

# Noninvasive continuous arterial pressure measurements in the assessment of acute, severe central hypovolemia

J Simon<sup>1</sup>, T Farkas<sup>1</sup>, Z Gingl<sup>2</sup>, A Csillik<sup>1</sup>, A Korsós<sup>1</sup>, L Rudas<sup>1</sup>, É Zöllei<sup>1</sup>

<sup>1</sup>Department of Anesthesiology and Intensive Care, University of Szeged, Szeged, Hungary

<sup>2</sup>Department of Technical Informatics, University of Szeged, Szeged, Hungary

Received: July 19, 2013

Accepted after revision: August 21, 2014

Acute, severe hypovolemia is a medical emergency. Traditional vital sign parameters allow no optimal triage. High predictive power of finger plethysmography-based stroke volume (SV) and pulse pressure (PP) was recently suggested. To assess the performance of the PP and SV parameters, lower body negative pressure of –40 mmHg, than –60 mmHg – corresponding to moderate and severe central hypovolemia – was applied in 22 healthy males (age  $35 \pm 7$  years). Slow breathing induced fluctuations in the above indices, characterized by stroke volume variability (SVV), and pulse pressure variability (PPV), were assessed. Responses in heart rate (HR) and shock index (SI) were also studied. Discriminative capacity of these parameters was characterized by the area under the ROC (receiver operating characteristic) curves (AUC). *Results:* In comparison of baseline to severe central hypovolemia SV, PP, HR and SI showed good discriminating capacity (AUC 99%, 88%, 87% and 93%, respectively). The discriminating capacity of SVV and PPV was poor (77% and 70%, respectively). In comparison of moderate and severe hypovolemia, the discriminating capacity of the studied parameters was uniformly limited. *Conclusions:* Plethysmography-based SV and PP parameters can be used to detect acute severe volume loss. Sensitive parameters discriminating moderate and severe central hypovolemia are still lacking.

**Keywords:** noninvasive finger blood pressure monitoring, pulse pressure, stroke volume, central hypovolemia

Acute hypovolemia due to severe hemorrhage is a leading cause of death in combat field injury as well as in civilian trauma (12, 25). Among the casualties, those, who are critically ill and those with minimal injuries, might be easily recognized. An intermediate group of patients, who show no alarming symptoms on presentation, however, do deteriorate later, represents a real diagnostic challenge. Traditional vital sign parameters are not sensitive enough for reliable classification (7). Refinement of the traditional tools, as well as search for new parameters, is badly needed (2).

In clinical research severe hypovolemia is often modelled by lower body negative pressure (LBNP) (2, 3, 9, 28). This type of volume loss, induced by redistribution of the blood into the lower body parts is referred to as “LBNP-induced central hypovolemia”. It has been concluded that LBNP between 20 and 40 mmHg corresponds to moderate (500–1000 ml), and LBNP of 40–60 mmHg corresponds to severe (>1000 ml) acute volume loss (9). The LBNP studies defined the hemodynamic responses to volume loss, and shed light on the underlying neuro-humoral adaptation (3, 4, 17, 20, 28). While providing valuable physiological information, many of the studied parameters are unsuited for everyday clinical practice. Recently, however, the importance of a long known, simple parameter, i.e.

---

Corresponding author: Prof. Dr. László Rudas

Department of Anesthesiology and Intensive Care, Faculty of Medicine, University of Szeged

Korányi fasor 7, H-6720 Szeged, Hungary

E-mail: rudas@icare.szote.u-szeged.hu

pulse pressure was reemphasized (4). Another important development is, that continuous noninvasive arterial pressure monitoring, based on the Peñáz-principle, has gained acceptance in emergency medicine (16). As a consequence, a further parameter, the stroke volume – as it is derived from the blood pressure signal – may also enter the practice of emergency care (20). In real life scenarios preload challenges (mostly postural manoeuvres), are often used to manifest latent hypovolemia (1, 13). Deep, patterned breathing could be regarded as one of these challenges (19). For this latter test, the monitored parameter, which reflects the preload changes, could be arterial pressure, stroke volume, diameter of the great veins, or aortic flow. It is, however, generally accepted that breathing based “dynamic preload assessment” requires positive pressure ventilation, with large tidal volumes (11, 22, 24, 27). At the time of the first medical contact with civilian and combat casualties, however, many victims require no positive pressure ventilation. These patients, on the other hand, may follow a slow, paced breathing pattern. The goal of our study therefore was to reassess the diagnostic strength of noninvasive arterial pressure monitoring in combination with deep, slow, controlled respiration in situation of simulated severe acute volume loss.

