Pulse Wave Analysis to Estimate Cardiac Output

Karim Kouz, M.D., Thomas W. L. Scheeren, M.D., Daniel de Backer, M.D., Bernd Saugel, M.D.

Cardiac output (CO)–guided therapy is a promising approach to hemodynamic management in high-risk patients having major surgery[1] and in critically ill patients with circulatory shock.[2] Pulmonary artery thermodilution remains the clinical reference method for CO measurement,[3] but the use of the pulmonary artery catheter decreased over the past two decades.[4] Today, various CO monitoring methods with different degrees of invasiveness are available, including pulse wave analysis.[5] Pulse wave analysis is the mathematical analysis of the arterial blood pressure waveform and enables CO to be estimated continuously and in real time.[6] In this article, we review pulse wave analysis methods for CO estimation, including their underlying measurement principles and their clinical application in perioperative and intensive care medicine.

Pulse Wave Analysis Methods and Underlying Measurement Principles

Pulse wave analysis methods estimate CO by mathematically analyzing the arterial blood pressure waveform. The arterial blood pressure waveform is a complex signal determined by various physiologic factors, including left ventricular stroke volume, aortic compliance, vascular resistance, and wave reflection phenomena.

In addition to CO, pulse wave analysis allows assessing dynamic cardiac preload variables, *i.e.*, pulse pressure variation and stroke volume variation related to positive pressure ventilation.[7] In patients with sinus rhythm and controlled mechanical ventilation with a tidal volume of at least 8 ml/kg predicted body weight, pulse pressure variation and stroke volume variation can be used to predict fluid responsiveness (*i.e.*, an increase in CO by fluid administration).[8]

Pulse wave analysis methods can be classified into invasive, minimally invasive, and noninvasive methods (fig. 1).[5,9] Pulse wave analysis methods can be further classified into externally calibrated, internally calibrated, and uncalibrated methods depending on the type of calibration they use to calibrate pulse wave analysis–derived CO.

Invasive Externally Calibrated Pulse Wave Analysis

Invasive externally calibrated pulse wave analysis methods calibrate pulse wave analysis–derived CO to an external reference CO value measured using an indicator dilution method (transpulmonary thermodilution or lithium dilution).[5,9] CO measurement using indicator dilution methods requires a (central) venous catheter for indicator injection upstream in the circulation and a dedicated arterial catheter and measurement system to detect downstream indicator temperature or concentration changes.[5,9–11]

The VolumeView system (Edwards Lifesciences, USA) and the PiCCO system (Pulsion Medical Systems, Germany) calibrate pulse wave analysis–derived CO to transpulmonary thermodilution–derived CO. To measure CO using transpulmonary thermodilution, a bolus of cold crystalloid solution is injected in the central venous circulation.[10] The cold indicator bolus injection causes changes in blood temperature that are detected downstream using a thermistor-tipped arterial catheter. From the thermodilution curve that represents the changes in blood temperature over time, CO can be calculated using a modified Stewart–Hamilton formula.[9,10] Transpulmonary thermodilution is considered a clinical reference method for CO measurement and has been validated against pulmonary artery thermodilution.[10,12] Common sources of measurement error include indicator loss, regurgitation, or recirculation that can affect the thermodilution curve and alter CO measurements.[10] Thus, regurgitation caused by valvulopathies and intracardiac shunts represents an important limitation.[10,13]

The VolumeView system is an invasive externally calibrated pulse wave analysis system that uses a thermistor-tipped femoral arterial catheter and a central venous catheter for transpulmonary thermodilution CO measurements.[14,15] To estimate CO, the VolumeView pulse wave analysis algorithm considers conventional arterial blood pressure waveform features based on a three-element Windkessel model to estimate aortic impedance and advanced waveform features. Advanced waveform features are derived from the entire arterial blood pressure waveform and reflect changes in vascular tone and compliance that can be assessed by skewness and kurtosis calculations.

