LESS AND NON-INVASIVE HEMODYNAMIC MONITORING TECHNIQUES

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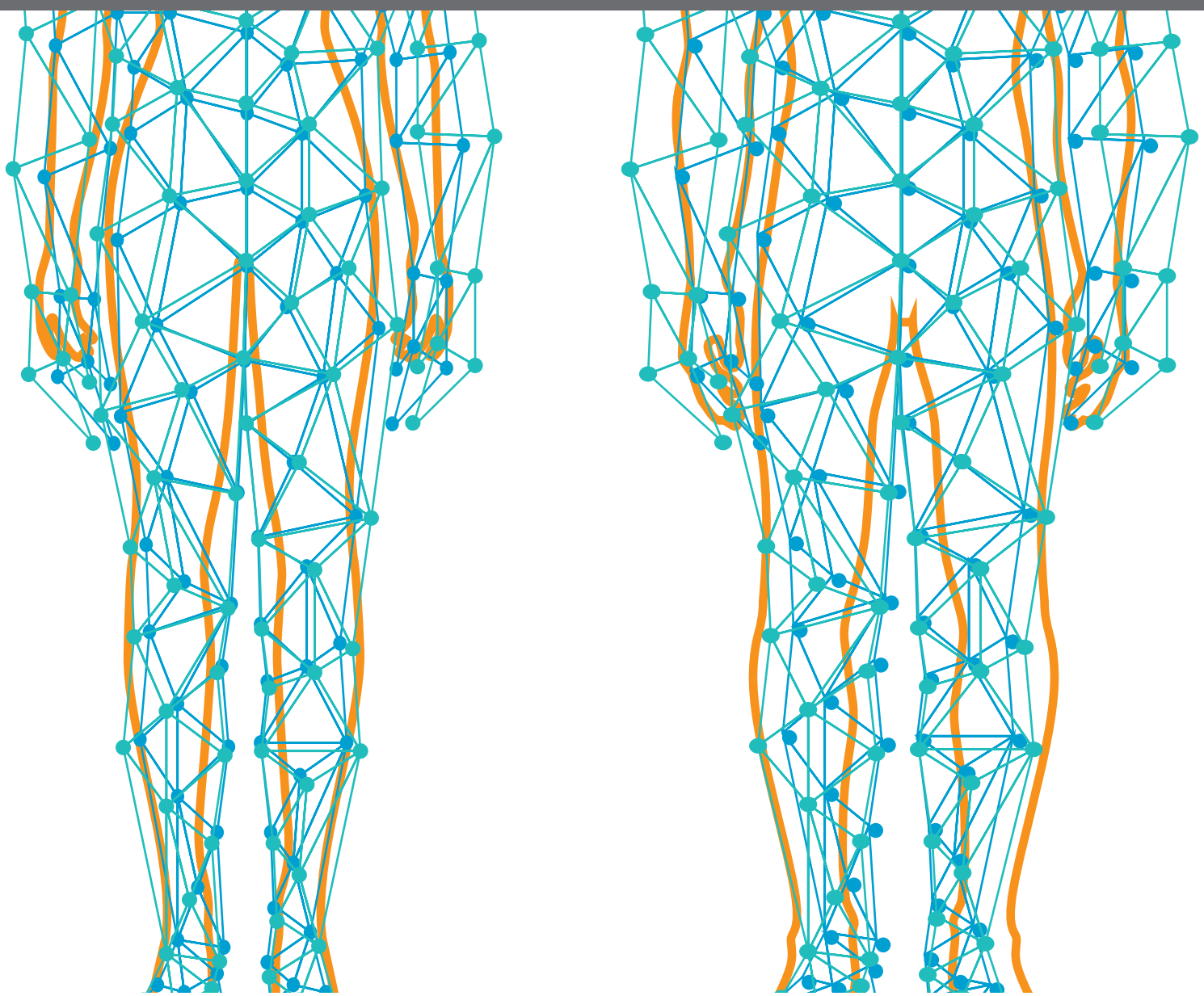

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LESS AND NON-INVASIVE HEMODYNAMIC MONITORING TECHNIQUES

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EDITORIAL
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Editorial: Less and Non-invasive Hemodynamic Monitoring Techniques

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Keywords: cardiovascular dynamics, cardiac output, blood pressure, intensive care medicine, anesthesiology, goal-directed therapy

Editorial on the Research Topic

Less and Non-invasive Hemodynamic Monitoring Techniques

The measurement or estimation of hemodynamic variables reflecting blood pressure, blood flow, cardiac contractility, cardiac preload, and cardiac afterload plays a pivotal role in the monitoring, diagnostic workup, and treatment of critically ill patients treated in the intensive care unit or in patients having major surgery.

Besides pulmonary artery catheterization that is established as a classical method to observe, measure, and derive a variety of variables reflecting cardiovascular and oxygen dynamics (1, 2) a variety of "modern" less- and non-invasive hemodynamic monitoring methods became available during the last decades (3, 4). The physical measurement principles, clinical applications, and limitations of these technologies are discussed in a series of articles that are part of the research topic "Less- and Non-invasive Hemodynamic Monitoring Techniques."

As a very basic hemodynamic variable and as a main determinant of the organs' perfusion pressure, arterial blood pressure is part of routine monitoring in intensive care medicine and anesthesiology. In a narrative review article, methods for non-invasive intermittent and continuous blood pressure monitoring are summarized (Meidert and Saugel). The authors recommend monitoring of blood pressure with intermittent oscillometry in hemodynamically stable, low-risk patients. In surgical patients at risk for hemodynamic instability, continuous non-invasive blood pressure monitoring with innovative techniques might become an option in the near future. In critically ill and high-risk surgical patients, continuous invasive blood pressure monitoring with an arterial catheter will be the method of choice in the foreseeable future. Based on these general recommendations, an article by Stenglova and Benes describes the evidence for the use of continuous non-invasive blood pressure monitoring during surgery and its potential to improve postoperative outcome by an early recognition (or even prediction) of hypotension.

In addition to blood pressure, the analysis of the arterial blood pressure waveform (pulse wave analysis) enables stroke volume, cardiac output, and dynamic cardiac preload parameters to be assessed using invasive (arterial catheter) or non-invasive (finger cuff) methods. Several articles discuss pulse wave analysis and its use in clinical practice.

Grensemann comprehensively explains the basic measurement principle of commercially available invasive monitoring systems using pulse wave analysis to estimate cardiac output. He emphasizes that pulse wave analysis is limited in patients with altered vascular tone and that uncalibrated systems should be used to follow cardiac output changes (trend monitoring) rather than to guide therapy based on absolute values of cardiac out. A review article by Yamada et al.

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describes how minimally invasive and non-invasive hemodynmaic monitoring techniques can be used to guide perioperative hemodynamic therapy and eventually improve postoperative outcome in surgical patients. The authors conclude that "monitoring equipment that can provide precise hemodynamic information without the complications and complexity of invasive techniques can facilitate individualized hemodynamic management and lead to improved outcomes."

In addition to this narrative review, a perspective article by Saugel and Reuter focuses on the use of invasive uncalibrated pulse wave analysis for perioperative hemodynamic management (often referred to as "perioperative goal-directed therapy"). The article briefly summarizes the evidence and concludes that perioperative goal-directed therapy based on pulse wave analysis-derived blood flow and dynamic cardiac preload variables can improve patient outcome in high-risk patients. This conclusion is in line with the results of recent meta-analyses showing that perioperative goal-directed therapy seems to reduce postoperative morbidity (5, 6). However, further well-designed and adequately powered studies are needed to answer open questions about optimal target variables and values and about how to implement these perioperative treatment strategies in clinical routine. Another perspective article written by Nicklas and Saugel discusses current evidence and open research questions related to completely non-invasive hemodynamic monitoring methods for perioperative hemodynamic management. Nguyen and Squara provide an in-depth review of non-invasive methods to estimate cardiac output besides pulse wave analysis. They explain the basic measurement principles and validation data of bioimpedance/bioreactance, partial carbon dioxide rebreathing, pulse wave transit time, ultrasonic methods, and inductance thoracocardiography. In particular, the authors focus on the feasibility of these methods in the intensive care unit setting and emphasize that hemodynamic monitoring of critically ill patients requires good measurement performance in terms of accuracy, precision, and step-response change. They conclude that "further developments are needed to provide clinicians with sufficiently accurate devices for routine use."

Optimization of oxygen delivery to the end-organs is the ultimate goal of therapeutic interventions aiming at an optimization of global cardiovascular dynamics. Accordingly, Molnar and Nemeth emphasize that—in addition to global blood flow variables such as stroke volume or cardiac output–markers of tissue oxygenation need to be considered during resuscitation of patients with circulatory shock. They explain the (patho)physiology of oxygen delivery, consumption, and extraction and discuss the value of central venous oxygen saturation to individually tailor therapeutic interventions to the individual patient's needs. The authors advocate for multimodal and individualized hemodynamic treatment strategies which should integrate various physiological variables (e.g., central venous oxygen saturation, lactate, venous-to-arterial carbon dioxide gap).

In summary, this series of articles reflects that a variety of innovative less- and non-invasive methods for advanced hemodynamic monitoring in intensive care and perioperative medicine are currently available. Future research needs to confirm that goal-directed optimization of global hemodynamics based on advanced less- and non-invasive hemodynamic monitoring can eventually improve oxygen delivery and have beneficial impact on patient outcome.

AUTHOR CONTRIBUTIONS

BS and SGS drafted the manuscript and approved the final version of the manuscript to be published.

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MINI REVIEW
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Techniques for Non-Invasive Monitoring of Arterial Blood Pressure

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Since both, hypotension and hypertension, can potentially impair the function of vital organs such as heart, brain, or kidneys, monitoring of arterial blood pressure (BP) is a mainstay of hemodynamic monitoring in acutely or critically ill patients. Arterial BP can either be obtained invasively via an arterial catheter or non-invasively. Non-invasive BP measurement provides either intermittent or continuous readings. Most commonly, an occluding upper arm cuff is used for intermittent non-invasive monitoring. BP values are then obtained either manually (by auscultation of Korotkoff sounds or palpation) or automatically (e.g., by oscillometry). For continuous non-invasive BP monitoring, the volume clamp method or arterial applanation tonometry can be used. Both techniques enable the arterial waveform and BP values to be obtained continuously. This article describes the different techniques for non-invasive BP measurement, their advantages and limitations, and their clinical applicability.

Keywords: blood pressure monitoring, perioperative monitoring, non-invasive blood pressure, arterial pressure, oscillometry, applanation tonometry, vascular unloading technique

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BACKGROUND

Monitoring of arterial blood pressure (BP) is a mainstay of hemodynamic monitoring in acutely or critically ill patients. Close monitoring of BP is of great importance to detect and treat hypotension and hypertension early. Both, hypotension and hypertension can impair the function of vital organs, such as the brain (1), the heart (2), and the kidneys (3).

The direct measurement of BP via arterial cannulation is regarded as the clinical reference method (criterion standard). In clinical routine, it is commonly performed during high-risk surgery and in intensive care medicine. The cannulation of an artery, however, can be time-consuming, needs to be done by a trained operator, and is associated—although very rarely (4)—with potential major complications such as embolism, lesion of nerves or vessels, or ischemia. For these reasons, BP is very commonly measured non-invasively.

There are several ways to non-invasively measure BP. Monitoring techniques can be classified according to their ability to measure BP intermittently or continuously (**Figure 1**). In this article, we describe techniques for non-invasive monitoring of arterial BP and discuss their advantages, limitations, and clinical applicability.

NON-INVASIVE INTERMITTENT TECHNIQUES

For intermittent BP measurement, an air-filled occluding cuff can be used that enables BP to be measured either manually or automatically. For all occluding cuffs, the right size is critical for valid measurement (5). Manual measurement of BP by an occluding cuff can be done either by palpation or auscultation (6).

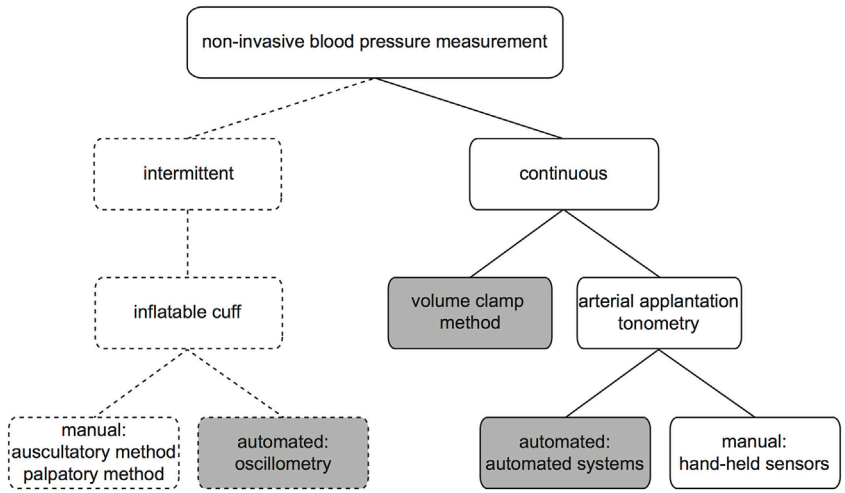

FIGURE 1 | Non-invasive blood pressure monitoring techniques.

With the palpatory method, an inflatable cuff is wrapped around the upper arm of a patient. The manometer connected to the cuff by a tube shows the pressure applied. The physician feels the radial pulse, inflates the cuff until the brachial artery collapses, and there is no blood flow any more. The pressure at which a pulse can be detected again while deflating the cuff corresponds to the systolic arterial pressure of the patient. This method does not need a stethoscope or any other specific skills or equipment and can also be performed in a noisy environment. However, it only provides the systolic arterial pressure. The auscultatory method is performed in a similar way; after inflation of the cuff to a pressure above the systolic pressure (verified by the vanished radial pulse), the typical Korotkoff sounds can be detected by a stethoscope applied distal of the upper arm cuff during slow deflation. The onset of the sounds corresponds to the patients' systolic arterial pressure, the last sound at decreasing cuff pressure equals the patients' diastolic arterial pressure. The advantage of this technique is that it provides the diastolic arterial pressure value, disadvantages include the need for training how to correctly apply this technique and the need of a stethoscope and a quiet environment.

An automated method to measure BP with the help of an occluding cuff employs the oscillometric technique. The cuff is inflated to a preset value automatically. Then, the pressure is gradually being reduced. The pressure wave causes oscillations in the vessel, which can be detected by the cuff. Mean arterial pressure corresponds to the maximum of oscillations (7); an algorithm applied to the change of oscillations sets systolic and diastolic arterial pressure values. These proprietary algorithms differ between manufacturers and are often not publicly available (8). The advantages of oscillometry are mainly the presence of reasonably accurate mean arterial pressure (in normal BP ranges) and the possibility of having an automated tool to determine a patient's BP at a preset interval. The disadvantages are the overestimation of low and underestimation of high values (9, 10) and the possibility to falsify measurements [e.g., by movement (detected as oscillations) or the patient's arm resting on the bed] (11).

The intermittent nature of BP measurements provided by all the techniques described earlier is a disadvantage they all have in common.

NON-INVASIVE CONTINUOUS TECHNIQUES

During the recent years, continuous non-invasive BP monitoring techniques became available that enable a real-time BP curve and numerical BP values to be assessed (just with direct BP measurement).

The continuous non-invasive measurement principles are based on either one of two different techniques, namely arterial applanation tonometry or the volume clamp method. Arterial applanation tonometry is based on the work of Pressman and Newgard (12), who found that a transducer strapped to an artery with a bone underneath, can obtain the arterial pulse wave. The technique has been refined and now is able to assess mean arterial pressure in the radial artery and allows the calculation of diastolic and systolic arterial pressure (e.g., using population-based algorithms) (13). The technique is used in cardiology to assess central vascular pressures (14). The pulse wave obtained by applanation tonometry can be analyzed and bears more information than systolic and diastolic pressure alone. However, these devices are not made for continuous patient monitoring as they have to be hand held by the examiner. A device allowing automated radial artery applanation tonometry is the T-Line system (Tensys Medical, San Diego, CA, USA) (15, 16). The system has been evaluated in various clinical settings (13, 16–20).

The second technique for non-invasive continuous BP measurement is called volume clamp method (or vascular unloading technology) based on the work by Penaz et al. (21). The BP is

measured at the finger with an inflatable cuff combined with a photodiode. The diameter of the artery in the finger is measured by the photodiode; the pressure in the cuff is adjusted to keep the diameter of the artery constant. From the pressure changes in the cuff, a BP curve can be calculated and transferred to correspond to brachial artery BP. Devices based on this technique are ClearSight (Edwards, Irvine, CA, USA) and CNAP (CNSystems Medizintechnik AG, Graz, Austria).

The continuous non-invasive devices are all sensitive to patient movement; therefore, monitoring of the conscious patient is possible but measurement results need to be checked for plausibility. In case of severe vasoconstriction, peripheral vascular disease, or distorted fingers due to arthritis, clinical experience has shown that it may be difficult to obtain a valid waveform using finger cuffs. Some patients report discomfort from the congestion in venous return from the fingertip where the cuff is place. For this reason, manufacturers recommend to change the cuff to another finger after a certain period of monitoring. In addition, compared to conventional intermittent devices for BP measurement, continuous BP monitoring is relatively expensive.

ARE THE TECHNIQUES RELIABLE?

Most clinicians ask themselves, whether the non-invasively obtained BP curve shows the "real" BP. Therefore, it is inevitable to discuss the measurement performance in terms of accuracy and precision of the various non-invasive devices. The pressure measured within an artery by means of arterial cannulation is regarded as the reference method of BP measurement. In the absence of direct BP measurement, the auscultatory method with a mercury column is regarded as the "gold standard." However, as Alpert and colleagues (11) point out, the cuff/stethoscope method itself sometimes differs considerably from intra-arterial pressure. Nonetheless, when evaluating a new non-invasive device using an occluding cuff, reference measurements are performed by the auscultatory method (22). This has led to the common belief that the upper arm cuff measurements represent the "real" BP of a patient. Since the auscultatory method is now widely replaced by devices that engage an oscillometric technology clinicians trust the values produced by the device with the upper arm cuff (23). A survey by Chatterjee and colleagues (23) showed that even in critically ill patients on vasopressors the non-invasive upper arm BP measurement was used to guide therapy by 47% of respondents, although intensivists would be expected to know about the limitations of oscillometric measurement in unstable patients. However, big data base analyses of simultaneous measurements on ICU an OR have demonstrated that the devices using an oscillometric method tend to overestimate hypotensive BP values and to underestimate hypertensive BP values (9, 10). Within the normal BP range, the measurement of mean arterial pressure seems to be sufficiently accurate (9, 10, 24). Studies on the accuracy of oscillometric mean arterial BP in critically ill patients demonstrated that a possible source for inaccuracy lies within the choice of the wrong cuff size (25, 26). However, even when the correctly sized cuff was used, the results still showed clinically unacceptable discrepancy between invasive and non-invasive values (25, 26). Focusing on a possible relationship between obesity and inaccuracy of non-invasive BP measurement, Araghi et al. (27) studied overweight patients in the ICU. The analysis revealed clinically relevant inaccuracy of both, auscultatory and oscillometric, techniques (27), which therefore should not be used to guide therapy in critically ill patients. A similar study compared invasive and oscillometric BP measurement in obese patients undergoing non-cardiac surgery (28). In addition, the same group also examined the cuff position at the forearm of patients. However, oscillometric measurement in these patients in both locations did not allow sufficiently accurate monitoring of BP (28). This leads to the question, whether BP values resulting from oscillometric measurement with other locations for the cuff than the upper arm can be used for guidance of therapy. A single-center study in ICU patients showed acceptable agreement for oscillometric mean arterial BP compared to intra-arterial BP when the cuff was placed at the upper arm, whereas the thigh and ankle location revealed inaccurate values (29). In accordance to these findings, Drake and Hill (30) performed upper arm and ankle measurements during elective cesarean section. The values from the different sites varied considerably; therefore, the oscillometric measurement at the ankle cannot be seen as an alternative to the upper arm (30).

The reliability of non-invasive intermittent BP measurement in patients with arrhythmia has been questioned (31). Two studies have shown recently that there is no relevant difference between oscillometric measurement in patients with or without arrhythmia (32, 33).

For all non-invasive devices that measure BP continuously, numerous validation studies exist (34–36). Kim et al. (35) pooled data from various studies comparing non-invasive continuous devices with direct BP, which have been published until 2013 and reported the mean of the differences with its SD. By this approach, they found an overall random-effect pooled bias for mean BP of 3.2 ± 8.4 mmHg. When stratifying the results according to the different measurement technologies described earlier, the analysis for mean BP yielded a bias and SD of 1.3 ± 5.7, 5.5 ± 9.3, and 3.5 ± 6.8 mmHg for the T-Line system, CNAP, and ClearSight, respectively (35). This analysis demonstrated that accuracy and precision of continuous non-invasive devices are not interchangeable with invasive BP measurement. Besides, the group criticized the lack of a recognized standard to define clinical acceptability (35). Vos et al. (37) concluded recently that non-invasive continuous monitoring with ClearSight was interchangeable with monitoring by an oscillometric technique. In their review from 2016, Bartels and colleagues (34) relate these findings to the well-known inaccuracy of oscillometry. The question is whether continuous non-invasive devices need to replace the direct measurement or rather fill the monitoring gap for patients who are insufficiently monitored by intermittent measurements only. Some clinicians find the ability to track changes in BP of the continuous devices particularly helpful in managing patient care.

In the end, the operator has to know about the limitations and pitfalls of any BP measuring technique, both non-invasive and invasive, to select the optimal technology for BP monitoring for the individual patient.

HOW SHOULD WE MEASURE BP?

The BP monitoring that we use for the individual patient needs to be tailored to the needs of the patients and the clinical setting.

For critically ill patients in the ICU, non-invasive BP monitoring is unlikely to play a big role in the foreseeable future. Although some researchers see the age of total non-invasive BP monitoring dawning (38), in our point of view critically ill patients need frequent arterial blood gas analysis as well as continuous and reliable measurement of absolute BP values.

In the emergency department, it is crucial to identify hemodynamic instability early. Intermittent BP monitoring, however, often is set at quite long intervals (e.g., 15 or 30 min) resulting in missing or only delayed detection of hypotension. There are studies that point out the advantage of continuous monitoring in terms early recognition of deterioration of the patient's hemodynamic status (39, 40).

For patients undergoing surgical procedures, the appropriate method of BP monitoring needs to be identified considering perioperative cardiovascular risk stratification. There are different types of hypotension during general anesthesia and surgery, e.g., post-induction hypotension, early intraoperative hypotension, and late intraoperative hypotension with different risk factors (41). There is a growing body of evidence that continuous monitoring can be beneficial in terms of BP stability. As Walsh et al. (3) showed even periods of hypotension as short as a few minutes can adversely affect organ function. Therefore, BP measurement should first of all enable the physician to maintain BP stability in the patient. Benes and colleagues (42) have demonstrated that continuous BP measurement helps to keep the BP stable during surgery in beach chair positioning compared to intermittent measurements taken every 5 min. Recently, it has been shown in 160 patients with a history of hypertension that there are significantly less hypotensive episodes during induction of general anesthesia when a continuous method is used instead of intermittent oscillometric measurements every 3 min (43). For patients undergoing planned cesarean section, continuous monitoring helped to detect hypotensive episodes earlier and more often (44).

In the perioperative setting, the likelihood for intraoperative hypotension and the patient's risk to develop hypoperfusion-induced organ failure should lead to the choice of which BP monitoring to use (**Figure 2**). We recommend advanced hemodynamic monitoring that allows monitoring of blood flow and fluid responsiveness parameters in the OR for high risk patients undergoing high-risk procedures (45) and in the ICU for patients with severe chronic and acute disease (**Figure 2**).

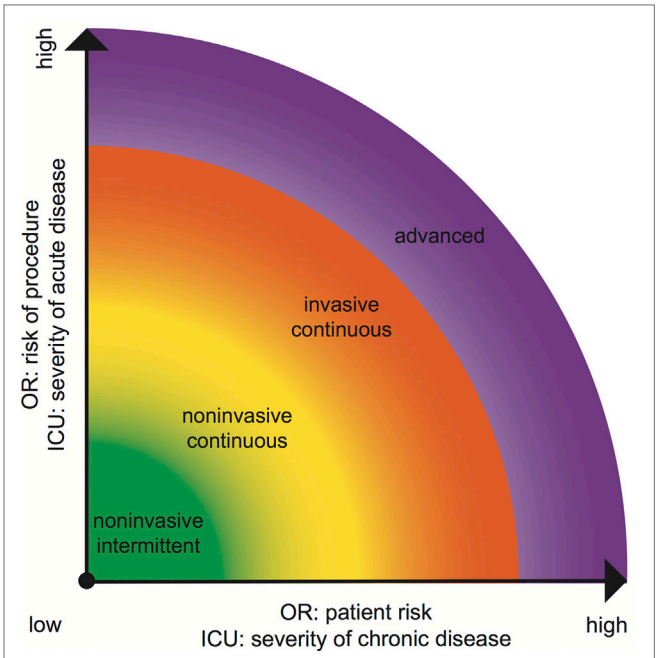

FIGURE 2 | Choice of adequate blood pressure monitoring equipment in ICU and OR according to patient and procedural risk (OR) (45) or chronic and acute disease (ICU).