## Materials and Methods

### *Subjects*

Twenty-two male volunteers were recruited from the medical staff our departments. Their mean age was  $35 \pm 7$  years (range 23–53 years). Only subjects with no known cardiovascular disease, or neuropathy were considered. The experiments were performed in our well-tempered laboratory, on the morning hours. Subjects were instructed to refrain from caffeine containing beverages on the day of the study. All volunteers received a verbal briefing and a written description of the procedures, and were made familiar with the laboratory, and the equipment. The study was approved by the local Ethics Board of the university, and participants gave their written consents to the investigations.

### *Experimental design*

On the day of the studies, the subjects assumed supine position in the airtight chamber, up to the level of their iliac crests. Subjects were instructed not to contract their leg muscles at any time of the study. The chamber was connected to a vacuum source, capable of generating rapid decompressions up to the range of  $-80$  mmHg. After about 20 minutes of adaptation to supine rest, the first period of patterned breathing with the frequency of 6/min was initiated and 3-minute segments of noise-free recordings were taken. Chamber decompression at  $-40$  mmHg was then started. Three-to-four minutes were used to allow the subjects to reach a steady-state status, during this period the subjects' respiration was not controlled. Subsequently, the 3-minute period of patterned breathing was repeated. The whole sequence with adaptation and metronomic breathing was then repeated with chamber decompression pressure of  $-60$  mmHg (Fig. 1).

---

### Abbreviations

HR: heart rate  
SV: stroke volume  
SAP: systolic arterial pressure  
DAP: diastolic arterial pressure

MAP: mean arterial pressure  
SI: shock index  
PPV: pulse pressure variability  
SVV: stroke volume variability

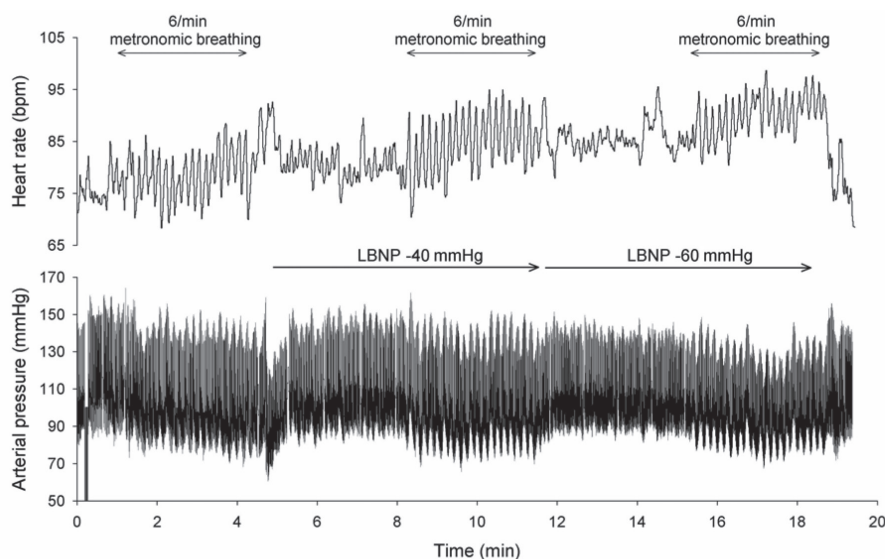


Fig. 1. Hemodynamic recordings of a volunteer at baseline, and during graded lower body negative pressure test