The PiCCO system is another invasive externally calibrated pulse wave analysis system. It uses the same external calibration principle as the VolumeView system and thus also combines pulse wave analysis and transpulmonary thermodilution. It requires a central venous catheter and

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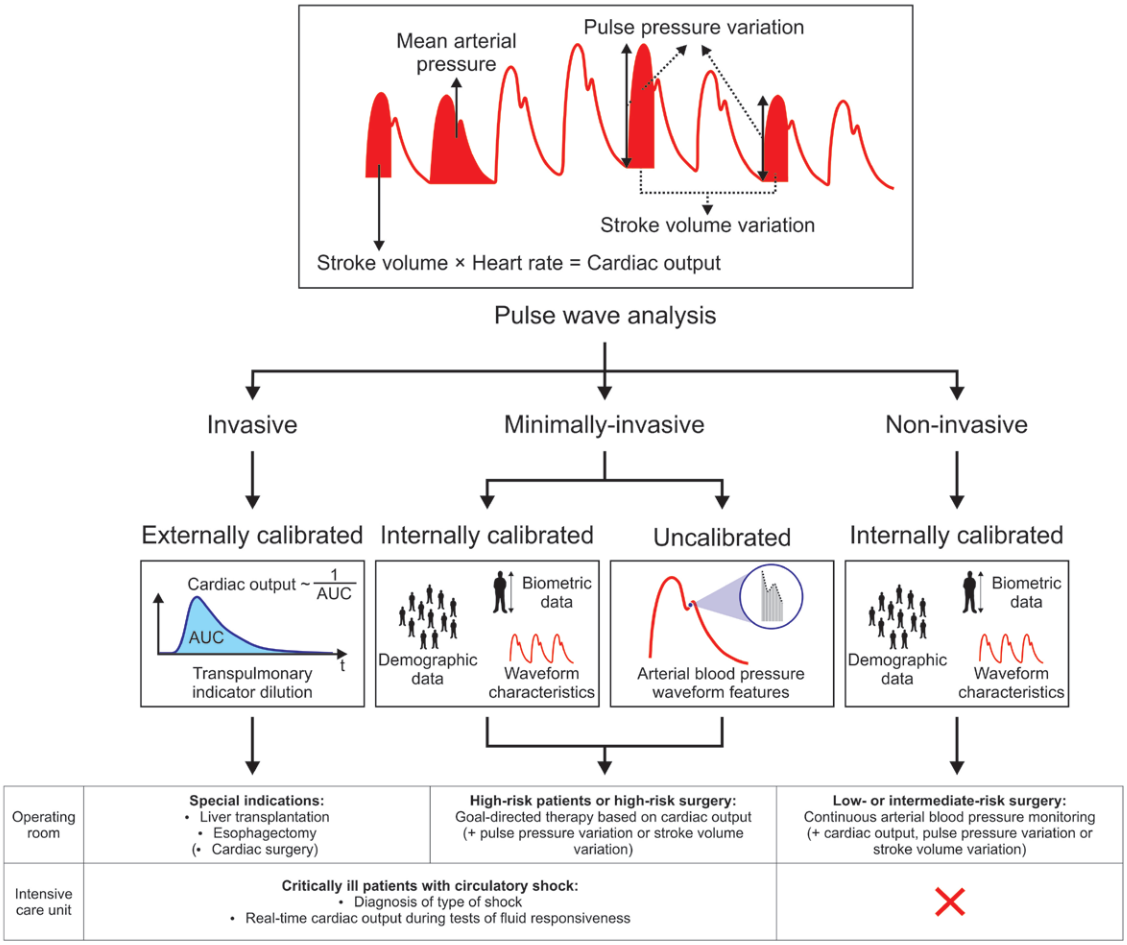