CONCLUSION

Blood pressure monitoring needs to be tailored to the individual patient. In stable, low-risk patients, intermittent oscillometric BP measurements are usually sufficient. Patients who are at risk for hemodynamic instability should be monitored by continuous BP measurement. Whether continuous non-invasive BP monitoring can improve patient outcome in certain patient collectives or clinical settings (perioperative medicine, emergency medicine) is the subject of the current clinical research. In critically ill patients, we still recommend the continuous invasive BP monitoring with an arterial catheter.

AUTHOR CONTRIBUTIONS

All authors listed, have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Cardiac Output Monitoring by Pulse Contour Analysis, the Technical Basics of Less-Invasive Techniques

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Routine use of cardiac output (CO) monitoring became available with the introduction of the pulmonary artery catheter into clinical practice. Since then, several systems have been developed that allow for a less-invasive CO monitoring. The so-called "non-calibrated pulse contour systems" (PCS) estimate CO based on pulse contour analysis of the arterial waveform, as determined by means of an arterial catheter without additional calibration. The transformation of the arterial waveform signal as a pressure measurement to a CO as a volume per time parameter requires a concise knowledge of the dynamic characteristics of the arterial vasculature. These characteristics cannot be measured non-invasively and must be estimated. Of the four commercially available systems, three use internal databases or nomograms based on patients' demographic parameters and one uses a complex calculation to derive the necessary parameters from small oscillations of the arterial waveform that change with altered arterial dynamic characteristics. The operator must ensure that the arterial waveform is neither over- nor under-dampened. A fast-flush test of the catheter–transducer system allows for the evaluation of the dynamic response characteristics of the system and its dampening characteristics. Limitations to PCS must be acknowledged, i.e., in intra-aortic balloon-pump therapy or in states of low- or high-systemic vascular resistance where the accuracy is limited. Nevertheless, it has been shown that a perioperative algorithm-based use of PCS may reduce complications. When considering the method of operation and the limitations, the PCS are a helpful component in the armamentarium of the critical care physician.

Keywords: hemodynamics, cardiac output, monitoring, physiologic, pulse contour analyses, waveform analysis, arterial wave property

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INTRODUCTION

Critically ill patients often receive extended hemodynamic monitoring with measurement or estimation of cardiac output (CO) as an aid for guiding fluid and vasopressor therapy. With the introduction of the pulmonary artery catheter by Swan et al., measurement of CO became available at the bedside by a thermodilution technique (1). However, routine use of the pulmonary artery catheter in critically ill patients has been questioned, presumably owing to its invasiveness, requiring an additional venous access with a dedicated catheter inserted into the pulmonary artery (2) and due to difficulties in the interpretation of the results (3).

In the following years, transpulmonary thermodilution techniques have been introduced, still allowing for a measurement of CO while less invasive, only requiring a central venous and an arterial line that are often used for standard hemodynamic monitoring in intensive care patients (4). However, the femoral access for the arterial line is preferred since the tip of the dedicated thermistor catheter must be placed in a central artery for correct measurements.

To further reduce the invasiveness of CO measurements, several new techniques have been evaluated and introduced into clinical practice in recent years. These include "non-invasive methods" and "less- or minimal-invasive methods."

The non-invasive methods estimate a CO, i.e., from changes in thoracic electrical impedance, from radial applanation tonometry (T-Line), or from finger blood pressure cuffs (Nexfin™/Clearsight™, CNAP-Systems).

The less- or minimal-invasive methods estimate a CO from an arterial pulse contour waveform (5–7) and require only a conventional arterial line to obtain an input signal. Although some systems may be calibrated by manually entering a CO measured with an independent reference technique (i.e., echocardiography), they do not include an independent calibration method and are thus also referred to as "uncalibrated pulse contour methods." Currently, four systems of this type have been introduced into clinical practice (see **Table 1**).

In addition, some systems have been introduced that combine a pulse contour analysis with an internal reference method and are referred to as "calibrated pulse contour methods." Two transpulmonary thermodilution systems are available that track CO by pulse contour analysis after an initial calibration with algorithms, which are similar to the ones used in the stand-alone uncalibrated PCS ($PiCCO_2$™: similar to Pulsioflex™, PULSION Medical Systems, Feldkirchen, Germany; EV1000™: similar to Vigileo™, Edwards LifeSciences, CA, USA). The algorithm of the LiDCOrapid™ is also used in the LiDCOplus™ System (Medtronic, MN, USA) that can measure CO by a lithium dilution method. Furthermore, a pulse contour analysis is available, that is calibrated by an esophageal Doppler included in the same monitor (CardioQ-ODM+, Deltex Medical, Chichester, UK). The use of the pulse contour analysis without the Doppler calibration is not possible.

The aim of this review is to focus on the technical basics of uncalibrated pulse contour methods for monitoring of CO.

BASIC CONSIDERATIONS

The uncalibrated PCS are designed to be connected to a radial or a femoral arterial catheter. CO is estimated continuously after an optional external calibration possible with some systems. Basically, all systems calculate CO by multiplying stroke volume (SV) and heart rate. Heart rate is usually equal to the pulse rate. The input of the device consists of a pressure measurement, the arterial waveform. Obtaining the pulse rate and hence the heart rate from the waveform is usually a straight-forward task by counting the number of upstrokes of the pressure curve over time. The calculation of the other required parameter, the SV is a difficult task since a pressure measurement must be converted to a volume measurement. This is done by estimating flow that is integrated over time leading to a volume. Deriving a flow from a pressure parameter requires concise information of the pressure–volume relation in the arterial system and especially the aorta. The systems use a refinement of Otto Franks Windkessel model dating back to 1899 that incorporates arterial impedance (Za), arterial compliance (Ca), and systemic vascular resistance (SVR) (8).

Arterial impedance is the ratio of pressure to flow in the central arteries and is determined by the physical properties of the arterial walls. It represents the forces opposing the propagation of the pressure wave transmitted along the arterial system. The arterial compliance is defined as the difference of blood volume induced by a difference in pressure and mainly depends on the elastic properties of the arterial walls. The SVR is the resistance of the total systemic vasculature to the blood flow.

Since arterial impedance and arterial compliance cannot be measured non-invasively, all PCS must obtain a good estimate of these parameters. All systems except one use internal nomograms or databases based on demographic data, i.e., age and gender.

OPERATING PRINCIPLES OF THE PCS

Vigileo™

The Vigileo™ monitor uses the proprietary FloTrac™ transducer that is attached to a standard radial or femoral arterial catheter. No external calibration is required. This system samples the arterial waveform at 100 Hz and then determines CO in 20 s intervals by a multiplication of the pulse rate with the SD of the arterial pressure

TABLE 1 | Overview of uncalibrated pulse contour systems.

System	Distributor	Method	External calibration	Requirements
FloTrac™/ Vigileo™[a]	Edwards LifeSciences, Irvine, CA, USA	Sampling at 100 Hz, multiplication of pulse rate with SD of arterial pressure and a conversion factor	No	Dedicated transducer
LiDCOrapid™	Medtronic, Minneapolis, MN, USA	PulseCO™ algorithm, waveform independent pulse power analysis	Yes—external cardiac output (CO) input	Keycard[b]
ProAQT™/ Pulsioflex™	PULSION Medical Systems, Feldkirchen, Germany	Sampling at 250 Hz, area under curve of the systolic portion of waveform multiplied by calibration factor	Yes—external CO input	Dedicated transducer
PRAM™/ MostCare™	Vytech, Padova, Italy	Pressure recording analytical method, sampling at 1,000 Hz, calculation from perturbations	No	Keycard[b]

[a]*Distribution of the Vigileo™ monitor has been discontinued, the FloTrac™ method is available in the EV1000™ monitor that also includes the transpulmonary thermodilution technique.*

[b]*A keycard is required for operation, on which either a number of booked applications or an unlimited activation code is encoded.*

over a certain period and a so-called "conversion factor" χ. This factor corresponds to the vascular tone and is calculated by means of a multivariate polynomial function. This function includes pulse rate, body surface area, aortic compliance, mean arterial pressure, and the SD of the arterial pressure over a certain time, as well as skewness and kurtosis of the waveform which describe the form of the arterial pressure curve. The aortic compliance is determined from an internal demographic data base (age, sex, height, and weight) and mean arterial pressure.

Over the years, the FloTrac™ algorithm has been refined. In the current software version 4.0, the internal database has been expanded, and an improved SV tracking has been added, electronically eliminating, and interpolating abnormal beats, i.e., in premature complexes.

Pulsioflex™

The Pulsioflex™ monitor is connected to the proprietary ProAQT™ transducer attached to a standard radial or femoral arterial catheter. A start CO may be determined by two methods. A CO may be manually entered if available from an external calibration method, i.e., echocardiography. Alternatively, the monitor may be "autocalibrated" thus estimating a CO from an internal database based on patient's characteristics (age, body height and weight, and gender).

For the continuous measurement of CO, the arterial waveform is sampled at a frequency of 250 Hz. The systolic portion of the arterial waveform is identified, and the area under the curve (AUC) integrated from pressure over time. At the start of CO measurements, an internal calibration factor is calculated from the CO and AUC. Since the AUC is proportional to CO, an increase of the AUC corresponds to an increase of CO, and a decrease of AUC corresponds to a decrease of CO. The algorithm also takes SVR and arterial compliance into account to improve measurements. The internal calibration factor basically corresponds to the arterial impedance.

LiDCOrapid™

This system is connected to any arterial line without a dedicated catheter. No special pressure transducer is required; the monitor can receive the pressure signal from a conventional vital signs monitor *via* an analog output. The system can be calibrated by manually entering a CO from a reference method.

The algorithm of this system for determining CO relies on calculation of SV by means of a so-called "pulse power analysis," which is independent of the shape of the arterial pressure curve. This algorithm determines a nominal aortic volume from a monitor-internal nomogram, in which age, gender, height, and other parameters are considered. The obtained volume is multiplied by an exponential function, that is affected by arterial blood pressure and an aortic compliance determined from an internal reference.

MostCare™

This system uses an algorithm called "pressure recording analytical method" (PRAM). The approach of this system is different from the other methods because the arterial impedance that is required for calculation of SV is estimated from perturbations of the arterial pressure waveform and not derived from internal nomograms based on demographic parameters (5). No external calibration is available with this system. The system does not require a dedicated pressure transducer.

The estimation of the arterial impedance relies on a complex theory of perturbations and is obtained from a morphological analysis of the pulsatile and the continuous components of the pressure waveform (9). When the pressure wave is propagated through the arterial system, the opposing force generated by the specific arterial impedance of the vasculature reflects parts of the pulse wave. The reflection leads to small oscillations ("perturbations") in the pulse wave that are recorded with a sampling frequency of 1,000 Hz. An increase of the impedance leads to a consecutive increase in the perturbations. These perturbations are obtained separately for the systolic and the diastolic part of the pulse wave. An arterial impedance is then estimated from the magnitude and the difference of systolic and diastolic of the perturbations.

Further calculations for SV use the area under the systolic part of the pressure curve divided by the arterial impedance. CO is obtained by the multiplication of pulse rate and SV.

PREREQUISITES FOR MONITORING

A good arterial waveform signal is an important prerequisite for correct measurements. Over-dampened and under-dampened waveforms indicate that the dynamic response characteristics of the arterial catheter system are insufficient and therefore not suitable for analysis (10). It has been estimated that approximately 30% of arterial waveforms in intensive care units are either over- or under-dampened (11). The PCS do not incorporate an automatic detection for inappropriate waveform readings thus requiring the operator to visually inspect and evaluate the arterial waveform regularly and confirm that the signal is correct.

A rapid flush test has been proposed to analyze the intrinsic resonance frequency of the catheter–transducer system and to verify for correct response characteristics (12, 13). After termination of the square wave from the rapid flush no visible oscillations of the wave indicate overdamping while several oscillations and "ringing" point to underdamping (14). The resonance frequency of the catheter–transducer system can be measured, and the damping coefficient calculated for a precise evaluation of the response characteristics that can be compared with the nomogram by Gardner (10). As a rule of thumb, an adequate response indicating appropriate dynamic response characteristics can be expected when the waveform returns to the pulse waveform after one to three undulations after the rapid flush test. The dynamic response characteristics change over time but may be corrected by a rapid flush (15). However, this requires a regular intervention by the operator.

Most systems rely on the recognition of the dicrotic notch to identify the systolic portion of the pulse waveform. In instances of over- or under-dampened catheter–transducer systems, the dicrotic notch may not be identified correctly, possibly leading to incorrect measurements (16).

Although these systems are designed to be used with any arterial waveform, concerns have been raised that femoral and radial waveforms are not interchangeable (17, 18). Trending analysis for one of the systems has been shown to be superior when the device was connected to a femoral catheter over a radial catheter (19).

LIMITATIONS TO PULSE CONTOUR MONITORING

As outlined earlier, the minimally invasive pulse contour analyses systems must convert a pressure measurement into a volume parameter. Since it is impossible to non-invasively measure the determinants needed for this transformation, this transformation is prone to error, especially during some underlying pathologies.

Systemic Vascular Resistance

As data show, agreement of the minimal-invasive methods with reference methods is poor, especially in patients during low SVR states such as sepsis and chronic liver failure (20–22). Apparently, there are no specific morphological patterns in the arterial waveform that are pathognomonic for low SVR. The difference of radial and central arterial pressure increases in low SVR (17), presumably reducing the ability of the systems to estimate adequate CO values. It has been shown that pulse contour monitoring systems are vulnerable in states of SVR changes, i.e., vasopressor therapy (21, 23). However, there are differences between the systems and some seem more robust than others (24).

The MostCare™ system that derives the arterial impedance from the pressure waveform itself and not from an internal nomogram overestimates CO in low SVR states (25), but data are sparse so far, and further validation in these patients is warranted.

The manufacturer of the LiDCOrapid™ system does not recommend its use during peripheral vasoconstriction.

Intra-aortic Balloon Pump

Due to the altered arterial waveform during intra-aortic balloon-pump therapy, most systems cannot identify the systolic and diastolic portion of the waveform correctly. Therefore, these systems are not able to display correct values. The use of the LiDCOrapid™, Vigileo™, and Pulsioflex™ systems is not recommended by the manufacturers. For the MostCare™ system, a study with 15 patients could show a good accuracy in patients with IABP, probably due to its different approach to measurements (26).

ACCURACY AND TRENDING ABILITY

The accuracy and trending ability are used for the evaluation of the pulse contour analysis systems. While accuracy is the agreement with an absolute value of a reference method, trending ability indicates the extent to which a change in CO over time is correctly estimated. As described earlier, none of the methods perform a measurement. Since the CO is only estimated according to different algorithms, the pulse contour analysis methods are error prone when used in critically ill patients who often have a low SVR, i.e., in septic shock as outlined earlier.

The Vigileo/FloTrac™ algorithm has been refined several times, and the manufacturer claimed an improvement in accuracy and trending ability with each iteration of the software. However, the available validation studies for the up to date fourth generation software could not show a sufficient accuracy or trending ability for this system when used in patients with changes in SVR or with low CO, although the performance has improved over the previous software versions (27–29). Concerning the Pulsioflex/ProAQT™ system data show that this system is also unable to adequately estimate the CO during low- or high-SVR. Concerning the trending ability, data are ambiguous, and the performance of this system may rely on the arterial access. The performance seems better when the system is connected to a femoral arterial catheter than to a radial arterial catheter (19, 21, 22). Similar to the other systems tested, accuracy of the LiDCOrapid™ monitor is below the acceptable limits (30). At first, validation studies of the MostCare/PRAM™ algorithm have shown a good agreement with thermodilution as reference method (31–33), followed by studies that have shown that accuracy is below acceptable limits (34, 35). This method should therefore be further evaluated.

In summary, none of the systems has a sufficient accuracy to be used in critically ill patients. Nevertheless, it must be noted that despite the inability to correctly estimate CO, it has been shown that these systems may improve outcome when used intraoperatively and algorithm based (36–39), although one large randomized study in high-risk abdominal surgery found no benefit (40).

Therefore, it is important that the pulse contour methods are used in a targeted manner in selected patients, where a benefit for their application could be shown. In critically ill patients or if accuracy plays a role, transpulmonary or pulmonary artery thermodilution methods should be used.

CONCLUSION

Uncalibrated PCS are less-invasive methods to estimate CO. Only a conventional arterial catheter that is present in many critically ill patients is required. For the transformation of the arterial waveform as a pressure signal to CO, assumptions on the dynamic characteristics of the arterial vasculature must be made. Most systems use internal databases or nomograms based on demographics, while one system uses a complex calculation to estimate the necessary parameters.

Special attention has to be given to the arterial waveform as the input signal of the pulse contour monitors. Neither over- nor under-dampened signals are suitable for analysis and regularly require the operator's intervention for the assessment of the dynamic response characteristics of the catheter–transducer system, i.e., by a fast-flush test. The operator must confirm that the waveform is correct before obtaining CO values from the monitor.

The use of PCS is limited in patients with large deviations from normal SVR or in patients receiving intra-aortic balloon pumps. The accuracy and trending ability of the CO estimation compared with thermodilution measurements is often limited. However, it has been shown that an algorithm-based use of PCS can improve the perioperative outcome of patients. Uncalibrated PCS represent a helpful, less-invasive tool in the hemodynamic armamentarium of the critical care physician.

AUTHOR CONTRIBUTIONS

The author listed has made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REVIEW
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Non-Invasive Monitoring of Cardiac Output in Critical Care Medicine

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Critically ill patients require close hemodynamic monitoring to titrate treatment on a regular basis. It allows administering fluid with parsimony and adjusting inotropes and vasoactive drugs when necessary. Although invasive monitoring is considered as the reference method, non-invasive monitoring presents the obvious advantage of being associated with fewer complications, at the expanse of accuracy, precision, and step-response change. A great many methods and devices are now used over the world, and this article focuses on several of them, providing with a brief review of related underlying physical principles and validation articles analysis. Reviewed methods include electrical bioimpedance and bioreactance, respiratory-derived cardiac output (CO) monitoring technique, pulse wave transit time, ultrasound CO monitoring, multimodal algorithmic estimation, and inductance thoracocardiography. Quality criteria with which devices were reviewed included: accuracy (closeness of agreement between a measurement value and a true value of the measured), precision (closeness of agreement between replicate measurements on the same or similar objects under specified conditions), and step response change (delay between physiological change and its indication). Our conclusion is that the offer of non-invasive monitoring has improved in the past few years, even though further developments are needed to provide clinicians with sufficiently accurate devices for routine use, as alternative to invasive monitoring devices.

Keywords: non-invasive monitoring, cardiac output, hemodynamics, critical care medicine, bioreactance

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INTRODUCTION

Hemodynamic instability requires cardiac output (CO) measurement and tracking to assess severity of disorders and to adjust treatments on a continuous basis. Invasive monitoring is widely used but is associated with inherent iatrogenic complications, notably for pulmonary catheters, esophageal probes, or arterial catheters (1–3). Therefore, non-invasive methods offer a safer approach even though their metrologic performance remains challenged, particularly in intensive care units (ICUs) (4, 5).

This article aims to review such non-invasive methods of CO monitoring excluding echographic, thermodilution, and pulse contour methods, already described in other sections. We will cover electrical bioimpedance and bioreactance, respiratory-derived CO monitoring technique, ultrasound CO monitoring, multimodal algorithmic estimation, and inductance thoracocardiography.

Devices are reviewed using three main metrologic criteria required for CO measurement: *trueness* (systematic error assessed by the closeness of agreement between the average of an infinite number of replicate measurements and the true or reference value), *precision* (random error assessed by the closeness of agreement between replicate measurements on the same or similar objects under

TABLE 1 | Summarizes the metrologic performance of these different technologies.

Device	Author	Year	Number of patients	ICU setting	Mean bias (l/min)	Percentage error (%)	Precision (repeatability)
Bioimpedance	Peyton and Chong (69)	2010	435 (pooled)	Yes	−0.1 ± 1.1	Mild	nd
Bioreactance	Squara (20)	2007	110	Yes	+0.16 ± 0.52	Mild	12%
CO_2 rebreathing	Kotake et al. (38)	2009	42	Yes	+0.18 ± 0.88	Mild	nd
	Peyton and Chong (69)	2010	167 (pooled)	Mixed	−0.05 ± 2.24	Mild	nd
	Opotowsky et al. (45)	2017	12232	Mixed	−0.4 ± 2.24	High	nd
Ultrasonic	Chong and Peyton (71)	2012	320 (pooled)	Yes	−0.39 ± 0.14	Poor	nd
Pulse wave velocity	Yamada et al. (51)	2012	213	Yes	+0.13 ± 1.15	Acceptable	nd
Inductance cardiography	Kaplan et al. (66)	2003	11	No	+0.2 ± 2.4	Mild	nd

specified conditions), and *step response change* (delay between physiological change and its indication) (6). **Table 1** summarizes the metrologic performance of all reviewed technologies.

BIOIMPEDANCE AND BIOREACTANCE

Bioimpedance was first described in aeronautical medicine 50 years ago (7). It shares physical principles with bioreactance. It involves delivery of a low-amplitude high-frequency electrical current (I) across the thorax and received voltage (V) by electrodes. Hemodynamic variables: stroke volume (SV), CO, and thoracic fluid content (TFC) are then derived from the output signal fluctuation. Thoracic impedance (Z) is defined by the ratio V/I. At baseline (Z_o) is the ratio of maximum values of V and I (V_o/I_o) and closely correlated changes in TFC (8–17). In the presence of flow through the aorta Z_0 Z decreases over time proportionally to the increase of water and iron located in the chest, thus, to the increase in blood volume. Traditional bioimpedance systems use amplitude modulation as signal whereas bioreactance systems use frequency modulation and phase shifts (see **Figure 1**) (18). The theoretical superiority of the frequency modulation is its easier electric noise filtration (19).

A basic hypothesis to derive CO from both impedance and reactance is that the heart chambers are electrically isolated. Indeed, relatively to the chest with the lungs, the myocardial wall effectively provides electrical isolation to the content of the heart; therefore, changes in chest impedance and reactance are closely linked to variations of aortic volume. SV is obtained from the product of the ventricle ejection time and the slope of the initial change of the aortic volume obtained from the first derivative of the impedance or reactance signal (dZ/dt_{max} or dX/dt_{max}). Since these changes only indicate relative changes of CO, a calibration factor (CF) is necessary, based on an initial cohort of patients to derive absolute values

$$SV = VET \times dZ/dt_{max} \times CF$$

$$SV = VET \times dX/dt_{max} \times CF.$$

Several physical and anatomical hypotheses are required, limiting the effectiveness of impedance/reactance, most notably when there is no association between aortic systolic deformation and the SV (i.e., aortic dissection, aortic prosthesis), when hematocrit is very low, when pulmonary arterial pressure is elevated (for which, correction factors exist) or because of physical abnormalities such as obesity and dehydration (20).

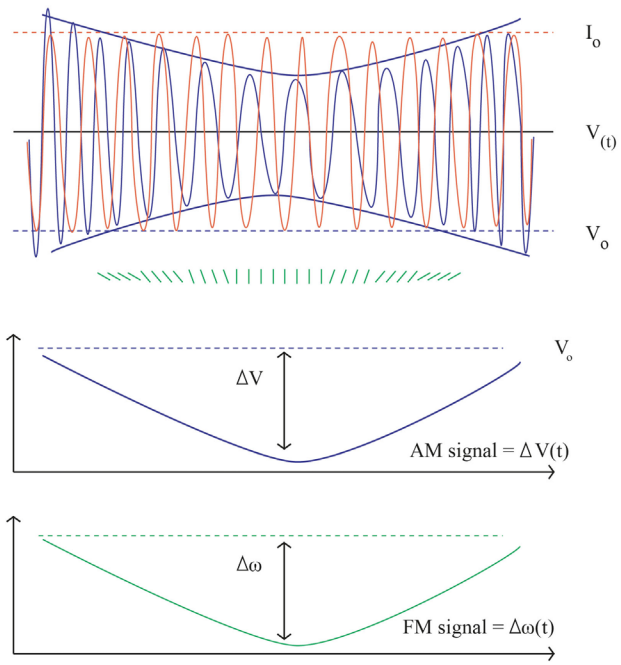

FIGURE 1 | Bioimpedance and bioreactance signal. Upper part, in orange the input constant alternating current: I_o = 5 mA, frequency 75 kHz (ω = 150,000 radians/s). In blue the output voltage. $V(t)$ = 200 ± 2 mV, frequency $F(t)$ = 75 kHz ± 5 Hz. The instantaneous changes in phase are figured in green. In the middle, the V_o envelope (AM component) is extracted from the envelope of V = 4 mV, corresponding to the bioimpedance signal (Z = 4/5 = 0.8 Ω). The lower part shows the corresponding changes in frequency as obtained by the sum of instant phase shift (FM signal) figuring the bioreactance signal: F = 10 Hz (ω = 20 radians/s). Using appropriate scaling the shape of the AM and FM signals is the same.