#### *Heart rate, blood pressure and stroke volume*

Arterial pressure was monitored by noninvasive finger plethysmography (Finapres 2300, Ohmeda). A Marquette Eagle bedside monitor served for continuous ECG recording. All signals were digitized at 500 Hz by the Dataq/WinDAQ system. The analysis was performed offline using the WinCPRS software package (Absolute Aliens Oy, Turku, Finland) (18). Mean arterial pressure was taken for each cardiac cycle as diastolic pressure plus one third of pulse pressure. The WinCPRS software served for stroke volume determinations. The technique to estimate SV is a simplified version of the pulse contour-based method, used in Portapres/Finometer (18). The above parameters were calculated from the whole patterned breathing segments of each test conditions (baseline, LBNP –40 mmHg, LBNP –60 mmHg).

#### *Pulse pressure variability (PPV), stroke volume variability (SVV) and shock index (SI)*

From the segments of metronomic breathing the first 6 contiguous cycles were selected, and for each cycles the maximum and minimum values of pulse pressure and stroke volume were calculated. Within one cycle the PPV was defined as  $100 \times (PP_{\max} - PP_{\min}) / ([PP_{\max} + PP_{\min}] / 2)$ , and SVV was defined as  $100 \times (SV_{\max} - SV_{\min}) / ([SV_{\max} + SV_{\min}] / 2)$  (14, 15, 23). A time honored parameter, shock index, defined as heart rate/systolic pressure, was calculated over each patterned breathing period.

#### *Statistical analysis*

Statistics were performed using the SigmaStat 2.03 software package. Repeated measures ANOVA was used to compare the different test conditions. For variables showing no normal distribution, the Friedman repeated measures analysis of variance on ranks was used. ROC curves were created for characterizing the performance of the studied parameters in discriminating the baseline and high chamber decompression (LBNP –60 mmHg) conditions, and also in discriminating the low and high levels of chamber decompression (LBNP –40 mmHg vs –60 mmHg).

## Results

Three subjects showed symptoms of syncope, or presyncope at LBNP –60 mmHg. Their studies were terminated prematurely, and their data were not included into the analysis. Hemodynamic data of the 19 subjects, who completed the protocol, are shown in Table I, and Fig. 2. Heart rate accelerated significantly with each steps of chamber decompression, and the range of individual values also increased. Systolic arterial pressure decreased slightly, but statistically significantly by the second step of LBNP only. Diastolic pressure, at the same time showed significant elevation, and as a result, mean arterial pressure remained unchanged. Both pulse pressure and stroke volume values declined markedly and significantly with LBNP steps. While increase in PPV and SVV reached significance only at a high level of chamber decompression, shock index increased significantly at both steps. The changes in PP and SV were associated with a narrowing of the range of individual values, thus favouring a better separation of study conditions. The opposite trend was seen with SI changes.

From the studied parameters stroke volume provided the best discrimination between baseline and high chamber decompression states, the AUC of the ROC curve being 99% (Fig. 3, Panel A). Pulse pressure, heart rate and shock index showed also good discrimination (AUC 93%, 88% and 87%, respectively). SVV and PPV on the other hand showed less discriminative capacity (AUC 77% and 70% respectively) (Fig. 3, Panel A). Discriminative capacity of the above parameters between low- and high level chamber decompression conditions was in general limited. AUC of the ROC curves of heart rate (76%) and shock index (74%) were similar to that of stroke volume (74%), and pulse pressure (72%). SVV performed in the same range (73%), and the AUC of the PPV ROC curve was somewhat inferior to the other parameters (66%) (Fig. 3, Panel B).