Fig. 1. Classification and clinical application of pulse wave analysis monitoring methods. Pulse wave analysis systems estimate cardiac output and other hemodynamic variables by analyzing the arterial blood pressure waveform. Pulse wave analysis methods can be classified according to their invasiveness into invasive, minimally invasive and noninvasive methods. Further, the methods can be classified based on their type of calibration into externally calibrated, internally calibrated, and uncalibrated methods. Invasive externally calibrated methods calibrate pulse wave analysis–derived cardiac output to an external reference cardiac output value measured using an indicator dilution method. Minimally invasive internally calibrated methods consider biometric, demographic, and hemodynamic data, as well as arterial blood pressure waveform characteristics, to estimate cardiac output without external reference cardiac output calibration. Minimally invasive uncalibrated methods do not use external or internal calibration at all and solely estimate cardiac output based on arterial blood pressure waveform features. Noninvasive methods analyze arterial blood pressure waveforms recorded continuously with noninvasive sensors and estimate cardiac output using internal calibration. In patients having surgery, invasive externally calibrated methods are reserved for special indications (*e.g.*, liver transplant surgery or esophagectomy). Minimally invasive internally calibrated and uncalibrated methods are used for perioperative goal-directed therapy in high-risk surgical patients. Noninvasive methods can be used for continuous arterial blood pressure and cardiac output monitoring in low- or intermediate-risk surgical patients. In critically ill patients treated in the intensive care unit, invasive and minimally invasive pulse wave analysis–derived continuous real-time cardiac output estimations can be used to monitor cardiac output during tests of fluid responsiveness (fluid challenges or passive leg raising test). AUC, area under the curve.

a thermistor-tipped arterial catheter (Pulsiocath; Pulsion Medical Systems) inserted in a central artery—most often the femoral artery, but catheters are also available for the axillary and brachial artery.[10] The PiCCO pulse wave analysis algorithm analyzes the systolic part of the arterial blood pressure waveform and uses the heart rate, a thermodilution-derived calibration factor, and the individual aortic compliance to estimate CO.[6] Calibrating pulse wave analysis–derived CO to transpulmonary thermodilution CO helps account for individual aortic compliance.

In contrast to the VolumeView and PiCCO systems, the LiDCOplus system (LiDCO, United Kingdom) does not use transpulmonary thermodilution but transpulmonary lithium dilution for external CO calibration. After lithium application *via* a peripheral or central venous catheter, the lithium–concentration–time curve is measured by a lithium-sensitive electrode integrated in an arterial catheter.[10,16] The area under this curve is inversely related to CO. The LiDCOplus pulse wave analysis algorithm tracks the power of the arterial blood pressure waveform and translates the arterial blood pressure waveform into a standardized volume waveform. CO is calculated based on different mathematical assumptions and the lithium dilution–derived CO.[11] A theoretical strength of the LiDCOplus system is that the arterial blood pressure waveform morphology is not as important for the estimation of CO as for other pulse wave analysis systems. Therefore, peripheral arteries can also be used for CO measurement, because disturbances caused by wave reflection phenomena are reduced, and the system is less affected by damping. However, in patients receiving lithium therapy, lithium dilution may overestimate CO, as in patients treated with certain muscle relaxants (*e.g.*, rocuronium, pancuronium), because they contain a positively charged quaternary ammonia ion in their chemical structure that can be detected by the lithium sensor.[10] Because of a potential lithium accumulation, the number of calibration measurements over a short time is limited.[10]

Minimally Invasive Internally Calibrated Pulse Wave Analysis

Minimally invasive internally calibrated pulse wave analysis methods consider biometric, demographic, and hemodynamic data, as well as arterial blood pressure waveform characteristics to estimate CO without external reference CO calibration. These systems only require an arterial catheter (most commonly inserted in the radial artery) and are therefore referred to as "minimally invasive" methods.[5] Compared with externally calibrated pulse wave analysis systems, all internally calibrated systems may exhibit poorer measurement performance and may become unreliable in patients whose biometric (*e.g.*, weight, height), demographic (*e.g.*, age, sex), and hemodynamic data used for statistical calibration are not in the standard range of the underlying database or physiologic assumptions of the pulse wave analysis system.[17] The latter may particularly occur during pathophysiologic conditions, *e.g.*, in patients having liver failure, septic shock, or rapid changes in vasomotor tone caused by rapid fluid or vasopressor administration. Additionally, the measurement performance is essentially determined by the quality of the arterial blood pressure waveform signal.

