The pulse pressure/heart rate ratio as a marker of stroke volume changes during hemorrhagic shock and resuscitation in anesthetized swine

Julien Pottecher, MD, PhD, Denis Chemla, MD, PhD, Lorenço Xavier, MD, Ngai Liu, MD, PhD, Thierry Chazot, MD, Jacques Marescaux, MD, PhD, Marc Fischler, MD, Pierre Diemunsch, MD, PhD, *and* **Jacques Duranteau, MD, PhD,** *Strasbourg, France*

BACKGROUND: Emergency physicians and anesthesiologists need accurate estimates of stroke volume when massive unexpected hemorrhage occurs. Using an animal model of hemorrhagic shock under general anesthesia, we hypothesized that the pulse pressure–heart rate ratio (PP/HR) would be an accurate marker of stroke volume changes during hemorrhage and resuscitation.

METHODS: In 16 swine under bispectral index-controlled, intravenous propofol-remifentanil anesthesia, pressure-controlled hemorrhagic shock was induced to achieve 30 mm Hg of mean arterial pressure, after which treatment was randomized to fluid (HES, n = 4), norepinephrine (NE, n = 4), both (HES + NE, n = 4), or neither (control, n = 4). Pulmonary artery thermodilution continuous cardiac output, stroke volume, and central arterial pressures were recorded at baseline (T0), after 30 minutes (T30) and 60 (T60) minutes of hemorrhage, during treatment (T90 and T120) and after blood retransfusion (T180).

RESULTS: At T60, blood withdrawal was 995 (301) mL (38 [8] mL/kg), resulting in a 70% decrease in stroke volume and a 3.3-fold decrease in PP/HR (each $p < 0.01$). When stroke volume data pointed at T0, T30 and T60 were plotted against the various hemodynamic variables under study, the PP/HR ratio exhibited the strongest relationship to stroke volume ($r^2 = 0.72$). The area under the receiver operating characteristic curve set to detect a 15% stroke volume decrease was larger for PP/HR (0.95 [0.94–0.97]) than for mean arterial pressure (0.91 [0.89–0.93]) ($p < 0.013$). During resuscitation in the HES and NE groups, correlation coefficients were significantly higher between stroke volume and PP/HR (0.75 [0.63–0.84] and 0.79 [0.67–0.86]) than between stroke volume and mean arterial pressure (0.52 [0.32–0.67], $p = 0.042$, and 0.49 [0.28–0.65], $p = 0.0018$, respectively).

CONCLUSION: The PP/HR ratio was strongly related to stroke volume during hemorrhagic shock and resuscitation in anesthetized swine. (*J Trauma Acute Care Surg*. 2013;74: 1438–1445. Copyright © 2013 by Lippincott Williams & Wilkins)

KEY WORDS: Hemorrhage; shock; pulse pressure; stroke volume; anesthesia.

Whether it occurs in the prehospital setting, in the emergency department or in the operative theater, massive hemorrhage is a highly challenging event. The caring physician has to lighten the depth of hypnosis and initiate fluid expansion, blood transfusion, and vasopressor infusion if hemorrhage is sustained. Along with mean arterial pressure (MAP),

Submitted: November 30, 2012, Revised: January 16, 2013, Accepted: January 21, 2013.

From the Hôpitaux Universitaires de Strasbourg (J.P.), Pôle Anesthésie Réanimation Chirurgicale SAMU, Service d'Anesthésie-Réanimation Chirurgicale, Hôpital de Hautepierre, 1 Avenue Molière 67098 Strasbourg Cedex, France; Université de Strasbourg, Faculté de Médecine, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Institut de Physiologie, Equipe d'accueil EA 3072, Strasbourg; Université Paris Sud (D.C.), Service de Physiologie, Equipe d'Accueil EA4046; APHP, Centre Hospitalier Universitaire de Bicêtre, Le Kremlin-Bicêtre; Hôpitaux Universitaires de Strasbourg (L.X.), Pôle Anesthésie Réanimation Chirurgicale SAMU, Service d'Anesthésie-Réanimation Chirurgicale, Hôpital de Hautepierre, 1 Avenue Molière 67098 Strasbourg Cedex; Hôpital Foch (N.L.), Service d'Anesthésie, Suresnes, Faculté de Médecine Paris-Ile-de-France-Ouest, Université Paris V; Hôpital Foch (T.C.), Service d'Anesthésie, Suresnes, Faculté de Médecine Paris-Ile de-France-Ouest, Université Paris V; Hôpitaux Universitaires de Strasbourg (J.M.), Nouvel Hôpital Civil, Service de Chirurgie Générale et Endocrinienne; Institut de Recherche contre les Cancers de l'Appareil Digestif (IRCAD) – European Institute of Telesurgery (EITS), Université de Strasbourg, Strasbourg; Hôpital Foch (M.F.), Service d'Anesthésie, Suresnes, Faculté de Médecine Paris-Ile de-France-Ouest, Université Paris V; Hôpitaux Universitaires de Strasbourg (P.D.), Pôle Anesthésie Réanimation Chirurgicale SAMU, Service d'Anesthésie-Réanimation Chirurgicale, Hôpital de Hautepierre, 1 Avenue Molière 67098 Strasbourg Cedex; I.R.C.A.D / E.I.T.S; Fédération de Médecine Translationnelle de Strasbourg, Institut de Physiologie, Equipe d'accueil EA 3072, Université de Strasbourg, Strasbourg; Centre Hospitalier Universitaire de Bicêtre (J.D.), Département d'Anesthésie-Réanimation; EA 3509, Université Paris Sud, Le Kremlin-Bicêtre; and Outcomes Research Consortium (N.L.), Cleveland, Ohio.

