Peripheral Perfusion Index as an Early Predictor for Central Hypovolemia in Awake Healthy Volunteers

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BACKGROUND: In healthy volunteers, we investigated the ability of the pulse oximeter–derived peripheral perfusion index (PPI) to detect progressive reductions in central blood volume.
METHODS: Twenty-five awake, spontaneously breathing, healthy male volunteers were subjected to progressive reductions in central blood volume by inducing stepwise lower body negative pressure (LBNP) with 20 mm Hg for 5 minutes per step, from 0 to −20, −40, −60, and back to 0 mm Hg. Throughout the procedure, stroke volume (SV), heart rate (HR), and mean arterial blood pressure were recorded using volume-clamp finger plethysmography. Assessment of the PPI was done by pulse oximetry. Additionally, the forearm-to-fingertip skin-temperature gradient was measured. Data are presented as mean ± SE. PPI underwent log transformation and is presented as median (25th–75th).
RESULTS: Of the 25 subjects, one did not complete the study because of cardiovascular collapse. After the first LBNP step (−20 mm Hg), PPI decreased from 2.2 (1.6–3.3) to 1.2 (0.8–1.6) ($P = 0.007$) and SV decreased from 116 ± 3.0 mL to 104 ± 2.6 mL ($P = 0.02$). The magnitude of the PPI decrease (41% ± 6.0%) was statistically different from that observed for SV (9% ± 1.3%) and HR (3% ± 1.9%). During progression of LBNP, SV decreased and HR increased progressively with the increased applied negative pressure, whereas the PPI remained low throughout the remainder of the protocol and returned to baseline values when LBNP was released. At −60 mm Hg LBNP, SV decreased and HR increased by 36% ± 0.9 % and 33% ± 2.4% from baseline, respectively. Mean arterial blood pressure remained in the same range throughout the experiment.
CONCLUSIONS: These results indicate that the pulse oximeter–derived PPI may be a valuable adjunct diagnostic tool to detect early clinically significant central hypovolemia, before the onset of cardiovascular decompensation in healthy volunteers. (Anesth Analg 2013;116:351–6)

Peripheral vasoconstriction is an early warning sign of circulatory shock in critically ill patients, when blood flow is diverted from less important tissues to maintain vital organ perfusion at the cost of peripheral circulation.[1,2] Because sympathetic neuroactivity predominates in the skin and muscle, the sympathetic neurohumoral response–induced vasoconstriction manifests primarily as decreased peripheral perfusion.[3,4] Unfortunately, standard physiologic measurements, such as mean arterial blood pressure (MAP), are poor indicators for the early assessment of shock.[5] Even standard examinations of mental status, pulse character, and heart rate (HR) provide late information about the severity of blood loss. Subsequently, the appearance of hypotension and other signs of shock do not mark the beginning of circulatory shock but rather represent the beginning of cardiovascular decompensation and do not allow for early intervention.[6] Therefore, a more practical and convenient method to detect early circulatory shock is needed.

The peripheral perfusion index (PPI), derived from the photoelectric plethysmographic signal of the pulse oximeter, is able to monitor vascular reactivity in adult critically ill patients.[2,7] Additionally, the PPI has been suggested to be a useful noninvasive method for the assessment of peripheral vasomotor tone in healthy volunteers, neonates, and critically ill patients.[2,8] This index is calculated as the ratio between the pulsatile component (arterial compartment) and the nonpulsatile component (venous and capillary blood and other tissues) of the light reaching the detector of the pulse oximeter. Therefore, peripheral vasoconstriction, mainly reducing the pulsatile component, directly affects the ratio and thus decreases the PPI.[9] Because a pulse oximeter is universally available in the operating room, emergency room, and intensive care unit, it could potentially be useful for the early detection of peripheral hypoperfusion in response to reductions in central blood volume in these settings.

In the present study, we investigated changes in PPI as an early marker of peripheral vasoconstriction induced by changes in central circulating volume, and hypothesized that PPI could be used for early detection of hypovolemia, before changes in conventional hemodynamic variables occur. To test this, we used a model of controlled central hypovolemia in healthy male volunteers by applying lower body negative pressure (LBNP). During application of LBNP, the circulating volume is progressively redistributed from the upper to the lower body, inducing

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central hypovolemia, which triggers similar compensatory mechanisms as during acute hemorrhage and clinical hypovolemia.[10] Using this approach, we were able to study the potential use of PPI during progressive reductions in central blood volume and determine whether changes in this index precede changes in frequently monitored vital signs.