The FloTrac system (Edwards Lifesciences) is a minimally invasive internally calibrated pulse wave analysis system based on the main assumption of a close relation between pulse pressure (the difference between systolic and diastolic arterial blood pressure) and CO. The system statistically analyzes pulse pressure characteristics and corrects them for waveform features resembling vascular tone. The system calculates the SD of successive pulse pressure measurements and estimates vascular tone using mean arterial blood pressure and arterial blood pressure waveform characteristics.[18]

The ProAQT/Pulsioflex system (Pulsion Medical Systems) is another minimally invasive internally calibrated pulse wave analysis system. It uses an algorithm very similar to the one used by its externally calibrated counterpart, the PiCCO system.[19] The system estimates CO based on the area of the systolic part of the arterial blood pressure waveform and takes into account empiric demographic and biometric data that are used to correct for aortic compliance.

The LiDCOrapid system (LiDCO) is based on the same algorithm as the LiDCOplus system. Instead of an external calibration by transpulmonary lithium dilution, it relies on nomograms that incorporate patient's age, height, and weight. These nomograms are used to estimate a calibration factor for the calculation of CO.[20]

The Argos CO monitor (Retia Medical, USA) uses an algorithm called multibeat analysis—a further development of long time interval analysis—to estimate CO.[21–24] The arterial blood pressure waveform is analyzed over long time scales that include multiple heartbeats, and an arterial blood pressure waveform that would be the response to a single cardiac contraction is estimated. This minimizes disturbing wave reflection phenomena, and a theoretical central arterial blood pressure waveform with a pure exponential pressure decay can be estimated.[22] Based on this central arterial blood pressure waveform and biometric patient data, the system estimates CO.

Minimally Invasive Uncalibrated Pulse Wave Analysis

Minimally invasive uncalibrated pulse wave analysis methods do not use external or internal calibration at all and solely estimate CO based on arterial blood pressure waveform features obtained *via* a radial or femoral arterial catheter. The MostCare system (Vygon, France) is currently the only commercially available minimally invasive uncalibrated pulse wave analysis system, and its CO values showed good agreement with those obtained by pulmonary artery thermodilution.[25] It uses the pressure recording analytical method algorithm to continuously estimate CO. The algorithm identifies specific ephemeral points of instability of the arterial blood pressure waveform that are mainly due to wave reflections by analyzing the arterial blood pressure waveform in a very high resolution.[26,27] This allows a beat-to-beat estimation of vascular impedance and makes the system robust against sudden changes in cardiovascular dynamics (*e.g.*, changes in heart rate, cardiac contractility, and vascular tone).[26] One major limitation of the MostCare system is its susceptibility to measurement errors caused by under- and overdamping of the arterial blood pressure waveform signal.[26,28] Thus, damping properties of the measurement systems have to be checked meticulously.

Noninvasive Pulse Wave Analysis

Noninvasive pulse wave analysis methods analyze arterial blood pressure waveforms recorded continuously with noninvasive sensors and estimate CO using internal calibration.[29,30] The use of noninvasive sensors to record the arterial blood pressure waveform makes cannulation of an artery or a central vein unnecessary. Noninvasive sensors include finger-cuffs and sensors placed on the skin above the radial artery.

The finger-cuff method uses the vascular unloading technology, also called the volume clamp method, to record the arterial blood pressure waveform and estimates CO using pulse wave analysis.[29,30] In general, inflatable finger-cuff sensors contain an infrared photodiode and light detector and allow high-frequent adjustments of cuff pressure. The blood volume in the finger arteries usually changes during the cardiac cycle. The finger-cuff sensor measures the blood volume in the finger arteries using the infrared photodiode and light detector and high-frequently adapts cuff-pressure to keep the blood volume in the finger arteries constant. These changes in cuff pressure are used to reconstruct the arterial blood pressure waveform, which is then further analyzed using pulse wave analysis. To scale the finger-cuff–derived arterial blood pressure to brachial arterial blood pressure, different systems use different approaches. Two commercially available finger-cuff systems for noninvasive pulse wave analysis are the ClearSight system (Edwards Lifesciences), formerly Nexfin (BMEye, The Netherlands), and the CNAP system (CNSystems Medizintechnik, Austria).

