



Advances in photoplethysmography: beyond arterial oxygen saturation

Progrès de la photopléthysmographie: au-delà de la saturation artérielle en oxygène

Karsten Bartels, MD · Robert H. Thiele, MD

Received: 7 April 2015 / Revised: 3 July 2015 / Accepted: 11 August 2015 / Published online: 19 August 2015
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Abstract

Purpose Photoplethysmography permits continuous measurement of heart rate and peripheral oxygen saturation and has been widely used to inform clinical decisions. Recently, a myriad of noninvasive hemodynamic monitoring devices using this same technology have been increasingly available. This narrative review aims to summarize the principles that form the basis for the function of these devices as well as to comment on trials evaluating their accuracy and clinical application.

Principal findings Advanced monitoring devices extend photoplethysmography technology beyond measuring oxygen concentration and heart rate. Quantification of respiratory variation of the photoplethysmographic waveform reflects respiratory variation of the arterial pressure waveform and can be used to gauge volume responsiveness. Both the volume-clamp and physiocal techniques are extensions of conventional photoplethysmography and permit continuous measurement of finger arterial blood pressure. Finger

arterial pressure waveforms can subsequently inform estimations of cardiac output.

Conclusions Although respiratory variations of the plethysmographic waveform correlate only modestly with the arterial blood pressure waveform, fluid responsiveness can be relatively consistently assessed using both approaches. Continuous blood pressure measurements obtained using the volume-clamp technique may be as accurate as conventional brachial noninvasive blood pressure measurements. Most importantly, clinical comparative effectiveness studies are still needed in order to determine if these technologies can be translated into improvement of relevant patient outcomes.

Résumé

Objectif La photopléthysmographie permet la mesure continue de la fréquence cardiaque et de la saturation en oxygène périphérique, et elle est largement utilisée pour les prises de décisions cliniques. Depuis peu, un très grand nombre de dispositifs non invasifs de surveillance hémodynamique utilisant la même technologie envahit le marché. Cette synthèse narrative vise à résumer les principes à la base du fonctionnement de ces dispositifs et à commenter les essais évaluant leur exactitude ainsi que leurs applications cliniques.

Constataions principales Les dispositifs de surveillance avancée étendent la technologie de photopléthysmographie au-delà de la mesure de la concentration en oxygène et de la fréquence cardiaque. La quantification de la variation respiratoire du tracé photopléthysmographique reflète la variation respiratoire du tracé de pression artérielle et peut servir à jauger la réactivité au volume. Les deux techniques de compression volumique (volume-clamp) au doigt et la technique physiocal sont des prolongements de

Author contributions Karsten Bartels wrote approximately 50% of the manuscript and critically edited the remainder. Robert H. Thiele wrote approximately 50% of the manuscript and critically edited the remainder.

K. Bartels, MD
Departments of Anesthesiology and Surgery, University of
Colorado Denver, Aurora, CO, USA

R. H. Thiele, MD (✉)
Divisions of Cardiac, Thoracic, and Critical Care
Anesthesiology, Departments of Anesthesiology and Biomedical
Engineering, University of Virginia School of Medicine,
Charlottesville, VA, USA
e-mail: thiele@virginia.edu

la photopléthysmographie et permettent une mesure continue de la pression artérielle au doigt. Les tracés de pression artérielle au doigt peuvent ensuite alimenter des estimations du débit cardiaque.

Conclusions Bien que les variations respiratoires du tracé pléthysmographique ne soient que modestement corrélées au tracé de la pression artérielle, la réactivité liquidienne peut être évaluée de façon relativement constante en utilisant ces deux méthodes. Les mesures continues de la pression artérielle obtenues par la technique de compression volumique peuvent être aussi précises que les mesures non invasives conventionnelles de la pression artérielle au niveau du bras. Plus important encore, les mesures d'efficacité clinique comparatives restent nécessaires afin de déterminer si ces technologies peuvent se traduire en améliorations pertinentes de l'évolution des patients.

Photoplethysmography

Photoplethysmography permits continuous measurement of heart rate and peripheral oxygen saturation, and its use in pulse oximetry has been used for decades to inform clinical decisions. A range of noninvasive hemodynamic monitoring devices are now using this same technology to further inform decisions on advanced hemodynamic management. The purpose of this article is to perform a critical analysis of recent advances in photoplethysmography. This narrative review examines the use of photoplethysmography to estimate vascular tone, blood pressure, stroke volume, and fluid responsiveness. Each device (or measurement technique) is reviewed in light of the physiologic basis on which the photoplethysmogram (PPG) is based, engineering considerations related to the biomedical devices which make these particular measurements, and available clinical data. The predominant source of information was original peer-reviewed articles that were sourced using PubMed. In instances in which the peer-reviewed literature was inadequate, intellectual property (i.e., patent) literature was used to supplement our understanding of the technical properties of these devices.

History and development of pulse oximetry

Qualitative analysis of the arterial pulse predates the development of pulse oximetry by centuries, with early accounts being attributed to the Egyptian, Greek, and Han Chinese societies.^{1,2} Nevertheless, it was not until 1876, when Karl von Vierordt described the impact of circulatory changes on the absorption of light, that the intellectual

foundation for pulse oximetry was laid.³ This work was largely unappreciated for a half century. Then, in Leipzig, Germany in 1939, Karl Matthes developed an ear probe capable of monitoring tissue oxygenation through the use of both a red (R) and infrared (IR) light source.⁴ J.R. Squire quickly followed this innovation by developing an absolute tissue oxygenation monitor that utilized a pressure cuff to remove blood from the “field of view” and, in so doing, allowed for calibration.⁵

In light of aviators losing consciousness during high-altitude dogfights in World War II, Glenn Millikan, in collaboration with John Pappenheimer at the University of Pennsylvania, successfully developed a feedback mechanism to adjust an aviator's oxygen supply based on the oxygen saturation measured using a portable IR light source.^{3,6} This device, like its precursors, was still not able to discriminate between arterial and venous blood. In the 1960s, the surgeon Robert Shaw added additional wavelengths to a tissue oximeter, which facilitated the calculation of carboxyhemoglobin and methemoglobin in addition to oxyhemoglobin and deoxyhemoglobin.⁷

In 1972, as Takuo Aoyagi was attempting to design a noninvasive cardiac output monitor using an indocyanine-green washout technique, he detected a pulsatile variation in the absorption of IR light attributable to the arterial pulse. Rather than silence this useful “artifact,” Dr. Aoyagi realized that this pulsatility might allow him to discriminate between arterial and venous blood and thereby calculate arterial oxygen saturation (as opposed to tissue oxygenation) with a two-wavelength oximetric device. Thus, somewhat by accident – but clearly not without hard work and deep understanding – the pulse oximeter was born.⁸

Physiology of the PPG

Aoyagi's major contribution to tissue oximetry was recognition that pulsations at the cardiac frequency allowed for the selective analysis of arterial blood. Indeed, it is still commonly thought that the “pulsatile” (or “AC” – analogous to the “alternating current” described by electrical engineers) component of the PPG is exclusively arterial in nature.⁹ The situation is more complex, however, and it is now appreciated that the systemic venous system and autonomic nervous systems play a large role in the development of the PPG waveform (Fig. 1).¹⁰ The interference with the PPG waveform attributed to the systemic venous system was identified over 25 years ago.¹¹ More recently, attempts have been made to analyze this venous interference in an effort to develop a noninvasive method of measuring venous oxygen saturation.^{12,13} Additionally, it is clear that