METHODS

Subjects

This study was conducted in a research laboratory at a university-affiliated teaching hospital. We recruited 25 awake, spontaneously breathing, healthy male volunteers without history of cardiac events nor receiving any vasoactive medication. To minimize potential confounding factors to different LBNP tolerances, all volunteers underwent an exercise electrocardiogram to determine equal physical fitness.[11] The volunteers were instructed not to consume caffeine-containing drinks or practice intensive exercise ≤12 hours before the experiments, but fluid intake was not standardized or regulated. The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam, and written informed consent was obtained from all subjects.

Measurements

Subjects were placed with their lower body in an air-tight chamber with a seal applied at the level of the iliac crests. The amount of negative pressure within the chamber could be manually adjusted using a variable vacuum source. Baseline recordings were made after a 10-minute stabilization period before LBNP application. LBNP was applied progressively in a 5-minute stepwise manner from 0 to −20, −40, and −60 mm Hg, followed by a second baseline measurement of 0 mm Hg 10 minutes after the last LBNP step. Data were gathered at the completion of every 5-minute LBNP step when the PPI signal was adequate and subjects were hemodynamically stable. In this regard, the different LBNPs simulate different levels of beginning hypovolemia and can be categorized as "mild" (−10 to −20 mm Hg, corresponding with 400–550 mL blood loss), "moderate" (−30 to −40 mm Hg, corresponding with 500–1000 mL blood loss), and "severe" (−40 to −60 mm Hg, corresponding with >1000 mL blood loss).[10,11] The LBNP protocol was immediately terminated if the subject developed presyncope, which was defined as a decrease in systolic blood pressure of >15 mm Hg from baseline, or if the subject experienced symptoms of impending syncope such as dizziness, light-headedness, nausea, sweating, or visual disturbances.

Global Hemodynamic Parameters

MAP, HR, and stroke volume (SV) were continuously and noninvasively measured using volume-clamp plethysmography (Nexfin; BMEYE, Amsterdam, The Netherlands) with the cuff placed around the left index finger. The Nexfin device is extensively described elsewhere and is validated technically to measure hemodynamic variables.[12,13] In brief, this method applies variable pressure in an inflatable cuff around the finger, countering the pulsatile arterial pressure. An optical plethysmograph placed in this cuff measures arterial volume and a calibration system determines the volume at which the artery is unloaded (i.e., when transmural pressure equals zero and no interference of the arterial wall occurs). Because brachial and finger arterial pressure are physiologically different, waveform transformation and correction are applied in order to reconstruct brachial arterial pressure.

Peripheral Perfusion Index

The PPI is derived from the photoelectric plethysmographic signal of the pulse oximeter Masimo SET Radical-7 (Masimo Corp., Irvine, CA). The adhesive sensor was attached onto the right index finger (Masimo SET® LNCS Adtx, adult sensor).[7] This index signal has been used as a noninvasive measurement of peripheral perfusion in critically ill patients.[2] The technique is based on 2 light sources that emit light at wavelengths of 660 and 940 nm through the cutaneous vascular bed of the distal side of the index finger. Because other tissues, such as connective tissue, bone, and venous blood, also absorb light, the pulse oximeter distinguishes the pulsatile component of arterial blood from the nonpulsatile component of venous and capillary blood, and other tissues. Using a 2-wavelength system, the nonpulsatile component is then discarded and the pulsatile component is used to calculate the arterial oxygen saturation (Spo_2). The PPI is calculated as the ratio between the amplitude of the pulsatile component (arterial compartment) and the nonpulsatile component (venous and capillary blood, and other tissues) of the light reaching the detector of the pulse oximeter. This ratio is independent of the hemoglobin oxygen saturation. Because a change in peripheral vasomotor tone primarily causes a corresponding change in the pulsatile component of the signal, the ratio changes accordingly. As a result, the PPI value reflects changes in peripheral vasomotor tone, with a median value of 1.4 for normality in healthy volunteers.[2] Simultaneously Spo_2 values were recorded.