The ClearSight system compensates for hydrostatic arterial blood pressure differences between the finger artery and the phlebostatic axis using a heart reference system to estimate brachial arterial blood pressure.[31,32] The underlying pulse wave analysis algorithm primarily analyzes the systolic part of the arterial blood pressure waveform and determines aortic impedance based on the assumption of a three-element Windkessel model.[33] The CNAP system scales the finger-cuff–derived arterial blood pressure waveform to brachial arterial blood pressure using intermittent upper-arm cuff oscillometry.[34] The pulse wave analysis algorithm of the CNAP system—called continuous noninvasive CO algorithm—estimates CO by analyzing the whole arterial blood pressure waveform and thereby accounting for preload, afterload, contractility, and vascular compliance.[35] A nomogram-derived calibration factor based on biometric data is used to obtain absolute CO values.

Radial artery applanation tonometry is another method for noninvasive pulse wave analysis using a mechanical sensor that is placed on the skin above the radial artery.[29,30,34,36] The mechanical sensor maintains a transmural pressure of zero by slightly compressing the radial artery and thereby enables continuous recording of the arterial blood pressure waveform.[34,36] Different systems for radial artery applanation tonometry are available. The DMP-Life system (Daeyomedi Co., South Korea) uses an array of sensors to estimate CO using an algorithm that analyzes the systolic part of the arterial blood pressure waveform and considers biometric and demographic data.[37,38] The T-Line system (Shanshi Medical, China; formerly, Tensys Medical, USA) uses a single sensor that is integrated in a bracelet and electromechanically adjusted to identify the optimal applanation pressure.[36] The system estimates CO using a complex mathematical model that incorporates arterial blood pressure waveform characteristics, biometric, and demographic data.[39]

General limitations for noninvasive pulse wave analysis methods are the same as those of invasive and minimally invasive pulse wave analysis methods. In addition, noninvasive pulse wave analysis methods have specific technical limitations. The main limitations for finger-cuff–based pulse wave analysis systems are clinical conditions impairing finger perfusion such as vascular diseases, circulatory shock, or high-dose vasopressor therapy.[34,40] The main limitation of radial artery applanation tonometry is that active or passive movements of the patient's extremity or the mechanical sensor disturb and impair the arterial blood pressure waveform signal quality and thus make pulse wave analysis unreliable.

Clinical Application of Pulse Wave Analysis

The decision to use—or not use—a certain pulse wave analysis system in an individual patient or clinical setting is influenced by numerous factors. These include patient-centered factors; the invasiveness, measurement performance, clinical applicability, and signal stability of the pulse wave analysis system; institutional factors such as the availability and the costs; and personal experience with monitoring systems of the caregiver.[41] A profound understanding of pulse wave analysis measurement principles and strengths and limitations of pulse wave analysis systems is important for clinicians to choose the appropriate pulse wave analysis system for the individual patient.

All pulse wave analysis systems discussed in this review have been investigated against pulmonary artery or transpulmonary thermodilution in method comparison studies.[10,17,42,43] Those method comparison studies are highly heterogenous regarding their study design, patient population, clinical setting, and results and, therefore, are hardly comparable with respect to the measurement performance of the investigated pulse wave analysis system. Even though there are studies showing clinical interchangeability between pulse wave analysis–derived CO measurements and reference indicator dilution CO measurements, the pooled overall results indicate that CO measurements by either method are not interchangeable.