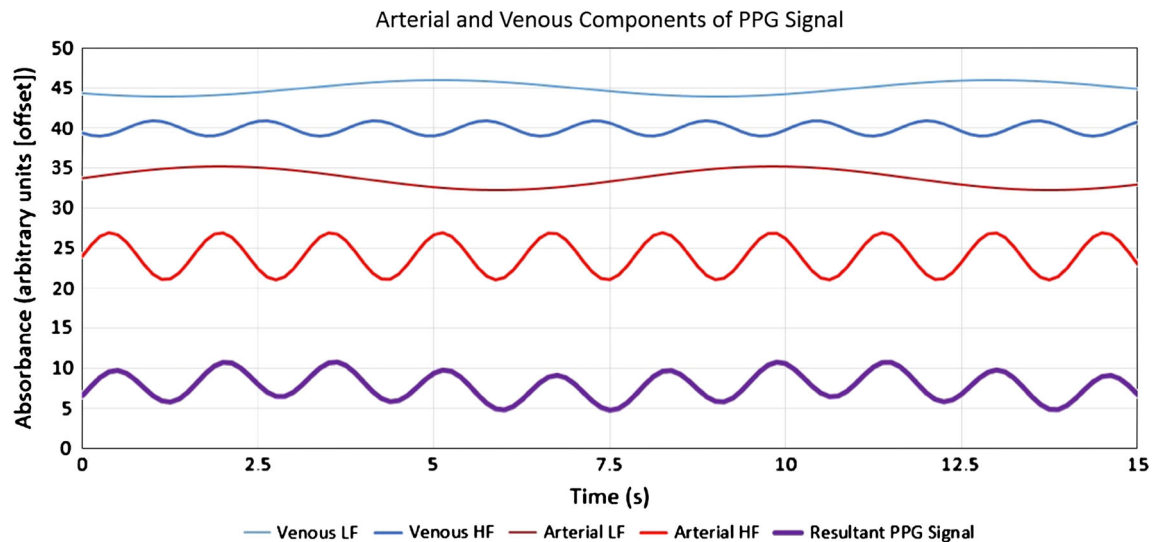


Fig. 1 The PPG signal is a combination of arterial (red) and venous (blue) signals, both of which oscillate at the cardiac and respiratory frequencies. Notice that the arterial and venous signals will be out of phase, further complicating the photoplethysmographic (PPG) signal

changes in autonomic tone induced by both temperature and pharmacology impact the PPG waveform.¹⁴⁻¹⁶ Despite this complexity, the *predominant* contributor to the pulsatility exhibited in PPG tracing is the arterial pressure waveform.

Pulse oximeters are highly sensitive to any changes in finger blood volume and can detect extremely low levels of pulsatility.^{17,18}

Systemic vascular resistance (SVR) and stroke volume

While several investigators have documented the impact of autonomic tone on the PPG waveform, initially, no attempts were made to quantify this relationship.¹⁴⁻¹⁶ Then, in 2007, Shelley's group attempted to use the PPG waveform to develop a quantitative estimate of SVR.¹⁹ Specifically, this group proposed that pulse width was correlated with SVR (Pearson correlation $r = 0.56$) as measured in patients undergoing cardiac surgery. By combining pulse amplitude and width as well as integrating oximeters from multiple sites (e.g., ear, finger), the correlation was marginally improved. A subsequent analysis of similar variables in cardiac surgical patients was not able to replicate these findings.²⁰ It should be emphasized that there were important differences between these two studies, including an intermittent *vs* a continuous thermodilution technique, different oximeter technology, multiple *vs* single-site measurements, and thus, the ability of the pulse oximeter waveform to predict changes in SVR has not been fully explored. It must also be pointed out that

(purple). To date, investigations using phasic information to separate the arterial from the venous components of the PPG are lacking; however, in theory this would be possible

both of these studies utilized oximetric equipment that gave the investigators access to the raw R and IR signals. In contrast, the PPG waveform displayed to the anesthesiologist is highly processed (e.g., high-pass filtered), and equations derived from the raw unprocessed waveforms (as in references)^{19,20} cannot be used on the processed PPG. That said, even an unprocessed PPG signal, when used alone, cannot yet be relied on for an accurate estimation of vascular resistance. Thus, clinicians should avoid utilizing the PPG waveform to detect changes in vascular tone.

Another interesting feature that can be extrapolated from the PPG waveform, at least in the presence of an electrocardiogram, is the pulse transit time (PTT), i.e., the time it takes the pulse wave to travel from the heart to the periphery where the PPG waveform is being measured. This is useful because, in laboratory conditions, for example, the velocity of a pulse wave travelling through an elastic tube can be described in terms of the diameter, elasticity, and wall thickness of the tube, as well as the density of the fluid contained within:^{21,22}

$$V = k(Eh/\rho D)^{1/2}$$

Equation 1: Moens-Korteweg Equation²³ describing fluid velocity (V) in an elastic tube in terms of wall thickness (h), tube diameter (D), vessel elasticity (E , Young's Modulus of Elasticity, [stress/strain]), fluid density (ρ), and $k = \text{constant}$

Because arteries behave to some extent as elastic tubes and thus can be modelled as such, changes in vascular tone that result in altered vascular impedance (i.e., changes in both cross-sectional diameter and blood vessel

compliance)²⁴ should, in theory, alter the speed at which a pressure wave travels through the arterial system.²² It is important to point out that this type of analysis neglects viscous properties of blood-filled arteries that, in reality, exhibit viscoelastic properties.²⁵

Greene *et al.* explored the relationship between pulse wave velocity (PWV), which is inversely proportional to PTT, and SVR over a range of hemodynamic conditions and found an independent relationship between PWV and SVR.²² Ishihara *et al.* explored the use of PTT to “correct” noninvasive cardiac output monitors for changes in peripheral tone.²⁶

The relationship between PTT and peripheral tone is further supported by the fact that decreased PTT (i.e., increased PWV) has been related to mortality after kidney transplantation. Specifically, in a cohort of 330 patients followed over an average of 3.8 years after renal transplantation, increased PWV was associated with a significant increase in age, systolic blood pressure, and pulse pressure. In this study, PWV and systolic blood pressure emerged as predictors of all-cause mortality.²⁷ In a related manner, some investigators have even begun to utilize changes in peripheral perfusion to assess the efficacy of peripheral nerve blockade which, when effective, leads to vasodilation with a corresponding change in the PPG waveform.²⁸

The PPG waveform is clearly related to the arterial pressure waveform, and the “area under the curve” (AUC) appears to be related to stroke volume in healthy volunteers who do not require vasopressors.²⁹ Nevertheless, there appears to be inadequate value in this isolated relationship for the anesthetized patient subjected to cardiac surgery.²⁰ Presumably, changes in vasomotor tone, temperature, and cardiac function all impact the PPG tracing, making simple analysis of the signal challenging and hence limiting the applicability of the AUC technique for the calculation of stroke volume in cardiac surgery patients. Given that this method has shown promise in healthy volunteers, it may be fruitful to test it in a more “intermediate” patient population, e.g. relatively healthy patients undergoing a non-cardiac surgical procedure.