Devices using bioimpedance include NCCOM (Bomed Medical, Irvine, CA, USA), BioZ (Cardiodynamics, San Diego, CA, USA), NICCOMO (MEDIS, Limenau, Germany), ICON (Osypka Cardiotronic, Berlin, Germany), ICG (Philips Medical Systems, Andover, MA, USA), NICOMON (Larsen and Toubro Ltd., Mumbai, India), the CSM3000 (Cheers Sails Medical, Shenzhen, China), and PHYSIOFLOW (Manatec Biomedical, Paris, France). The NICaS system (NI Medical, Petah-Tikva, Israel) uses the same principles but applied to the whole body. In the ECOM system (Ecom Medical, San Juan Capistrano, CA, USA), the transmitting and receiving electrodes are located on

the cuff of an endotracheal tube, therefore close to the ascending aorta, in order to minimize the impact of analogous signals from other cardiac structures. Bioreactance is used by two products from the same company NICOM and Starling (Cheetah medical, Wilmington, DE, USA).

Bioimpedance and bioreactance have the strong advantage of being totally non-invasive and low costs. Literature on bioimpedance includes hundreds of articles, dozens of which are clinical trials set in a wide range of situations from ambulatory patients at home, to patients in a physiology laboratories, during surgery and in a ICU. Results are somewhat contradictory (21). At least a third of the publications failed to assess bioimpedance as a reliable mean to assess CO (22–25). Focusing on positive articles, most of them took place outside from an ICU setting most often in situations where the absolute value of CO has less importance than relative changes (26–30). This may be explained as electronical environment is heavier in ICU (due to the number of monitoring devices) compared to traditional medicine department; the higher the level of noise, the lesser bioimpedance would be accurate because of an unfavorable signal/noise ratio. Moreover, total body impedance is less accurate than localized thoracic impedance. Finally, even though last iterations of this technology seem more advanced (such as electrical velocimetry), results are not quite as clear either (31, 32). As of today, bioimpedance is not consensually viewed as accurate enough to estimate CO in ICU.

Bioreactance on the other hand has scarcer documentation. Theoretical superiority of bioreactance over bioimpedance was hinted in small sample studies set, in quite homogeneous patients of cardiac surgery ICU where the CF was derived (33, 34). In two studies, the accuracy, delay and amplitude of the signal were found similar to that of continuous thermodilution, although a bias up to 20% was found in 20% of patients. In other words, bioreactance-measured CO was similar to that of thermodilution in 80% of patients, but in those in whom it was not, bias could be as high as 20%. In several other studies investigating more heterogeneous patients, results were not considered as acceptable (35, 36). Concerns may be raised about decrease in accuracy during low-flow state and when electrocauterization was performed.

Further developments may be required to improve bioimpedance and bioreactance performance focusing or better understanding of the signal composition and better extraction of the aortic expansion signal. The auto calibration process may also be improved to fit better the studied population.

RESPIRATORY DERIVED CO MONITORING SYSTEM: PARTIAL CO_2-REBREATHING

Applying Fick principles to exhaled gases allows measuring CO, by assessing oxygen consumption (VO_2) and the difference of arterial (CaO_2) and venous (CvO_2) blood oxygen contents. This method was first described for intubated, sedated and ventilated patients (who did not present severe gas-exchange abnormality), using either oxygen (O_2) or carbon dioxide (CO_2) exhaled gas, and requires invasive arterial and mixed venous blood sampling, obeying the following equations (37):

$$CO = VO_2 / CaO_2 - CvO_2$$

$$CO = VCO_2 / CaCO_2 - CvCO_2.$$

A non-invasive method has since been developed, using the slope of CO_2 dissociation curve (S) and the end tidal CO_2 concentration (S. $etCO_2$) as a surrogate of $CaCO_2$. Since the $CvCO_2$ is more difficult to estimate, it is derived considering two periods of time: normal respiration (n) and a 30-s period of rebreathing (r). Assuming that the CO and the $CvCO_2$ remain unchanged during the two periods of time, the two equations become as follow:

$$VO_2 / CaO_2 - CvO_2 = nVCO_2 / n\left(S \,.\, etCO_2\right) - CvCO_2$$

$$VCO_2 / CaCO_2 - CvCO_2 = rVCO_2 / r\left(S \,.\, etCO_2\right) - CvCO_2$$

$$\text{Hence: } CO = nVCO_2 / n\left(S \,.\, etCO_2\right) - CvCO_2$$
$$= rVCO_2 / r\left(S \,.\, etCO_2\right) - CvCO_2$$

$$\text{Finally: } CO = \Delta VCO_2 / \Delta\left(S \,.\, etCO_2\right).$$

$etCO_2$ can be measured in exhaled gas with a sealed facial mask. This partial CO_2-rebreathing method hence allows measuring CO without the need of intravascular monitoring devices. Practical use involves an extra loop of ventilatory circuit to create a transient partial CO_2 rebreathing system (i.e., $etCO_2$) (see **Figure 2**).

The NICO-sensor (Philips Respironics, Eindhoven, the Netherlands) and INNOCOR (Innovision ApS, Denmark) are based on these principles (38, 39). Several limitations surround this method: (a) the smallest variations in CO_2 can lead to significant differences in CO measurements, i.e., the slightest leaks in facial mask can induce measurement bias, (b) changes in ventilation modify end-tidal CO_2 requiring patient respiratory state to be steady, i.e., not applicable in ICU, and (c) differences in VCO_2 and end-tidal CO_2 only account for that part of the lung which is ventilated, hence, atelectasis or intrapulmonary shunts need to be adjusted for, which in an ICU setting can prove difficult when patients present with several lung diseases (40–42). The two most recent validation articles published were small-sample studies in which this method was compared with thermodilution. Both failed to prove the equivalence between the two methods (43, 44).

A very recent retrospective study, in more than 12,000 patients who underwent right heart catheterization but were not necessarily hospitalized in ICU, found between thermodilution and an oxygen-uptake-based Fick method, an acceptable systematic bias of 0.4% but poor limits of agreement from −1.31 to +1.27 l/min; and a difference of more than 20% between measured CO in 40% of patients (45).

Hence, partial CO_2-rebreathing is still hard to routinely use in ICU but fields of development include better rebreather-face interface to avoid leaks (i.e., masks) and correction algorithms which may take into account changes in end-tidal CO_2, all the more in ICU setting. Indeed, this latter concern seems particularly difficult to address, as acute respiratory disease (including acute pulmonary edema, pneumonia and chronic obstructive

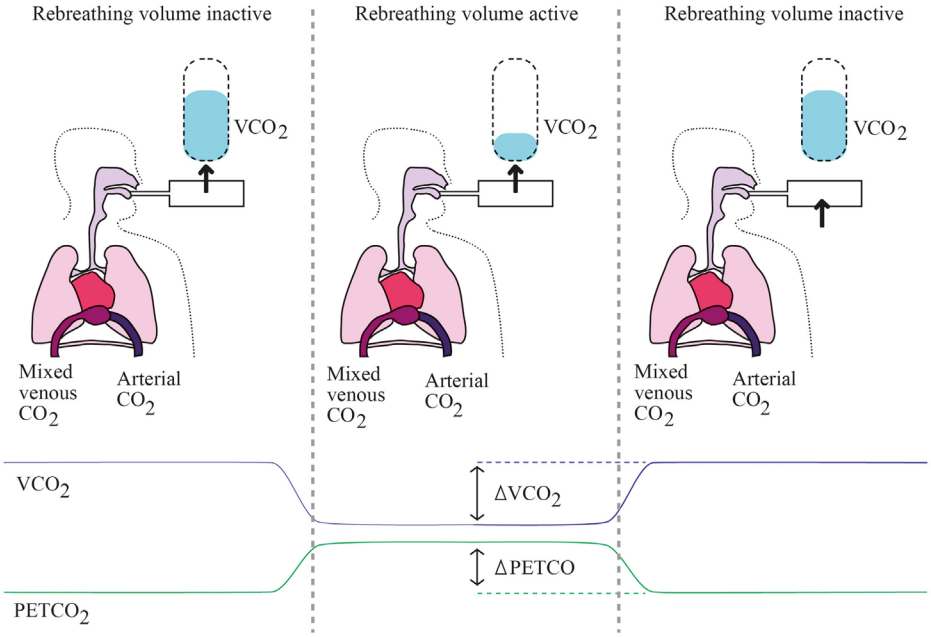

FIGURE 2 | Partial rebreathing principles. Left panel represents baseline state, where the rebreathing valve is off and every parameter is at baseline levels. Middle panel represents early rebreathing time, when the valve is put; there is a decrease of VCO_2 with simultaneous rise in $PaCO_2$ and $PETCO_2$. Right panel represents late rebreathing time when valve is off again and all parameters return to baseline levels, while mixed venous PCO2 has varied.

pulmonary disease exacerbation) represents the most prevalent cause of admission in ICU.

PULSE WAVE TRANSIT TIME (PWTT)

Pulse wave transit time is the time required for a pulse pressure wave to travel between two points. It can be estimated from the time interval between the development of the R-wave on the electrocardiogram and its peripheral detection (see **Figure 3**). Approximating systemic blood circulation to a three-component Windkessel circuit (integrating aortic characteristic impedance, arterial compliance, and systemic vascular resistance) and neglecting vascular inertance, blood pressure can be associated with blood flow hence CO in a complex non-linear function (46, 47). PWTT is then considered inversely correlated with the SV (48). With increasing blood pressure, increasing arterial distending pressure and decreasing arterial compliance, pulse-wave velocity increases and PWTT shortens. Hence, PWTT was suggested as a surrogate measure of blood pressure changes. Given a known and fixed distance between the heart and the extremity on which the measurement is made, PWTT can be computed using the following Bramwill and Hill formula (49):

$$\mathrm{PWV} = \mathrm{d}P.V / \rho.\mathrm{d}V,$$

where PWV = pulse wave velocity; ρ = density of blood; V = initial vessel volume; dP = the change in pressure; and dV = the change in vessel volume.

One product uses this technology (EsCCO, Nihon Kohden, Japan). Continuous CO is estimated with a multimodal algorithm

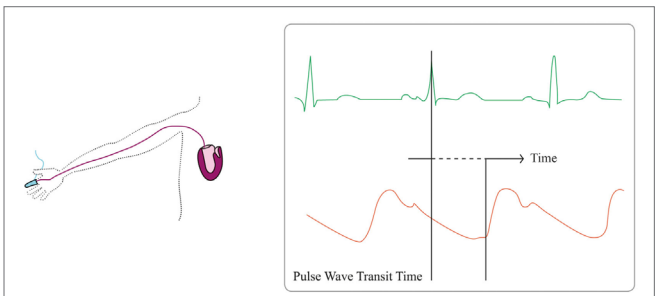

FIGURE 3 | Pulse wave transit time principles. Pulse wave transit time is based on the delay of the generation of a stroke volume (orange line) after the generation of the R-wave on the electrocardiogram (green line).

PWV and using patients' characteristics and several measurements such as pulse oximeter waveform, non-invasively measured blood pressure and electrocardiogram. The final formula is given by:

$$\mathrm{SV} = K \times (\alpha \times \mathrm{PWTT} + \beta),$$

where the unique variable is PWTT then inversely proportional to velocity. Other determinants are $\alpha = -0.3$, experimental proportional constant according to unpublished preliminary data and K and β are individual CFs based on physical profile (age, weight, height) and the initial measurement of the pulse pressure. Interestingly, initial CO was estimated only by this non-invasive patient information calibration (50). Even if later refined by an automated exclusion algorithm, several concerns were raised as

to its accuracy in ICU setting (51–55). Indeed, although systematic bias was acceptable with 0.13 l/min, limits of agreement were poor (between −2.13 and 2.39 l/min) (51). Limitations include vasoconstriction, cold extremities and arrhythmias all of which induce bias in measurements. Moreover, while calibration with invasive means seems to enhance the trueness of this device; there is uncertainty as to its stability (51). Finally, catecholamines infusions are a limitation to the use of plethysmographic-variability-based indices in critically ill patients (56, 57).

While EsCCO has not been quite validated in ICU, devices using pulse wave contour analysis, working quite closely to pulse wave velocity analysis are more promising. EsCCO suffers mainly from initial individual calibration issues, which are reduced to a crude algorithm aggregating a few variables which may not be sufficient to account for the wide variability of patients presenting in ICU. Indeed, the two main issues are (i) the heterogeneity of patients' profiles, for which an overall algorithm may be statistically true for most but containing an inherent percentage error, making individual prediction hard to assess and (ii) the interpatient variability in the course of his treatment and care in ICU (accounting for volemia, vasoconstriction or vasodilation, catecholamine use and arrhythmia, to name a few).

ULTRASONIC METHODS

Product of aortic blood flow velocity and area of a section of the aorta equals to the CO measured in the aorta. Blood flow velocity can be measured using ultrasound and Doppler effect

$$SV = VTI \,.\, CSA,$$

where VTI = aortic flow velocity time integral and CSA = aortic cross-sectional area. Hence, a non-invasive measurement method would require a device continuously measuring aortic blood flow, in a fixed manner (see **Figure 4**). This method is used in the ultrasonic cardiac output-monitoring (USCOM) device. USCOM requires the precalculation of the aortic valve area based on patient's age and weight. Moreover, ICU setting seems to be inadequate for using USCOM (58–60). Limitations include (i) the difficulty of keeping the USCOM Doppler probe in a steady position on a critically ill patient, (ii) the lack of echogenicity in patients who underwent cardiac surgery (61), and (iii) the reliability of the valve area estimation based on age and weight tends to decrease with population age (62, 63).

A few articles highlight the feasibility of using USCOM in ICU, with a systematic bias of −0.36 l/min however limits of agreement were poor ranging from −2.34 to 1.62 l/min and the reported percentage error (29%) seemed too high for daily use (64).

To put it in a nutshell, although point-of-care ultrasonic evaluation of CO is widely used in ICU, continuous echocardiographic monitoring of CO by USCOM remains largely debated. Indeed, a high percentage error, either due to errors in valve area estimation or probe displacement, make it hard to routinely apply. However, initial calibration on actual echocardiographic assessment of the valve area and regular signal-quality checks may improve this technique.

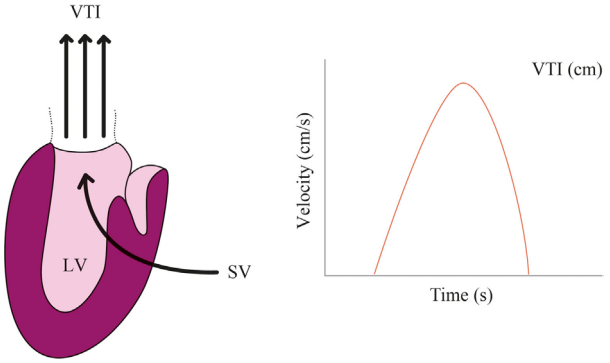

FIGURE 4 | Echocardiographic monitoring. Aortic flow velocity time integral (VTI) multiplied by the cross-sectional area (CSA) allows to compute stroke volume (SV) ejected by the left ventricle (LV). Heart rate (HR) then allows to compute cardiac output (CO) = VTI × CSA × HR.

INDUCTANCE THORACOCARDIOGRAPHY

This method allows the computation of ventricular volume curves from ECG-triggered ensemble respiratory waveform of an inductive plethysmographic transducer. The latter is placed on the thorax by surrounding with a belt. Impedance varies according to respiration and cardiac ejection. Because the transducer is positioned in front of the heart, heartbeat-related ventricular volume variations are detected and adjusting the signal on respiratory-related impedance signal allows computing specific cardiac changes. The only device using this technology is Respitrace (Noninvasive Monitoring Systems, Miami, FL, USA) (65).

Main limitation of this method resides in the fact that it only detects relative variations in cardiac volumes (66, 67), hence, at least one calibration per patient is required to get an absolute value (68). Moreover, if thoracic compliance is very low, cardiac volume variations can be undetectable. Finally, although the method was published at the end of the 90s, only a few publications have since been written by a few authors only, making external validation difficult to assess. In 2017, inductance thoracocardiography seem like it fell out of clinical practice, maybe to the exception of a few experimental settings.

DISCUSSION

The need for a non-invasive, true and precise CO measurement in the ICU is, as of yet, still unsatisfied (69, 70), despite acceptable results on other settings. As recent reviews demonstrated, overall, validation articles available in the field of non-invasive hemodynamic monitoring showed too large heterogeneity and devices, insufficient levels of agreement. Thus, further research may be warranted in the field, as hemodynamic monitoring is bound to be less and less invasive in the future.

Extensive reviewing of published data on diagnostic performance of monitoring devices, be they invasive or not, shows heterogeneity in reporting of performance. Specifically, *accuracy*, i.e., how close a single measurement value is to the true value of

the measurand can never be numerically assessed. Indeed, the true value of the measurand can only be approximated by a reference method or, when available, a gold-standard. Theoretically, if someone could repeat the measurement an infinite number of times to estimate the same measurand value, the only difference between the averaged observed value and the true value would equal the systematic measurement error (i.e., systematic bias qualifying the trueness). Statistical analyses are aimed for adjusting for such bias, however, most methods derive from population-based algorithms, hence do not account for individual variability. Therefore, non-invasive devices are characterized by acceptable mean interpatient bias but poor individual calibration. *Precision*, as defined by metrological standards, represents the repeatability and reproducibility of the method, i.e., the degree to which repeated measurements using the same method to estimate the same measurand value, produce the same observed value. Inherently, it relates to random measurement error (as opposed as systematic measurement error represented by the bias). As such, most publications do not specify precision but rather publish the standard deviation of the bias in the cohort, i.e., interpatient bias. A higher precision allows for fewer measurements in order to have an estimation of the measurand. Hence, *precision* has a direct practical impact on the usability of devices, especially in the step time response of the device. Indeed, very few articles describe how many measurements were taken to obtain a value, and similarly, manufacturers do not always specify how many measurements are necessary to be within acceptable error limits. In practice, non-invasive devices present the obvious advantage of allowing repeated measures to obtain more accurate value, given they would be adequately calibrated. However, if a given device takes too long to estimate a measurand, its usefulness may be challenged, however accurate it can be.

Hence, the risk of misdiagnosis or delay to diagnosis from an insufficiently accurate non-invasive device remains real. Indeed, they represent the counterparts of invasive device-related complications, be they infections or hemorrhages. Consequently, properly assessing the need for invasive monitoring remains a clinical challenge in ICU, to which, the only acceptable solution would be equally efficient non-invasive devices.

Interestingly, obtaining the true value of a measurand would not necessarily be the most important feature that one might require from a hemodynamic monitoring device. Indeed, ability to observe variations in hemodynamics is equally important, if not more; implying fast step-time response and precision. Observing the decrease in CO may be as useful as knowing this exact value. In the end, the difference between trueness and precision may be analogous to that of diagnosis or monitoring.

CONCLUSION

Non-invasive monitoring has evolved in the past few years, seeing the appearance of promising new devices. Further developments may be warranted to validate their use and increase their metrologic performance in ICU. Even though some have successfully deployed such device, the need for a non-invasive, true and precise CO measurement in ICU is, as of yet, still unsatisfied.

AUTHOR CONTRIBUTIONS

LN and PS contributed equally to the manuscript.

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frontiers in Medicine

REVIEW
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Monitoring of Tissue Oxygenation: an Everyday Clinical Challenge

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Purpose of review: The aim of this article is to study the overview of pathophysiology and clinical application of central venous oxygen saturation monitoring in critically ill patients and during the perioperative period.

Recent findings: There are several clinical studies and animal experiments evaluating the effects of goal-directed hemodynamic stabilization on critically ill patients. Recent systematic reviews and meta-analyses found that advanced hemodynamic endpoints-targeted management has a positive effect on outcome in high-risk surgical patients. As all interventions aim to improve tissue oxygenation, it is of utmost importance to monitor the balance between oxygen delivery and consumption. For this purpose, central venous blood gas analysis provides an easily available tool in the everyday clinical practice. The adequate interpretation of central venous oxygen saturation renders the need of careful evaluation of several physiological and pathophysiological circumstances. When appropriately evaluated, central venous oxygen saturation can be a valuable component of a multimodal individualized approach, in which components of oxygen delivery are put in the context of the patients' individual oxygen consumption. In addition to guide therapy, central venous oxygen saturation may also serve as an early warning sign of inadequate oxygen delivery, which would otherwise remain hidden from the attending physician.

Summary: With the incorporation of central venous oxygen saturation in the everyday clinical routine, treatment could be better tailored for the patients' actual needs; hence, it may also improve outcome.

Keywords: venous oxygen saturation, central venous oxygen saturation, oxygen debt, hemodynamic monitoring, oxygen delivery, oxygen consumption, goal-directed therapy

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INTRODUCTION

Interventions to improve oxygen delivery and decrease oxygen consumption are the cornerstone of resuscitation in the critically ill patients and during the perioperative period of high-risk patients. Early recognition of the patients at risks and the implementation of adequate monitoring-guided interventions can have a profound effect on outcome. On the contrary, delaying adequate interventions will inevitably lead to hypoperfusion, tissue hypoxia, and multiple-organ failure affecting both outcome and wasting of resources and costs (1). Therefore, the use of appropriate indices, which are able to detect the imbalance between oxygen delivery (DO_2) and consumption (VO_2), is mandatory for adequate management (2). Conventional parameters such as heart rate, mean arterial blood pressure, mental status, and urine output are robust warning signs of inadequate tissue perfusion, but for fine tuning of therapy detailed hemodynamic monitoring is warranted (3). The recent FENICE (Fluid Challenges In Intensive Care) trial indicate that there is a considerable gap between the accumulating knowledge about the benefits of advanced hemodynamic

monitoring based optimization and the actual clinical practice. In more than 2,000 patients, fluid challenges were evaluated. The main indicator of administering fluid boluses was hypotension in 57%, and in 43% of cases, no hemodynamic variable was used to predict fluid responsiveness (4). Detailed assessment of global hemodynamic indices such as cardiac output (CO) and derived variables and also the measures of oxygen delivery and uptake should be taken into account to provide appropriate therapy for these patients (5, 6). Furthermore, in addition to the optimization of global hemodynamic parameters, indicators of tissue perfusion should also be monitored to verify the effectiveness of our interventions (7). To monitor changes in tissue oxygenation, central or mixed venous blood gas measurements can give more detailed information, which should be incorporated into a multimodal approach that can lead to a better, individualized, patient-centered care. The goal of this review is to highlight the importance of central venous oxygen saturation in this multimodal, individualized hemodynamic management in the context of the pathophysiological background and the results of recent clinical and experimental studies.

PHYSIOLOGICAL ISSUES

Tissue oxygenation is the net product of oxygen delivery and oxygen consumption, which can be described by the following formulae (8):

$$DO_2 = CO \times CaO_2.$$
$$CaO_2 = Hb \times 1.34 \times SaO_2 + 0.003 \times PaO_2.$$
$$DO_2 = CO \times (Hb \times 1.34 \times SaO_2 + 0.003 \times PaO_2).$$
$$VO_2 = CO \times (CaO_2 - CcvO_2).$$
$$VO_2 = CO \times [(Hb \times 1.34 \times SaO_2 + 0.003 \times PaO_2) - (Hb \times 1.34 \times ScvO_2 + 0.003 \times PcvO_2)].$$
$$\text{Oxygen extraction } (O_2ER) = VO_2/DO_2.$$
$$O_2ER: (SaO_2 - ScvO_2)/SaO_2.$$

If SaO_2 is taken as 1, as under normal circumstances, the hemoglobin is almost fully saturated with oxygen, and the other hemodynamic variables are kept constant, then:

$$O_2ER \approx 1 - ScvO_2$$

DO_2, oxygen delivery; CO, cardiac output; Hb, hemoglobin; SaO_2, arterial oxygen saturation; PaO_2, partial pressure of oxygen in the arterial blood; CaO_2, arterial oxygen content; VO_2, oxygen consumption; $ScvO_2$, central venous oxygen saturation; $CcvO_2$, central venous oxygen content; O_2ER, oxygen extraction; $PcvO_2$, central venous partial pressure of oxygen.