Pulmonary artery thermodilution remains the clinical reference method for CO monitoring.[3] Pulmonary artery catheterization additionally provides numerous advanced hemodynamic variables that help guiding therapy in patients having cardiac surgery (in combination with transesophageal echocardiography) or liver transplant surgery or in patients with pulmonary hypertension or right ventricular failure.[5] However, pulmonary artery catheterization is an invasive procedure associated with potential complications. This may be one of the reasons for a decrease in the use of the pulmonary artery catheter over the last years.[4]

Although the CO measurement performance of pulmonary artery thermodilution is superior to that of pulse wave analysis, pulse wave analysis may be a reasonable choice for CO monitoring in a broad spectrum of surgical and critically ill patients.

Pulse Wave Analysis in Perioperative Medicine

Major surgery under general anesthesia causes marked hemodynamic alterations and impaired tissue oxygenation.[44] Perioperative goal-directed therapy based on advanced hemodynamic monitoring has thus been proposed to optimize CO and global oxygen delivery. Goal-directed therapy refers to protocolized hemodynamic treatment strategies that are used to titrate fluids, vasopressors, and inotropes to predefined target values of hemodynamic variables to optimize global cardiovascular dynamics and maintain adequate organ perfusion pressure and oxygen delivery.[45] There is evidence that goal-directed therapy can improve postoperative outcomes and reduce postoperative mortality in high-risk patients having major surgery.[46,47] Pulse wave analysis is frequently used in studies of goal-directed therapy because it provides CO and dynamic cardiac preload variables that can be used as target variables.[46,48]

Minimally invasive internally calibrated pulse wave analysis (ProAQT/Pulsioflex system) was used in a multicenter randomized controlled trial in patients having major abdominal surgery investigating the impact of goal-directed therapy on postoperative complications compared with routine care.[49] In goal-directed therapy group patients, the individual optimal CO was determined after anesthetic induction by giving fluids until pulse pressure variation was less than 10%. During surgery, fluids, vasopressors, and inotropes were titrated according to pulse pressure variation, the individual CO, and a mean arterial blood pressure of more than 65 mmHg. Patients treated with goal-directed therapy had significantly less postoperative complications compared with routine care patients.[49]

In the Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome (OPTIMISE) trial,[47] the to-date largest randomized controlled trial on goal-directed therapy, minimally invasive internally calibrated pulse wave analysis (LiDCOrapid system), was used to optimize blood flow by maximizing stroke volume with repetitive colloidal fluid boluses and the inotrope dopexamine in high-risk patients having major abdominal surgery. The primary endpoint—a composite of moderate or severe postoperative complications—occurred less frequently in goal-directed therapy group patients compared with routine care group patients. However, the clinically important difference in the incidence of postoperative complications was not statistically significant.

Based on the OPTIMISE trial, the OPTIMISE II trial—an international multicenter pragmatic randomized controlled trial in high-risk patients having major surgery—is currently being carried out.[50] Minimally invasive internally calibrated (FloTrac system) or noninvasive (ClearSight system) pulse wave analysis is used to maximize stroke volume with fluid challenges and low-dose dobutamine or dopexamine. Stroke volume variation less than 5% or an absence of a sustained rise in stroke volume after a fluid challenge are considered indicators of fluid nonresponsiveness. The primary endpoint of the study is the incidence of postoperative infection within 30 days of randomization.

For goal-directed therapy to be even more effective, personalized target values based on patients' preoperative baseline cardiovascular dynamics may be promising.[51] In this regard, noninvasive pulse wave analysis systems enable clinicians to determine baseline CO before surgery (*e.g.*, the day before surgery on the ward). In the Targeting Preoperatively Assessed Personal Cardiac Index in Major Abdominal Surgery Patients (TAPIR) trial,[52] noninvasive pulse wave analysis (CNAP system) was used to determine the individual patient's baseline cardiac index the day before surgery. In patients assigned to personalized management, clinicians strove to maintain this baseline cardiac index during surgery—where cardiac index was measured using minimally invasive internally calibrated pulse wave analysis (ProAQT/Pulsioflex system)—by using fluids and dobutamine based on a goal-directed therapy algorithm. The primary outcome, a composite of major postoperative complications or death within 30 days of surgery, occurred less frequently in patients in the personalized management group compared with patients in the routine management group.