This study was presented in part at the 21st European Society of Intensive Care Medicine Annual Congress, September 22, 2008, in Lisbon, Portugal.

This study was performed at the Institut de Recherche contre les Cancers de l'Appareil Digestif (I.R.C.A.D) / European Institute of Telesurgery (E.I.T.S), Hôpitaux Universitaires de Strasbourg 1, place de l'Hôpital, 67091 Strasbourg Cedex, France.

This study is attributed to the Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire de Hautepierre, Hôpitaux Universitaires de Strasbourg and Fédération de Médecine Translationnelle de Strasbourg, Institut de Physiologie, Equipe d'accueil EA 3072, Université de Strasbourg, both in Strasbourg, France.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for reprints: Julien Pottecher, MD, PhD, Hôpitaux Universitaires de Strasbourg, Pôle Anesthésie Réanimation Chirurgicale SAMU, Service d'Anesthésie-Réanimation Chirurgicale, Hôpital de Hautepierre, 1 Avenue Molière 67098 Strasbourg Cedex, France; Université de Strasbourg, Faculté de Médecine, Fédération de Médecine Translationnelle de Strasbourg, Institut de Physiologie, Equipe d'accueil EA 3072, Strasbourg, France; email: julien.pottecher@wanadoo.fr.

DOI: 10.1097/TA.0b013e31828c3565

stroke volume (SV) is the key variable to target during resuscitation. Indeed, SV is an early indicator of blood loss;[1] it possesses a prognostic value,[2] and its optimization reduces hospital length of stay and morbidity.[3] Unfortunately, in many situations, the bleeding patient is not currently equipped with sophisticated hemodynamic monitoring. When invasive SV monitoring is not available, the physician has to rely on surrogate markers of SV such as end-tidal CO_2 (ET_{CO_2}), systolic (SAP), mean or diastolic (DAP) arterial blood pressures.

Pressure-derived estimates of SV such as pulse pressure (PP = SAP − DAP) have demonstrated their sensitivity in detecting hypovolemia in conscious volunteers.[4] However, its precision to track norepinephrine-induced changes in SV has been challenged.[5] It has been demonstrated that pressure-derived estimates of fluid responsiveness such as respiratory variations in arterial pulse pressure (PPV) track blood volume loss during acute hemorrhage in swine.[1,6] Nevertheless, concerns have been raised as to the ability of PPV to predict fluid responsiveness in hemorrhaged animals when norepinephrine is administered.[7,8]

In an attempt to maintain cardiac output (CO), the acute reduction in SV associated with hypovolemia is physiologically countered by reflex increases in heart rate (HR).[9] This provides the pathophysiologic basis for using the shock index,[10] namely the ratio between HR and systolic blood pressure. The pulse rate over pressure evaluation (ROPE) index was recently demonstrated as a method to predict early hemorrhagic compensation in healthy patients donating blood with a proportionally greater mean increase compared with the shock index.[11] The aim of our study was to document relationship between the PP/HR ratio (PP/HR) and SV during hemorrhage and resuscitation, mimicking clinical scenario. Using an animal model of hemorrhagic shock under controlled anesthesia, our goals were as follows:

To determine the value of PP/HR as a marker of SV decrease during hemorrhage, compared with other available hemodynamic variables

To assess the value of PP/HR as an estimate of SV changes during hemorrhage resuscitation consisting in volume expansion, vasopressor infusion, or both.

MATERIALS AND METHODS

The institutional review board for the care of animal subjects approved the study and care, and handling was in accord with the French Institute of Health guidelines for ethical animal research (authorization number 67–147). Twenty-one immature Large White swine of either sex (5 (1) months) were fasted overnight, with free access to water.