Taking a 75-kg healthy adult man when resting, the relationship between DO_2 and VO_2 can be estimated as:

Oxygen delivery:

$$CO = 70ml \times 70/min \sim 5{,}000\,ml/min.$$
$$CaO_2 = (150g/l \times 1.34\,ml \times 1.00) + (0.003 \times 100\,mmHg) \sim 200\,ml/l.$$
$$DO_2 \sim 1{,}000\,ml/min.$$

Oxygen consumption:

$$CO = 70ml \times 70/min \sim 5{,}000\,ml/min.$$
$$CcvO_2 = (150\,g/l \times 1.34\,ml \times 0.75) + (0.003 \times 40\,mmHg) \sim 150\,ml/l$$
$$VO_2 = 5l/min \times (200\,ml/l - 150\,ml/l) \sim 250\,ml/min.$$

Oxygen extraction:

$$O_2ER: 250\,ml/min/1{,}000\,ml/min \times 100 = 25\%.$$

The main difference between the equations of DO_2 and VO_2 is the oxygen content (CaO_2 versus $CcvO_2$), especially the central venous oxygen saturation ($ScvO_2$). Therefore, it can be useful to assess the imbalance between DO_2 and VO_2 in the critically ill.

When the arterial oxygen content (CaO_2) and/or CO becomes impaired, DO_2 decreases, which is often accompanied by a parallel decrease in VO_2. The most frequently occurring scenarios are represented in **Figure 1**. In the early phase of decreasing DO_2, the circulation can compensate to some extent, and VO_2 remains stable. However, beyond a critical point, any further drop in DO_2 will result in a decrease in VO_2. From this point, VO_2 becomes dependent on DO_2, and aerobic metabolism will have to be switched to anaerobic metabolism, leading to low $ScvO_2$, hyperlactatemia, metabolic acidosis, and oxygen debt (9).

The principle task of early resuscitation is to regain balance by optimizing the VO_2/DO_2 ratio. However, it is also important to define the endpoints of resuscitation to avoid overresuscitation. In the case of fluid resuscitation, for example, unnecessary administration of fluids will lead to hypervolemia, which increases morbidity and mortality to a similar extent to that of hypovolemia (10, 11). Unjustified blood transfusions also carry the risk of hypervolemia and transmission of infections (12) or allergic reactions (13). There is evidence that prolonged use of catecholamines is associated with poor outcome (14). Therefore, it is important to recognize the point when tissue perfusion has been normalized, oxygen debt has been resolved, and resuscitation has been terminated.

INDIVIDUALIZED GOAL-DIRECTED HEMODYNAMIC THERAPY

The multimodal concept in hemodynamic monitoring enables us to appreciate that each patient is different, hence the so-called normal values, which are more or less appropriate for a given population may be inadequate for the given patient. Therefore, this concept can be translated into the individualized or personalized use of target endpoints to avoid underresuscitation or overresuscitation.

PARAMETERS FOR ASSESSMENT OF TISSUE METABOLISM

Mixed Venous and Central Venous Oxygen Saturation

Mixed venous oxygen saturation (SvO_2) measured in the pulmonary artery *via* a pulmonary artery catheter, and its surrogate,

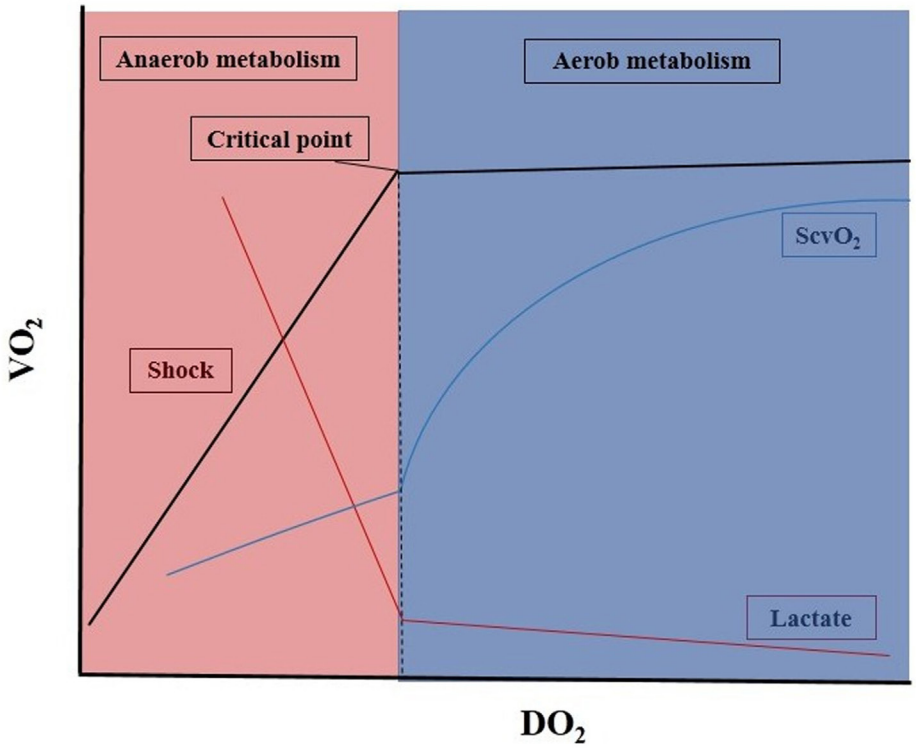

FIGURE 1 | Oxygen delivery and consumption in critically ill patients. DO_2, oxygen delivery; VO_2, oxygen consumption; $ScvO_2$, central venous oxygen saturation ratio. For details, see main text.

central venous oxygen saturation ($ScvO_2$) measured in the superior vena cava are the most commonly used parameters to assess global oxygen extraction (VO_2/DO_2). As central venous catheters are frequently applied in most critically ill patients, $ScvO_2$ is more readily available compared to SvO_2. Although the absolute values of $ScvO_2$ are 5% higher than SvO_2 on average, but changes usually occur in a parallel manner (15), therefore $ScvO_2$ is regarded as a surrogate marker in the clinical setting (16, 17).

The main factors, which influence $ScvO_2$, are hemoglobin, arterial oxygen saturation of hemoglobin, CO, and oxygen consumption. There are multiple physiologic, pathophysiologic, and therapeutic factors that influence venous oxygen saturation such as anemia, hypovolemia, contractility, bleeding, sedation, fever, and pain (18).

$ScvO_2$ in Intensive Care Patients

During sepsis, organ dysfunction is most likely the result of inadequate tissue perfusion causing cellular hypoxia. Interventions improving the balance between DO_2 and VO_2 may prevent the development of tissue hypoperfusion, organ dysfunction syndrome, and thus improve the outcome of septic patients. In patients with early phase of severe sepsis, septic shock, early goal-directed intervention guided by continuous monitoring of $ScvO_2$, central venous pressure and mean arterial pressure (MAP), with target values of CVP 8 to 12 mmHg, MAP > 65 mmHg and $ScvO_2$ > 70%, reduced mortality from 46.5 to 30.5% at the 28th day (19).

Although this study has been criticized for several reasons and these results could never be repeated, there is international consensus that that low $ScvO_2$ values are very important warning signs of inadequate DO_2 and can prognosticate complications and poor outcome. However, recent data suggest that high $ScvO_2$ values may also have adverse outcomes in septic patients (20). Due to deranged microcirculation when shunting is present on the level of capillaries, impaired oxygen utilization can lead to normal or supraphysiological $ScvO_2$ values, which represent an inability of the cells to extract oxygen in sepsis (21). In patients with $ScvO_2$ > 70% complementary blood gas parameters, such as elevated venous-to-arterial CO_2 gap (dCO_2) (>6 mmHg), increased or persistently elevated serum lactate levels could help the clinicians to identify tissue hypoxia. In a retrospective analysis, septic patients with physiological $ScvO_2$ and abnormal dCO_2 mortality was significantly higher as compared to patients with normal dCO_2 values (22).

In patients treated on intensive care units, heart failure is often present resulting impaired CO, hence decreased oxygen delivery (23), and resulting oxygen extraction imbalance that could be detected by low $ScvO_2$ (24). In a clinical study after myocardial infarction in patients with heart failure and cardiogenic shock, SvO_2 was 43%, while in patients with heart failure without shock, it was 56% compared to patients without heart failure with an SvO_2 of 70% (25). It may also be useful in patients with cardiogenic shock requiring the support by intraaortic balloon counter pulsation. In a study during weaning period, intraaortic balloon

pump assist ratio was decreased from 1:1 to 1:3. In the weaning failure group, decreased support was accompanied by a drop in $ScvO_2$, while it remained constant in the successful group (26). In patients with chronic heart failure, $ScvO_2$ can be chronically low. However, during acute decompensation, major cardiac events were observed in 81% of patients with $ScvO_2 \leq 60\%$ at 24 h after ICU admission, while it was only 13% in patients with higher $ScvO_2$ (27).

$ScvO_2$ and Blood Transfusion

In addition to heart failure, anemia is another frequent cause of impaired DO_2 in critically ill patients, and almost 40–45% of patients will receive blood transfusion during the treatment period (28). As large multicenter trials (TRICC and TRISS) suggest that patients with hemoglobin levels above 10 mg/dl usually do not require transfusion, while red blood cell administration is usually beneficial if the hemoglobin level is below 7 mg/dl (29, 30). Between these values, physicians have to make decisions according to clinical signs like mental status, tachycardia, tachypnea, blood pressure, and diuresis. To be able to give additional objective data about oxygen debt of organs, $ScvO_2$ may offer an easily obtainable tool to detect a low hemoglobin-related altered O_2ER and hence may serve as a physiological trigger for blood transfusion (30). In human studies, both on volunteers and retrospective data in critically ill patients suggest that lower levels of hemoglobin compared to that of recommended by international guidelines were well tolerated and did not produce hemodynamic instability, and when oxygen imbalance occurred, it was accompanied by a significant drop in SvO_2 (30–32). In our recent animal experiment on isovolemic anemia, we have found that anemia-induced change in VO_2/DO_2 showed significant correlation with changes of $ScvO_2$ (33); hence, $ScvO_2$ may be used as a "physiologic transfusion trigger" in otherwise hemodynamically stable patients.

$ScvO_2$ and High-Risk Surgery

High-risk surgical patients are at an increased risk of developing imbalance between VO_2 and DO_2 in the perioperative period; therefore, monitoring $ScvO_2$ may have a rationale during both the intraoperative and postoperative managements.

It has been shown that patients with low $ScvO_2$ values preoperatively, intraoperatively, or postoperatively are at an increased risk for complications and poor prognosis (34). Therefore, it seems to be logical to maintain $ScvO_2$ in normal range during the perioperative care. We reported in a small, single-center prospective randomized study about continuously measured $ScvO_2$-assisted intraoperative hemodynamic optimization (CeVOX Maquet® Munich Germany) during major abdominal surgery. In the conventional group, patients were treated according to mean arterial and central venous pressure, while in the $ScvO_2$ group, additionally venous oxygen saturation was also measured *via* fiberoptic catheter placed in the superior vena cava. $ScvO_2$ monitorization resulted in more interventions, more fluid boluses and more blood transfusion compared to the conventional group. These intervention resulted in better organ functions, less complication rate, and better 28 days of survival (35). These results are in accord with the results of an earlier single-center study, where $ScvO_2$ over 73% directed group had fewer postoperative complications and had shorter length of hospital stay compared to patients in whom hemodynamic stabilization was guided according to MAP and central venous pressure (36). However, it is important to considerate that in anesthetized, mechanically ventilated patients, "physiological" values of $ScvO_2$ are 5–10% higher (i.e., 75–80%) because of the decreased oxygen extraction of the brain. Second, when bleeding is present and blood loss is replaced by crystalloids, considerable hemodilution can take place. In our experimental stroke volume-guided hemorrhage and fluid resuscitation animal model, $ScvO_2$ normalized at the end of resuscitation, but returned to a significantly lower level (with a mean of 5%) as the hemodilution caused significant drop in hemoglobin levels (37). In a clinical study performed on patients with esophagectomy, $ScvO_2$ could indicate decreased DO_2 caused by low hemoglobin levels; therefore, the authors suggest to use $ScvO_2$ as complementary transfusion trigger to hemoglobin in the perioperative period (32).

High-risk patient with major surgery benefits most from goal-directed therapy with significant reduction in mortality and morbidity compared to patients with low-risk interventions (38). $ScvO_2$ is an important element of this complex perioperative multimodal monitoring-based concept, including advanced hemodynamic monitoring and assessment of VO_2/DO_2, what we call the individualized, multimodal approach (39).

COMPLEMENTARY BLOOD GAS PARAMETERS

Venous-to-Arterial CO_2 Gap (dCO_2)

Mixed-, or central venous-to-arterial carbon dioxide gap is an easily attainable parameter when patients has arterial and central venous lines *in situ*. The physiological value is ≤6 mmHg, and this holds true for both mixed- ($Pv\text{-}aCO_2$) and central venous-to-arterial ($Pcv\text{-}aCO_2$) CO_2 gap values. Therefore, the central venous $Pcv\text{-}aCO_2$-gap can be useful surrogate of $Pv\text{-}aCO_2$ in the everyday practice.

Increased CO_2 gap of >40 mmHg was described 30 years ago during cardiac arrest in patients who were monitored with pulmonary artery catheters and also in an animal experiment on cardiopulmonary resuscitation (40). After these landmark studies, increased dCO_2 was detected in several low-flow states (41–43). During anaerobic metabolism, increased production of hydrogen ions are buffered by bicarbonate presented in the cells, and this process will generate CO_2 production (44). When the Fick principle is applied for carbon dioxide, there is an inverse relationship between the CO and dCO_2 (45); in other words, increased levels of dCO_2 should reflect low-flow states. Indeed, it has been shown that in sepsis, heart failure, and severe hypovolemia, its value can be elevated (46, 47).

In the perioperative setting, dCO_2 also has a strong predictive value. Patients with high dCO_2 had significantly higher mortality compared to patients with normal values (36.4 versus 4.5%) (48). High-risk surgical patients admitted to intensive care unit postoperatively with high dCO_2 also developed more complications. The cutoff value was 5.8 mmHg (49), and in a different

clinical study, a $dCO_2 > 5$ mmHg had 96% sensitivity to predict the occurrence of postoperative complications in patients with physiological (≥71%) $ScvO_2$ (50). In critically ill patients, the dCO_2 shows good inverse correlation with the CO (42), and it has also been shown to be a good predictor for bad outcome in patients with septic shock (41). In cases like septic shock, when due to microcirculatory or mitochondrial defects oxygen uptake is insufficient, $ScvO_2$ can be supranormal. Previous studies have suggested that under such circumstances the increased value of dCO_2 (>5 mmHg) and increased lactate level can help the physician in detecting inadequate flow to the tissues; hence, the complementary use of $ScvO_2$ and dCO_2 is recommended (50, 51).

CONCLUSION

Early and adequate interventions to improve hemodynamics, oxygen delivery, and reducing oxygen needs have a significant effect on outcome. Protocolized care with predefined values of certain physiological indices, such as blood pressure, CO, may benefit the majority of the population, but these values may be inadequate for the rest; hence, they will remain either underresuscitated or overresuscitated. Therefore, individualizing treatment should be desirable. For this purpose, additional physiological parameters like central venous oxygen saturation, lactate, and venous-to-arterial CO_2 gap should be assessed together with other hemodynamic variables to get a detailed picture about the hemodynamic status of our patients. Putting the pieces of the puzzle together in context is what we define as multimodal, individualized hemodynamic support, in which $ScvO_2$ has a pivotal role.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Continuous Non-Invasive Arterial Pressure Assessment during Surgery to Improve Outcome

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Blood pressure (BP) is one of the most important variables evaluated during almost every medical examination. Most national anesthesiology societies recommend BP monitoring at least once every 5 min in anesthetized subjects undergoing surgical procedures. In most cases, BP is monitored non-invasively using oscillometric cuffs. Although the risk of arterial cannulation is not very high, the invasive BP monitoring is usually indicated only in the case of high-risk patients or in complex surgical procedures. However, recent evidence points out that when using intermittent BP monitoring short periods of hypotension may be overlooked. In addition, large datasets have demonstrated that even short periods of low BP (or their cumulative duration) may have a detrimental impact on the development of postoperative outcome including increased risk of acute kidney or myocardial injury development. Recently marketed continuous non-invasive blood pressure monitoring tools may help us to recognize the BP fluctuation without the associated burden of arterial cannulation filling the gap between intermittent non-invasive cuff and continuous invasive arterial pressure. Among others, several novel devices based either on volume clamp/vascular unloading method or on applanation tonometry are nowadays available. Moreover, several near-future smart technologies may lead to better hypotension recognition or even prediction potentially improving our ability to maintain BP stability throughout the anesthesia or surgical procedure. In this review, novel or emerging technologies of non-invasive continuous blood pressure assessment and their potential to improve postoperative outcome are discussed.

Keywords: blood pressure, non-invasive monitoring, volume clamp, vascular unloading, applanation tonometry, intraoperative hypotension, goal-directed hemodynamic therapy, postoperative outcomes

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INTRODUCTION

Since the end of nineteenth century, when non-invasive monitoring using Riva-Rocci sphygmomanometer was improved and implemented into wide clinical praxis by Harvey Cushing, blood pressure (BP) became one of the three most important vital signs evaluated in the perioperative care. It is quite difficult to ascertain the contribution of BP monitoring to the improvement of postoperative

Abbreviations: AAMI, Association for the Advancement of Medical Instrumentation; AKI, acute kidney injury; A-line, arterial cannulation; ASA, American Society of Anesthesiologists; BP, blood pressure; CNBP, continuous non-invasive blood pressure; GDFT, goal-directed fluid therapy; HD, hemodynamic monitoring; IOH, intraoperative hypotension; MAP, mean arterial pressure; MI, myocardial injury; NIBP, non-invasive blood pressure; PPV, pulse pressure variation; SBP, systolic blood pressure; TWA, time-weighted average.

outcome at that time, however, performing nowadays any anesthesia procedure without knowing patient's BP is literally inconceivable. The American Society of Anesthesiologists (ASA) recommends in the Standards for basic anesthetic monitoring, that BP should be monitored in all anesthetized persons at least at 5-min intervals (1). The same recommendation (BP at least each 5 min) was incorporated into the World Health Organization's "Guidelines for Safe surgery 2009" (2). Intermittent automated non-invasive oscillometric cuffs integrated into classic anesthesia monitors are mostly used for this purpose. This approach is convenient, safe, and reliable. However, motion artifacts, the need for adequate cuff size, and prolonged inflation/deflation times can pose significant drawbacks in routine care. The general perception of oscillometric non-invasive blood pressure (NIBP) accuracy has been also tempted (3). Until recently, more reliable and in particular continuous BP monitoring has been possible only using arterial catheterization (A-line) and direct pressure measurement. The arterial cannulas are usually well tolerated and pose only limited risk to the patient (4), but still this technique is usually limited to the high-risk cases only. However, even among high-risk surgical patients in about 50% the NIBP is used (5).

Using the intermittent cuff, NIBP monitoring may leave BP fluctuations undetected or may lead to late recognition and delayed correction (6, 7). Several recent large scale observational studies have demonstrated, that not only the "intensity" (depth of hypotension) but also the "dose" (cumulative time spent in hypotension) are associated with severe postoperative complications [myocardial infarction, stroke, or acute kidney injury (AKI)] (8–11). Recently, several monitors enabling for continuous non-invasive blood pressure (CNBP) monitoring have been marketed. These new technologies combine the advantages of both non-invasive cuffs and arterial catheters. They offer reliable real-time estimation of actual BP and display pressure curve making advanced analyses possible (i.e., calculation of pulse pressure variation, maximal pressure change, or hemodynamic variables using pulse contour/power analysis). Further use of smart technologies and software prompts enables not only fast recognition but even prediction of further BP course decreasing the risk of hypotension-associated complications. In this review, we discuss several novel aspects of up-to-date BP monitoring and their possible impact on patients' outcome.

INTRAOPERATIVE HYPOTENSION (IOH) AND PERIOPERATIVE OUTCOME

In this literature, we may find numerous definitions of IOH. Bijker et al. have identified 140 different definitions in 130 studies (12) ranging from systolic blood pressure (SBP) below 100 mmHg to a complex definition based on absolute SBP and mean arterial pressure (MAP) values and their relative decrease to baseline. Naturally, the incidence of IOH varied significantly (from 5 to 99%). The authors of that study suggested a dynamic approach to the IOH, rather than arbitrarily chosen thresholds (12). As an example of answering individual needs of pressure targets, the SEPSISPAM study may serve to show the profit of higher pressure in the critically ill with chronic hypertension (13). Several other authors have studied the issue of IOH and increased risk of organ complications.

Salmasi et al. (9) have demonstrated on a large database (57,315 non-cardiac surgery patients) that risk of acute kidney injury (AKI) and myocardial injury (MI) starts to increase when intraoperative BP declines below 65 mmHg or more than 20% from baseline (defined as an average of all MAP readings over 6 months prior hospitalization). The risk further increased with profound hypotension. Besides, the effect was "time-dose" dependent. Similar pattern of AKI and MI risk increase, but with the lower threshold (MAP of 55 mmHg) was observed by Walsh et al. (8) in another large retrospective single-center database cohort (33,330 non-cardiac surgery patients). These findings were further supported in a prospective way by Sun et al. (11), who found a strong association between AKI development and MAP < 60 mmHg lasting more than 20 min or MAP < 55 mmHg more than 10 min. None of these studies have performed separate analysis in patients with chronic hypertension [though they created 48% in Sun et al. (11) and 49% in Salmasi et al. (9)], albeit the higher risk was observed in these patients.

The association between low intraoperative pressures and increased risk of vascular brain injury (namely stroke) and increased mortality was stressed by the results of the POISE trial (14). The extended release metoprolol administration was protective against MI in elective non-cardiac surgery patients, but it led to increase in stroke incidence and death in patients with a history of cardiac, peripheral artery disease, or stroke. IOH associated with metoprolol administration was deemed to be the culprit of this unfavorable outcome of this prospective randomized trial. In another large population retrospective (48,241 non-cardiac and non-neurosurgical patients), Bijker et al. (10) supported this association. Each minute of IOH defined as a MAP drop of more than 30% from baseline increased the odds ratio of postoperative stroke within 10 days after surgery by 1.013 (95% confidence interval 1.000–1.025).

Intraoperative hypotension and higher occurrence of organ complications may be also linked to increased postoperative mortality in non-cardiac surgery patients as demonstrated by Mascha et al. (15). Naturally, the pressure thresholds were much lower to induce fatal complications. Time-weighted average (TWA) of MAP equal to 50 mmHg increased the 30-day mortality more than three times compared to 80 mmHg. Interestingly, short-time variability of BP had much lower effect than long-term trends. In the retrospective analysis of 46,496 procedures performed on 30,650 patients in six American Veteran hospitals by Monk et al. (16), IOH, but not hypertension, was coupled with increased 30-day mortality after major non-cardiac surgery. Thresholds found in this were basically similar to Mascha et al. (15): absolute SAP < 67–70 mmHg or MAP < 49 mmHg for more than 5 min and relative MAP drop more than 50% of baseline for 5 min.

Based on all these large population samples, the risks of IOH are undeniable, especially in non-cardiac surgery patients. Moreover, the inconsistency of IOH thresholds leading to different complications may be attributed to different organ needs and population under study. The threshold of AKI and MI

increased risk of MAP below 60–65 mmHg corresponds with the lower inflection point of renal and myocardial autoregulation curves. Because the brain autoregulation's plateau starts at lower MAPs, the threshold observed is lower (drop of more than 30% of chronic MAP). Finally, the burden of global hypoperfusion has to be much higher to induce life-threatening situation—i.e., TWA MAP 50 mmHg corresponds with profound hypotension throughout the procedure as well as SAP lower than 70 mmHg or MAP drop of 50%. Therefore, nowadays, the question should not state: "Is IOH dangerous?" but "How the IOH could be prevented…" Several hints may be already found in the literature. First the "Triple low study" (17) and its followers (18, 19) have demonstrated, that unnecessarily deep anesthesia in frailty individuals may significantly contribute to the risk of IOH with its consequences. More recently, the retrospective analysis from Germany (20) pinpointed that not every IOH is the same: the IOH within 20–30 min after induction (post-induction hypotension) has slightly other background than IOH occurring later on. Low pre-induction SAP, older age, and emergency surgery contributes to both types of IOH, but the use of supplementary epidural or spinal anesthesia, male sex, and the American Society of Anesthesiologists physical status grade 4 was associated with hypotension occurring later on during the procedure. Another possibility is to use continuous BP monitoring which may help to identify hypotensive periods more swiftly and hence decrease the time dose (7).