In addition to the use of pulse wave analysis for goal-directed therapy in high-risk patients having major surgery, noninvasive pulse wave analysis may be useful for continuous arterial blood pressure monitoring in low- or intermediate-risk patients that would otherwise have only intermittent arterial blood pressure monitoring. Recent randomized controlled trials in patients having moderate-risk noncardiac surgery revealed that continuous noninvasive arterial blood pressure monitoring reduces the amount of intraoperative hypotension compared with intermittent blood pressure monitoring using upper-arm cuff oscillometry.[53,54]

Pulse Wave Analysis in Intensive Care Medicine

In critically ill patients with complex circulatory shock, CO monitoring is recommended to diagnose the type of shock and to evaluate the response to fluids or inotropes.[2] For the diagnosis of the type of shock, pulmonary artery thermodilution or transpulmonary thermodilution are recommended[2] because the diagnosis depends on accurate and precise absolute CO measurements and additional hemodynamic variables.[55]

Because pulse wave analysis provides CO continuously and in real time, it is recommended to monitor CO during tests of fluid responsiveness (fluid challenges[56] or passive leg raising test[57]).[2] Circulatory shock—especially septic shock—is characterized by marked alterations in systematic vascular resistance.[55] Invasive externally calibrated pulse wave analysis systems offer the opportunity to frequently recalibrate pulse wave analysis–derived CO estimations and thereby improve the measurement performance regarding absolute CO values. In patients with circulatory shock, absolute CO measurement by minimally invasive internally calibrated or uncalibrated pulse wave analysis systems may become unreliable because of marked alterations in vasomotor tone.[17] Noninvasive pulse wave analysis systems are not recommended in critically ill patients with shock because these patients will be equipped with an arterial catheter anyway.[9]

Conclusions

Pulse wave analysis is the mathematical analysis of the arterial blood pressure waveform and enables CO to be estimated continuously and in real time. In addition to CO, pulse wave analysis allows assessing dynamic cardiac preload variables, *i.e.*, pulse pressure variation and stroke volume variation that can be used to predict fluid responsiveness in patients with sinus rhythm and controlled mechanical ventilation. Pulse wave analysis methods are classified into invasive, minimally invasive, and noninvasive methods. Pulse wave analysis methods are further classified into externally calibrated, internally calibrated, and uncalibrated methods depending on the type of calibration they use to calibrate pulse wave analysis–derived CO values. In high-risk patients having major surgery, pulse wave analysis–derived CO and dynamic cardiac preload variables can be used for perioperative goal-directed therapy. In critically ill patients, pulse wave analysis–derived continuous real-time CO estimations can be used to monitor CO during tests of fluid responsiveness (fluid challenges or passive leg raising test).

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Competing Interests

Dr. Saugel has received honoraria for consulting, honoraria for giving lectures, and refunds of travel expenses from Edwards Lifesciences (Irvine, California); honoraria for consulting, institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from Pulsion Medical Systems (Feldkirchen,Germany); institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from CNSystems Medizintechnik (Graz, Austria); institutional restricted research grants from Retia Medical (Valhalla, New York); honoraria for giving lectures from Philips Medizin Systeme Böblingen (Böblingen, Germany); and honoraria for consulting, institutional restricted research grants, and refunds of travel expenses from Tensys Medical (San Diego, California). Dr. Scheeren has received research grants and honoraria for consulting and lecturing from Edwards Lifesciences and Masimo (Irvine, California) and honoraria for lecturing from Pulsion Medical Systems. Dr. de Backer has received honoraria for consulting from Edwards Lifesciences and honoraria for giving lectures from Fresenius Kabi (Bad Homburg, Germany).

Correspondence

Address correspondence to Dr. Saugel: Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg–Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. bernd.saugel@gmx.de.

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