measurements (because they rather represent single measurements for changing multiple true values per subject). This statistical paper illustrates that correctly applying statistical tests and assessing the "precision of method" is challenging in CO method comparison studies.

8 Survey on the use of hemodynamic monitoring

Bignami et al. [63] published a survey study of current clinical practice in hemodynamic monitoring and vasoactive medication use from 71 of 92 centers (77%) across Italy. The survey, a 33 item question translated from a previous similar German one [64], was aimed at cardiac surgery patients and units and dates from June to December 2013, such is the delay between data collection to finally reaching press. The paper contains descriptive data on current hemodynamic management practices across Italy. Of greatest note for our monitoring journal readers was that (a) all units completing the survey have transesophageal echo and nearly all have transthoracic echo (96%); (b) only 18% of units were still regularly using pulmonary artery catheters and (c) although available in just under half of units surveyed, minimally invasive CO monitoring was rarely used (3%). The tendency was to use dynamic indices of hemodynamic response such as SVV rather than a straight forward increase in stroke volume or CO to assess therapy. Volume replacement therapy was mostly based on balanced colloids (87%), although starches were still being used in 2013. Dobutamine and adrenaline were the main inotropes.

9 Hemodynamic monitoring: impact on patient outcome and clinical decision-making

As hemodynamic monitoring can only improve patient outcome if coupled with therapeutic interventions the JCMC welcomes studies investigating the impact of hemodynamic management on clinical decision-making and outcome.

As hemodynamic goal-directed therapy (GDT) is well known to improve outcome following elective major surgery, in the issue of February, Pavlovic et al. [65] studied GDT during emergency surgery. In this randomized, controlled trial, 50 patients with hypovolemic or septic conditions needing surgery were enrolled and two algorithms for hemodynamic optimization were compared [65]. Two groups were defined, the standard of care group with the use of PPV (control group) and the optimized group with the measurement of CI, global end-diastolic volume index (GEDVI), and SVV using the PiCCO system (Pulsion Medical Systems SE, Feldkirchen, Germany). Patient outcome was evaluated using the SOFA Score trend following the 3 days after surgery, major complications, and postoperative outcome. Data from 43 patients were analyzed (control group, $N=23$; optimized group, $N=20$). Paradoxically, major complications occurred more frequently in the optimized group (19 (95%) vs. 10 (40%) in the control group, $P<0.001$) [65]. Likewise, SOFA scores following surgery days were higher in the optimized group than in the control group [65]. The present paper is of interest for our readers, as it underlines that during emergency surgery, hemodynamic optimization using an advanced hemodynamic monitoring may be associated with a less favorable postoperative outcome [65]. A key point in this notable study is the fact that dobutamine was given intraoperatively in 45% optimized patients but in no control patients [65]. The present piece of information may explain these results, as we may expect that over treating patients with drugs, having potential adverse events, is harmful. The second take home message is to keep in mind that an advanced hemodynamic monitoring is of interest only if the measured variables agree with a body of clinical and para-clinical arguments [66].

In the issue of October, Perel et al. considered another question on advanced hemodynamic monitoring [67]. The authors designed a study to answer the following questions: (1) how accurate is our clinical assessment of important cardiopulmonary variables in critically ill patients in comparison with advanced hemodynamic monitoring? (2) How does the information provided by this advanced hemodynamic monitoring affect our therapeutic decisions in this patient population? The method used consisted in asking experienced physicians involved in the patient's care in European mixed ICUs to fill in a questionnaire [67]. They were asked to indicate the existing clinical and classical

hemodynamic information before any advanced hemodynamic monitoring with the TPTD technique was used [67]. Following that, TPTD measurements were undertaken to measure CO, GEDVI, and extravascular lung water index (EVLWI). The rational was to compare physician's own prediction of expected values of physiological variables with the same values obtained using TPTD. The study demonstrated that the physicians are not always able to predict physiological variables in the absence of advanced hemodynamic monitoring [67]. Moreover, a relevant proportion of them changed their major therapeutic decisions originally made when they obtained TPTD measurements [67]. The finding of a limited ability of experienced clinicians to accurately assess physiological variables of blood circulation from clinical assessment and classical hemodynamic monitoring is rational. As already stated by the authors, this fact is not related to a "learning contamination bias" but certainly to the complexity of ICU patient's disease. Indeed, for instance, patients undergoing mechanical ventilation, dialysis and/or hypothermic therapy are out off physiological clinical ranges as positive intra-thoracic pressure, fluid balance, and low body temperature affect macro- and microcirculation [68]. From that, our readers may understand that presuming CO, GEDVI, and EVLWI measurements in these settings is a very difficult task.

Compliance with ethical standards

Conflicts of interest BS collaborates with Pulsion Medical Systems SE (Feldkirchen, Germany) as a member of the medical advisory board. BS received honoraria for giving lectures and refunds of travel expenses from Pulsion Medical Systems SE (Feldkirchen, Germany). BS received institutional research grants and unrestricted research grants from Tensys Medical Inc. (San Diego, CA, USA). BS received honoraria for giving lectures and refunds of travel expenses from CNSystems Medizintechnik AG (Graz, Austria). BS received research support from Edwards Lifesciences (Irvince, CA, USA). KB has no conflicts of interest to declare. LAC has no conflicts of interest to declare. SR has received speaker's fees from Edwards Lifesciences (Irvine, CA, USA). TWLS received honoraria from Edwards Lifesciences (Irvine, CA, USA) and Masimo (Irvine, CA, USA) for consulting and from Pulsion Medical Systems SE (Feldkirchen, Germany) for lecturing.

Informed consent Not applicable.

Research involving human participants and/or animals This is a review article not including human participants and/or animals.

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