CONTEMPORARY POSSIBILITIES OF CONTINUOUS NIBP ASSESSMENT

Since the second half of twentieth century, several technologies of continuous NIBP assessment have been available. Unlike the occlusive technique used in standard pressure cuffs (both Riva-Rocci–Korotkoff and oscillometric methods), these techniques are non-occlusive based on pressure transduction over the vessel wall under dedicated conditions. Important base for this research was Etienne-Jules Marey's development of former Vierordt's sphygmograph into portable form in 1860. In his later works, Marey described the relationship between the amplitude of pulse and pressure imposed on the vessel wall from the outside: i.e., the largest oscillations are observed in the moment of zero transmural pressures. Besides, the contemporary technologies of continuous NIBP monitoring (**Figure 1**) are based on two major principles: volume clamp and applanation tonometry. Numerous validation studies were performed under divergent conditions; their results are so far not entirely satisfactory as demonstrated by large meta-analysis by Kim et al. (21). On the other hand, there is currently no widely accepted standard or methodology how to evaluate the accuracy of such new devices and the Association for the Advancement of Medical Instrumentation (AAMI) standard (22) does not seem to be the best option (23).

Volume Clamp Method

The Czech physiologist Jan Peňáz first described the volume clamp method in 1973. In this semiocclusive technique, the volume of finger arteries is assessed using infrared photo-plethysmography. Next, using fast reacting inflatable pressure cuff, the volume of blood is held constant. The pressure which is needed to maintain a constant blood volume is proportional to the BP. To obtain real BP values (not only a proportional estimate), the zero transmural pressure needs to be obtained. Under zero transmural pressures (the so-called vascular unloading), the pressure outside (i.e., in the finger cuff) and inside the vessel are equal hence enabling the reconstruction of BP curve and assessment of numerical values. Based on the Marey's experiments, the zero transmural pressure is accompanied by the maximal amplitude of pulse oscillations. However, the vascular tone may change in time making the vascular unloading far from being constant. In the 1995, Karel Wesseling developed the Physiocal™ algorithm for automatic vascular unloading set point assessment that leads to gross improvement in the device accuracy. The device enabling non-invasive finger cuff was later marketed under the name Finapress/Portapress. Nowadays, different methods of vascular unloading are used by divergent devices. Because the pressure tracing monitored using this technique corresponds with the pressure inside finger arteries, a further mathematical processing is needed to reconstruct either radial or better brachial pressure curve or values.

A higher than venous pressure inside the finger cuff leads to venous congestion distally to the probe. This so-called blue finger syndrome is mostly regarded as unpleasant or disturbing. In any case, it may limit the length of the monitoring in conscious subjects. Under several non-frequent conditions—as for instance Raynaud's syndrome—this method of pressure monitoring is better to be avoided. The accuracy of the monitoring may be significantly affected in patients with finger edema or low perfusion

FIGURE 1 | Currently available continuous non-invasive blood pressure monitors: **(A)** ClearSight with EV 1000 monitoring platform, **(B)** CNAP HD device, **(C)** T-line 400 device. Device photographs for publication's purpose were provided with permission to re-use by the manufacturers or distributors.

due to blood redistribution (low cardiac output), chronic vascular disease, or peripheral vasoconstriction (hypothermia, shock states).

ClearSight (Former Nexfin)

ClearSight technology marketed by Edwards Lifesciences Inc. (Irvine, CA, USA) is a direct successor of former Finapress and Nexfin (BMEYE B.V., Amsterdam, The Netherlands) devices encompassing the Physiocal™ vascular unloading algorithm. A disposable single-use cuff is placed around the second phalanx of finger (usually index, but middle or ring finger use is also possible) connected to a band held pressure controller. The pressure inside the finger cuff is determined by the photoplethysmographic sensors inside the cuff at a rate of 1,000 Hz. Within a time span of 5–70 beats the set point is reassessed using Physiocal™ algorithm. Mathematical inversed transfer function reconstructs the brachial BP curve out of the finger tracing and heart reference system is available to eliminate inaccuracies induced by hand vertical movements. Using the pulse contour analysis (adapted Modelflow method), advanced hemodynamic variables are calculated from the reconstructed pressure curve. The results of validation studies concerning BP and cardiac output accuracy performed using Nexfin device are also applied to the ClearSight, because this technology is a direct successor of the former one.

CNAP

The CNAP device (CNSystems, Graz, Austria) is second currently available device based on the Peňáz's principle. In contrast to the ClearSight, the finger probes of CNAP are more robust and durable. Two neighbor fingers (either index and middle or middle and ring finger) are inserted into a double lumen plastic tunnel encompassing the inflatable finger cuffs. This setting enables periodical finger switch and to avoid the prolonged venous congestion of the acral part. A system of interlocking control loops (VERIFIY algorithm) is used for optimal vascular unloading. Upper arm oscillometric cuff calibration (or any other external input) is necessary for brachial pressure reconstruction. According to the manufacturer, such calibration should be performed in 15- to 30-min window; however, frequent recalibrations (each 5 min) are probably more appropriate to maintain adequate accuracy (24). However, the inaccuracy of the oscillometric cuff pressure reading mentioned previously (3) may concomitantly affect accuracy of CNAP monitoring, especially in high and low BP range too. The most recent device version (CNAP HD) provides calculation of hemodynamic variables.

T-Line

The T-line (Tensys Medical Inc., San Diego, CA, USA) is the last commercially (and globally) available option of continuous NIBP monitor. Unlike previous ones, T-line is based on radial arterial wall applanation based on the Pressman and Newgard device described in the 1963 (25). A pressure transducer is placed over an artery supported by a bony structure hence enabling its compression (applanation). For T-line, a reusable bracelet with singe use interface is placed over the wrist, enabling a close contact between the sensor and radial artery. Based on the third Newton's law, the pressure inside is directly proportional to the force which induces flattening of a ball surface and indirectly proportional to the area of contact. Creating a zero transmural pressure leads to obtaining maximal pulsations and hence accurate MAP assessment. A mathematical correction for elastic tissues lying between the artery and sensor is needed [the detailed technology is described in the original article by Pressman (25) and in the excellent review by Matthys et al. (26)]. An important drawback to the technology is the extreme sensitivity of the sensor position; therefore, two servo motors automatically and continuously reassess the sensor position. Similar to previous devices, the reconstructed arterial wave enables calculation of different advanced hemodynamic variables, including cardiac output (27). Several validation studies exist for the different T-line generations, mostly with accuracy comparable to volume clamp devices as demonstrated in the meta-analysis by Kim et al. (21).

NON-INVASIVE PRESSURE ASSESSMENT TO IMPROVE OUTCOME

Basically, the described CNBP monitoring tools may help to improve perioperative care in two ways. First to replace contemporary invasive means and second to improve monitoring in patients who were deemed too good to have such invasive BP assessment. In 2012, Kirov et al. (28) have proposed a two-dimensional decision table for intraoperative monitoring. Given current possibilities, this table may be adapted into current form (**Figure 2**).

The first option, decreasing monitoring associated burden in patients currently monitored using invasive arterial pressure, seems to be far less important in the clinical routine. First, the risks associated with arterial cannulation, especially radial, are not negligible (4), but rather small and easily outweighed by the

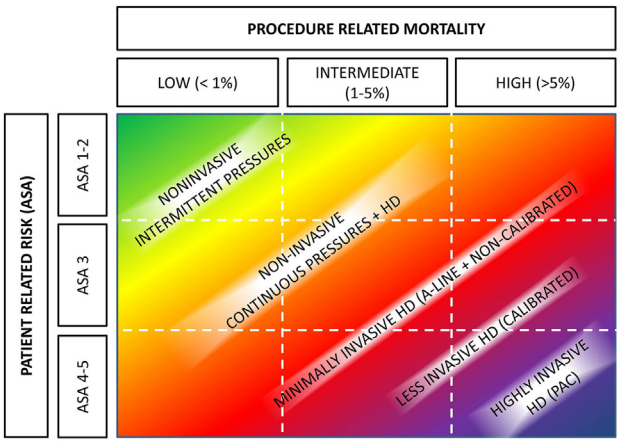

FIGURE 2 | Hemodynamic monitoring based on patients' and operative risks. Abbreviations: A-line, arterial cannulation; ASA, American Society of Anesthesiologists physical status; HD, hemodynamic monitoring. Authors' own design based on Kirov et al. (28).

risks of the procedure. Second, the A-line is inserted not only for BP monitoring but also to facilitate blood sampling and gas analysis, things not possible with CNBP. And finally, the CNBP readings would have to be fully reliable under all conditions. Adherence to the AAMI standards would not help us in this issue (23). The validations of current CNBP devices have been performed using the old Bland–Altman methodology, but possibly we should go further into more elaborate analyses using error grams (29), four-quadrant, and polar plots (30) as described by Critchley. At any circumstances, the reliability of current CNBP seems not to reach this (21).

From this perspective, the second option (increasing the spectrum of monitoring in "good patients") might be far more clinically relevant. Because of the intermittent nature of NIBP, BP fluctuations may be missed. In 2012, Chen et al. (6) have demonstrated that as monitored by Nexfin device in average 7 ± 1 min of hypotension and 7 ± 2 min of hypertension per 1 h of general and orthopedic surgery time were missed when NIBP with 5 min period was used. Later on that year, Ilies et al. (31) used CNAP device during Cesarean section under general anesthesia and observed similar results: CNAP was able to identify hypotensive periods (SAP < 100 mmHg) in 91% of parturient (as compared to 55% by NIBP each 3 min) with prolonged duration. It is important to note that the umbilical venous pH was significantly more deranged in these newborns whose mothers were identified to be hypotensive by CNAP. In both these trials, CNBP devices were used to monitor, but not to intervene, the BP fluctuations. In another study, Benes et al. (7) have compared CNAP device to NIBP (at least each 5 min) in a randomized fashion to intervene BP fluctuations in patients undergoing thyroid gland surgery in half-sitting (beach chair) position. The results have clearly demonstrated that using continuous monitoring time spent in hypotension (20% decrease from preoperative values) may be significantly shortened (12 [4–20] vs. 27 [16–34] min), although not eliminated. Finally, recent randomized trial by a German group has demonstrated that use of CNBP even without any dedicated protocol led to higher BP stability and fewer hypotensive events (32). However, none of these trials has demonstrated any clinically relevant benefit in CNBP monitored patients. The only data demonstrating that maintaining BP in range ±10% of patient's resting systolic BP in major surgery has impact on postoperative organ dysfunction by day 30 as compared to standard care come from recently published INPRESS trial (33). Patients at risk of renal dysfunction were studied and radial arterial cannulation was used to monitor continuous BP in this trial. Hence, the real clinically relevant impact of decreased IOH occurrence based on CNBP monitoring on postoperative outcome (organ dysfunctions, etc.) in intermediate risk patients is still speculative and opens a wide arena of possibilities for future research.

However, decreasing the risks of IOH is not the only possibility how CNBP devices may impact on rate of postoperative complications. Given the reconstruction of arterial curve, a beat-to-beat analysis of hemodynamic variables and/or their induced fluctuations are inevitably part of the displayed information. Variation in pulse pressure (PPV) induce by mechanical ventilation has been shown to be an excellent predictor of fluid responsiveness (34). The use of invasive PPV (or its surrogates) for goal-directed fluid therapy (GDFT) has been associated with improved outcomes in high-risk surgical patients (35). Moreover, the PPV assessed using CNBP devices seems to be as accurate as the invasively obtained one (36–38). Based on these findings, it seems rational that GDFT principles may be transposed to lower risk patients' groups. So far, two studies have been published proving such concept, but multiple others are ongoing (for example, NCT02950649, NCT02135146, NCT02382185, NCT02479321, NCT02343601, and NCT03189550). In our institution, we have started to implement CNAP device for intraoperative monitoring of patients undergoing total hip or knee replacement (39). A before-and-after evaluation revealed significant decrease in transfusion needs and resulting number of infectious and organ complication in the GDFT group managed using PPV as compared to historical control (39). More recently, Broch et al. (40) have published results of their GDFT study using Nexfin device. On a small sample size, the authors were able to demonstrate the feasibility of the concept of non-invasive GDFT, naturally because of small numbers included, they have failed to demonstrate improvement in patients' outcome (40).

At any case, use of CNBP devices for intraoperative hemodynamic care seems to offer a large field of small improvements in patients' care and may be deemed as a natural part of current and future Enhanced Recovery programs. However, it should be noted that at current state large outcome data (i.e., mortality or morbidity benefit) as well as cost-effectiveness studies are missing. This coupled with price of the equipment and/or disposables create a not negligible impediment in routine use. At the end of the day, BP and flow are only global hemodynamic indicators and possess only limited information about end-organs perfusion and tissue metabolic well-being. Future clinical research should therefore try to couple these macrohemodynamic indices with monitoring of organ perfusion and assess impact of both these factors on patients' postoperative outcome.

EMERGING AND FUTURE CONCEPTS

Because the ability to assess the patients' hemodynamic status is so appealing for the domain of anesthesiology, perioperative and intensive care multiple further technologies are in the pipeline of development. Practical applications based on pulse transit time (41, 42) and pulse decomposition analysis (43, 44) are currently available even though their validations for given field is still insufficient and probably multiple improvements in mathematical models used will be necessary prior clinical routine use. Besides, several patents are placed on use of superficially placed optical (patent US 20050228299A1), piezoelectric (45), or mechanical (surface acoustic wave—patent US 20110208066A1) continuous non-invasive pressure sensors. As pointed recently in futuristic views of hemodynamic monitoring in the 2050 will be "NEWS"—Non-invasive, Easy to use, Wireless and wearable, and first of all Smart (46).

Such Smart software development may significantly alter the way patients will be monitored in the future. Over the

past decade, we have significantly improved the way how we analyze the arterial pressure curve, but still the modality is not fully exploited. Assessing dynamic arterial elastance to predict pressure response on fluid administration is still in its basics (47), but may play important part in future decision-making how to treat hypotensive periods in the future. Use of closed-loops systems to deliver fluids (48) or vasopressors (49, 50) is now limited in their clinical applicability, but when combined with neuronal networks able to recognize the source of hemodynamic instability may open the door for their routine use. A combination of more information sources together (i.e., pulse transit time, finger volume clamp, and surface sensor) may further improve the way we perform hemodynamic monitoring. For instance, taking together more vital signs (like the Vital Sign Index by Visensia™ monitor, OBS Medical, IN-USA) may help to predict cardiac instability (51) or assessing the heart rate variability from electrocardiography may be useful in predicting hypotension (52). Another example may be the recently approved Hypotension Probability Indicator by Edwards Lifesciences Inc. which should be able to predict hypotension based on analysis of multiple domains including arterial pressure curve complexity, heart rate variability, and others by proprietary algorithm combined with machine learning. Merging non-invasive hemodynamic (not only pressure) sensors with automated signal analysis may promote current trend of expanding postoperative intensive care into the standard wards or even home without decreasing patients safety (53).

CONCLUSION

Blood pressure monitoring is a vital part of perioperative care. Current technologies (although not perfect) enable much wider application of continuous monitoring hopefully leading to decrease in undesired BP fluctuations and hypotensive periods. Sophisticated analyses of arterial pressure curve make possible to monitor not only BP but also blood flow (and its variations). These new monitoring tools available today may significantly influence perioperative care especially in intermediate risk patients. However, to which extent the macrohemodynamic parameters improvement impact postoperative outcome in this patient population has to be determined in forthcoming studies. Future developments in this field coupled with smart technologies and in conjunction with other possibilities to assess end-organ perfusion may further improve patient care.

AUTHOR CONTRIBUTIONS

AS and JB both wrote the manuscript, performed the literature search needed, and approved the final form of the text.

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Perioperative Goal-Directed Therapy Using Invasive Uncalibrated Pulse Contour Analysis

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"Perioperative goal-directed therapy" (PGDT) aims at an optimization of basic and advanced global hemodynamic variables to maintain adequate oxygen delivery to the end-organs. PGDT protocols help to titrate fluids, vasopressors, or inotropes to hemodynamic target values. There is considerable evidence that PGDT can improve patient outcome in high-risk patients if both fluids and inotropes are administered to target hemodynamic variables reflecting blood flow. Despite this evidence, PGDT strategies aiming at an optimization of blood flow seem to be not well implemented in routine clinical care. The analysis of the arterial blood pressure waveform using invasive uncalibrated pulse contour analysis can be used to assess hemodynamic variables used in PGDT protocols. Pulse contour analysis allows the assessment of stroke volume (SV)/cardiac output (CO) and pulse pressure variation (PPV)/stroke volume variation (SVV) and thus helps to titrate fluids and vasoactive agents based on principles of "functional hemodynamic monitoring." Pulse contour analysis-based PGDT treatment algorithms can be classified according to the hemodynamic variables they use as targets: PPV/SVV, SV/CO, or a combination of these variables. From a physiologic point of view, algorithms using both dynamic cardiac preload and blood flow variables as hemodynamic targets might be most effective in improving patient outcome. Future research should focus on the improvement of hemodynamic treatment algorithms and on the identification of patient subgroups in which PGDT based on uncalibrated pulse contour analysis can improve patient outcome.

Keywords: hemodynamic monitoring, cardiac output, stroke volume, pulse pressure variation, stroke volume variation, pulse wave analysis

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BACKGROUND

"Perioperative goal-directed therapy" (PGDT), i.e., the assessment and goal-directed optimization of hemodynamic variables, might improve the quality of perioperative care and patient outcome. PGDT aims at an optimization of basic and advanced global hemodynamic variables to maintain adequate oxygen delivery to the end-organs. PGDT protocols help to titrate fluids, vasopressors, or inotropes to hemodynamic target values that can be assessed with different hemodynamic monitoring technologies.

The analysis of the arterial pressure waveform using uncalibrated pulse contour analysis can be used to estimate stroke volume (SV), cardiac output (CO), and dynamic variables of cardiac preload [pulse pressure variation (PPV), stroke volume variation (SVV)].

In this article, we will describe the physiological background and the clinical application of PGDT using invasive uncalibrated pulse contour analysis for the assessment of hemodynamic values.

PGDT: A GAP BETWEEN EVIDENCE AND CLINICAL PRACTICE

Numerous randomized-controlled trials and meta-analyses demonstrate that there is an increasing body of evidence that PGDT can contribute to an improvement in patient outcome (1–9) and guidelines and consensus statements recommend PGDT in major surgery patients (10–12).

A meta-analysis including 29 studies demonstrated that preemptive PGDT strategies targeting cardiac index (CI) or oxygen delivery improve patient outcome in terms of mortality and postoperative complications in moderate- and high-risk surgical patients (1).

In accordance, a meta-analysis including 32 randomized-controlled trials showed that protocol-based optimization of tissue perfusion in terms of optimization of hemodynamics decreases postoperative mortality and organ dysfunction in high-risk surgical patients, particularly when CI, oxygen delivery, and oxygen consumption are used to guide therapy (2).

Another meta-analysis confirmed that PGDT improves postoperative mortality and morbidity in high-risk surgical patients undergoing major non-cardiac surgery when fluids and inotropes are used to achieve CI or oxygen delivery target values (3).

A Cochrane meta-analysis including 31 randomized-controlled trials concluded that a perioperative increase in global blood flow to explicitly defined goals with fluids and/or inotropes reduces complications and length of hospital stay, but not mortality, in adult patients (4). An updated version of this Cochrane meta-analysis included in the paper reporting the OPTIMISE trial (13) provided further evidence that PGDT increasing global blood flow to explicitly defined goals reduces postoperative complications.

Despite the evidence that PGDT can improve postoperative outcome in high-risk patients undergoing major surgery, PGDT strategies aiming at an optimization of blood flow seem to be not well implemented in routine perioperative care. This is reflected by the fact that there is a wide variation in clinical practice and that in only about 10–20% of major non-cardiac surgery patients CO monitoring is used during perioperative care (14). Moreover, it has been shown that, in general, CO monitoring is used only by about one-third of anesthesiologists in Europe and the United States (15). Suggested explanations for the fact that advanced hemodynamic monitoring is rarely used in perioperative care include a lack of experience or knowledge regarding monitoring technologies and local factors such as a lack of available technical equipment or problems with reimbursement (14).

INVASIVE UNCALIBRATED PULSE CONTOUR ANALYSIS: BASIC MEASUREMENT PRINCIPLES

One technique that can be used to assess hemodynamic variables for PGDT is invasive uncalibrated pulse contour analysis. The analysis of the arterial blood pressure waveform (pulse contour analysis) allows not only the monitoring of arterial blood pressure but also the estimation of SV, CO, and PPV/SVV (**Figure 1**). An arterial catheter is placed in most high-risk patients undergoing major surgery for invasive ("direct") continuous arterial blood pressure monitoring and for point of care blood gas analysis. Therefore, pulse contour analysis can be used for PGDT without the need for the placement of additional intravascular catheters.

There are a variety of different algorithms for pulse contour analysis that enable SV to be estimated from the arterial blood pressure waveform (16, 17). These algorithms analyze the shape and characteristics of the waveform considering that the waveform is determined by left-ventricular SV and arterial impedance (i.e., ventriculo-arterial coupling). Other factors influencing pulse pressure and the arterial blood pressure waveform are the cardiac contractility, the vascular compliance, and the peripheral vascular resistance. Some hemodynamic monitors combine pulse contour analysis with a second CO measurement technique (e.g., transpulmonary thermodilution or lithium dilution) to calibrate the continuous pulse contour-derived CO signal to an independent external CO value (18). This external calibration increases the accuracy and precision of pulse contour-derived CO measurements, but also increases the invasiveness of the monitoring technology and is, therefore, recommended in patients with rapid changes in vasomotor tone that require frequent recalibration (19, 20). In the perioperative setting, however, uncalibrated pulse contour analysis only requiring an arterial catheter can be used. The term uncalibrated pulse contour analysis is misleading, because even uncalibrated systems perform an "autocalibration" of the CO signal (using data from large patient databases, biometric data, or characteristics of the arterial blood pressure waveform) (18).

Besides the estimation of SV, pulse contour analysis allows the assessment of dynamic cardiac preload variables (PPV, SVV) that—based on heart-lung interactions during mechanical ventilation—can be used to predict fluid responsiveness (21).

Although pulse contour analysis can be easily used in patients with an arterial catheter, the method has several limitations that are crucial to know to avoid erroneous measurements. First, pulse contour analysis depends on an optimal arterial pressure signal. Therefore, to assure impeccable arterial blood pressure waveform recording, one has to meticulously avoid clotting of the arterial catheter, over- or underdamping of the tubing system, or incorrect zeroing of the pressure transducer and monitoring system. In addition, the clinical usefulness of pulse contour analysis is limited in patients with high-grade cardiac arrhythmias and rapid changes or profound abnormalities in vasomotor tone (e.g., in septic patients or patients with cardiocirculatory alterations due to advanced liver disease) (22). The use of PPV and SVV is limited to patients with sinus rhythm, mechanical ventilation, and tidal

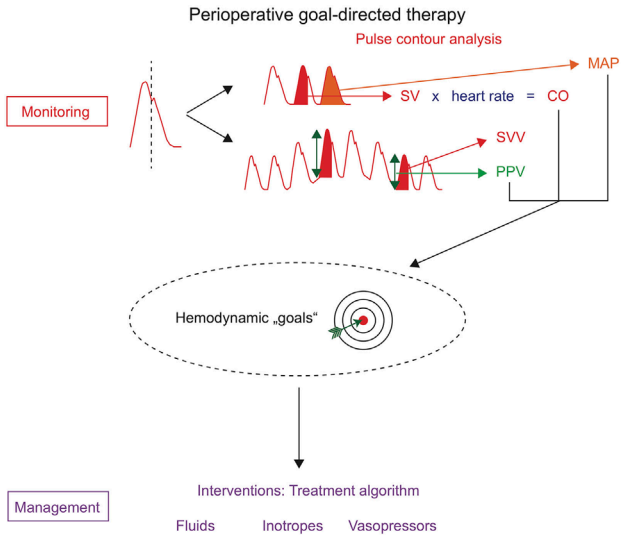

FIGURE 1 | Perioperative goal-directed therapy based on uncalibrated pulse contour analysis. Hemodynamic monitoring with uncalibrated pulse contour analysis allows the assessment of mean arterial pressure (MAP), stroke volume (SV), cardiac output (CO), stroke volume variation (SVV), and pulse pressure variation (PPV). These hemodynamic variables can be used as hemodynamic "goals" in treatment algorithms that trigger therapeutic interventions (hemodynamic management).

volumes ≥8 mL/kg predicted body weight. Of note, the capabilities of PPV to predict fluid responsiveness are limited for PPV values between 9 and 13% (gray zone for the prediction of fluid responsiveness) (23).