The experimental protocol is presented in Figure 1. In premedicated animals (azaperone, 2 mg/kg), inhaled anesthesia was induced with isoflurane in pure oxygen. When end-tidal isoflurane concentration reached one minimum alveolar concentration, a 22-gauge catheter was inserted into an ear vein. Depth of anesthesia was checked by paw pinch. Endotracheal intubation was facilitated with intravenously administered pancuronium (0.1 mg/kg) that was perfused continuously (0.1 mg/kg/h) to maintain zero response at the train-of-four. Mechanical ventilation was controlled with an Aespire 7900 Anesthesia Workstation (GE Healthcare, France) in pure oxygen. Tidal volume was set at 10 mL/kg to 12 mL/kg, and minute ventilation was adjusted to keep ET_{CO_2} between 35 mm Hg and 45 mm Hg. Throughout the instrumentation and stabilization procedures, saline (7 mL/kg/h) was intravenously infused and stopped at the beginning of hemorrhage. After forehead shaving, Bispectral Index (BIS) Quatro Sensor electrodes (Covidien, Dublin, Ireland) were firmly secured to the skin. Isoflurane was turned off, and closed-loop total intravenous anesthesia combining propofol (DIPRIVAN, AstraZeneca, Rueil-Malmaison, France) and remifentanil (ULTIVA, GlaxoSmithKline, Marly-Le Roi, France) was then administered using a computer-based Proportional-Integral-Derivative algorithm[12] steered to maintain a 40 to 60 BIS value target throughout the protocol (see Text, Supplemental Digital Content 1, http://links.lww.com/TA/A249, and Video, Supplemental Digital Content 2, http://links.lww.com/TA/A250, which shows an example of pressure-controlled hemorrhagic shock and resuscitation in BIS-controlled intravenously anesthetized swine, for the detailed description).

Indwelling catheters were inserted into the proximal femoral arteries (4 Fr width, 10 cm length, Leader-Cath, Vygon, Ecouen, France). A balloon-tipped pulmonary artery catheter was inserted into the right internal jugular vein (Swan-Ganz CCOmbo CCO/SvO_2, Edwards Lifesciences, Maurepas, France) to measure continuous thermodilution CO (CCO) and mixed venous oxygen saturation (SvO_2). Esophageal temperature was kept constant between 37°C and 38°C by means of a forced air warming blanket.

After a 30-minute instrumentation period and a 30-minute stabilization period, pressure-controlled hemorrhagic shock was induced through rapid venous blood withdrawal to reach a 30 mm Hg of MAP target during 30 minutes (hemorrhage phase on Fig. 1). Additional small blood volume withdrawal was allowed to maintain the 30 mm Hg of MAP target for the next 30 minutes (target MAP, 30 mm Hg). Blood was collected in anticoagulated bags (Macopharma, Mouvaux, France) that were weighed to assess shed-blood volume. Animals were then randomized according to a computer-generated table to one of the following four groups:

1. Control group, bled animals received no other treatment until T120, when shed blood was retransfused up to T180.
2. HES group, animals were fluid resuscitated with 6% hydroxyethyl starch (Voluven, Fresenius Kabi, France) titrated to reach a 70 mm Hg of MAP between T60 and T120, at which time shed blood was retransfused up to T180.
3. NE group, continuous intravenous norepinephrine was introduced at T60 (0.05 μg/kg/min increments every 5 minutes) and maintained to achieve the same goal (70 mm Hg of MAP) before T120, at which time shed blood was retransfused up to T180.
4. HES + NE group, bled animals were first fluid resuscitated with a 15-mL/kg infusion of hydroxyethyl starch (from T60 to T90) followed by intravenous norepinephrine infusion (from T90 to T120) titrated to a 70 mm Hg of MAP before T120, at which time shed blood was retransfused up to T180.