As mentioned above, PTT has been utilized in the development of a noninvasive cardiac output monitor that relies only on the use of electrocardiography and PPG (esCCO, Nihon Kohden, Japan). While one study has shown sufficient accuracy for clinical use,³⁰ subsequent studies have not been so favourable.^{31,32}

Blood pressure

Because the PPG waveform is in part determined by changes in blood pressure, attempts have been made to

correlate changes in PPG amplitude to changes in blood pressure; however, this has been largely unsuccessful.^{10,33} One reason for the lack of success is the fact that the PPG measures changes in light absorption, which are not easily translated to changes in pressure –especially when neither the width nor compliance of the finger are known. In addition, the modified Beer-Lambert law, which is integral to pulse oximetry and other similar technologies, is an oversimplification of light behaviour through tissue. Indeed, light is affected by scattering and other complexities that are, at best, challenging to model.^{10,34}

Assuming cardiac output is constant, which of course is rarely the case, changes in SVR manifest as changes in blood pressure. Thus, some investigators have attempted to estimate blood pressure noninvasively by measuring PTT. A small study did suggest that PTT derived from a pulse oximeter could be used to estimate blood pressure in anesthetized patients;³⁵ however, this early study was refuted by a larger multicentre analysis.³⁶ More recently, oximeter-based PTT has been used to obtain accurate measurements of changes in blood pressure that occur during induction of general anesthesia as well as to achieve rapid detection of the onset of hypotension in patients undergoing spinal anesthesia for Cesarean delivery.^{37,38} While more validation studies are needed, the near instantaneous response time shown in both of these studies is encouraging.^{33,34} In aggregate, these data suggest that PTT, at least over *short time periods*, provides useful information for immediate detection of hemodynamic changes that might be missed if only an oscillometric cuff method is used for periodic blood pressure assessments.

Peripheral perfusion

The fact that vascular compliance of the finger is not known, combined with the complexities of light scattering, makes it impossible to formulate a direct comparison between the PPG waveform and the arterial pressure waveform. That said, over short periods of time, assuming that finger compliance and scattering effects remain stable, changes in pulse amplitude may be indicative of changes in perfusion.

Fluid responsiveness

One of the most exciting physiologic discoveries over the last century is the appreciation that the dynamic interaction between the cardiovascular and pulmonary systems can be assessed, at least in part by analysis of the arterial and PPG waveforms.³⁹ Because changes in intrathoracic volume that

occur with each breath (particularly with positive pressure breathing) cyclically alter left ventricular preload and right ventricular afterload, patients positioned at the peak of the Frank-Starling curve (i.e., with optimal intravascular volume) will exhibit very little alteration in the arterial or PPG signals with each breath. In contrast, those positioned on the “steep” ascending portion of the curve (i.e., relatively “underfilled”) exhibit respiratory variation.⁴⁰ Indeed, animal data suggest that respiratory variation and hemorrhagic fluid losses are linearly related but can be reversed with fluid resuscitation.⁴¹ Furthermore, there is an inverse relationship between the magnitude of respiratory variation, which is typically elevated in hypovolemic patients, and left ventricular end-diastolic volume.⁴² These data have led to the paradigm-shifting concept of “fluid responsiveness” in which clinicians shift their focus away from static measures of intravascular volume, e.g., central venous pressure, and towards predictive metrics that correspond to changes in cardiac output following a fluid bolus.

In fact, data in a systematic review of nearly 700 patients collected in 29 studies suggest that *arterial* respiratory variation outperforms central venous pressure, pulmonary capillary wedge pressure, and end-diastolic volume as a predictor for the response to fluid administration.⁴³ These findings were echoed in a large trial by Cannesson *et al.* that included more than 400 patients at multiple centres.⁴⁴ The clinical relevance of this new measurement class has recently been established, with at least five studies using arterial respiratory variation as a physiologic endpoint for patient intraoperative fluid management. The studies have shown significant reductions in hospital length of stay as well as other relevant outcomes—our own analysis revealed a mean weighted reduction in length of stay of 2.3 days, but it was widely variable with a standard deviation of 3.9 days.^{45–50} Importantly, at least one negative study has also been published.⁴⁷ Unfortunately, Buettner *et al.* did not report fluid administration in this negative study, making it difficult to interpret its negative meaning. For example, if fluid administration was identical between groups, we would not expect a difference.⁴⁷

A limited number of patients receive arterial catheters for monitoring. Indeed, only 16% of patients undergoing general anesthesia at major academic medical centres receive an intra-arterial catheter.⁵¹ Thus, it is of particular importance to find out if arterial and PPG-derived indices of respiratory variation are interchangeable. While some studies have shown a meaningful correlation between the two,^{52,53} the majority of studies comparing arterial and PPG respiratory variation point to a relatively weak correlation.^{54–58} Solus-Biguenet *et al.*, for instance, found a weak correlation of 0.29.⁵⁴ Nevertheless, despite this

weak correlation, the majority of fluid responsiveness studies suggest that the respiratory variation in the PPG tracing is predictive of the hemodynamic response to fluid loading,^{59–63} although this finding is not universal.^{64,65}

Surprisingly, despite the fact that the physiologic meaning of *arterial* respiratory variation has been understood for decades, extrapolation to the PPG waveform was completely missed by the manufacturers of pulse oximeters who considered this information “noise” and filtered it out through the application of high-pass filters.⁶⁶ Masimo Corporation was the first commercial entity to bring a PPG-based respiratory variation algorithm to market. The pleth variability index (PVI) feature of the Radical-7 pulse oximeter (Masimo Corporation; Irvine, CA, USA) is expressed as:

$$\text{PVI} = \frac{\text{PP}_{\max} - \text{PP}_{\min}}{\text{Average}[\text{PP}_{\max}, \text{PP}_{\min}]}$$

Equation 2: PP represents the amplitude of the PPG waveform (in arbitrary units)

The PVI is therefore analogous to pulse pressure variation (PPV)⁶⁷ from the arterial waveform, but it differs in that the PPG waveform contains varying amounts of venous information not present in the arterial waveform.^{11,68,69} This information, along with the dependence of PVI on signal quality, may explain why arterial and PPG-based estimates of respiratory variation do not correlate well. Despite the poor correlation with PPV, PVI seems to be fairly predictive of fluid responsiveness, at least at tidal volumes above 8 mL·kg⁻¹.^{57,64,70–72}

Høiseth *et al.*'s analysis of PPV, SVV, ΔPOP (a non-proprietary estimate of PPG-based respiratory variation), and PVI in patients subject to pneumoperitoneum (i.e., which leads to increased intra-abdominal pressure, increased central venous pressure, and decreased venous return)^{73–75} revealed an increase in ΔPOP and PVI but not in PPV or SVV,⁶⁵ supporting the hypothesis that a physiologically meaningful venous contribution to the photoplethysmographic waveform may explain the relatively poor correlation between ΔPOP (or PVI) and PPV.