Skin Temperature

We obtained the peripheral skin-temperature gradient (*T*skin-diff) from 2 skin probes (Hewlett Packard 21078A, Palo Alto, CA) attached to the right ring finger and to the radial side of the forearm, midway between the elbow and the wrist. At constant environmental conditions, *T*skin-diff increases during vasoconstriction and thereby provides a better measurement of peripheral vasomotor tone compared with only the local skin temperature. The ambient temperature was therefore actively set at 22°C during the entire protocol. Basically, when vasoconstriction decreases fingertip blood flow, finger skin-temperature decreases, and *T*skin-diff increases. This temperature gradient was previously validated as an independent measurement of peripheral perfusion.[14]

Statistics

Unless otherwise specified, data are presented as mean ± SE. For statistical analysis, the different LBNP levels (0, −20, −40, −60, and 0 mm Hg) were plotted as points over time. Accordingly, HR, MAP, SV, *T*skin-diff, and PPI were plotted versus the level of LBNP. PPI underwent log-transformation (Kolmogorov-Smirnov test $P < 0.05$) to achieve close to normal distribution and then qualified for longitudinal testing. Assuming equal variances and the same correlation

between measures for all variables (Mauchly criterion "test for sphericity" not significant), statistical significance of differences between the progressive LBNP levels was explored using repeated-measures analysis of variance with a Bonferroni correction for multiple comparisons. Changes from baseline were computed dividing the parameter value at specific time points into the baseline value and was expressed as percentile changes (% of baseline × 100). We compared the magnitude of changes among PPI, SV, and HR at specific time points and differences were tested with the use of Mann-Whitney test for unpaired data. In case of cardiovascular collapse, data were excluded from the repeated-measurements analysis. We used SPSS software (version 20.0; SPSS Inc., Chicago, IL) for statistical analysis. $P < 0.05$ was regarded as statistically significant.

RESULTS

Of the 25 male subjects recruited, one did not complete the study because of cardiovascular collapse and was excluded from further analysis, but the results of this excluded subject are presented and discussed below. The mean ± SD of age, weight, and height of the remaining 24 subjects were 23 ± 6 years, 82 ± 2 kg, and 182 ± 1 cm, respectively.

Baseline values for global hemodynamic variables, PPI, and *T*skin-diff stratified by the progressive LBNP levels are presented in Table 1. The mean PPI decreased substantially from baseline during the onset of mild central hypovolemia (i.e., LBNP −20 mm Hg) and remained in the same range during the remainder of the experiment (Fig. 1). SV progressively decreased and HR progressively increased in an opposite manner to the level of negative pressure in the chamber. On average, the magnitude of PPI decreasing (41% ± 6.0%) in the first LBNP step was statistically different from that observed for SV (9% ± 1.3%) and HR (3% ± 1.9%) (Fig.1). Progressive hypovolemia (i.e., LBNP = −60 mm Hg) resulted in a mean decrease in SV of 36% ± 0.9 % from baseline and a mean increase in HR of 33% ± 2.4% from baseline. MAP did not change significantly during progressive LBNP exposure (Table 1). Accordingly, *T*skin-diff and Spo_2 remained unchanged during the LBNP protocol (Table 1). Upon cessation of LBNP, all systemic hemodynamic variables and PPI returned to baseline values (Fig. 1, Table 1).

Figure 2A shows HR, SV, and PPI in the subject who experienced cardiovascular collapse during LBNP. Figure 2B shows a representative subject with a normal response. The subject who experienced cardiovascular collapse started with a low PPI (approximately 1) and displayed a lack of appropriate sympathetic baroreflex activation as reflected by an absence of an increase in HR, despite a significant decrease in SV. Directly after the start of −60 mm Hg LBNP, this volunteer already had signs of nausea and dizziness, which were followed by signs of impending cardiovascular collapse with a further decrease in SV from 82 to 57 mL, and concomitant decreases in HR from 76 to 56 bpm, systolic blood pressure from 136 to 97 mm Hg, diastolic blood pressure from 83 to 68 mm Hg, and a decrease in MAP from 88 to 63 mm Hg. Paradoxically, his PPI increased from 2.1 to 8.4 (suggesting vasodilation), simultaneous to the development of clammy skin. Thereafter, decompression was immediately initiated, followed by discontinuance of the protocol. During this collapse, *T*skin-diff did not change.