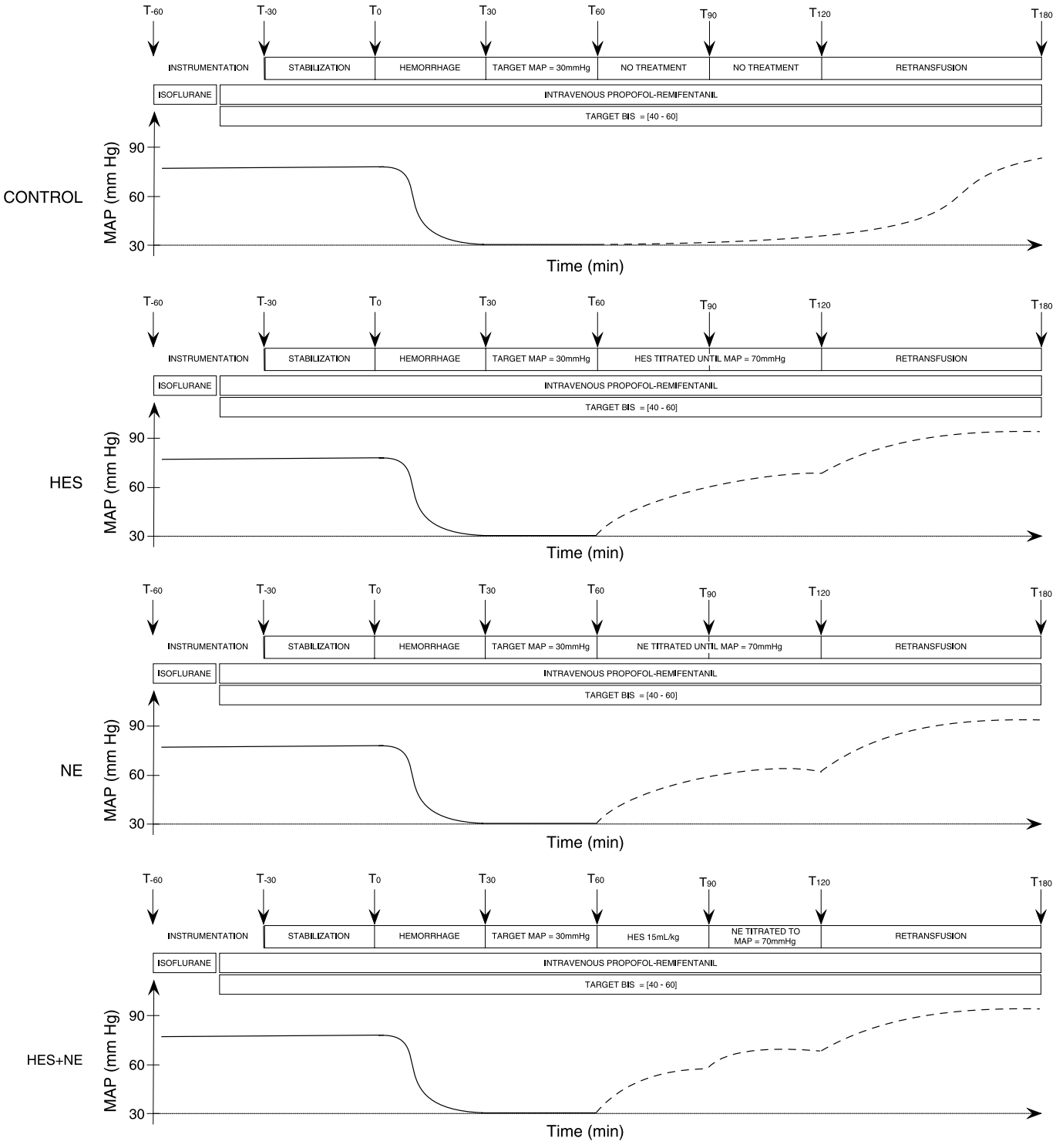

Figure 1. Timeline of the experimental protocol and description of the four treatment groups.

At the end of the study, animals were euthanized by massive propofol overdose and a hypertonic potassium solution.

The following hemodynamic variables were continuously measured (Datex OhmedaS/5 monitor, Finland), sampled every 5 seconds on a Microsoft Excel sheet (see Figure, Supplemental Digital Content 3, http://links.lww.com/TA/A248) and finally recorded at end expiration: the time-averaged MAP, SAP, DAP, PP, HR, SvO_2, and CO obtained in the rapid mode (STAT CCO). This allowed the calculation of SV (SV = CO / HR) and of the PP/HR ratio. Rapidly changing CO values during

the early hemorrhage period were analyzed at 2.5-minute intervals (to take the time response of CCO measurements into account[13]), providing 13 CO and SV values for the 30-minute hemorrhage. Experimental time markers (T30, T60…) were indicated online on the recording Microsoft Excel sheet. The total arterial compliance (C) was estimated by using the SV/PP ratio.[14] The PPV as defined by Michard et al.[15] was intermittently recorded at T0, T30, T60, T90, T120, and T180 on frozen monitor screen as described by Gouvea and Gouvea[16] over one single breath. It is assumed that the tip of the catheter was located at the aortic level and thus that the pulse wave amplification phenomenon was small enough to be negligible.[17]

Statistical Analysis

The distribution of data sets was checked for normality using the Shapiro-Wilk test. In the case of non-Gaussian distribution, data were expressed as the median [interquartile range] and analyzed with Mann-Whitney U-test, Spearman correlation ρ, Wilcoxon matched pairs test and Friedman test followed by the Wilcoxon test with the Bonferroni correction. Normally distributed data were expressed as mean (SD) and analyzed using paired Student' *t* test and repeated-measures analysis of variance. Univariate regression analysis was performed using the least squares method with the Poon correction when pooled data sets were used.[18] Comparison between correlation coefficients was performed using analysis of covariance. We compared the ability of PP/HR and MAP to detect a 15% decrease in SV during hemorrhage by constructing receiver operating characteristic (ROC) curves. Indeed, reproducibility data with commercially available devices indicate that a minimal difference of 15% between determinations of consecutive COs is required to suggest clinical significance.[19] A p value of <0.05 was considered statistically significant. Data were analyzed using StatEl, adScience, (Paris, France; www.adscience.eu) and Prism4, GraphPad (San Diego, CA).

RESULTS

Animals Included

Twenty-one animals were entered into the study, and 16 animals weighing 28 (4) kg (76%, 4 swine per group) completed the entire protocol. The reasons for withdrawal were the following: impossibility to reach the MAP target within 30 minutes (n = 1, NE); death between T30 and T60 (n = 1, control); profound hypothermia that prevented CO measurement (n = 1, HES); technical failure of the pressure recording system (n = 1, HES + NE); and early circulatory failure at the onset of blood withdrawal (n = 1, control).