It is important to point out that data are lacking to determine if peripheral venous pressure variation is predictive of fluid responsiveness. That said, there are data to suggest that venous oscillations (i.e., as measured in the inferior vena cava via ultrasound) are predictive of fluid responsiveness.⁶⁸ Even more interesting, Alian *et al.* recorded the peripheral venous pressure waveform during simulated hypovolemia (lower body negative pressure [LBNP]) and found an increase in spectral power at the respiratory frequency at moderate levels of LBNP, followed by near complete abolition of respiratory variation at LBNP levels leading to symptoms.⁶⁹ This suggests that there are complex interactions between the systemic arterial and venous systems in the setting of hypovolemia.

The PVI has been used as an endpoint in at least two published protocols utilizing intraoperative *goal-directed therapy*. One procedure showed a reduction in lactate at various time points during and after major abdominal surgery, and the other showed reduced length of stay and hospital costs when PVI was used to guide intraoperative fluid management as part of an Enhanced Recovery After Surgery protocol.^{76,77} In both instances, the PVI-guided group received less overall fluid than the control. Recently, PVI has been expanded beyond fluid responsiveness and has been used to predict both hypotension after induction of anesthesia and the hemodynamic impact of positive end-expiratory pressure.^{78,79}

Venous oxygenation

Multiple authors have described the presence of venous “interference” in the PPG signal.^{11,80,81} The venous contribution to the PPG signal should not, however, be thought of as interference. Rather, it provides additional information, the utility of which has yet to be fully understood. Indeed, attempts have been made to utilize the venous component of the PPG signal to estimate venous oxygen saturation, although these findings have not been validated.^{12,13}

Volume-clamp technique

History and development

Over 40 years ago, the Czech physiologist, Jan Peñáz, developed the *volume-clamp* technique to measure peripheral arterial pressure.⁸² The basic principle of the Peñáz approach was to establish a control loop between pressure applied to a circumferential finger bladder and finger blood volume as determined by plethysmographic IR light – absorption of IR light in the finger increases with increasing blood volume during systole. In response, a finger cuff is inflated to counteract the increasing systolic blood pressure and stabilize blood volume. The cuff is then deflated with decreasing blood volume in the finger during diastole, thereby keeping the blood vessel diameter in the finger constant.⁸³ The pressure waveform in the finger cuff required to maintain constant blood volume (and constant IR absorption) is equal to the arterial blood pressure.

Continuous measurement of blood pressure in the finger

Technologic principles

While an ultrafast control loop between a finger bladder and an IR emitter/detector can recreate the shape of a

pressure waveform, more information is needed to translate this information into a numerical estimate of blood pressure. Continuous application of pressure such that arterial blood volume is constant (as described above) maintains the artery in what is referred to as an “unstretched” or “unloaded” state in which the arterial diameter is held constant, not by wall stress but by externally applied pressure. A useful analogy would be the decreased wall tension observed after externally compressing an inflated balloon.^{84,85} When the finger artery remains in an “unstretched” state, the blood pressure measured in the finger cuff is reflective of mean arterial blood pressure; thus, the key to the numerical determination of blood pressure is identification of this “unstretched” state.

To determine the pressure at which the artery is “unstretched”, finger bladder pressure is held constant for brief periods of time and increased stepwise while continuously analyzing the PPG waveform. Once the PPG amplitude is at its maximum, the feedback point for the mechanism is set (this is referred to as the *volume clamp*). Wesseling combined the volume-clamp technique with earlier work by Peñáz, leading to the development of the FinapresTM (Finapres Medical Systems BV, Amsterdam, The Netherlands) device in the 1980s.^{84,86,87} Determination of the correct unstretched state of a finger artery is complicated by frequent dynamic changes to the arterial compliance (e.g., as can occur with changes in temperature-mediated sympathetic tone).

The volume-clamp technique used in the Finapres device formed the basis for continuous finger blood pressure measurements used in newer generation devices on the market today, which differ slightly in how they achieve vascular unloading. The ClearSightTM (Edwards Lifesciences, Irvine, CA, USA) device, previously known as the Nexfin[®] (BMEYE, Amsterdam, The Netherlands), is based on the Finapres and utilizes the *physiocal* approach (see below) to maintain the finger arteries in an unstretched state. Another device, CNAP[®] (CNSystems, Graz, Austria) for monitoring continuous non-invasive arterial pressure, uses the Vasomotoric Elimination and Reconstructed Identification of the Initial setpoint (VERIFI) algorithm to maintain the finger arteries in an unstretched state and also utilizes a standard upper arm oscillometric blood pressure measurement to calibrate the finger measurements.

In the *physiocal* (physiological calibration) technique, periodic change in the finger bladder pressure is induced for continuous reanalysis of the PPG waveforms. New feedback points are determined as necessary if different finger bladder pressures result in higher PPG amplitude. The feedback setpoint is thereby constantly adjusted in order to maintain the finger artery in a maximally unloaded state.⁸⁴ A combination of the *volume-clamp* and *physiocal*

techniques enables continuous noninvasive blood pressure measurement in the finger (Fig. 2).⁸⁴

The CNAP approach, an alternative to the physical approach used for Nexfin/ClearSight, is based on the VERIFI algorithm to account for distortion caused by the non-instantaneous feedback mechanism (i.e. a small but mathematically relevant time lag between the cuff and the IR detector).⁸⁸ The VERIFI approach initially uses a brachial artery cuff (noninvasive blood pressure [NIBP]) to estimate a starting value of mean arterial pressure - this is the initial set point. The volume-clamp technique is still used to estimate finger blood volume as a function of time, $V(t)$; however, continuous determination of the set point differs from the physical solution.⁸⁹

Just as auditory waveforms contain multiple frequency components (e.g., middle C on the piano and clarinet both oscillate primarily at 262 Hz), physiologic waveforms (e.g., pressure and flow) are complex and contain a range of frequencies (Fig. 3).²

Using frequency domain analysis techniques, the VERIFI algorithm decomposes the volume signal $V(t)$ into three components: $V_{VLF}(t)$ = very low frequency volume; $V_{LF}(t)$ = low frequency volume; and $V_{AC}(t)$ = pulsatile volume. Volume and pressure are related to each other by gain (or the degree of amplification, G , analogous to the resistance that relates current and voltage in Ohm's law). At very low frequencies, gain is assumed to be zero. Gain at low and "pulsatile" frequencies (G_{LV} and G_{AC} , respectively) is determined by comparing the signal amplitude with various fixed cuff pressures and developing a transfer function (T) that relates the two (Fig. 4).⁸⁹

For a comparison between Nexfin / ClearSight and CNAP technology see Table 1.