DISCUSSION

We induced progressive central hypovolemia by controlled application of LBNP and studied changes in PPI. We found that PPI changed significantly with the onset of mild hypovolemia, and may have reflected induced compensatory peripheral vasoconstriction. In addition, PPI changed earlier than the peripheral *T*skin-diff, suggesting that PPI may be a useful early indicator of mild central hypovolemia in an acute setting.

Early detection of hypovolemia is of key importance in the management of circulatory shock. Circulatory changes

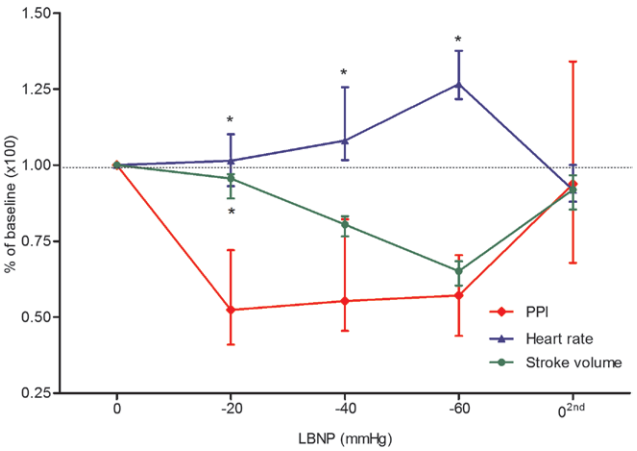

Figure 1. Peripheral perfusion index (PPI) (red line), heart rate (blue line), and stroke volume (green line) plotted as proportional changes from baseline during progressive application of lower body negative pressure (LBNP) from 0 to −60 mm Hg and back to 0 mm Hg. Bars represent mean ± 95% confidence interval ($n = 24$). Changes in PPI were statistically different from those observed for stroke volume and heart rate (*$P < 0.05$ versus PPI, by Mann-Whitney test).

Table 1. Descriptive Analysis

	LBNP level				
	0 mm Hg	−20 mm Hg	−40 mm Hg	−60 mm Hg	0 mm Hg(2nd)
Heart rate (bpm)	63 ± 1.8	64 ± 1.5	72 ± 1.5*	83 ± 2.0*	59 ± 1.7
Mean arterial blood pressure (mm Hg)	89 ± 1.8	92 ± 1.8	90 ± 1.4	86 ± 1.7	90 vs 1.5
Stroke volume (mL)	116 ± 3.0	104 ± 2.6*	91 ± 2.4*	74 ± 2.1*	112 ± 2.1
*T*skin-diff (°C)	0.0 ± 0.2	−0.1 ± 0.3	0.1 ± 0.2	0.9 ± 0.2	0.0 ± 0.3
PPI (a.u.)	2.2 (1.6–3.3)	1.2* (0.8–1.6)	1.2* (0.9–1.8)	1.3* (0.9–1.7)	2.2 (1.4–3.4)

Data are presented as mean ± SE and median (25th–75th) for PPI.

Systemic hemodynamic variables, skin-temperature difference between finger and forearm (*T*skin-diff), and peripheral perfusion index (PPI) during progressive application of lower body negative pressure (LBNP) from 0 to −60 mm Hg and back to 0 mm Hg(2nd).

*$P < 0.05$, vs LBNP = 0 mm Hg.