At T60, blood withdrawal was 995 (301) mL, which corresponded to 38 (8) mL/kg and 55% (11%) of total estimated blood volume (70 mL/kg). For the whole population, it took 22 (12) minutes to reach the 30 mm Hg of MAP target. This duration was not statistically different between groups (control, 16 (5) minutes; HES, 21 (4) minutes; NE, 33 (19) minutes; HES + NE, 18 (7) minutes). The hemodynamic effects of hemorrhage for the entire animal population are summarized in Table 1. The table in Supplemental Digital Content 4 (see Table, Supplemental Digital Content 4, http://links.lww.com/TA/A251) depicts hemodynamic changes during hemorrhage and resuscitation in the four predefined groups. Metabolic variables are summarized in Supplemental Digital Content 5 (http://links.lww.com/TA/A252). The volume of fluid infused during the 60-minute treatment period in HES group animals was 525 mL [478–663 mL], corresponding to 20 mL/kg [17–25 mL/kg]. Animals treated in the NE group received a maximum infusion of 0.375 μg/kg per minute [0.275–0.465 μg/kg/min] of norepinephrine. In the HES + NE group, swine were resuscitated with 402 mL [369–448 mL] (corresponding to 15 mL/kg [14.9–15.1 mL/kg]) of hydroxyethyl starch and a maximum norepinephrine infusion rate of 0.225 μg/kg per minute [0.2–0.325 μg/kg/min].

Characteristics of the Closed-Loop Anesthesia

Propofol and remifentanil infusion rates for the entire protocol were 172 (46) μg/kg per minute and 0.78 (0.25) μg/kg per minute, respectively. Total intravenously administered anesthesia (propofol + remifentanil) accounted for a total volume of 248 (99) mL, representing 9.0 (3.6) mL/kg, 12.9% (5.2%) of actual blood volume, and 23.5% (9.4%) of actual blood loss during the whole protocol duration from instrumentation to end retransfusion. However, if we only consider the resuscitation phase (from T60 to T120), fluid volume associated with intravenously administered anesthesia represented 71 mL on average (2.6 mL/kg, 3.7% total blood volume, and 6.7% blood loss) and did not substantially contribute to effective resuscitation by itself. BIS value was maintained within the 40-to-60 range for 52% (23%) of the overall duration of the procedures and did not differ significantly between groups (Tables, Supplemental Digital Content 6, http://links.lww.com/TA/A253, and Supplemental Digital Content 7, http://links.lww.com/TA/A254).

TABLE 1. Hemodynamic Parameters in Swine (n = 16) Studied at Baseline (T0) and After 30 minutes (T30) and 60 minutes (T60) of Hemorrhage

	T0	T30	T60	ANOVA
HR, beats per minute	77 (16)	99 (27)*	123 (35)*†	0.001
CO, L/min	3.9 (1.0)	2.0 (0.4)*	1.8 (0.4)*	0.001
SV, mL	53 (21)	22 (6)*	16 (7)*	0.001
MAP, mm Hg	69 (14)	34 (10)*	31 (5)*	0.001
SAP, mm Hg	95 (18)	44 (12)*	42 (12)*	0.001
DAP, mm Hg	53 (11)	27 (7)*	26 (8)*	0.001
PP, mm Hg	41 (10)	18 (6)*	16 (7)*	0.001
PP/HR, 100× mm Hg/ beats per minute	57 (21)	19 (9)*	15 (10)*	0.001
PPV, %	9 (3)	48 (19)*	64 (26)*†	0.001
TPR, dyne·s/cm^5	1,496 (498)	1,349 (366)	1,381 (277)	0.37
C, mL/mm Hg	1.33 (0.50)	1.36 (0.57)	1.15 (0.42)	0.39

*$p < 0.05$ versus T0.
*†$p < 0.05$ versus T30. Only statistical significance is figured.
Values are presented as mean (SD).
ANCOVA, analysis of covariance; C, the estimated total arterial compliance; TPR, total peripheral resistance.

Standard Hemodynamic Variables for the Entire Population During Hemorrhage

Baseline measurements (T0) were obtained after 30 minutes of stable hemodynamic conditions, during which there were no significant change in HR (from 79 (15) beats per minute to 77 (16) beats per minute, $p = 0.82$), SAP (from 96 (12) mm Hg to 95 (18) mm Hg, $p = 0.73$), MAP (from 70 (9) mm Hg to 69 (14) mm Hg, $p = 0.81$), and DAP (from 53 (8) mm Hg to 53 (11) mm Hg, $p = 0.85$). There was a marked decrease in MAP, SAP, and DAP at T30 when compared with T0 values. A 58% decrease in SV and a 28% increase in HR resulted in a 49% decrease in CO. As compared with T0, relative decreases in MAP, SAP, and DAP were less than 2.5 at both T30 and T60. As compared with T0, there was a 5-fold increase in PPV, a 3-fold decrease in PP/HR, and a 2.3-fold decrease in PP at T30. As compared with T30, there was a continuous slight increase in PPV, while PP and PP/HR remained unchanged at T60. As compared with T0, there was a 7.1-fold increase in PPV, a 2.6-fold decrease in PP, and a 3.8-fold decrease in PP/HR at T60. The estimated total arterial compliance and total peripheral resistance did not change significantly over time (Table 1).