Table I

	Baseline	LBNP –40 mmHg	LBNP –60 mmHg
Heart rate $\pm$ SD (bpm)	73 $\pm$ 8	80 $\pm$ 11*	96 $\pm$ 13**, #
SAP $\pm$ SD (mmHg)	118 $\pm$ 19	113 $\pm$ 17	105 $\pm$ 15**, #
DAP $\pm$ SD (mmHg)	62 $\pm$ 13	67 $\pm$ 11*	68 $\pm$ 10**
MAP $\pm$ SD (mmHg)	80 $\pm$ 15	83 $\pm$ 12	81 $\pm$ 11
PP $\pm$ SD (mmHg)	57 $\pm$ 12	46 $\pm$ 10*	36 $\pm$ 9**, #
SV (ml)	75 $\pm$ 14	52 $\pm$ 12*	38 $\pm$ 9**, #
SI $\pm$ SD	0.63 $\pm$ 0.1	0.72 $\pm$ 0.2*	0.95 $\pm$ 0.3**, #
PPV $\pm$ SD (%)	15 $\pm$ 6	18 $\pm$ 7	25 $\pm$ 9**
SVV $\pm$ SD (%)	19 $\pm$ 8	24 $\pm$ 15	32 $\pm$ 11**, #

\*  $p < 0.05$  LBNP –40 mmHg vs baseline

\*\*  $p < 0.05$  LBNP –60 mmHg vs baseline

#  $p < 0.05$  LBNP –40 mmHg vs LBNP –60 mmHg

SAP: systolic arterial pressure, DAP: diastolic arterial pressure, MAP: mean arterial pressure, PP: pulse pressure, SV: stroke volume, SI: shock index, PPV: pulse pressure variability, SVV: stroke volume variability

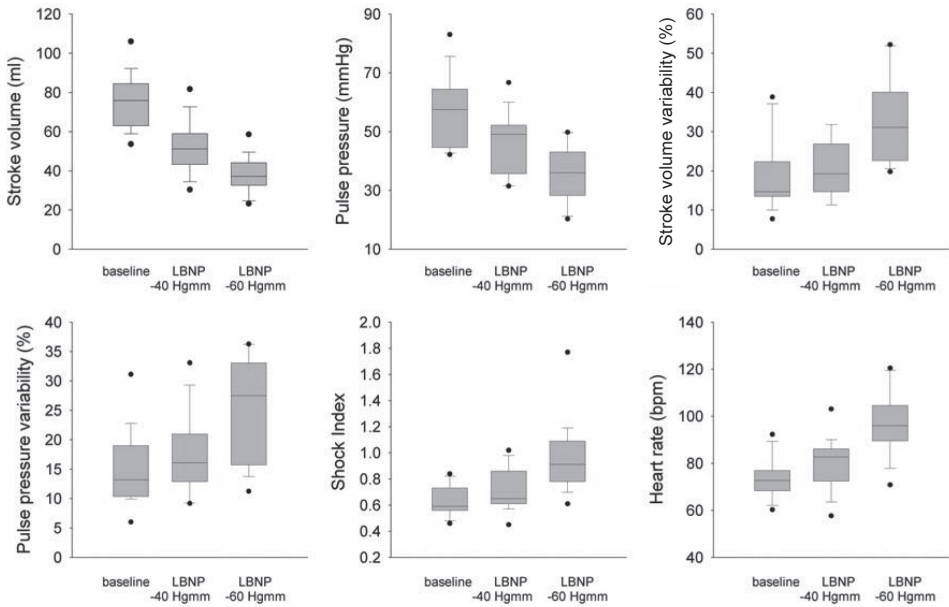


Fig. 2. Distribution of the hemodynamic changes in response to moderate and severe central hypovolemia.

The box plots indicate medians, interquartile ranges, 5<sup>th</sup> and 95<sup>th</sup> percentiles, the minimum and also the maximum values