Accuracy and limitations

A meta-analysis of continuous NIBP monitors, which included both the NexFin and CNAP devices as well as the T-Line (Tensys Medical Systems, Irvine, CA, USA), recently showed a bias of 3.2 mmHg and limits of agreement of -13.4 to 19.7 mmHg from pooled data from 28 studies including 919 patients. The T-Line uses tonometry to estimate blood pressure. A pressure-sensitive piezoelectric device placed directly over the radial artery "senses" the amount of pressure inside the radial artery, which is essentially a digitized version of a practitioner placing a finger on the radial artery to make a qualitative assessment of the intensity of the pulse. Mean arterial pressure is derived from identification of the maximal pulse waveform amplitude. Systolic and diastolic blood pressure values are then calculated.⁹⁰ Because the limits of agreement were not reported for each device individually (i.e., the tonometry devices were not separated from the volume-clamp devices), it is difficult to interpret the results of this meta-analysis specifically in the context of the volume-clamp device classification.⁹¹

Vasoconstriction can occur during shock or with the use of vasopressors. Insufficient peripheral circulation can subsequently make finger blood pressure measurement impossible in affected patients. In an earlier study of six gynecologic surgery patients who had a total of 378 paired (finger/brachial) blood pressure measurements using the

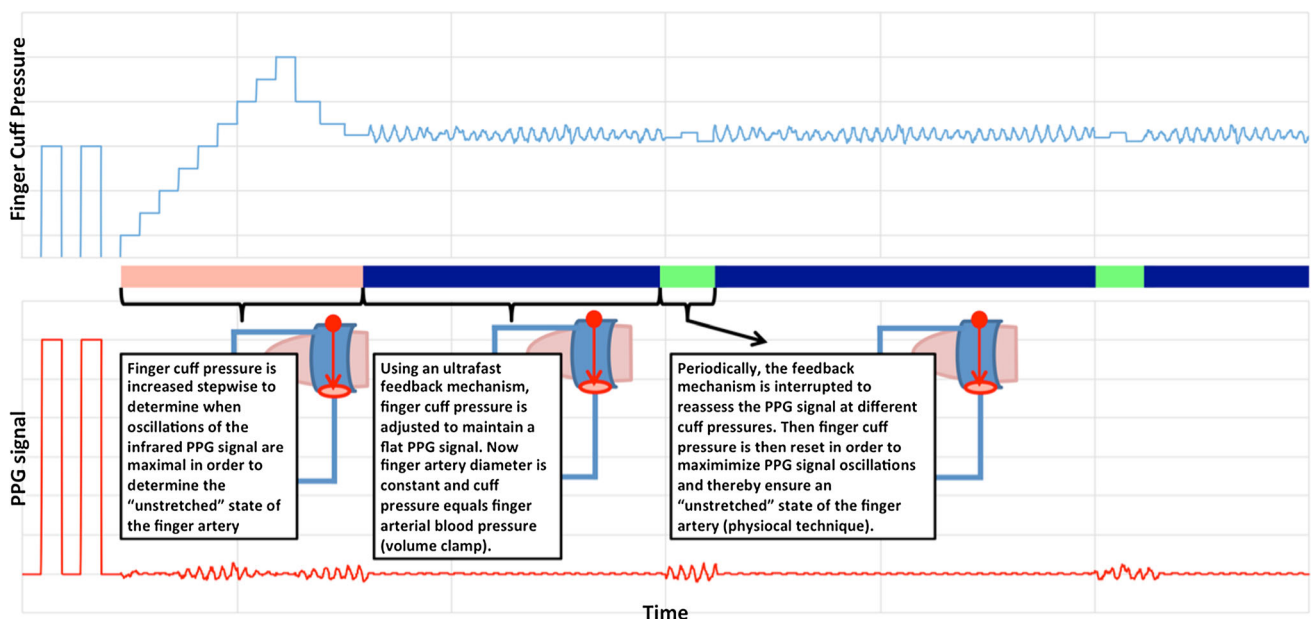


Fig. 2 Finger blood pressure measurement using photoplethysmography using the volume-clamp and physical approaches.⁸³

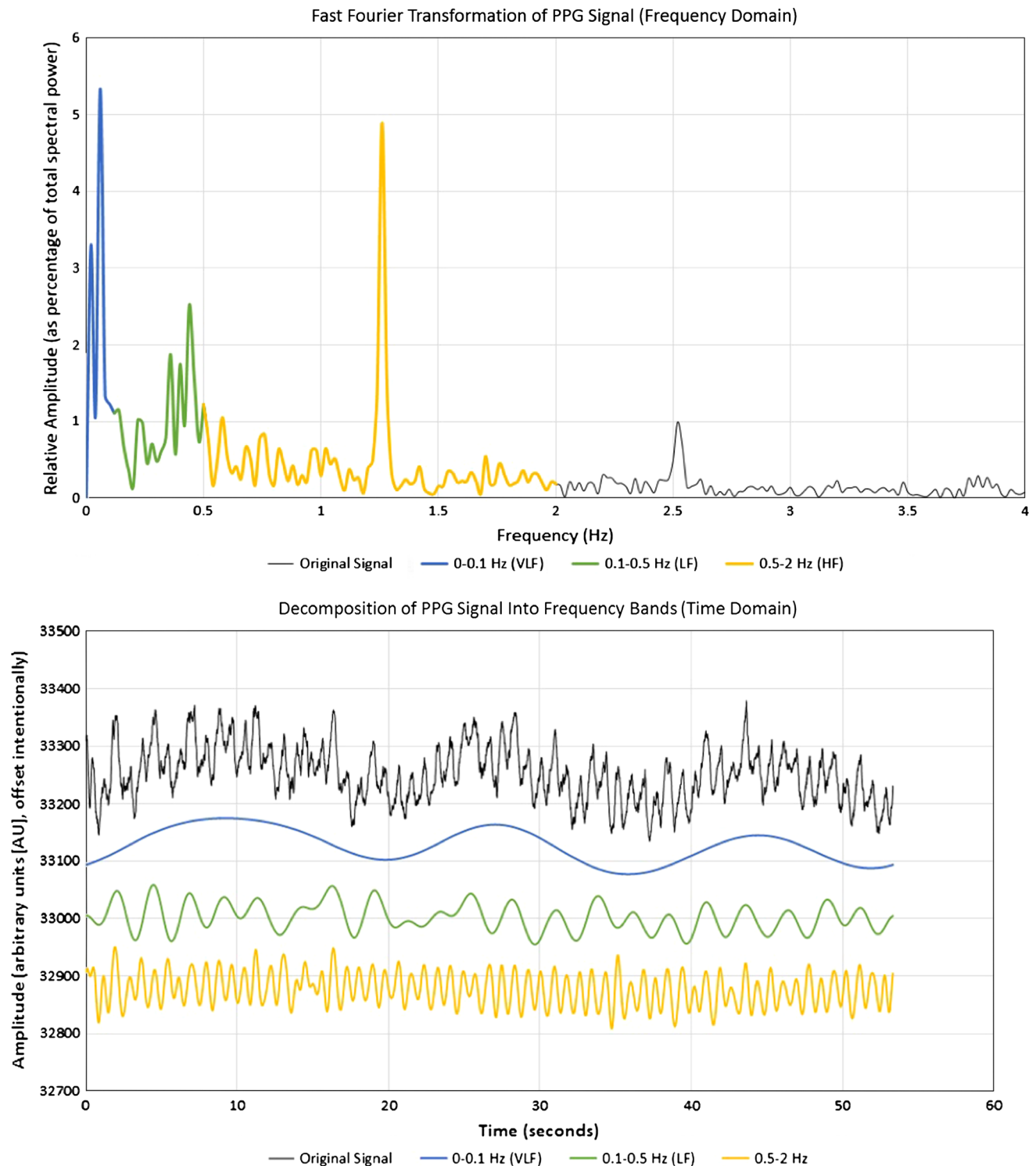


Fig. 3 Decomposition of a standard pulse oximetry signal into three bands: a very low frequency band (0-0.1 Hz), a low frequency band (0.1-0.5 Hz), and a pulsatile band (0.5-2 Hz)