HOW TO USE INVASIVE UNCALIBRATED PULSE CONTOUR ANALYSIS FOR PGDT: PHYSIOLOGIC BACKGROUND

The cardiac function curve (i.e., Frank–Starling curve) describes the relation of ventricular preload or left-ventricular end-diastolic pressure and SV. A left ventricle functioning on the steep part of the cardiac function curve will increase SV after an increase in cardiac preload (e.g., due to fluid administration). This state of "preload reserve" is clinically referred to as "fluid responsiveness," i.e., an increase in blood flow following fluid administration. Because ventricular function is a major determinant of the shape of the cardiac function curve, fluid administration must be performed cautiously to avoid fluid overload and circulatory failure, especially in patients with poor ventricular function in whom the heart is already working on the flat part of the curve.

Based on these basic physiologic principles, pulse contour analysis provides crucial hemodynamic variables reflecting fluid responsiveness (PPV, SSV) and blood flow (SV, CO) that can be used in PGDT protocols to titrate fluids and vasoactive agents based on principles of "functional hemodynamic monitoring" (24). Functional hemodynamic monitoring using pulse contour analysis can be used to predict fluid responsiveness using the dynamic cardiac preload variables PPV or SVV and to assess the dynamic response to fluid administration using real-time CO monitoring. The diagnostic passive leg raising test, that was proposed to assess fluid responsiveness in critically ill patients (25), cannot be routinely performed intraoperatively and is usually not part of PGDT protocols. In addition to fluid therapy, pulse contour analysis enables vasopressors and inotropes to be titrated according to arterial blood pressure and SV/CO, respectively.

HOW TO USE INVASIVE UNCALIBRATED PULSE CONTOUR ANALYSIS FOR PGDT: CLINICAL APPLICATION

Invasive uncalibrated pulse contour analysis is frequently used for the assessment of hemodynamic variables within PGDT protocols (8, 9, 13, 26, 27). Numerous different algorithms for pulse contour analysis-based PGDT have been proposed.

These treatment algorithms can be classified according to the hemodynamic variables they use as targets: some algorithms are solely based on either dynamic cardiac preload variables (PPV, SVV) or blood flow variables (SV, CO/CI); other algorithms combine these dynamic cardiac preload and blood flow variables (9).

The OPTIMISE trial is an example for a study using pulse contour analysis solely to optimize blood flow (13). In this largest available multicenter randomized-controlled trial, uncalibrated pulse contour analysis was used to maximize SV with repetitive colloidal fluid boluses (250 mL over 5 min) (13). Maximal SV was defined "as the absence of a sustained rise in SV of at least 10% sustained for 20 min or more in response to a fluid challenge" (13). After the first fluid bolus, patients in the treatment group also received inotropic support (dopexamine in a fixed dose) to achieve the maximal value of SV (13). In the OPTIMISE trial, PPV or SVV were not part of the treatment algorithm. In the study group, the composite endpoint of predefined moderate or severe postoperative complications and mortality at day 30 after surgery occurred less frequently in the intervention group (36.6%) compared with the control group (43.4%), but this finding did not reach statistical significance (13).

Compared with the approach of maximizing SV by using the full cardiac preload reserve, PGDT algorithms targeting both dynamic cardiac preload parameters and SV/CO may help to better tailor the hemodynamic management to the individual patient (28, 29).

In the ongoing follow-up study of the OPTIMISE trial (OPTIMISE II[1]), SVV is included in the hemodynamic management protocol in addition to the SV target (fluid challenge not recommended if SVV is <5%).

In a multicenter randomized-controlled trial in major abdominal surgery patients, uncalibrated pulse contour analysis was used to define an optimal CI value after the induction of general anesthesia and before surgical incision (26). The post-induction preload optimized CI value was defined as the CI value that was observed when the PPV was less than 10% (either spontaneously or after fluid administration) and was used to

[1]http://optimiseii.org.

trigger inotropic therapy with dobutamine during the intraoperative period (26). The use of this algorithm combining targets for PPV, CI, and mean arterial pressure resulted in a clinically relevant and statistically significant reduction in postoperative complications compared with the control group treated without PGDT (26).

A recently started study on individualized PGDT in major abdominal surgery patients (iPEGASUS[2]) uses a similar treatment algorithm, but a higher threshold for PPV (12%). The use of a higher PPV cutoff value [closer to the upper range of the "gray zone" (23)] represents a more restrictive approach to fluid administration.

CONCLUSION

Perioperative goal-directed therapy protocols help to titrate fluids, vasopressors, or inotropes to predefined target values of hemodynamic variables in order to optimize global hemodynamics and eventually maintain or restore adequate oxygen delivery to the end-organs.

There is considerable evidence that PGDT can improve patient outcome in high-risk patients if both fluids and inotropes are administered to target hemodynamic variables reflecting blood flow.

Despite this evidence, PGDT strategies aiming at an optimization of blood flow seem to be not well implemented in routine clinical care.

The analysis of the arterial blood pressure waveform using invasive uncalibrated pulse contour analysis can be used to assess hemodynamic variables used in PGDT protocols. Pulse contour analysis allows the assessment of SV/CO and PPV/SVV and thus helps to titrate fluids and vasoactive agents based on principles of "functional hemodynamic monitoring."

Pulse contour analysis-based PGDT treatment algorithms can be classified according to the hemodynamic variables they use as targets: PPV/SVV, SV/CO, or a combination of these variables. From a physiologic point of view, algorithms using both dynamic cardiac preload and blood flow variables as hemodynamic targets might be most effective in improving patient outcome.

Future research should focus on the improvement of hemodynamic treatment algorithms and on the identification of patient subgroups in which PGDT based on uncalibrated pulse contour analysis can improve patient outcome.

AUTHOR CONTRIBUTIONS

BS and DR conceived the study, performed the literature search, drafted the manuscript, and approved the final version of the manuscript to be published.

[2]www.clinicaltrials.gov, identifier NCT03021525.

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Non-Invasive Hemodynamic Monitoring for Hemodynamic Management in Perioperative Medicine

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BACKGROUND

In perioperative medicine, hemodynamic management aims at an optimization of perfusion pressure and oxygen delivery in order to maintain or restore adequate cellular metabolism (1). To optimize cardiopulmonary function, hemodynamic management triggers the administration of fluids and vasoactive agents according to predefined target values of hemodynamic variables. This is often referred to as "goal-directed therapy" (GDT). Although the general and vague term GDT comprises various (in part very different) hemodynamic treatment strategies (2), GDT has been shown to improve patient outcome, especially in high-risk patients undergoing major surgery (3–11). Besides basic hemodynamic variables (blood pressure and heart rate), GDT treatment algorithms usually include advanced hemodynamic variables such as pressure- or volume-based cardiac preload variables (central venous pressure, pulmonary capillary wedge pressure, global end-diastolic volume), dynamic cardiac preload variables (pulse pressure variation, stroke volume variation), and blood flow variables (stroke volume, cardiac output). A variety of invasive, less-invasive, and non-invasive hemodynamic monitoring technologies are nowadays available to assess hemodynamic variables in the operating room or the intensive care unit. In this opinion paper, we will discuss how innovative non-invasive hemodynamic monitoring might be used for hemodynamic management in perioperative medicine.

HEMODYNAMIC MONITORING TECHNOLOGIES USED FOR GDT

Until recently, the measurement of advanced hemodynamic variables used in GDT protocols required invasive hemodynamic monitoring such as invasive pulse contour analysis (arterial catheter), transpulmonary thermodilution (dedicated arterial catheter and central venous catheter), or pulmonary artery thermodilution (pulmonary artery catheter). However, during the last decades, the use of the pulmonary artery catheter in perioperative medicine and critical care is declining (12, 13) and the routine use of the pulmonary artery catheter is not recommended for surgical patients undergoing non-cardiac surgery (14). Advanced hemodynamic monitoring using the transpulmonary thermodilution technique, often called a less-invasive alternative to the pulmonary artery catheter, is also used only in a minority of patients in the perioperative period (15). Especially in the UK, the esophageal doppler is used to assess blood flow for perioperative GDT (3). Many recent studies on perioperative GDT used un-calibrated invasive pulse contour analysis (arterial catheter) to assess blood pressure, dynamic cardiac preload parameters, or cardiac output (3, 4, 16–18).

In the recent years, different completely non-invasive hemodynamic monitoring technologies were proposed (19). Measurement principles of these innovative hemodynamic monitoring technologies are, among others, bioimpedance and bioreactance, pulse wave transit time, partial carbon dioxide rebreathing, and non-invasive pulse contour analysis (19–27). It is beyond the scope of this article to discuss in detail the underlying measurement principles. In general, the main advantage of these new technologies is that they allow the estimation of cardiac output and other advanced hemodynamic variables without the need for arterial or central venous cannulation. In addition, using these technologies in clinical practice is relatively easy and does not require extensive training. On the other hand, all of the available technologies still have technical limitations with regard to their clinical applicability (19). Furthermore, the numerous validation studies comparing these innovative measurement technologies with established reference methods revealed contradicting results (19, 28–31).

In the following, we want to describe how these innovative technologies can be used for hemodynamic management in perioperative medicine.

NON-INVASIVE HEMODYNAMIC MONITORING FOR PERIOPERATIVE HEMODYNAMIC MANAGEMENT—AVAILABLE DATA

There are still only a few studies available that investigated the feasibility and usefulness of perioperative GDT based on completely non-invasive hemodynamic monitoring technologies.

In a prospective randomized controlled trial, Benes et al. (32) evaluated the impact of continuous non-invasive blood pressure monitoring using the volume clamp method (finger cuff) on blood pressure stability in patients undergoing thyroid gland surgery in an upright position ("beach chair position"). Patients were randomized to the study group (continuous blood pressure monitoring) or to the control group (intermittent blood pressure monitoring with oscillometric upper arm cuff). Continuous non-invasive blood pressure monitoring significantly decreased the time spent in intraoperative hypotension defined as blood pressure −20% below the individual patient's target blood pressure (14 vs. 34%; $p = 0.003$). However, the study was too small to adequately evaluate whether this reduction of time spent in hypotension translates into an improvement in postoperative patient outcome.

Fellahi and colleagues (33) evaluated the impact of intraoperative GDT based on stroke volume variation and cardiac index assessed with an endotracheal bioimpedance cardiac output monitor on postoperative outcome after coronary artery bypass surgery in a prospective, controlled, parallel-arm trial. In patients in the study group, the proportion of patients receiving fluid loading and dobutamine was higher compared with the control group. Although the primary endpoint (time to hospital discharge) was not different between the groups, the time to extubation was statistically significantly shorter in the GDT intervention group.

In a similar setting, Leclercq et al. (34) evaluated the feasibility and clinical utility of an endotracheal bioimpedance cardiac output monitoring to optimize intraoperative hemodynamics and improve short-term outcome in patients undergoing off-pump coronary artery bypass grafting surgery. The authors compared 20 patients in whom hemodynamics were monitored with the bioimpedance technology with a historic control of 42 patients. The primary endpoint, the rate of postoperative intensive care unit admission, occurred significantly less often in the bioimpedance group than in the control group (55 vs. 90%; $p = 0.008$). In addition, the time to extubation, the length of stay in the intensive care unit, and the lactate level 6 h after surgery were significantly lower in the bioimpedance group. The authors thus concluded that the systematic use of endotracheal bioimpedance cardiac output monitoring is associated with a reduction in the rate of intensive care unit admission and an improvement in immediate postoperative outcome in patients undergoing off-pump coronary artery bypass grafting surgery.

Broch et al. (35) investigated the feasibility and clinical impact (postoperative complications up to 28 days and length of hospital stay) of GDT based on non-invasive pulse contour analysis (volume clamp method) in patients undergoing elective major abdominal surgery. In their randomized controlled trial, patients in the study group who were treated according to an algorithm based on non-invasively assessed cardiac index and pulse pressure variation were compared with patients in the control group ("standard of care"). The total number of complications was lower in the study group compared with the control group without reaching statistical significance (94 vs. 132; $p = 0.22$). There was also no clinically relevant or statistically significant difference in hospital length of stay or mortality. Thus, the authors conclude that this study demonstrates the general feasibility of a non-invasive GDT approach for hemodynamic optimization in major abdominal surgery. However, following this specific GDT protocol did not improve outcome.

The pleth variability index (i.e., the variability in the pulse oximeter plethysmogram) can be used as a non-invasive dynamic cardiac preload parameter. Forget et al. (36) randomized 82 major abdominal surgery patients into two groups to compare intraoperative fluid management guided by the pleth variability index and mean arterial pressure vs. standard fluid management based on mean arterial and central venous pressure. Interestingly, the amount of intraoperatively administered crystalloids and the total volume of fluids infused were significantly lower in the pleth variability index-GDT group. Lactate levels (primary endpoint) were significantly lower in the GDT group compared with the control group during surgery and 48 h after surgery.

In the multicenter (six tertiary hospitals) randomized clinical POEMAS trial (37), it was evaluated whether perioperative GDT based on non-invasive bioreactance monitoring decreases the incidence of postoperative complications and hospital length of stay in 142 major abdominal surgery patients requiring intensive care unit admission. The GDT protocol included the administration of fluids and vasoactive agents to target values for mean arterial pressure and cardiac index. In the study group, colloid boluses, red blood cell units, and dobutamine was used more often compared with the control group. The study failed to demonstrate a beneficial impact of GDT on patient outcome

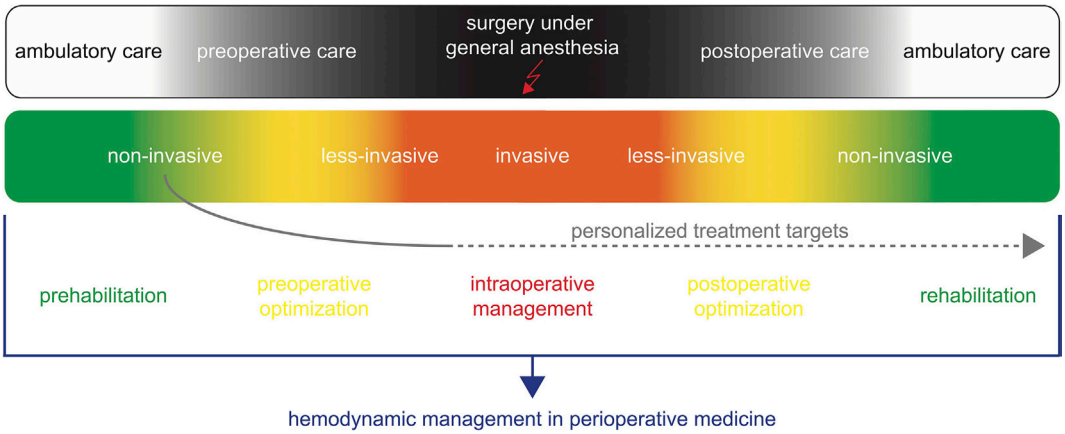

FIGURE 1 | Non-invasive hemodynamic monitoring for hemodynamic management in perioperative medicine. Non-invasive hemodynamic monitoring might be applied for prehabilitation and preoperative optimization during the ambulatory and preoperative care. In addition, it can be used to define personalized targets for the intraoperative hemodynamic management and postoperative optimization.

in terms of overall complications or length of stay between the intervention group and the control group.

We soon will report the results of a monocenter randomized controlled trial in high-risk patients undergoing major abdominal surgery (https://clinicaltrials.gov: NCT02834377) in which we performed "personalized hemodynamic management" (1) by applying a protocol for intraoperative GDT to target the patients' personal normal cardiac index values as measured the day before surgery using the non-invasive volume clamp method.

NON-INVASIVE HEMODYNAMIC MONITORING FOR PERIOPERATIVE HEMODYNAMIC MANAGEMENT—FUTURE PERSPECTIVES

As discussed above, to date, there are still limited data on the use of non-invasive hemodynamic monitoring technologies for perioperative GDT.

Nevertheless, in the future, these innovative technologies for continuous non-invasive advanced hemodynamic monitoring might offer a variety of opportunities to improve and expand perioperative GDT strategies.

Non-invasive monitoring technologies might enable hemodynamic management strategies to be applied in different new clinical settings (intermediate and low risk surgery) and in patient groups in which advanced hemodynamic monitoring was so far usually not applied (e.g., in patients without arterial catheter or in patients undergoing surgery in regional peripheral or neuraxial anesthesia).

In addition, with non-invasive monitoring technologies, the patients' hemodynamic status can be assessed even before induction of anesthesia and after surgery (**Figure 1**). Non-invasive hemodynamic monitoring might thus be applied for prehabilitation [i.e., optimizing the patient's hemodynamic status in the weeks before surgery (38)] and preoperative optimization. In addition, values of hemodynamic variables assessed at different time points in the preoperative phase might be used as targets to guide intraoperative hemodynamic management and postoperative optimization (1). The availability of non-invasive technologies for the assessment of advanced hemodynamic variables might thus open a window for perioperative concepts of "personalized hemodynamic management" that aims to optimize cardiovascular dynamics based on the patient's personal hemodynamic profile (1). Because these innovative technologies enable blood pressure, blood flow, and dynamic cardiac preload variables to be estimated in a completely non-invasive manner even in the preoperative evaluation clinic or on the normal ward, they can be used to determine a patient's personal normal values of these hemodynamic variables prior to induction of anesthesia and surgery (1). Thus, non-invasive hemodynamic monitoring technologies might help to assess and define personal target values for perioperative GDT in contrast to conventional GDT often using predefined fixed population-based "normal" values as hemodynamic target values (1).

In the future, further technical and digital innovations [e.g., implantable, wireless, or wearable sensors (39, 40)] might further pave the way for GDT based on non-invasive hemodynamic monitoring in perioperative medicine.

CONCLUSION

Perioperative hemodynamic management based on the assessment of advanced hemodynamic variables aims at an optimization of cardiovascular dynamics to improve postoperative patient outcome. Until recently, hemodynamic management required invasive hemodynamic monitoring (arterial catheter, central venous catheter, pulmonary artery catheter). Recently, different monitoring technologies that enable advanced hemodynamic variables to be estimated non-invasively became available. In theory, these innovative technologies for continuous non-invasive advanced hemodynamic monitoring might offer a variety of opportunities to improve and expand hemodynamic

management strategies and to personalize hemodynamic management (1) in the perioperative phase. However, there are still only a few studies available investigating perioperative GDT based on these innovative technologies with regard to the clinical feasibility and the impact on patient outcome; thus, further research is needed to evaluate and establish non-invasive hemodynamic monitoring for hemodynamic management in perioperative medicine.

AUTHOR CONTRIBUTIONS

JYN and BS both contributed substantially to the conception of the work and drafted the manuscript. The authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated. JYN and BS approved the final version of the manuscript to be published.

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REVIEW
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Improving Perioperative Outcomes Through Minimally Invasive and Non-invasive Hemodynamic Monitoring Techniques

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An increasing number of patients require precise intraoperative hemodynamic monitoring due to aging and comorbidities. To prevent undesirable outcomes from intraoperative hypotension or hypoperfusion, appropriate threshold settings are required. These setting can vary widely from patient to patient. Goal-directed therapy techniques allow for flow monitoring as the standard for perioperative fluid management. Based on the concept of personalized medicine, individual assessment and treatment are more advantageous than conventional or uniform interventions. The recent development of minimally and noninvasive monitoring devices make it possible to apply detailed control, tracking, and observation of broad patient populations, all while reducing adverse complications. In this manuscript, we review the monitoring features of each device, together with possible advantages and disadvantages of their use in optimizing patient hemodynamic management.

Keywords: hemodynamic monitoring, non-invasive, perioperative complications, outcomes, hemodynamic, blood pressure, perioperative outcomes, monitor

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INTRODUCTION

While medicine is moving toward standardized care, the 2015 Precision Medicine Initiative aimed to understand how a person's genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease. It is now possible to improve patient outcomes by setting individualized hemodynamic parameters according to specific and customized comorbidities or current pathologies. Enhanced Recovery After Surgery (ERAS) protocols recommend individualized intraoperative fluid optimization through integrated hemodynamic monitoring (1).

For patients and healthcare providers, blood pressure (BP) is one of the most important vital signs monitored. The recent development of monitoring technologies allows clinicians to obtain both minimally invasive and continuously non-invasive BP. Hemodynamics describes a patients' BP, cardiac output (CO), and systemic vascular resistance (SVR). Appropriate and precise evaluations of these parameters make it possible to evaluate tissue perfusion. Although the optimal hemodynamic parameters for each patient are undefined, patient outcomes can potentially be improved by applying therapeutic strategies based on hemodynamic information (2). Poor perioperative hemodynamic management of surgical patients can extend beyond cardiovascular complications. Appropriate management can potentially lead to a decrease in neurologic complications, kidney injury, and even mortality.

The goal of this review is to describe the existing scientific scholarship on perioperative hemodynamic monitoring techniques and patient outcomes. We will describe different monitoring techniques as well as the advantages and disadvantages of each device. By using tailored monitoring tools, it is possible to adjust therapeutic decisions for each patient individually and for specific situations.

HEMODYNAMIC PHYSIOLOGY

Blood circulation supplies the necessary nutrients and oxygen to each tissue and collects unnecessary or toxic substances. The proper maintenance of pressure is necessary to distribute enough blood so that the organism can adapt to vigorous activity. Normally, organisms maintain their circulation homeostasis adequately, but surgery, anesthesia, and/or critical illness may disturb this homeostasis. Accurate hemodynamic monitoring is mandatory in these situations, most particularly with vulnerable patients who might not be able to adequately adapt to these unique conditions. Accurate monitoring provides necessary and invaluable information to launch appropriate interventions.

Circulatory systems are often compared to electric circuits and are explained by Ohm's law. Ohm's law relates pressure, flow, and resistance by a simple mathematical expression that can be applied to the human circulatory system. In the human body, the amount of electrical current is translated to CO. Electrical resistance correlates to vascular resistance (**Figures 1A,B**). Consider the following three simple examples as treatment interventions for hypotension after induction of anesthesia: (1) administration of phenylephrine increases SVR, with an increase of BP; (2) administration of dobutamine increases CO, leading to an increase of BP; (3) fluid loading increases CO, with increase of BP. While we recognize BP as an important vital sign, we do not have the tools to directly manipulate BP. It is also not possible to directly measure SVR. By determining BP, CO, and SVR, it is possible to understand which intervention needs to be addressed and which drugs to select and administer. Control of BP is, in essence, hemodynamic management based on CO measurement.

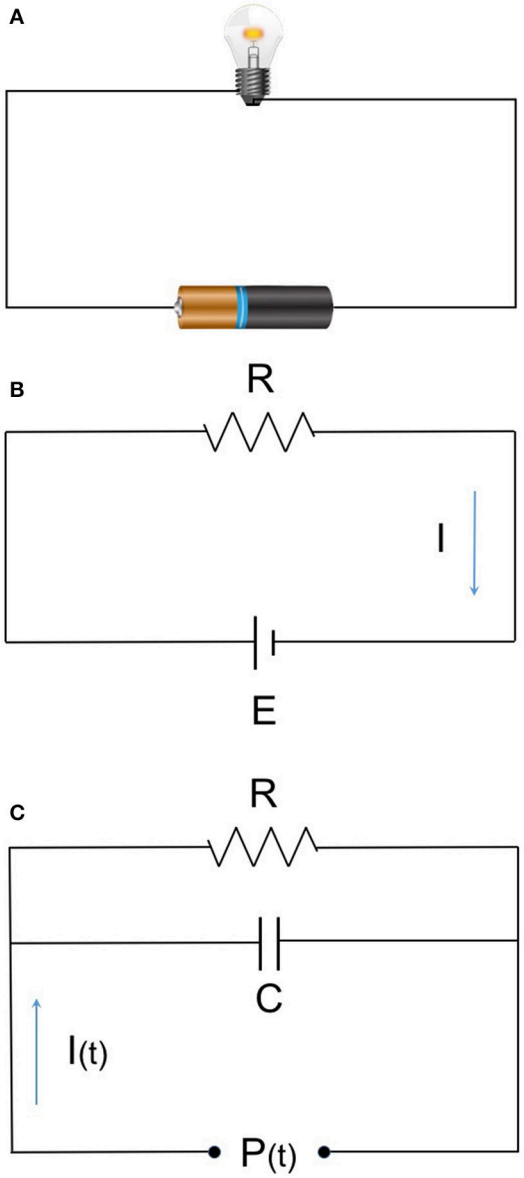

FIGURE 1 | (A) Ohm's low and hemodynamic equation. **(B)** E (voltage) = I (current) × R (resistance) (MAP-CVP) = CO × SVR. MAP, mean arterial pressure; CVP, central venous pressure; CO, cardiac output; SVR, systemic vascular resistance. **(C)** The basic 2-element Windkessel model. Elastic artery has specific compliance and behaves as a capacitor. The relation given as:

$$I(t) = \frac{P(t)}{R} + C\frac{dP(t)}{dt}$$

The 3- and 4-element models as a succeeding model are used in recent devices with more accuracy.