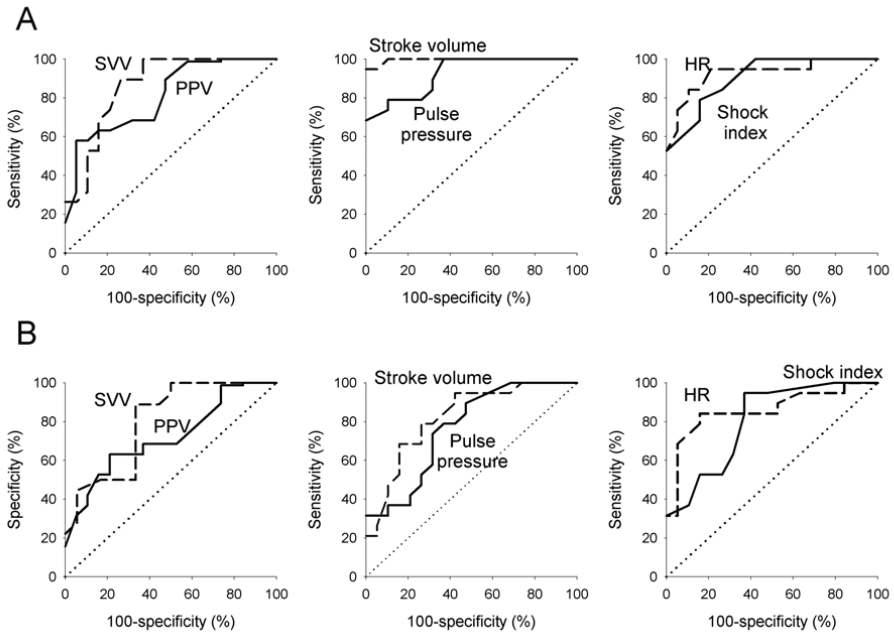


Fig. 3. Receiver operating characteristic curves illustrating the diagnostic performance of various hemodynamic parameters in comparison of the state of severe central hypovolemia to the baseline, (upper panels; A), and comparison of moderate to severe central hypovolemia states (lower panels; B)

## Discussion

Hemodynamic adaptation to acute volume loss serves to maintain perfusion pressure to vital organs. Conservation of mean arterial pressure, even up to the level of pre-syncope, is well documented (9, 4, 17, 28). Exemplifying common clinical knowledge, our data indicates that systolic, diastolic and mean arterial pressure changes are of little value in predicting hypovolemia. Heart rate acceleration in our study was quite characteristic for moderate-to-severe volume depletion. Our studies, however, were restricted to young male subjects. The limited heart rate acceleration in the elderly upon acute volume unloading is well documented (17, 26), therefore generalizability of our observation in this regard is questionable. Since systolic arterial pressure responses were minimal, the marked shock index responses were basically driven by tachycardia, therefore the above limitations hold for this parameter as well.

Our study confirms previous findings that pulse pressure is a sensitive indicator of volume loss (4). Importantly, it has been also documented in real life situations, using data of true trauma victims that unlike other arterial pressure values, pulse pressure does differ between survivors and nonsurvivors (10). Pulse pressure changes in response to volume depletion in some extent mirrors those of stroke volume (4). As it has already been shown by Reisner et al., stroke volume might be an even more sensitive parameter of hypovolemia than pulse pressure (20). Our study is in line with their observation. The method of pulse wave analysis for assessment of stroke volume, without invasive calibration may be imprecise (21), however, in emergency medicine the distinctive capacity of a parameter is important, rather than its precisity, compared to a “gold standard”. The scarce availability of stroke volume analysis is a limitation yet. Unlike stroke volume, pulse pressure values can be easily obtained by various invasive or noninvasive manometers. Although pulse pressure, obtained by traditional manometers, has already demonstrated good diagnostic power (10), continuous recording may enhance the reliability of measurements. It has been noted that arterial pressure exhibits remarkable fluctuations in the state of severe hypovolemia (5). These fluctuations, which might be generated by forceful respiration, may render intermittent blood pressure measurements by traditional manometers unreliable.

There is a long clinical tradition of preload challenges, mostly based on postural volume shifts (1, 13). These manoeuvres, however, do not suit well the scenes of mass casualties. In 1987 Perel et al. published their observation that graded hemorrhage in animal model resulted in augmented respiratory blood pressure variation (19). The phenomenon was attributed to augmented stroke volume fluctuation. Stroke volume swings during positive pressure ventilation are determined, however, not only by the volume state of the subject, but also by the applied tidal volume. It is generally accepted that positive pressure ventilation with a large tidal volume is a prerequisite of any blood pressure variability study (11, 22, 24, 27). Therefore the researchers' interest shifted to ventilated patients, and the scene of their studies confined to the operating theatres and ICUs. Our observations could not refute the previous consensus. Although SVV in our study was not inferior to the other studied parameters in discriminating between moderate and severe volume loss, unfortunately, none of these parameters was sensitive enough for this purpose (Fig. 3, Panel B).