Finapres device, the diastolic and mean pressures were found to be 9-10 mmHg lower in the finger compared with the brachial artery, whereas the systolic pressure in the finger was 7 mmHg higher on average than in the arm.⁹²

Given that about half of the measurements in this study were obtained in a state of *local* vasoconstriction (defined as a 50% reduction in the PPG amplitude), the authors concluded satisfactory performance of finger blood

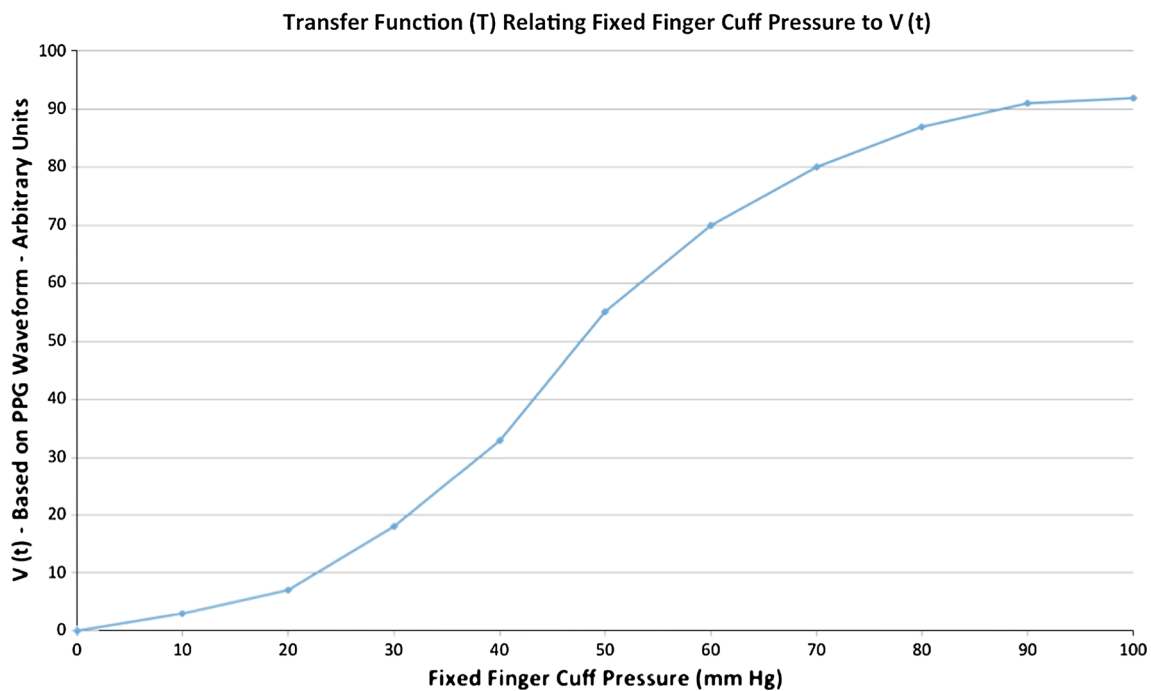


Fig. 4 Transfer function (T) showing the relationship between $v(t)$ and fixed pressures. The pressure at which the slope of the transfer function is steepest is used as the “set point” in the VERIFI algorithm

Table 1 Comparison between Nexfin / ClearSight™ and CNAP® technology. “Biometric calibration” refers to estimation of vascular impedance using patient characteristics such as age, gender, height, and weight

Characteristic	Nexfin / ClearSight™	CNAP®
Number of fingers used	1-2	2
Algorithm to account for changes in vasomotor tone	Physiocal	VERIFI
Algorithm for stroke volume estimation	Pulse contour analysis and biometric calibration	Pulse contour analysis using CNCO® algorithm and biometric or manual calibration

pressure measurements in this study. The PPG amplitude is widely accepted to reflect changes in *local* vasomotor tone;¹⁵ whether these changes translate to global changes in vascular resistance is discussed in the *Systemic vascular resistance* section, above.

Interestingly, finger arterial blood pressure measurements appear to be most accurate when obtained from a cuff placed on the thumb.⁹³ Conceivably, the slightly larger thumb arteries could be less affected by vasoconstriction than smaller finger arteries. Furthermore, measurements should be taken with the finger at the level of the heart to avoid introduction of hydrostatically induced error.⁹⁴ Many studies have compared the ability of Nexfin / ClearSight and CNAP technology to measure blood pressure with standard methods, most often with continuous blood pressure measurement using an arterial catheter (Table 2). While the majority of studies show

good agreement between different measurement standards, studies in hemodynamically unstable patients have sometimes been less favourable.

Clinical context

It is impossible for a noninvasive device to be *more* accurate than the gold standard, i.e., invasive arterial catheterization; thus, the crucial clinical question is how the accuracy of the volume-clamp devices compares with that of the current *noninvasive* standard, the NIBP cuff. While there is a lack of three-way comparisons of NIBP, volume-clamp devices, and arterial catheterization, Wax *et al.* retrospectively compared NIBP with arterial catheter readings from over 15,000 non-cardiac anesthetics in which both modalities were used. Their study results showed that the standard deviation of the difference between the two devices was approximately ± 12

Table 2 Comparison studies between blood pressure measured by Nexfin / ClearSight™ or CNAP® technology and other reference methods in humans