Relationship Between SV, CO, and Pressure-Derived Variables

When SV data points at T0, T30, and T60 were pooled together and plotted against the various hemodynamic variables under study, the PP/HR ratio exhibited the strongest relationship to SV ($r^2 = 0.72$) (Table 2).

In all 16 animals with values obtained every 2.5 minutes (208 paired values), the data set of early hemorrhage (T0–T30) were pooled together. The study of linear regression of PP/HR to SV with Poon correction revealed a high correlation coefficient of $r^2 = 0.89$ (Fig. 2). Similar analysis could not be performed with PPV because the latter was intermittently measured at only 6 predefined time points.

In the control group, which experienced the more severe shock (sustained hypotension and lower SV), the PP/HR ratio was significantly more correlated to SV ($r^2 = 0.80$ [0.69–0.87], considering all time points) than in the other experimental groups ($p < 0.0001$; HES, $r^2 = 0.57$ [0.39–0.71]; NE, $r^2 = 0.62$ [0.45–0.74]; HES + NE, $r^2 = 0.61$ [0.41–0.76]).

TABLE 2. Correlation Matrix of SV and Stroke Index Throughout the Hemorrhage Period

	SV	Stroke Index
HR	0.36 (−)	0.40 (−)
MAP	0.47	0.48
SAP	0.54	0.54
DAP	0.39	0.44
PP	0.63	0.57
PP/HR	0.72	0.70
PPV	0.58 (−)	0.47 (−)

Data at T0, T30, and T60 were pooled together (each n = 48), and the value of coefficient r^2 is indicated. Positive linear relationships were observed except where indicated (negative relationship (−)).

Stroke index = SV per kg body weight.

Each $p < 0.01$.

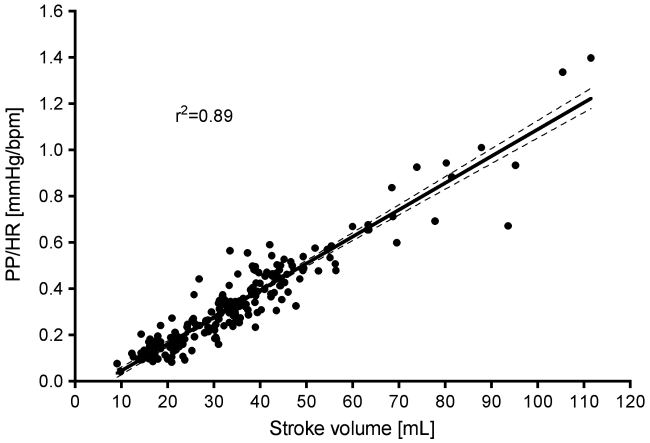

Figure 2. Linear regression of PP/HR to SV with Poon correction using pooled data sets during hemorrhage period (n = 16).

Accuracy of PP/HR and MAP to Track Rapid SV Changes During Hemorrhage

We compared the ability of PP/HR and MAP to detect a 15% decrease in SV during hemorrhage. The area under the ROC curve was larger for PP/HR (area under the curve, 0.95 [0.94–0.97]; sensitivity, 83%; specificity, 94%) than for MAP (area under the curve, 0.91 [0.89–0.93]; sensitivity, 77%; specificity, 91%; $p < 0.013$) (Fig. 3). ROC curve analysis for the 5% and the 10% thresholds are provided in Supplemental Digital Content 8 (see Table, Supplemental Digital Content 8, http://links.lww.com/TA/A255). When the best cutoffs were used to detect a 15% decrease in SV, the PP/HR provided a warning signal 2.5 minutes to 5 minutes earlier than MAP.

Accuracy of PP/HR and MAP to Track SV Changes During Resuscitation of Hemorrhage

Correlations between SV and either PP/HR or MAP were studied according to the four resuscitation strategies (Table 3). In the HES and NE groups, correlation coefficients were significantly higher between SV and PP/HR than between SV and MAP.

DISCUSSION

The main result of our study is that the PP/HR ratio was strongly related to SV during severe hemorrhage and different resuscitation strategies (fluid expansion, norepinephrine infusion, or both) in anesthetized swine.

Hemodynamic Correlates of PP During Hemorrhage and Resuscitation

In our study, hemorrhage was associated with marked decreases in PP, and this is consistent with a study by Dark et al.[20] in immature swine. Pulse pressure arises mainly from

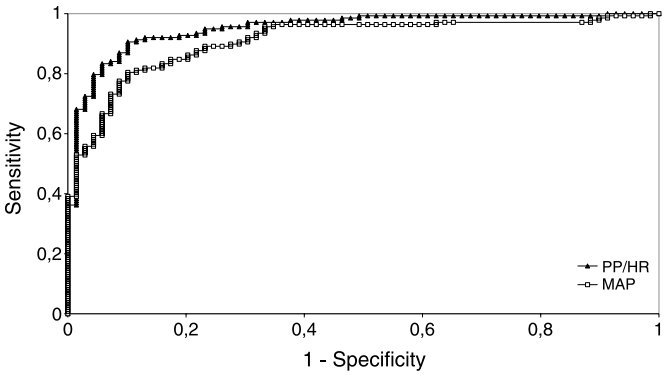

Figure 3. ROC curves comparing the ability of the PP/HR and MAP variations to detect a 15% SV decrease.

the combined influences of SV and total arterial compliance.[14,21] Consistently, our study showed a strong relationship between SV and PP, with SV accounting for 63% of PP variability.