MONITORING TECHNOLOGY

Non-invasive Continuous Monitoring

Blood Pressure

Volume clamp

The most popular, noninvasive continuous BP monitor uses finger cuff. Small cuff(s) with photoplethysmogram (PPG) are applied to the fingers. The cuff inflates to cancel out changes in the PPG. The balanced pressure represents the patients' blood pressure at the cuff site. The equipment reconstructs brachial arterial pressure from the finger BP waveform's transformation. It calculates arterial BP using estimated arterial resistance based on the patients' physical characteristics. When a patients' vessel characteristics differ greatly from the installed software, the obtained value may differ greatly from the actual and real value. This technique is still subject to some controversy: while some studies report it as a reliable, others conclude it to be inaccurate.

Table 1 summarizes recent studies investigating accuracy of this technique. According to the Association for the Advancement of Medical Instrumentation (AAMI), product standard uses the mean difference in BP measurements between these devices and "gold standard" measurements should be <5 mmHg, with a standard deviation <8 mmHg (3). Alfano et al. compared finger-cuff with a conventional oscillometric method in 40

TABLE 1 | Accuracy study of noninvasive continuous blood pressure.

Study	Device	Setting	No. of subjects	Comparison	No. of measured values	SBP	MAP	DBP
Ilies et al. (4)	Finger cuff (CNAP®)	ICU	104	Invasive line (same side radial artery)	11,222	4.3 ± 11.6, 22.8%	−6.1 ± 7.6, 18.4%	−9.4 ± 8.0, 25.6%
Gayat et al. (5)	Finger cuff (CNAP®)	OR (including cardiac surgery)	52	Invasive line (same side radial artery)	5,174	−2 ± 22, 37%	−8 ± 12, 32%	−11 ± 14, 37%
Hahn et al. (6)	Finger cuff (CNAP®)	OR (non-cardiac surgery)	50	Invasive line	237,562	0.9 ± 13.2, NA	−3.1 ± 9.45, NA	−2.8 ± 8.6, NA
Ameloot et al. (7)	Finger cuff (Nexfin®)	ICU	45	Invasive line (femoral artery)	225	8.3 ± 13.8, 22%	−1.8 ± 5.1, 12%	−9.4 ± 6.9, 23%
Vos et al. (8)	Finger cuff (Nexfin®)	OR (non-cardiac surgery)	110	Invasive line (radial artery)	758	NA	2 ± 9, 22%	NA
Hofhuizen et al. (9)	Finger cuff (Nexfin®)	ICU (post cardiac surgery)	20	Invasive line (radial artery)	66	2.7 ± 11.3, NA	4.2 ± 7.0, NA	4.9 ± 6.9, NA
Langwieser et al. (10)	Tonometory (T−line™)	Cardiac ICU	30	Invasive line (radial artery)	7,304	−6 ± 11, 20%	2 ± 6, 17%	4 ± 7, 23%
Meidert et al. (11)	Tonometory (T−line™)	ICU	24	Invasive line (radial artery)	2,993	−3 ± 15, 23%	2 ± 6, 15%	5 ± 7, 22%
Saugel et al. (12)	Tonometory (T−line™)	ICU (medical patient)	22	Invasive line	330	−8 ± 13, NA	0 ± 6, NA	4 ± 6, NA
Findlay et al. (13)	Tonometory (Vasotrac™)	OR (liver transplant)	14	Invasive line (radial artery)	6,468	7.6 ± 13, NA	5.4 ± 10, NA	3.3 ± 8, NA

SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure. Values of SBP, MAP and DBP are represented as mean difference ± standard deviation in mmHg and percentage error.

hemodynamically stable hemodialysis patients (14) and found that the measured values were significantly different between the two methods. This study included an elderly population (65% of whom were over 65 years of age), where vascular calcifications are recognized in up to 88% of the patients. This study looked into patients with diabetes, neuropathy, and increased systolic BP, accounting for its low accuracy measurement. Also, dialysis patients have altered blood vessel characteristics, consistent with concerns derived from the calculation principle. These issues largely overlap with geriatric patient populations. Thus, careful judgment is required regarding the reliability of finger cuff method on elderly patients, especially those with complications as described above and in the cited study. As continuous counter pressure on finger may interfere peripheral blood circulation, these devices set the time limit for continuous use or use two fingers alternately for secured safety.

Tonometry

Applanation tonometory, on the radial artery, continuously measures the tone calibrated with a conventional arm cuff. Although the first machine was invented in 1963, a major disadvantage of this monitor has been the difficulty in sensor fitting (15). Frequent positioning adjustment and calibration could possibly compensate for errors. When sensor fitting is adequate, a fine arterial pressure waveform is obtained and the system can output both continuous blood pressure and CO values using waveform analysis. Short measurements are widely used for arterial compliance studies. However, long time measurement is currently not common and not commercially distributed.

Pulse wave transit time (emerging)

Pulse wave transit time (PWTT) is recognized as a parameter related to hemodynamics, especially SV, BP, and vascular resistance. The device is comprised of a common basic sensor, such as an electrocardiogram and a pulse wave detector on finger (often a pulse oximeter), possibly adding a phonocardiograph. The use of a phonocardiograph can help to provide more precise measurements. In recent years, time resolution, analytical algorithm, and its speed were improved by computer performance and cuff-less BP measurements (16). PWTT is still in development and its accuracy remains poor. Further improvements are needed for its performance, particularly when there is a sudden change in vascular resistance.

Cardiac Output

Bioimpedance and reactance

This method measures the impedance or reactance between a pair of electrodes on the chest wall or on the tracheal tube while applying an imperceptible alternating current that estimates changes in blood volume present in the thorax, particularly in the aorta. Changes in impedance or reactance during one cardiac cycle is considered to reflect stroke volume. This method estimates the stroke volume based on an internal database according to the patients' physical characteristics. Deviation from the database may enhance measurement errors (17). While it is non-invasive, easy to apply and no reported complication associated with an electromagnetic application, it does not detect pure CO. It is also considered to be inaccurate in patients with pulmonary and cardiac pathology. Measurement values will be

affected in patients with chronic lung disease, heart, or valvular disease.

Ultrasound (echocardiography/transesophageal/transthoracic doppler)

There are roughly two methods to measure flow rate using an ultrasound device: one obtains the SV as the difference of the left ventricular end diastolic volume and the end systolic volume, while the other calculates the SV from the product of a certain cross-sectional area and velocity time integral. Minimally invasive and noninvasive CO monitors are designed with the latter method, which is simple and can reduce operator-dependent discrepancies (18). A variety of dedicated probes are developed for various sites, such as aortic valve, carotid artery, descending aorta, or pulmonary artery. Software can often estimate both the cross-sectional area and proportion of blood flow against SV based on the age and physical characteristics of the patient. This method can be operator dependent and patients' anatomy can sometimes interfere with accurate measurement. The dedicated esophageal probe for CO measurement has a small diameter and low heat emission. Probe insertion and manipulation is rarely associated with oropharyngeal, esophageal, or gastric trauma, but requires appropriate sedation.

Pulse transit time

Emerging BP and CO monitoring devices using the relation of SV with PWTT are commercially available and tested (19). Although Pulse Transit Time still needs improvements to increase accuracy, CO can be measured with conventional electrocardiograms and pulse oximeters, and does not require any special sensors or operating techniques. It is considered to be an easy monitor to set up with the added advantage of being noninvasive.

Minimally Invasive Continuous CO Monitoring

Pulse Contour Analysis

Pulse contour analysis has been investigated and modified since it was first developed. Improved algorithms have been adopted by various commercial devices. Pulse contour analytic CO monitors calculate SV from arterial pressure waveform based on the Windkessel model (**Figure 1C**) and/or wave reflex phenomenon principle. Pressure waveforms are obtained noninvasively (finger cuff) or minimally invasively (peripheral arterial catheter). In the equation allowing for CO calculation, a constant (κ) reflecting vascular compliance is determined from a preset database that is based on the patients' data (gender, age, height, weight). The databases were developed from a general population, so for patients with complex comorbidities (such as different vascular characteristics, arrhythmia, or valvular heart disease), measurement errors will increase.

Additionally, counter analysis has developed some secondary parameters such as Pulse Pressure Variation (PPV) and Stroke Volume Variation (SVV). These dynamic parameters are used as an index for fluid responsiveness, allowing for appropriate fluid management. The risk of arterial catheter-related infection was reported 1.3% and comparable with 2.7% of central venous catheters (20).

Transpulmonary Thermodilution

Blood temperature changes are detected by a special arterial cannula which has a thermistor on its tip. Cold fluid boluses are injected through a central venous catheter, which is then sensed in the thermistor tip. CO is calculated from the thermodilution curve according to the Stewart–Hamilton equation. Following this intermittent manual measurement, it continuously calibrates the pulse contour analysis and displays CO. Since calibration is carried out every time the thermodilution is performed, the value is fairly accurate (21). Unlike with pulmonary arterial catheter (PAC), the detected temperature curve is achieved after passing through the pulmonary circulation. The assumption that intra-thoracic blood volume has 1.25 times of global end-diastolic volume allows the system to estimate extravascular lung water without double dilution indicator technique as in the past. Some conditions such as post lung resection or cardiac shunt deteriorate the premise and calculation. The catheter is relatively long and thicker than a regular arterial catheter needing careful insertion to avoid injury.

Partial CO_2 Rebreathing

The Fick principle calculates CO with oxygen consumption and arterial and venous oxygen tension. The same principle can be applied to calculate CO_2 production and blood CO_2 tension, the indirect Fick method. A dedicated rebreathing loop is connected to the patients' breathing circuit and the system measures CO by calculating carbon dioxide metabolism with partial rebreathing technology. This technology is not affected by vessel anatomical abnormalities or peripheral circulatory insufficiency, as it only needs information from exchange gases. Several validation studies have been published, mainly in the ICU setting (22). This method can only be applied to intubated and mechanically ventilated patients.

Severe lung disease can affect the measurement accuracy due to increased deadspace/tidal volume ratio changing the relationship between $PaCO_2$ and $PetCO_2$. Acute respiratory distress syndrome is a severe and most common limitation of partial CO_2-rebreathing. Also, hemoglobin concentration can change the balance between bicarbonate ion and carbon dioxide affecting measurement. It is also not a good method to use in patients with pulmonary hypertension or increased intracranial pressure since they will probably not tolerate CO_2 retention.

Indicator Dilution

The Stewart Hamilton equation is behind the basic physics of the indicator dilution method. CO can be measured by an appropriate indicator dye and corresponding detector. Available detectors that do not require blood withdrawal are arterial catheters with a lithium sensor (minimally invasive) and fingertip photometric sensors, which detect indocyanine green (non-invasive). The advantage of products using arterial catheters is that they continuously measure the pulse contour analysis. Repeated measurements with frequent indicator can lead to dye accumulation, resulting in measurement errors

and adverse effects. Muscle relaxants (specifically, quaternary ammonium ion) can disturb the lithium ion sensor and rare allergic reactions have been reported with indocyanine green.

A summary of noninvasive and minimally invasive continuous cardiac output monitors available can be found in **Table 2**.

TABLE 2 | Non-minimal invasive continuous cardiac output monitors.

Basic principle	Requirements	Advantage	Disadvantage
NON-INVASIVE			
Bioimpedance and reactance	Chest wall electrode	Easy installation Continuous measurement	Susceptible to noise
	Dedicated tracheal tube	Continuous measurement	Need Intubation
Ultrasound	TTE probe	Evaluate cardiac preload and motion	Chest wall access Operator's skill
	Transthoracic Doppler probe	Simple and small probe PA based measurement available	Unstable probe direction
Pulse transit time	ECG and pulse oximeter	Calculated from basic monitoring Continuous measurement	Not available in dysrhythmia
MINIMAL INVASIVE			
Ultrasound	TEE probe	Evaluate cardiac preload and motion	Esophageal access Operator dependent
	Esophageal Doppler probe	Simple and Small diameter probe GDT Evidence	Esophageal access
Pulse contour analysis	Arterial line	Continuous measurement Evaluate SVV/PPV	Arterial cannulation (covered by noninvasive continuous finger cuff/tonometoric BP technology)
Transpulmonary Thermodilution	Dedicated arterial catheter	Continuous measurement Evaluate preload information (SVV, GEDV, etc)	Central arterial cannulation Manual calibration with cold water injection
Partial CO2 rebreathing	Dedicated breathing circuit	Vascular disease independent	Need intubated and ventilated CO2 loading
Indicator dilution	Dedicated arterial catheter or photometric sensor	Evaluate blood volume	Indicator accumulation/allergy

TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; ECG, electrocardiogram; GDT, goal directed therapy; SVV, stroke volume variation; PPV, pulse pressure variation; GEDV, global end-diastolic volume.

POSTOPERATIVE OUTCOMES

The appropriate BP values vary from patient to patient, and the "correct" BP may differ depending on the surgery requirements or current situation. A surgical insult may cause the rapid or abrupt change in hemodynamic parameters, making it imperative to continuously monitor BP or other hemodynamic parameters. While controversial, hypotensive anesthesia is practiced with the goal to reduce intraoperative blood loss. This technique requires careful monitoring to avoid dramatic and sudden changes. Patients that have known vascular pathology are also candidates for continuous BP measurement.

Studies showed that sustained intraoperative hypotension is associated with adverse patient outcomes, including increased mortality and organ injury. The duration of hypotension is also an important contributing factor for poor outcomes. **Table 3** summarizes several studies that link low BP and adverse outcomes. While there is no definite consensus on the specific degree and duration of hypotension involved, these studies demonstrate the importance of hemodynamic maintenance with individualized considerations. The duration of hypotension was also shown to be an important contributing factor for poor outcomes. Continuous monitoring of hemodynamic parameters would likely reduce the duration of less than desirable BP values and noninvasive, continuous BP monitoring could possibly become the new standard.

The perioperative hemodynamic management of surgical patients extends beyond cardiovascular complications. Delayed recovery of cognition, whether delirium (an acute attentional deficit which waxes and wanes), or the long-lasting phenotype termed postoperative cognitive decline (POCD), has been linked to intraoperative blood pressure fluctuations (23) or maintained hypotension in the intraoperative period (24). The use of vasopressors during surgery and/or postoperative hypertension is associated with new-onset dementia after surgery (25). With more than 46 million Americans over the age of 65, postoperative delirium is a major public health issue with an projected annual cost of over $150 billion. It is estimated that 30–40% of delirium cases might be preventable (26). Prevention and optimization is the most effective strategy for minimizing neurologic injury. Hemodynamic monitoring using minimally invasive and noninvasive monitors can optimize the cognitive recovery and perioperative experience of surgical population. This might lead to improve neurologic outcomes, decrease hospital length of stay, reduce the amount of postoperative mechanical ventilation, lessen ICU length of stay, cut back healthcare costs in general, and patients' functional decline.

CARDIAC OUTPUT

In the Operating Room

Numerical, target-oriented volume and inotropic management based on hemodynamic measurement is crucial for a rapid recovery. It is increasingly accepted that the traditional fixed volume therapy should be abandoned and the administration of fluids to achieve a certain volume (goal-directed fluid therapy) improves outcomes. In addition to pressure measurement, hemodynamic parameters such as SV need to be calculated (27) and minimally invasive devices can be used, for example in high risk ERAS cases.

TABLE 3 | Intraoperative hypotension and adverse outcome.

Study	Study design	Type of surgery	No. of patients	Evaluation of hypotension	Outcome measurement	Result	Remarks
Sun et al. (28)	Retrospective cohort	Non-cardiac surgery	5,127	MAP < 55, 60, 65 mmHg for 5, 10, 20 min	AKI	MAP < 60 for >10 min associated with AKI	Patients needed invasive BP monitoring
Mascha et al. (29)	Retrospective cohort	Non-cardiac surgery	104,401	Time-weighted average intraoperative MAP	30-day mortality	Intraoperative MAP associated with mortality	Decrease in MAP 80–50 mmHg increased mortality
Monk et al. (30)	Retrospective cohort	Non-cardiac surgery	18,756	Areas under MAP-2SD Absolute BP Percent change from baseline	30-day mortality	Low BP deviation associated with mortality	Absolute BP and % change also associated
Walsh et al. (31)	Retrospective cohort	Non-cardiac surgery	33,330	MAP < 55∼75 mmHg for 5, 10, 20 min	AKI and myocardial injury	MAP < 55 associated with AKI and myocardial injury	
Bijker et al. (32)	Case-control	Non-cardiac, non-neurosurgical surgery	294	A priori definition in systolic and mean pressure (40–100 mmHg), Decrease 10–40% of baseline	Ischemic stroke within 10 POD	30% decrease in MAP associated with stroke	Includes 20 CEA patients
Yocum et al. (33)	Cohort	Lumbar spine surgery	45	Absolute BP value	Neuropsychometric performance after 1 day and 1 month	Low minimum MAP associated with low performance	In hypertensive patients
Bijker et al. (34)	Cohort	General and vascular surgery	1,705	A priori definition in SBP and MAP (40–100 mmHg), Decrease 10–40% of baseline	1 year mortality after surgery	Low BP and aging associated with mortality	
Monk et al. (35)	Prospective cohort	Non-cardiac surgery	1,064	SAP < 80 mmHg	1 year mortality	SBP < 80 related to mortality	
Wang NY et al. (36)	Randomized controlled trial	Orthopedic surgery	103	MAP < 80 mmHg	Postoperative delirium at day 2	MAP <80 mmHg associated to delirium	
Sessler DI et al. (24)	Retrospective	Non-cardiac surgery	24,120	MAP < 75 mmHg	Length of stay and 30-day mortality	Low MAP indicator of mortality	

BP, blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; CEA, carotid endarterectomy; AKI, acute kidney injury; SD, standard deviation.

In the Intensive Care Unit (ICU)

The International Guidelines for Management of Severe Sepsis and Septic Shock brought further attention to the need for hemodynamic assessment in critically ill patients (37). Management in the ICU is based on a detailed assessment, which includes infusion loading, diuretics, dialysis, cardiovascular drugs, ventilator setting, rehabilitation care, and timing. Along with patient recovery, removing unnecessary invasive monitors, and their replacement with minimally invasive techniques can reduce mechanical and infectious complications, facilitating early mobilization and recovery. Many patients have an arterial line for frequent blood sampling in ICU. Pulse contour analysis monitor is therefore an option since CO and other parameters can be obtained without inserting an additional catheter.

DISCUSSION

No single monitor is able to comprehensively identify the spectrum of pathophysiologic changes for high risk patients, despite various commercially available devices with a range of differing measurement principles.

Understanding the measurement principles behind minimally invasive and noninvasive techniques can facilitate accurate evaluation of patients' hemodynamic status, even taking into consideration a possible measurement mismatch. When choosing and applying these monitors, it is important to clarify the purpose for monitoring and how to correctly employ the obtained parameters. The development of minimally invasive and noninvasive devices derives from the need to reduce complications from invasive tools. The application of two complementary devices, with different background principles, might even be an alternative to an invasive technology.

In order to improve patient outcomes, monitoring itself should not be the goal. Monitoring principles need to be understood to guide therapy and decision making. New techniques have led to the development of new hemodynamic parameters. Dynamic parameters such as SVV and PPV are now widely recognized as important signs that can be used to

guide fluid management. SVV has been shown to be a valid measure of fluid responsiveness (38, 39) and many different technologies are available for measuring SVV at the bedside (40). An estimate of both SVV and PPV is displayed in real time by the PiCCO plus system (Pulsion Medical Systems AG) (38, 41) as well as by the LiDCO system. The pulse contour method measures SVV through a femoral catheter (transcardiopulmonary thermodilution) (42, 43). Another device that measures SVV, the FloTrac/Vigileo system (Edwards Lifesciences LLC), requires standard arterial access and is considered minimally invasive and easy to use (44). In an RCT in patients who had undergone elective cardiac surgery ($N = 40$), SVVs assessed using the FloTrac/Vigileo and the PiCCOplus systems performed similarly in predicting fluid responsiveness (42). Today many studies have demonstrated the ability of this algorithm to predict fluid responsiveness in the operating room. It is also possible to assess surrogates for SVV and PPV non-invasively. Attached noninvasively to a finger (45), the pulse oximeter probe can be used to detect changes in blood volume at the site of measurement (46) and respiratory variations in the pulse oximeter plethysmographic waveform amplitude (ΔPOP) have been shown to be related to PPV and SVV (47). This index is also sensitive to changes in preload (48), and can predict fluid responsiveness in mechanically ventilated patients (46, 49–52). The Pleth Variability Index (PVI) is a clinical algorithm that allows for noninvasive, automated, continuous calculation of ΔPOP using a pulse oximeter in mechanically-ventilated patients during general anesthesia (40, 45, 53). PVI is calculated as the dynamic changes in perfusion index (PI)—the ratio of non-pulsatile to pulsatile blood flow through the peripheral capillary bed—occurring during a complete respiratory cycle (40, 54). PVI has been shown to predict fluid responsiveness with good sensitivity and specificity: in mechanically ventilated patients (45). Today, SVV is also available non-invasively using Bioreactance (NICOM, Cheetah) and technologies based on non-invasive blood pressure monitoring (Clearsight, CNAP devices). It is possible that the future will bring us even better indicators derived from advanced method and analysis. Although the comparative examination on the accuracy of the new equipment will require intensive studies, we can wait in anticipation of these new technologies.

The assessment of hemodynamics allow for a customized approach to patient management, one in which treatment decisions are being guided by more precise, multimodal and technologically sophisticated monitoring of physiological variables. Monitoring equipment that can provide precise hemodynamic information without the complications and complexity of invasive techniques can facilitate individualized hemodynamic management and lead to improved outcomes and many other positive contributions to the field.

AUTHOR CONTRIBUTIONS

TY, SV, and MC are responsible for manuscript research, writing, editing, and review. YG is responsible for manuscript review.

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The Predictive Value of Integrated Pulmonary Index after Off-Pump Coronary Artery Bypass Grafting: A Prospective Observational Study

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Background: The early warning scores may increase the safety of perioperative period. The objective of this study was to assess the diagnostic and predictive role of Integrated Pulmonary Index (IPI) after off-pump coronary artery bypass grafting (OPCAB).

Materials and Methods: Forty adult patients undergoing elective OPCAB were enrolled into a single-center prospective observational study. We assessed respiratory function using IPI that includes oxygen saturation, end-tidal CO_2, respiratory rate, and pulse rate. In addition, we evaluated blood gas analyses and hemodynamics, including ECG, invasive arterial pressure, and cardiac index. The measurements were performed after transfer to the intensive care unit, after spontaneous breathing trial and at 2, 6, 12, and 18 h after extubation.

Results and Discussion: The value of IPI registered during respiratory support correlated weakly with cardiac index (rho = 0.4; $p = 0.04$) and $ScvO_2$ (rho = 0.4, $p = 0.02$). After extubation, IPI values decreased significantly, achieving a minimum by 18 h. The IPI value ≤9 at 6 h after extubation was a predictor of complicated early postoperative period (AUC = 0.71; $p = 0.04$) observed in 13 patients.

Conclusion: In off-pump coronary surgery, the IPI decreases significantly after tracheal extubation and may predict postoperative complications.

Keywords: postoperative respiratory failure, coronary artery bypass grafting, monitoring, microstream capnography, integrated pulmonary index

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INTRODUCTION

Cardiac surgery can be complicated by respiratory failure that may contribute to increased morbidity and additional health-care costs (1, 2). The outcome of coronary artery bypass grafting can be significantly influenced by decompensation caused by chronic pulmonary diseases and other complications (atelectases, pleuritis, etc.) (3–5). Therefore, the thorough postoperative monitoring of pulmonary function during both mechanical ventilation and spontaneous breathing may be of a great value. Notably, the modern monitoring devices should be accurate and non- or minimally invasive with measurements that are continuous and results easily interpreted (6).