Nexfin / ClearSight™ study	Population	Comparator	Agreement
Eeftinck Schattenkerk 2009 ⁽¹¹⁶⁾	Supine volunteer test persons (<i>n</i> =104)	Riva-Rocci/Korotkoff (RRK)	Nexfin–RRK median IQR differences were 5.4 [–1.7–11.0] mmHg for SBP and –2.5 [–7.6–2.3] mmHg for SBP
Akkermans 2009 ⁽¹¹⁷⁾	Volunteer pregnant test persons (<i>n</i> =33)	Mercury sphygmomanometer	Mean (SD) differences were 2.3 (6.8) mmHg for SBP and 0.8 (6.3) mmHg for DBP
Stover 2009 ⁽¹¹⁸⁾	Critically ill patients (<i>n</i> =10)	Arterial catheter Pulmonary artery catheter	Correlation $r^2 = 0.67$ (MAP)
Martina 2010 ⁽¹¹⁹⁾	Patients with cardiopulmonary bypass (<i>n</i> =18)	Arterial catheter	During CPB, Nexfin NAP-IAP average (SD) difference was –1.3 (6.5) mmHg. Correlation r^2 values were 0.65–0.99 for individual patients.
Maggi 2010 ⁽¹²⁰⁾	Patients undergoing electrophysiology procedures (<i>n</i> =22)	Arterial catheter	Correlation coefficient 0.81
Hofhuizen 2010 ⁽¹²¹⁾	Pediatric patients undergoing congenital heart surgery (<i>n</i> =10)	Arterial catheter	Correlation coefficient: 0.98 (MAP)
Nowak 2011 ⁽¹²²⁾	Acutely ill emergency room patients (<i>n</i> =40)	Automated brachial cuff measurement	Correlation coefficients: 0.75 (DBP), 0.83 (SBP), 0.81 (MAP)
Martina 2012 ⁽⁹⁶⁾	Cardiac surgery patients (<i>n</i> =50)	Arterial catheter	Correlation coefficients were SBP 0.96 (0.91–0.98), DBP: 0.93 (0.87–0.96), MAP 0.96 (0.90–0.97)
Fischer 2012 ⁽¹²³⁾	Intensive care patients after cardiac surgery (<i>n</i> =50)	Arterial catheter	SPB $r^2=0.56$, DBP $r^2=0.61$, and MAP $r^2=0.77$
Garnier 2012 ⁽¹²⁴⁾	Pediatric patients admitted to intensive care (<i>n</i> =41)	Arterial catheter	Mean (SD) bias for SBP, MAP, and DBP estimated were –13.5 (13.4), –2.6 (7.7), and 0.2 (6.6) mmHg
Broch 2013 ⁽¹²⁵⁾	Patients undergoing coronary surgery (<i>n</i> =50)	Arterial catheter (radial and femoral)	Femoral MAP before CPB $r=0.64$, after CPB $r=0.57$. Radial MAP before CBP $r=0.53$, after CPB $r=0.54$.
Ameloot 2014 ⁽¹²⁶⁾	Critically ill patients (<i>n</i> =45)	Arterial catheter (PiCCO)	$r^2 = 0.88$ for MAP
Vos 2014 ⁽¹²⁷⁾	Elective general surgery patients (<i>n</i> =112)	Arterial catheter	Compared with MAP, invasive modified Bland–Altman analysis revealed a bias (SD) of 2 (9) mmHg. Percentage error was 22%.
Weiss 2014 ⁽⁹⁷⁾	Elective surgery patients (<i>n</i> =31)	Arterial catheter	Bias limits of agreement of arterial SBP variations were –0.5 mmHg (–31.2 to 30.2) and –9.4 mmHg (–31.3 to 12.6) from baseline to nadir and from baseline to peak, respectively.
CNAP® study Biais 2010 ⁽¹⁰³⁾	Major vascular surgery patients (<i>n</i> =25)	Arterial catheter	Bias and 95% limits of agreement were respectively 7.2 mmHg (–17.7 to 32.2) for SBP, –1.8 mmHg (–22.0 to 18.3) for MAP, and –7.5 mmHg (–27.3 to 12.4) for DBP
Jelezov 2010 ⁽⁹⁸⁾	Patients undergoing elective abdominal surgery, cardio-, or neurosurgery (<i>n</i> =88)	Arterial catheter	Limits of agreement were ± 17.6 mmHg (SBP), ± 11.4 mmHg (DBP), and ± 12.0 mmHg (MAP)
Schramm 2011 ⁽¹²⁸⁾	Patients undergoing transfemoral aortic valve implantation with sedation (<i>n</i> =29)	Arterial catheter	CNAP accuracy was –8.3, 6.4, and 0.6 mmHg in normotensive, –20.5, 4.4, and –5.5 mmHg in hypertensive, and –4.8, 9.4, and 4.5 mmHg in hypotensive conditions. The frequency of AP pairs with a difference of ± 15 mmHg (limits of agreement) or less was 59.5, 71.7, and 76.5% in normotensive, 33.1, 72.9, and 66.9% in hypertensive, and 59.5, 71.7, and 76.5% in hypotensive periods for SBP, DBP, and MAP, respectively

Table 2 continued

Nexfin / ClearSight™ study	Population	Comparator	Agreement
Ilies 2012 ⁽¹²⁹⁾	Patients under general anesthesia (<i>n</i> =85)	Arterial catheter	Mean (SD) bias during maintenance of anesthesia was: SBP: 4.2 (16.5) mmHg; MAP: -4.3 (10.4) mmHg; and DBP: -5.8 (6) mmHg. In patients with a MAP < 70 mmHg: SBP: -0.3 (9.7) mmHg; MAP: -6.8 (7.6) mmHg; and DBP: -7.9 (7.2) mmHg
Hahn 2012 ⁽¹⁰⁴⁾	Patients undergoing elective surgery with general anesthesia (<i>n</i> =100)	Arterial catheter	The mean (SD) bias of the MAP in the first 50 patients was -2.9 (10.6) mmHg, LOA -23.7 to 17.9. Following improvement of the CNAP software in the consecutive 50 patients, the mean (SD) bias was -3.1 (9.5) mmHg, LOA -21.6 to 15.4.
McCarthy 2012 ⁽¹⁰⁵⁾	Elective Cesarean delivery patients (<i>n</i> =59)	Intermittent oscillometric blood pressure measurement	Mean bias and limits of agreement (± 2 SD mean bias) for SBP, DBP, MAP respectively were +1.3 (± 26.0), -2.9 (± 21.8) and +2.6 (± 20.4) mmHg
Jagadeesh 2012 ⁽⁹⁹⁾	Cardiac surgical intensive care unit patients (<i>n</i> =30)	Arterial catheter	SBP bias was 10.415 mmHg; DBP bias was -5.3386 mmHg; MAP bias was 0.03944 mmHg. Percentage within limits of agreement was 94.5%, 95.1%, and 99.4% for SBP, DBP, and MAP, respectively. Calculated limits of agreement were -4.60 to 25.43, -13.38 to 2.70 and -5.95 to 6.03, respectively.
Gayat 2013 ⁽¹³⁰⁾	Patients undergoing surgery with general anesthesia (<i>n</i> =52)	Arterial catheter	Bias was 5 and -7 mmHg for peak and nadir SBP, with upper and lower limits of agreement of (42;-32) and (27;-42), respectively.
Kako 2013 ⁽¹³¹⁾	Surgical pediatric patients, weighing 20-40 kg (<i>n</i> =20)	Arterial catheter	Correlation coefficient was 0.48 (SBP), 0.60 (DBP), and 0.64 (MAP).
Dewhirst 2013 ⁽¹⁰⁰⁾	Pediatric patients undergoing surgery in the prone position (<i>n</i> =20)	Arterial catheter	MAP bias of 0.26 mmHg, with upper and lower limits of agreement of 12.18 to -11.67
Schramm 2013 ⁽¹⁰⁶⁾	Patients undergoing elective transfemoral aortic valve implantation under monitored anesthesia care (<i>n</i> =33)	Arterial catheter	Overall bias (SD) was -6.3 (18.9) SBP, 7.4 (10.5) DBP, and 4.0 (11.3) MAP mmHg. Bias increased during episodes of hypotension (rapid pacing) to 11.8 (14.5), 13.8 (12.4), and 12.9 (12.4) mmHg, respectively.
Tobias 2014 ⁽¹⁰¹⁾	Severely obese subjects undergoing weight loss surgery (<i>n</i> =18)	Arterial catheter	Correlation coefficient was 0.655 (SBP), 0.667 (DBP), and 0.783 (MAP) Precision and bias (SD) were 0.3 (14.2) mmHg (SBP), -1.3 (9.5) mmHg (DBP), and -0.6 (8.6) mmHg (MAP)
Ilies 2015 ⁽¹⁰²⁾	Cardiovascular surgical critical care patients (<i>n</i> =104)	Arterial catheter	Biases (SD) for all patients were 4.3 (11.6) mmHg (SDP), -9.4 (8) mmHg (DBP) and -6 (7.6) mmHg (MAP)
Kumar 2015 ⁽¹³²⁾	Cardiac surgery patients (<i>n</i> =60)	Arterial catheter	Bias was 5.98 mmHg (SBP), -3.72 mmHg (DBP), and -0.02 mmHg (MAP)
Wagner 2015 ⁽¹³³⁾	Intensive Care Unit patients (<i>n</i> =55)	Arterial catheter	Mean difference (SD), 95% limits of agreement, percentage error for MAP +1 (9) mmHg, -16 to 19, 22%; for SBP -10 (6) mmHg, -42 to 21, 27%; and for DBP +7 (9) mmHg, -10 to 24, 28%.