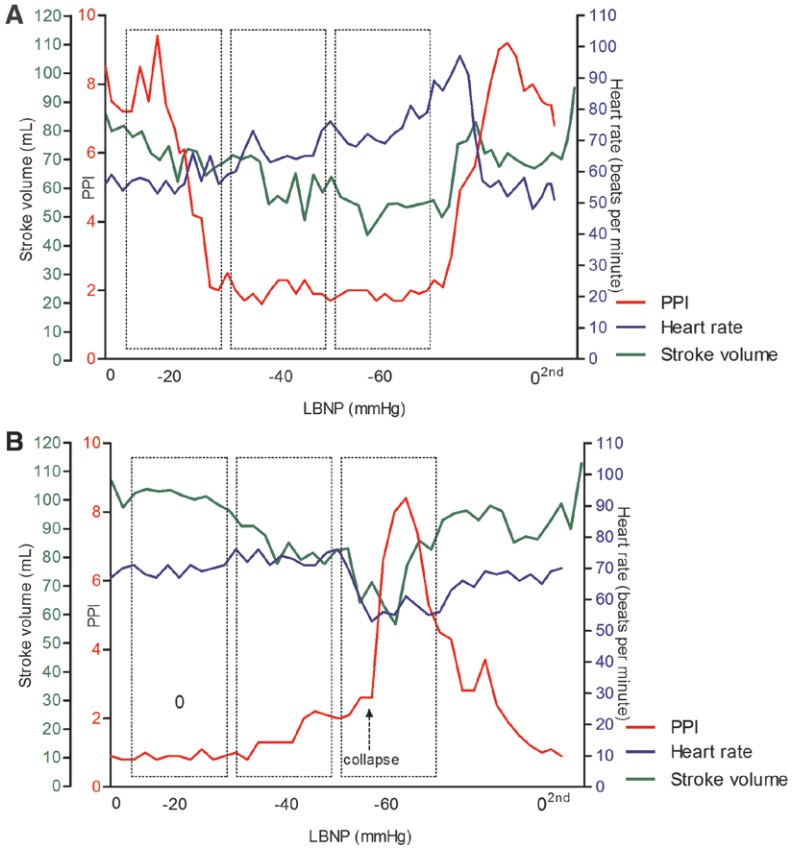

Figure 2. Heart rate, stroke volume, and peripheral perfusion index (PPI) during the application of lower body negative pressure (LBNP). A, Representative subject with a normal response. B, Subject who experienced cardiovascular collapse during progressive LBNP. The subject who experienced cardiovascular collapse displayed a remarkably low PPI at baseline, indicative of peripheral vasoconstriction well before the application of LBNP. Subsequently, with progressive stroke-volume reduction, collapse occurred with a simultaneous decrease in heart rate and sudden increase in the PPI. LBNP was released immediately, leading to the subject's recovery and return to baseline levels (0^{2nd}) of heart rate, stroke volume, and PPI.

during LBNP resemble hemodynamic responses similar to those reported during acute hemorrhage, such as tachycardia and reductions in SV as result of a neurohumoral response.[3,10] However, physiologic compensatory factors, such as increased HR, limit the use of blood pressure and cardiac output as indicators for mild central hypovolemia in the early setting.[6] Thus, hypotension is a late marker of hypoperfusion, and almost 30% of circulating volume may already be lost before hypotension occurs.[15] Therefore, recognizing hemodynamic instability before this point is of prime importance in the prevention of hypoperfusion-induced organ failure.

To this end, monitoring the early compensatory mechanisms that act on the peripheral circulation might provide a better indication of the onset of compensated shock than systemic hemodynamic variables.[16] PPI is able to reflect rapid changes in the peripheral vascular diameter.[7] We chose the LBNP model to test our hypothesis, because previous studies, including those of our own group, have shown that peripheral vasoconstriction is a frequent abnormality in peripheral perfusion of critically ill patients, and its persistence has been associated with increased lactate levels and organ failure.[2] Moreover, PPI has been linked to HR and the abdominal flank-to-forearm skin-temperature gradient, particularly in neonates.[17] The marked decrease in PPI in our model provides evidence that PPI can be used to detect changes in peripheral vasomotor tone as an additional tool for hemodynamic monitoring. Our study expands these observations with the demonstration that PPI decreases well before the onset of cardiovascular instability. Thus, PPI seems to provide an early and continuous indication of central hypovolemia during preshock hemorrhage when arterial blood pressure and HR remain within clinically normal levels.

Except for the volunteer who collapsed, MAP was maintained around baseline levels during the entire protocol, which indicated adequate compensation of the reduced circulating volume. It should be noted, however, that PPI did not decrease further during progression of hypovolemia and did not differentiate between mild hypovolemia and progressive hypovolemia, which might be of vital importance for follow-up and resuscitation. It is important to note that there is no direct causal relation implied between hypovolemia and PPI. We demonstrated that PPI reflects the condition of peripheral vasomotor tone, such as hypovolemia-induced peripheral vasoconstriction, but one cannot predict hypovolemia looking at a single PPI value. Instead, one should look at the physiologic behavior of PPI as a marker of variations in peripheral vasomotor tone. Although changes in the PPI preceded significative changes in HR, our data demonstrate that measuring PPI together with HR can be a more elegant noninvasive technique to detect the onset of hypovolemia, and therefore can reflect hemodynamic instability earlier than arterial blood pressure. In this regard, the development of an algorithm capable of providing changes in the PPI together with HR could provide a valuable clinical tool for the early detection of hemodynamic instability in trauma and intensive care patients.