The present study took advantage of the expected increases in HR at the initial stages of the hemorrhage[9] and during norepinephrine infusion in hypovolemic animals.[22] Experimental[23] and clinical[24] observations also indicate that increases in HR can independently account for a reduction in central PP owing to a direct reduction in wave reflection. As a result, the tachycardia tied with reduced SV simultaneously decreased the numerator and increased the denominator of the PP/HR ratio, providing a magnifying effect. In the first part of the study, the PP/HR ratio was recorded in a semicontinuous fashion (every 2.5 minutes) during active bleeding and proved to be tightly correlated with SV within this time frame ($r^2 = 0.89$ with Poon correction, Fig. 2). As a result, we believe that this ratio would be of great value if measured during active bleeding in the trauma patient. Moreover, the PP/HR ratio performed better in the most severe and underresuscitated group (control), suggesting that its correlation to SV could be best in the most severe cases.

SV, PP, PP/HR, and PPV During Hemorrhage

In 14 healthy awake volunteers exposed to lower-body negative-pressure, Convertino et al.[4] reported that PP decreased linearly with the magnitude of central hypovolemia and that PP positively correlated with SV, with $r^2 = 0.91$.

Several authors have reported a correlation between PPV and either SV[6] or shed blood volume,[25] and this was confirmed in our study. However, in our study, SV was more closely related to PP/HR ($r^2 = 0.72$) than to PP ($r^2 = 0.63$) and to PPV ($r^2 = 0.58$). First, PPV is expected to parallel the amount of the preload in reserve, not the snapshot value of SV.[15] Second, in previous studies,[1,6,25] PPV was measured under steady-state conditions following several hemorrhagic steps, whereas we used a continuous hemorrhage protocol.

SV, MAP, and PP/HR During Resuscitation

In our study, MAP was an acceptable estimate of SV during hemorrhage, and this confirms the study by Dalibon et al.,[26] but MAP was much less accurate than PP/HR during fluid and norepinephrine resuscitation. Norepinephrine may have both recruited blood from unstressed blood volume (increasing venous return and SV) and increased arteriolar resistance (increasing MAP without change in SV).[27] One hypothesis could be that norepinephrine was started in deeply hypovolemic animals in which the splanchnic reservoir was fully depleted. As a result, the expected increase in venous return could hardly take place, and the prevalent effect was an increase in arteriolar resistance without any significant increase in SV.

Technical Aspects and Relevance of Our Model

The hemorrhage protocol was designed to provide the same hemodynamic compromise in all animals. This was achieved by using the isobaric hemorrhage model described by Wiggers and Ingraham[28] and a closed-loop bispectral index-controlled anesthesia regimen that both provided greater reproducibility between animals as compared with uncontrolled models.[29] The 70 mm Hg of target MAP for resuscitation was chosen because it was recently proposed to be the optimal MAP for postbleeding resuscitation.[30]

In our model, as in others,[6,8,20] the sympathoexcitatory response to hemorrhage was attenuated, with moderate tachycardia and no increase in peripheral resistances despite a large reduction in circulating blood volume. This suggests that our anesthesia regimen profoundly depressed sympathetic and baroreflex activity. This also implies that the PP/HR ratio would rather outperform MAP as an indicator of blood loss during hemorrhage in the nonanesthetized animal since MAP is longer maintained during hemorrhage in the conscious state. In our view, a single PP/HR value would not be more useful than a unique SV value during resuscitation, providing a single snapshot of the hemodynamic situation that is not meaningful enough to drive resuscitation. The trending values of the PP/HR ratio would provide more useful information to the caring physician, indicating the imminence of cardiovascular collapse and the clinical response to hemodynamic interventions.

One strength of our study was the BIS-controlled, intravenously administered anesthesia protocol. As it continuously titrated drugs infusion against BIS, the dual loop controller has offset drug overdosing and limited the interindividual variability. Our protocol also mimicked the clinical situation in which the physician reduces the rate of drug infusion while maintaining anesthesia in patients with severe hemorrhage.[31]

TABLE 3. Correlation Coefficients Between SV and Either PP/HR or MAP in the Four Treatment Groups

Group	SV vs. PP/HR	SV vs. MAP	Difference in Slopes
Control	0.89 [0.83–0.93]	0.70 [0.55–0.81]	NS
HES	0.75 [0.63–0.84]	0.52 [0.32–0.67]	0.042
NE	0.79 [0.67–0.86]	0.49 [0.28–0.65]	0.0018
HES + NE	0.78 [0.64–0.87]	0.74 [0.58–0.85]	NS

Comparison between correlation coefficients was performed using analysis of covariance. NS, not significant. Correlation coefficients are expressed as value [95% confidence interval]