CPB = cardiopulmonary bypass; CNAP = continuous noninvasive arterial pressure; DBP = diastolic blood pressure; IAP = intra-arterial blood pressure; LOA = limits of agreement; MAP = mean arterial pressure; NAP-IAP = Nexfin arterial pressure-intra-arterial pressure; PiCCO = continuous pulse contour cardiac analysis; SBP = systolic blood pressure; IQR = interquartile range; SD (standard deviation)

mmHg at the mode (75 mmHg MAP).⁹⁵ While these authors did not calculate the limits of agreement, a rough estimate that does not take into account repeated measures suggests that the confidence intervals of standard NIBP are worse than those reported in a number of volume-clamp studies [e.g., Martina (Nexfin),⁹⁶ Weiss (Nexfin),⁹⁷ Jelezov (CNAP),⁹⁸ Jagadeesh (CNAP),⁹⁹ Dewhirst (CNAP),¹⁰⁰ Tobias (CNAP),¹⁰¹ and Ilies (CNAP)]¹⁰² but similar to those in other volume-clamp studies [Biais (CNAP),¹⁰³ Hahn (CNAP),¹⁰⁴ McCarthy 2012 (CNAP),¹⁰⁵ and Schramm (CNAP)].¹⁰⁶ At the extremes (significantly above or below a MAP of 75 mmHg), when accurate measurement of blood pressure is increasingly important, NIBP performance deteriorated.⁹⁵ It is important to point out that the retrospective nature of the Wax study precludes standardization of some important practice elements, e.g., location of transducer height. Thus, while the means by which volume-clamp devices perform in relation to NIBP has not been definitively answered, tentatively, it appears that there may be an advantage in terms of accuracy, and certainly the continuous nature of the measurements is desirable.

Measurement of stroke volume

Technologic principles

Newer generation devices that are based on volume-clamp technology, e.g., Nexfin / ClearSight and CNAP, use the PPG signal to determine the diameter of the finger arteries. As discussed above, a closed loop system utilizes this information to adjust the pressure of a finger cuff, thereby maintaining the artery in an “unstretched” state and permitting estimation of the finger arterial blood pressure through constant measurement of the finger cuff pressure.⁸³ Blood pressure can thereby be measured continuously, and the resultant curve can be used for pulse contour analysis.¹⁰⁷

Briefly, most pulse contour analyses are based on the Windkessel model of blood flow developed by Frank.¹⁰⁸ The aorta represents a capacitor - storing blood ejected during systole - whereas the arterioles represent a resistor for blood ejected into the arterial system. A detailed discussion of arterial waveform analysis is beyond the scope of this review, but for more information, we refer the reader to a recent review focused on the physiologic basis of these algorithms.¹⁰⁹ Bear in mind that, in uncalibrated devices, aortic impedance is estimated based on characteristics such as height, weight, and age. In general, stroke volume can be estimated by the following equation:

$$SV = k \times P (1 + A_s / A_d)$$

Equation 3: Stroke volume calculation based on arterial pressure waveform analysis. With SV = stroke volume, k = constant, P = estimate of pressure, A_s = v area under the pressure curve during systole, A_d = area under the pressure curve during diastole

Limitations and clinical data

A comparison of cardiac output measurements in patients following cardiac surgery was performed before and after fluid challenge using the Nexfin device vs thermodilution cardiac output measurement via a Swan-Ganz catheter.¹¹⁰ On the basis of 47 paired measurements in 22 patients, a correlation coefficient of 0.71 before and 0.70 after fluid challenge was described. This correlated with an average change in cardiac output from 4.9 to 5.6 L·min⁻¹ for the Swan-Ganz and from 5.0 to 5.6 L·min⁻¹ for the Nexfin device. The authors concluded that the Nexfin device can reliably detect cardiac output changes after fluid challenge. Other studies have also reported favourably on the Nexfin's ability to measure cardiac output accurately, e.g., compared with rebreathing methods,¹¹¹ or with transthoracic Doppler.¹¹² These results contrast with other studies that reported far inferior performance of the Nexfin device when comparing the noninvasively derived cardiac output measurements with thermodilution in critically ill patients^{113,114} and cardiac ultrasound.¹¹⁵

It is important to point out that, relative to other noninvasive cardiac output devices (e.g., over 3,000 patients in 16 studies comparing the FloTrac [uncalibrated] with thermodilution, over 1,400 patients in nine studies comparing the PiCCO [calibrated] with thermodilution, and almost 400 patients in three studies comparing the LiDCO [calibrated] with thermodilution),¹⁰⁷ there are very few data comparing volume-clamp-based estimates of SV or cardiac output with gold standards. Additionally, volume-clamp-based devices cannot possibly perform better than arterial-based devices, because they use the same algorithms to estimate stroke volume but apply them to an estimate of the arterial waveform (not the true waveform). Thus, the relatively poor performance of arterial waveform analysis, in particular for uncalibrated devices, against clinical standards suggests that accurate measurement of stroke volume will be a challenge for this class of device.¹⁰⁷

Summary

Photoplethysmography offers the clinician more than just a determination of oxygenation status and heart rate.

Respiratory variation of the PPG waveform mirrors respiratory variation of the arterial pressure waveform and can be used to gauge volume responsiveness. The volume-clamp technique pioneered by Peñáz, expanded by Wesseling, and now improved with the physioal and VERIFI algorithms, permits continuous noninvasive measurement of arterial blood pressure with accuracy that is likely intermediate between NIBP and invasive catheters. Noninvasively derived arterial pressure waveforms can be used to estimate cardiac output but appear to lose accuracy in critically ill patients. While the value of packaged interventions that include noninvasive means to guide fluid therapy has been shown, additional investigations are required to determine if these devices alone can provide any meaningful improvement in outcome.

Key points

- In addition to peripheral arterial oxygenation, photoplethysmography can provide clinically useful information such as fluid responsiveness;
- Photoplethysmography in combination with the volume clamp and the physioal technique permits blood pressure and cardiac output measurements. These measurements of blood pressure are likely more accurate than sphygmomanometric measurements but less accurate than the invasive gold standards;
- The majority of data suggest that volume-clamp devices may be more accurate than noninvasive blood pressure for the measurement of mean arterial pressure; however, this question will not be answered definitively until three-way comparisons are made;
- It remains to be seen whether the expanded technical capabilities of these devices can be translated into improved clinical outcomes for patients.

Conflicts of interest None declared.

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