To maintain respiratory function, the cardiosurgical patients are monitored using pulse oximetry, capnography, respiratory rate, and discrete blood gas analysis (7–9). Although blood gas analyses are the gold standard for early detection of different types of respiratory failure, they are invasive,

cannot be measured continuously, and frequently impose a delay between sampling and availability of results (10). Thus, the early warning systems allowing early recognition of critical respiratory events might be of value when patient is monitored both in the intensive care unit (ICU), postoperative ward, and high dependency unit. This approach can be particularly useful with a limited number of medical staff. Several observational studies indicate that early warning systems improve detection of complications (11), and their use is recommended by the World Federation of Societies of Anesthesiologists to facilitate the work of nurses and physicians in the ICU (12, 13).

The Integrated Pulmonary Index (IPI) is an automated value calculated by one monitor (Capnostream-20, Medtronic, Israel) and can be considered as an automated early warning system. The IPI algorithm utilizes the real time measures and interactions of four parameters—end-tidal CO_2 ($PetCO_2$), respiration rate, pulse rate, and oxygen saturation (SpO_2) to provide an assessment of the patient's respiratory status. The calculation of the IPI is based on the fuzzy logic principle, a mathematical model, which mimics human logic thinking; detailed description of the algorithm was provided by Ronen et al. (14) The values of IPI below 7 have been suggested to be an indicator for respiratory deterioration (14).

Currently, only few investigations of IPI were performed during non-cardiosurgical procedures (14–18) In these studies, IPI algorithm correlated with the respiratory status and has demonstrated the ability for promoting early awareness to changes in a patient's respiratory system.

The aim of our study was to assess the diagnostic and predictive role of IPI during the discontinuation from mechanical ventilation and in the early postextubation period after off-pump coronary artery bypass grafting (OPCAB).

MATERIALS AND METHODS

The study was performed in a 900-bed university hospital (City Hospital #1 of Arkhangelsk, Russia). During 2015, 40 adult patients undergoing elective OPCAB were enrolled into an observational prospective study. The study design and the informed consent form were approved by the Ethical Committee of Northern State Medical University (Arkhangelsk, Russian Federation) and registered with http://ClinicalTrials.gov (ref: NCT02524522). Written informed consent was obtained from every patient. Exclusion criteria were age <18 and >80 years, morbid obesity with body mass index >40 kg/m^2, and constant atrial fibrillation.

All patients were intubated using the standard induction technique with sodium thiopental (4 mg/kg), fentanyl (2.5–3.0 μg/kg) and pipecuronium bromide (0.1 mg/kg). Anesthesia was maintained using sevoflurane (0.5–3.0 vol.% at the end of expiration) and fentanyl (2.0–4.0 μg/kg/h). Depth of anesthesia was adjusted to maintain BIS values between 40 and 60 (LifeScope, Nihon Kohden, Japan).

In all cases, preoxygenation with 80% O_2 was provided during 3–5 min before anesthesia. After tracheal intubation, patients were ventilated using a protective volume-controlled mode (Dräger Primus, Germany) with tidal volume of 6–8 mL/kg of predicted body weight, flow of 1 L/min and positive end-expiratory pressure (PEEP) of 5 cm H_2O. FiO_2 was set to at least 50% or higher to achieve intraoperative SpO_2 above 95%. The respiratory rate was adjusted to maintain $PetCO_2$ value within 30–35 mmHg.

After surgery, all patients were transferred to the postoperative cardiac ICU and shortly sedated with continuous infusion of propofol (2–4 μg/kg/h) to maintain BIS values within 60–70. Respiratory support in ICU was provided by a G5 ventilator (Hamilton Medical, Switzerland) using pressure controlled ventilation mode with parameters of intraoperative ventilation. Additionally, all patients received recruitment maneuver by raising the PEEP to 20 cm H_2O for 5 min.

After the initial measurements, sedation was stopped, and the weaning from respiratory support was initiated. The weaning protocol included gradual reduction of inspiratory pressure and mandatory respiratory rate, as well as spontaneous breathing trial. After passing the 30-min spontaneous breathing trial, all the patients were immediately extubated. After extubation, the patients received a supplementary oxygen flow of 4 L/min *via* a nasal catheter. During the weaning process and in the early postextubation period, all the patients received continuous infusion of fentanyl and discrete administration of paracetamol for multimodal analgesia. In addition, the postoperative therapy included aspirin, low-molecular weight heparins, and bisoprolol.

The measurements included ventilator parameters, blood gas analyses (ABL800Flex, Radiometer, Denmark), $PetCO_2$, SpO_2, respiratory rate, pulse rate, and IPI (Capnostream-20, Medtronic). The IPI measurement is based on continuous transformation of SpO_2, $PetCO_2$, pulse rate, and respiratory rate values into a single index from 1 to 10, where "10" indicates a normal respiratory status, and "1" indicates that patient requires immediate intervention. We distributed patients into two subgroups: with optimal (IPI 9–10) and suboptimal (IPI ≤ 8) IPI values (**Table 1**). After tracheal extubation, for a more accurate assessment of the IPI, all the values were measured following breathing during 5 min without supplemental oxygen (FiO_2 0.21), avoiding the reduction of SpO_2 less than 88%. Continuous hemodynamic measurements included ECG monitoring, invasive arterial pressure and cardiac output measured with pulse wave transit time (esCCO, Nihon Kohden, Japan).

All these parameters were registered after transfer to the ICU, as well as after spontaneous breathing trial and at 2, 6, 12, and 18 h after extubation. In addition, we recorded the preoperative EuroScore II, perioperative fluid balance, left ventricle ejection fraction assessed by transthoracic echocardiography before and 24 h after surgery, duration of postoperative mechanical ventilation and ICU stay, as well as early postoperative complications and hospitalization time. Postoperative complications were assessed according to the categories as predefined the study protocol: arrhythmias, hemorrhage, respiratory complications,

TABLE 1 | The clinical interpretation of Integrated Pulmonary Index (IPI) (14).

IPI	Patient status	Subgroups
10–9	Normal	Optimal values
8	Within normal range	Suboptimal values
7	Close to normal range; requires attention	
5–6	Requires attention and may require intervention	
3	Requires intervention	
1–2	Requires immediate intervention	

neurological complications, and postoperative myocardial damage. Arrhythmic complications were comprised of any episode of atrial fibrillation, ventricular arrhythmia, or fibrillation requiring therapeutic intervention. Hemorrhagic complications were defined as drainage blood loss of more than 200 mL/h for three consecutive hours or re-sternotomy. Respiratory complications were reintubation, need for prolonged oxygen therapy, pneumothorax, hydrothorax, chylothorax, or pneumonia. Patients were considered as requiring prolonged oxygen therapy after extubation in case if needed oxygen insufflation more than 12 h to maintain $SpO_2 > 93\%$. Neurological complications were defined as postoperative delirium or stroke. The postoperative myocardial damage was defined as an increase in the plasma concentration of creatine kinase-MB > 50 pg/mL.

Statistical Analysis

For data collection and analysis, we used SPSS software (version 17.0; SPSS Inc., USA) and MedCalc software (version 12.3, MedCalc Software, Belgium). Due to pilot design of the study, the sample size was limited by 40 patients. All the variables were expressed as median (25^{th}–75^{th} interquartile interval). The groups were compared using Mann–Whitney test. The intragroup comparisons were performed by Friedman and *post hoc* Wilcoxon tests with Bonferroni correction. For correlation analysis, we used Spearman test. Nominal data were compared using χ^2 test and expressed as patient number. To evaluate the ability of IPI and $PetCO_2$ to predict cardiac index <2.5 L/min/m^2 during mechanical ventilation, we performed ROC-curve analysis and calculated area under the ROC curve (AUC). The ROC analysis was also used to assess the capability of IPI and PaO_2/FiO_2 measured at 6 h after extubation for prediction of postoperative complications during 24 h. The optimal cutoff point for IPI was determined by maximum value of the Youden Index (maximizing sensitivity and specificity). For *post hoc* intragroup comparisons, p value < 0.013 was considered as statistically significant. In all other cases, p value < 0.05 was regarded as statistically significant.

RESULTS

We enrolled 30 males and 10 females. Demographic and baseline characteristics of the patients, as well as postoperative complications are shown in **Table 2**.

After admission to the ICU, we had difficulties in registration of the IPI value only in one patient. Notably, 10 min later IPI was registered in 100% of patients. After admission to the ICU, 5% of patients required attention according to their respiratory status and had IPI < 7. Simultaneously, 63% of patients had PaO_2/FiO_2 < 300 mmHg. The IPI values, measured after ICU admission, weakly correlated with cardiac index (rho = 0.4, $p = 0.04$) and $ScvO_2$ (rho = 0.4, $p = 0.02$). The decreased values of IPI and $PetCO_2$ during controlled mechanical ventilation were associated with CI < 2.5 L/min/m^2 (cutoff point for IPI ≤ 8, sensitivity 84%, specificity 53%, positive predictive value 64%, negative predictive value 75%, AUC = 0.72, $p = 0.02$; cutoff point for $PetCO_2 \leq 30$ mmHg, sensitivity 78%, specificity 68%, positive predictive value 70%, negative predictive value 76%, AUC = 0.73, $p = 0.02$, **Figure 1**).

TABLE 2 | The patient characteristics during perioperative period.

Characteristics	Value
Age, years	62 (55–70)
BMI, kg/m^2	30 (27–31)
EuroScore II, points	1.15 (0.85–1.59)
Duration of surgery, min	210 (185–250)
Grafts, number	3 (2–4)
Intraoperative fluid balance, mL	900 (563–1,238)
Baseline characteristics after admission to the ICU	
IPI	9 (8–10)[a]
PaO_2/FiO_2, mmHg	270 (193–332)
SpO_2, %	100 (98–100)
$PetCO_2$, mmHg	30 (28–34)
PR, bpm	61 (54–75)
RR/min	15 (13–15)
$PaCO_2$, mmHg	39 (36–41)
Cardiac index, L/min/m^2	2.41 (2.04–2.76)
Duration of postoperative ventilation, min	193 (138–258)
Duration of ICU stay, h	24 (24–66)
Postoperative complications (n = 13)	
Arrhythmia	5
Respiratory complications	6
Hemorrhagic complications	1
Neurological complications	1
Myocardial damage	0

[a]*n = 39; in all other cases n = 40.*

Data presented as median (25th–75th percentile), percentage or numbers.

BMI, body mass index; PR, pulse rate; RR, respiratory rate; ICU, intensive care unit; IPI, Integrated Pulmonary Index.

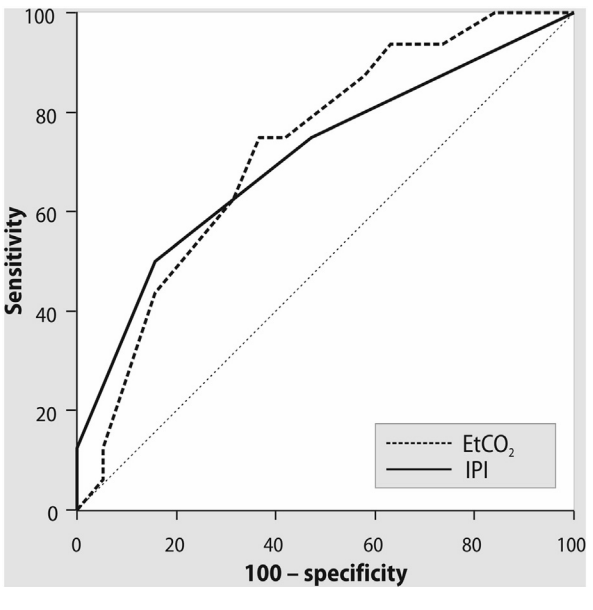

FIGURE 1 | ROC curves for Integrated Pulmonary Index (IPI), end-tidal CO_2, and cardiac index < 2.5 L/min/m^2 during mechanical ventilation. AUC = 0.72, $p = 0.02$; cutoff point of IPI ≤ 8, with sensitivity 84%, specificity 53%, positive predictive value 64%, negative predictive value 75%. AUC = 0.73, $p = 0.02$; cutoff point of $PetCO_2 \leq 30$ mmHg, with sensitivity 78%, specificity 68%, positive predictive value 70%, negative predictive value 76%.

All patients were successfully weaned from mechanical ventilation. PaO_2/FiO_2 ratio was stable both during the spontaneous breathing trial and after tracheal extubation. In contrast, IPI

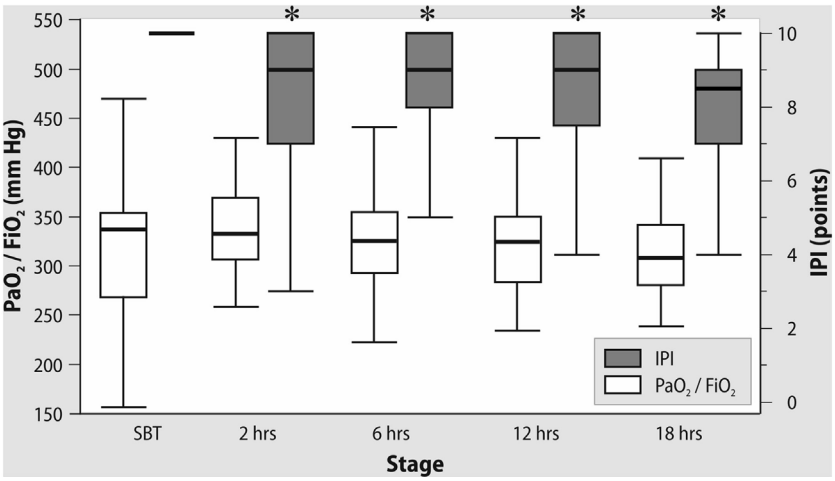

FIGURE 2 | Changes in PaO_2/FiO_2 and Integrated Pulmonary Index (IPI) after tracheal extubation. *Wilcoxon test, $p < 0.01$.

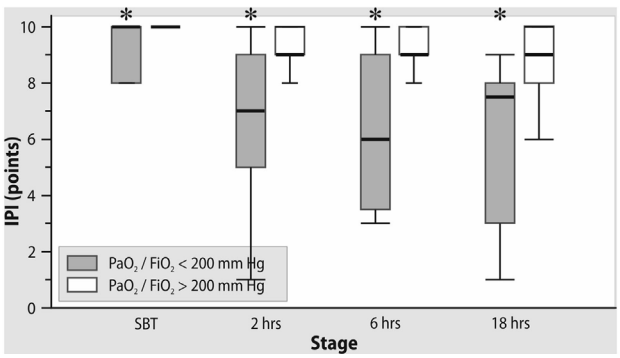

FIGURE 3 | The changes in Integrated Pulmonary Index (IPI) after extubation in subgroups with PaO_2/FiO_2 <200 mmHg and >200 mmHg on admission to the intensive care unit. *Mann–Whitney test, $p < 0.05$.

TABLE 3 | Comparative characteristics in subgroups of patients with optimal (>8) and suboptimal (≤8) IPI values at 2 h after extubation.

Characteristics	$IPI_{optimal}$ ($n = 25$)	$IPI_{suboptimal}$ ($n = 13$)	*p*-Value
Age, years	63 (55–70)	65 (56–74)	0.69
BMI, kg/m²	29 (27–32)	30 (28–32)	0.63
EuroScore II, points	1.01 (0.84–1.5)	1.4 (1.2–2.05)[a]	**0.03**
EF before surgery, %	60 (55–66)	52 (46–60)[a]	**0.02**
EF after surgery, %	63 (60–68)	57 (52–62)[a]	**0.007**
SpO_2, %	95 (93–98)	93 (89–95)[a]	**0.045**
$etCO_2$, mmHg	37 (35–39)	33 (30–35)[a]	**0.03**
PR, bpm	77 (70–88)	88 (75–99)[a]	**0.04**
RR/min	14 (14–18)	15 (15–18)	0.33
PaO_2/FiO_2, mmHg	324 (301–349)	317 (293–331)	0.32
PaCO2, mmHg	38 (36–39)	36 (31–39)	0.58
Fluid balance, mL	320 (−110 to 498)	−225 (−337 to +275)[a]	**0.03**
Urine output, mL/kg/h	1.0 (0.7–1.3)	1.2 (1.0–1.6)	0.06
Administration of diuretics	4	11[b]	**0.05**
Duration of surgery, min	195 (172–237)	245 (202–255)	0.13
Duration of ICU stay, h	24 (24–72)	24 (24–48)	0.30
Hospitalization time, days	9 (7–10)	9 (8–12)	0.35

Data presented as median (25th–75th percentile), percentage or numbers.
BMI, body mass index; EF, ejection fraction; PR, pulse rate; RR, respiratory rate; ICU, intensive care unit.
Bold font indicates statistical significance with $p < 0.05$.
[a]*Mann–Whitney test, $p < 0.05$.*
[b]*χ^2, $p < 0.05$.*

decreased significantly after OPCAB with a minimal value at 18 h after extubation (**Figure 2**). As shown in **Figure 3**, in patients with $PaO_2/FiO_2 < 200$ mmHg on ICU admission, the IPI values at 2, 6, 12, and 18 h after extubation did not exceed suboptimal range (≤8) ($p < 0.05$ as compared to IPI values of the subgroup with $PaO_2/FiO_2 > 200$ mmHg).

In addition, the suboptimal IPI values at 2 h after tracheal extubation were associated with higher preoperative EuroScore and decreased left ventricular ejection fraction before and after OPCAB (**Table 3**). In the subgroup with IPI ≤ 8, we observed decreased SpO_2 and $etCO_2$, as well as increased pulse rate. Higher IPI values were associated with positive fluid balance and decreased rate of diuretic administration at the first day of ICU stay.

The length of ICU and hospital stay did not differ between the patients with optimal and suboptimal IPI values. We did not find any associations between PaO_2/FiO_2 ratio and the length of ICU stay either. However, IPI value ≤9 at 6 h after extubation demonstrated moderate predictive ability for early postoperative complications (AUC = 0.707; $p = 0.04$, with sensitivity 92% and specificity 48%, positive predictive value 89%, **Figure 4**). PaO_2/FiO_2 ratio at 6 h after extubation did not demonstrate any predictive ability for postoperative complications (AUC = 0.543; $p = 0.67$).

DISCUSSION

Our study has shown that IPI can provide important information about respiratory and hemodynamic status of the cardiosurgical patient, especially during the postextubation period.

In our study, we observed difficulties in registration of the IPI value after admission to the ICU in one patient from 40 enrolled into the study; this problem can be explained by decreased perfusion, leading to low SpO_2 signal. Low perfusion as well as

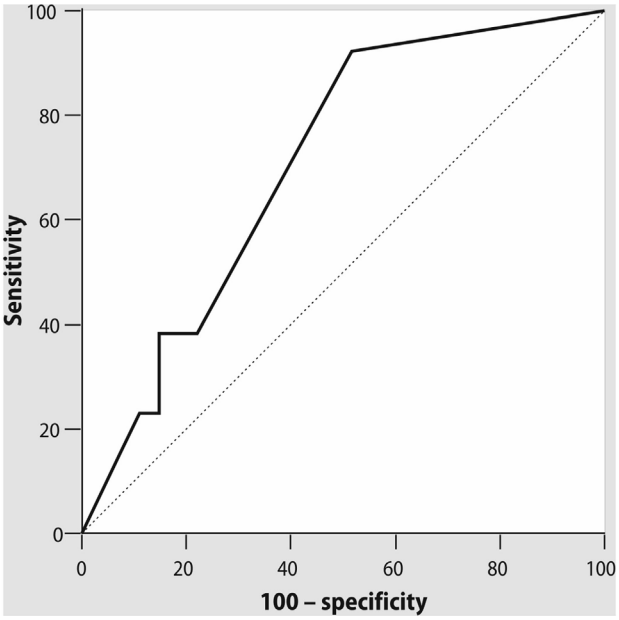

FIGURE 4 | ROC curve for Integrated Pulmonary Index (IPI), measured at 6 h after tracheal extubation, and early postoperative complications. AUC = 0.71; $p = 0.04$, cutoff point of IPI ≤ 9 with sensitivity 92% and specificity 48%, positive predictive value 57%, negative predictive value 89%.

motion artifacts are the well-known limitations of pulse oximetry observed in the early postoperative period after cardiac surgery (19).

After admission to the ICU, the number of patients with compromised respiratory function according to their PaO_2/FiO_2 values (63%) was higher than the number of patients requiring attention according to the IPI values (5%). During controlled mechanical ventilation, several components of IPI like respiratory rate, SpO_2, and $PetCO_2$, are determined mainly by the operator-depending settings of the ventilator that may not reflect the complex respiratory status. The association of IPI, measured after admission to the ICU, with cardiac index and $ScvO_2$, observed in our study can be explained by the relationship between cardiac output, $PetCO_2$, and oxygen transport (20). Although the described correlations were weak that can be caused by dependence of end-tidal CO_2 not only from cardiac output but also from ventilation, metabolism, and other factors, our findings are consistent with other investigations in this field. In several studies, authors demonstrated that $PetCO_2$ and cardiac output had a positive association in different categories of patients (21–23). Thus, Baraka and colleagues have shown that cardiac output correlated with $PetCO_2$ during partial cardiopulmonary bypass and following weaning from bypass (22). In this study, $PetCO_2 > 30$ mmHg during partial bypass predicted an adequate cardiac output after perfusion. At the same time, $PetCO_2 < 30$ mmHg may correctly denote a low cardiac output only in combination with low $ScvO_2$ (22). This relationship between $PetCO_2$ and cardiac function can be relevant not only for cardiac surgery; thus, Dunham and colleagues have found that a decline in $PetCO_2$ correlates with decrease in noninvasive cardiac output in emergently intubated trauma patients (23). Notably, the addition of pulse rate into the algorithm for calculation of IPI could improve the ability of this parameter to predict decreased cardiac output compared with $PetCO_2$ alone. However, our ROC analysis has shown equal AUC to predict $CI < 2.5$ L/min/m^2 both for IPI < 8 and for $PetCO_2 < 30$ mmHg. The possible explanation for this finding could be that the heart rate is just one of the determinants of cardiac output, thus $PetCO_2$ alone may have similar accuracy with IPI in predicting cardiac output after OPCAB.

Notably, reduced IPI values during controlled mechanical ventilation observed in our study can be explained by decreased $PetCO_2$ levels. During spontaneous breathing with ambient air (FiO_2 21%), suboptimal IPI was also associated with decreased SpO_2 values and increased pulse rate, aiming to maintain adequate cardiac output and oxygen delivery. We suppose that, summarizing the key cardiovascular and respiratory parameters, IPI can be a useful tool for postoperative assessment of patient in addition to PaO_2/FiO_2 ratio, which has a limited value due to dependence on FiO_2 (24) This can explain the stable values of PaO_2/FiO_2 with simultaneous reduction of SpO_2 and IPI after extubation while breathing with ambient air. It is important to mention that the measurement of IPI does not replace postoperative blood gases but it can potentially reduce the number of blood gas samples, is continuous as compared to discrete blood gases and can serve as a "monitoring bridge" after discontinuation of mechanical ventilation and invasive monitoring.

The association of suboptimal IPI values with preoperative EuroScore and ejection fraction before and after intervention demonstrates the relationship of IPI and severity of cardiac comorbidities. Several studies have shown that decreased ejection fraction after cardiac surgery may be associated with risk of sepsis, postoperative respiratory failure and prolonged mechanical ventilation (25, 26). Thus, the reduction of IPI after cardiac surgery can detect patients who require more complex hemodynamic monitoring and optimization including fluids, diuretics, inotrope/vasopressor support, and other therapies.

Association between IPI value ≤9, recorded at 6 h after extubation and the incidence of early complications after OPCAB seems to be relevant for prediction of the course of postoperative period. We did not find in other studies the data about the opportunity of IPI to predict the course of postoperative period, although IPI was effective in detection of clinically significant events, such as hypoxia or bradypnea, during the intraoperative period (16, 17). The complications observed during our study (predominantly, atrial fibrillation and respiratory failure) are accompanied by changes in respiratory and hemodynamic status of the patient. The patients after cardiac surgery can have a higher alert threshold of IPI as compared to other settings where the attention is required when IPI is ≤7. The diagnostic capabilities of IPI need further validation and studies including the assessment of IPI as a marker for the safe transfer from ICU.

Study Limitations

Our findings have a limitation due to relatively small sample size. In addition, all the patients from our study received bisoprolol postoperatively that may influence the heart rate, as well as the IPI value.

CONCLUSION

Integrated pulmonary index is associated with changes in cardiac output and may predict the postoperative complications during the discontinuation from mechanical ventilation and in the early postextubation period after OPCAB. This index may be a valuable adjunct to the routine monitoring during spontaneous breathing, but not during controlled mechanical ventilation.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the ethics committee of the Northern State Medical University (Arkhangelsk, Russian Federation). All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of the Northern State Medical University (Arkhangelsk, Russian Federation).

AUTHOR CONTRIBUTIONS

All authors had contributed equally.

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