Limitations: In contrast to the traditional “vital signs”, we have no population-wide data bases regarding the proposed new parameters. Our studies were restricted to young male subjects the results therefore are not representative of females. There is an indication that the hypovolemic pulse pressure response may be dependent on the subjects' age (26). Children may also exhibit different responses. These populations were not addressed in our study.

Another limitation of our study is that only the pattern, but not the volume of ventilation was controlled. Although, the tidal volume of volunteers during patterned breathing in steady state condition would adjust automatically to maintain normocapnia (8), progressive reduction in central blood volume can induce unproportional tidal volume augmentation at near syncope (6). Further studies are needed to clarify these issues.

## Conclusions

**Declaration:** Decreased pulse pressure amplitude is a sensitive indicator of acute hypovolemia. Noninvasive, continuous monitoring by Peñáz-principle based finger plethysmography allows onsite or even remote assessment of this parameter. Application of uncalibrated stroke volume calculation programs to the same device provides an additional sensitive hypovolemia-indicator. SVV and PPV calculated during unassisted spontaneous breathing are not sufficiently sensitive indicators of hypovolemia.

## Acknowledgements

The publication is supported by the European Union and co-funded by the European Social Fund. Project title: “Telemedicine-focused research activities on the field of Mathematics, Informatics and Medical Sciences”. Project number: TÁMOP-4.2.2.A-11/1/KONV-2012-0073.

## REFERENCES

1. Birkhahn RH, Gaeta TJ, Terry D, Bove JJ, Tloczkowski J: Shock index in diagnosing acute hypovolemia. *Am. J. Emerg. Med.* 23 (3), 323–326 (2005)
2. Carrico CJ, Holcomb JB, Chaudry IH: PULSE Trauma Work Group: Scientific priorities and strategic planning for resuscitation research and life saving therapy following traumatic injury: report of the PULSE Trauma Work Group. *Acad. Emerg. Med.* 9 (6), 621–626 (2002)
3. Convertino VA, Cooke WH: Relationship between stroke volume and sympathetic nerve activity: new insights about autonomic mechanisms of syncope. *J. Gravit. Physiol.* 9 (1), P63–P66 (2002)
4. Convertino VA, Cooke WH, Holcomb JB: Arterial pulse pressure and its association with reduced stroke volume during progressive central hypovolemia. *J. Trauma* 61 (3), 629–634 (2006)
5. Convertino VA, Ryan KL, Rickards CA, Salinas J, McManus JG, Cooke WH, Holcomb JB: Physiological and medical monitoring for en route care of combat casualties. *J. Trauma* 64 (4 Suppl), S342–S353 (2008)
6. Convertino VA, Rickards CA, Lurie KG, Ryan KL: Hyperventilation in response to progressive reduction in central blood volume to near syncope. *Aviat. Space Environ. Med.* 80 (12), 1012–1017 (2009)
7. Convertino VA, Moulton SL, Grudic GZ, Rickards CA, Hinojosa-Laborde C, Gerhardt RT, Blackburn LH, Ryan KL: Use of advanced machine-learning techniques for noninvasive monitoring of hemorrhage. *J. Trauma* 71 (1 Suppl), S25–S32 (2011)
8. Cooke WH, Cox JF, Diedrich AM, Taylor JA, Beightol LA, Ames JE 4<sup>th</sup>, Hoag JB, Seidel H, Eckberg DL: Controlled breathing protocols probe human autonomic cardiovascular rhythms. *Am. J. Physiol.* 274 (2 Pt 2), H709–H718 (1998)
9. Cooke WH, Ryan KL, Convertino VA: Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. *J. Appl. Physiol.* 96 (4), 1249–1261 (2004)
10. Cooke WH, Salinas J, Convertino VA, Ludwig DA, Hinds D, Duke JH, Moore FA, Holcomb JB: Heart rate variability and its association with mortality in prehospital trauma patients. *J. Trauma* 60 (2), 363–370 (2006).
11. De Backer D, Heenen S, Piagnerelli M, Kock M, Vincent JL: Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med.* 31 (4), 517–523 (2005)