Interestingly, the subject who experienced cardiovascular collapse was already vasoconstricted at baseline

(Fig. 2A). At the beginning of −60 mm Hg, his HR suddenly decreased followed by a rapid increase in PPI (vasodilation) and the actual collapse. Apparently, loss of sympathetic tone resulted in a simultaneous decrease in HR and a decrease in peripheral vasomotor tone, leading to low cardiac output and cardiovascular collapse. This observation emphasizes the value of the PPI as a monitor of sympathetic activity. Previous studies demonstrated the phenomenon of paradoxic vasodilation in patients with depressed baroreceptor unloading[18] and congestive heart failure[19] during mild central hypovolemia induced by LBNP. Cardiovascular collapse becomes imminent when sympathetic activity decreases or vagal tone increases and cardiac chronotropic and peripheral vasoconstrictive mechanisms can no longer adequately compensate for progressive hypovolemia, resulting in reduced HR and vasodilation that occur at, or before, the onset of cardiovascular collapse.[3,20]

Although *T*skin-diff is associated with vasoconstriction, and is an independent indicator of peripheral blood flow,[14] we found that changes in PPI occurred earlier than changes in the *T*skin-diff. Because PPI is based on the photoelectric plethysmographic signal of the pulse oximeter, it can reflect real-time changes in the peripheral vasomotor tone, and therefore peripheral blood flow. In contrast, it takes much more time for the skin temperature to decrease as a result of peripheral vasoconstriction. This explains why the skin-temperature gradient takes longer to reflect variations in peripheral blood flow. PPI may therefore be more suitable as an early indicator of acute changes in peripheral vasomotor tone in response to changes in central blood volume.

During hemorrhage, vasoconstriction is heterogeneous throughout the body, predominantly affecting peripheral skin and muscle and splanchnic circulation, to redirect blood flow to the heart and brain.[21–23] As previously proposed by Lima et al., changes in peripheral circulation in critically ill patients can be reflected by changes in PPI.[2] By using PPI in such a way, and in combination with HR, it can be used as a complementary hemodynamic monitoring technique for the early detection of conditions that can trigger variations in peripheral circulation secondary to hemodynamic instability in trauma and intensive care patients.

This study has some limitations that should be acknowledged. First, although volume redistributions with LBNP are similar to those that occur during hemorrhage, we did not induce severe hypovolemia or hypovolemic shock. Nevertheless, the LBNP model of moderate hypovolemia provides an excellent opportunity to collect physiologic data on healthy human subjects, without confounding factors such as tissue injury, anesthesia, or hypothermia. Hence, we were interested in the ability of PPI to indicate the onset of clinically significant central hypovolemia. This was clearly demonstrated, as changes in PPI occurred before systemic hemodynamic changes. Our results may be the first to strictly reflect the relationship between reduced central blood volume and PPI in humans. Second, PPI changes as local vasomotor tone changes. Vasomotor tone is not only influenced by sympathetic activity due to hypovolemia and hypotension but also due to pain, emotional stress, or local conditions such as hypothermia. Such external factors should be considered when interpreting the PPI. Furthermore, our study involved awake, young, healthy subjects, which might not exactly mimic physiologic responses in older, ill patients, especially under general anesthesia. Third, we used a commercial pulse oximeter system with the Masimo SET software incorporated to derive the PPI. The sensors in such systems are not without limitations, and pulse oximeter–derived PPI can be affected by incorrect sensor placement and motion artifacts. Last, we did not measure MAP and SV with invasive methods such as an arterial or pulmonary artery catheter, but instead used the noninvasive Nexfin device. Although the Nexfin has been validated previously[12] and was shown to provide accurate measurements of MAP and SV during a LBNP protocol,[24] it still might lead to inaccuracies when compared with conventional techniques that are frequently used in the clinical setting.[25]

In conclusion, the pulse oximeter–derived PPI may be a valuable adjunct to systemic monitoring to detect acute hemodynamic responses to central hypovolemia, even before the onset of cardiovascular decompensation. Because the pulse oximeter is used extensively in many different clinical environments, the PPI can be easily obtained and can be used as a complementary hemodynamic monitor for the early detection of hemodynamic instability in trauma and intensive care patients.

DISCLOSURES

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