12. Kelly JF, Ritenour AE, McLaughlin DF, Bagg KA, Apodaca AN, Mallak CT, Pearse L, Lawnick MM, Champion HR, Wade CE, Holcomb JB: Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003–2004 versus 2006. *J. Trauma* 64 (2 Suppl), S21–S27 (2008)
13. McGee S, Abernethy WB, Simel DL: The rational clinical examination. Is this patient hypovolemic? *JAMA* 281 (11), 1022–1029 (1999)
14. Michard F, Chemla D, Richard C, Wysocki M, Pinsky MR, Lecarpentier Y, Teboul JL: Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am. J. Resp. Crit. Care Med.* 159 (3), 935–939 (1999)
15. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL: Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am. J. Resp. Crit. Care Med.* 162 (1), 134–138 (2000)
16. Nowak RM, Sen A, Garcia AJ, Wilkie H, Yang JJ, Nowak MR, Moyer ML: Noninvasive continuous or intermittent blood pressure and heart rate patient monitoring in the ED. *Am. J. Emerg. Med.* 29 (7), 782–789 (2011)
17. Olsen H, Verneris E, Länne T: Cardiovascular response to acute hypovolemia in relation to age. Implications for orthostasis and hemorrhage. *Am. J. Physiol.* 278 (1), H222–H232 (2000)
18. Penttilä J, Snapir A, Kentala E, Koskenvuo J, Post J, Scheinin M, Scheinin H, Kuusela T: Estimation of cardiac output in a pharmacological trial using a simple method based on arterial blood pressure signal waveform: A comparison with pulmonary thermodilution and echocardiographic methods. *Eur. J. Clin. Pharmacol.* 62 (6), 401–407 (2006)
19. Perel A, Pizov R, Cotev S: Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology* 67 (4), 498–502 (1987)
20. Reisner AT, Xu D, Ryan KL, Convertino VA, Rickards CA, Mukkamala R: Monitoring non-invasive cardiac output and stroke volume during experimental human hypovolaemia and resuscitation. *Br. J. Anesth.* 106 (1), 23–30 (2011)
21. Remmen JJ, Angevaeren WRM, Verheugt FWA, van der Werf T, Luijten HE, Jansen RWM: Finapres arterial pulse wave analysis with the Modelflow is not a reliable non-invasive method for assessment of cardiac output. *Clin. Sci.* 103 (2), 143–149 (2002)
22. Renner J, Cavus E, Meybohm P, Tonner P, Steinfath M, Scholz J, Lutter G, Bein B: Stroke volume variation during hemorrhage and after fluid loading: impact of different tidal volumes. *Acta Anesthesiol. Scand.* 51 (5), 538–544 (2007)
23. Reuter DA, Felbinger TW, Kilger E, Schmidt C, Lamm P, Goetz AE: Optimizing fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations. Comparison with aortic systolic pressure variations. *Br. J. Anaesth.* 88 (1), 124–126 (2002)
24. Reuter DA, Bayerlein J, Goepfert MSG, Weis FC, Klinger E, Lamm P, Goetz AE: Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. *Intensive Care Med.* 29 (3), 476–480 (2003)
25. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, Pons PT: Epidemiology of trauma deaths: a reassessment. *J. Trauma* 38 (2), 411–417 (1995)
26. Shi X, Huang G, Smith SA, Zhang R, Formes KJ: Aging and arterial blood pressure variability during orthostatic challenge. *Gerontology* 49 (5), 279–286 (2003)
27. Szold A, Pizov E, Perel A: The effect of tidal volume and intravascular volume state on systolic pressure variation in ventilated dogs. *Intensive Care Med.* 15 (6), 368–371 (1989)
28. Van Hoeyweghen R, Hanson J, Stewart MJ, Dethune L, Davies I, Little RA, Horan MA, Kirkman E: Cardiovascular responses to graded lower body negative pressure in young and elderly man. *Exp. Physiol.* 86 (3), 427–435 (2001)