BIS is considered a reasonable tool to monitor hypnosis in large animals[32–34] where it reflects the anesthetic depth and is not modified by hypotension[34] until a state of lethal hypotension (<20 mm Hg) is unable to sustain brain electrical activity.[35] Finally, the closed-loop anesthesia protocol performed as well and allowed similar depth of anesthesia for the four groups despite the use of specific pharmacokinetic model for propofol.[34]

Limitations

The beat-to-beat SV was not measured in our experiments, where SV was calculated as the ratio of CCO divided by HR. When compared with aortic transit-time flow probe, CCO measurements are of reasonably good accuracy and precision in pigs, even in severe hypovolemia conditions.[36] New devices relying on pulse contour CO analysis allow beat-to-beat SV monitoring, but in a severe hemorrhagic shock model, such devices are inaccurate, unless frequently recalibrated by pulmonary thermodilution.[37] When comparing pulse contour CO analysis with CCO in hemorrhaged pigs treated with norepinephrine, Bein et al.[38] established that, unlike pulse contour CO, CCO demonstrated good agreement with bolus thermodilution CO.

The clinical implications of our results must be carefully extrapolated for the following reasons. First, subgroup patient populations presenting with cardiac dysautonomia (e.g., diabetic patients) or receiving chronic treatment with β-adrenergic blocking agents are expected to exhibit only mild changes in HR during hemorrhage; hence, further studies are needed to test our PP/HR index under such clinical conditions. Second, our results should be tested in humans when arterial pressure is measured with a peripheral radial artery or a brachial cuff. Indeed, PP measurements in the low value range may not be sufficiently accurate.[39] Consequently, the PP/HR ratio should not be used in place of established SV monitoring devices in elective situations but could be of real value in emergency circumstances (prehospital setting, trauma bay) when such devices are not readily available. Third, our hemorrhage protocol was coupled with minor tissue injury and does not encompass the full spectrum of hemodynamic changes associated with trauma hemorrhagic shock. Last, our model was associated with only a moderate increase in arterial lactate and the absence of a preshock and postshock difference in arterial base excess and bicarbonate levels, probably owing to the short duration of shock. In a previous study by our group, Collange et al.[40] found that blood lactate increased to more than 4 mmol/L but only when low MAP (40 mm Hg) was maintained for 3 hours. Yet, we believe that the PP/HR ratio would be even more sensitive in a more severe hemorrhage model because the intensity of the decrease would be larger.

In conclusion, the PP/HR ratio was strongly related to SV during severe hemorrhage and resuscitation in anaesthetized swine even when norepinephrine was used during resuscitation. An early marker of acute decreases in SV may be especially valuable in cases of acute blood loss in anaesthetized patients, and furthermore, studies are needed to investigate whether this new, easy-to-obtain, and continuous index may improve the rationale management of hemorrhagic shock patients.

AUTHORSHIP

J.P. performed the literature search and participated in the study design, data collection, data analysis, data interpretation, writing, critical revision, and submission. D.C. participated in the data analysis, data interpretation, writing, critical revision, and submission. L.X. performed the literature search and participated in the study design, data collection, data analysis, and critical revision. N.L. participated in the study design, data analysis, writing, and critical revision. T.C. participated in the study design, data collection, data analysis, and critical revision. J.M. participated in the study design and critical revision. M.F. performed the literature search and participated in the study design, data analysis, data interpretation, writing, and critical revision. P.D. participated in the study design, data collection, data analysis, data interpretation, writing, and critical revision. J.D. performed the literature search and participated in the study design, data analysis, data interpretation, writing, critical revision, and submission.

ACKNOWLEDGMENT

We are greatly indebted to Nancy Richardson-Peuteuil, for her editorial assistance.

DISCLOSURE

Financial support for this study was provided exclusively by institutional department funds. Edwards Lifesciences kindly provided pulmonary artery catheters. GlaxoSmithKline kindly provided remifentanil flasks (ULTIVA).

REFERENCES

1. Westphal G, Garrido Adel P, de Almeida DP, Rocha e Silva M, Poli-de-Figueiredo LF. Pulse pressure respiratory variation as an early marker of cardiac output fall in experimental hemorrhagic shock. *Artif Organs*. 2007;31:284–289.
2. Giordano S, Biancari F, Loponen P, Wistbacka JO, Luther M. Preoperative haemodynamic parameters and the immediate outcome after open repair of ruptured abdominal aortic aneurysms. *Interact Cardiovasc Thorac Surg*. 2009;9:491–493.
3. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ*. 1997;315:909–912.
4. Convertino VA, Cooke WH, Holcomb JB. Arterial pulse pressure and its association with reduced stroke volume during progressive central hypovolemia. *J Trauma*. 2006;61:629–634.
5. Monnet X, Letierce A, Hamzaoui O, Chemla D, Anguel N, Osman D, Richard C, Teboul JL. Arterial pressure allows monitoring the changes in cardiac output induced by volume expansion but not by norepinephrine. *Crit Care Med*. 2011;39:1394–1399.
6. Berkenstadt H, Friedman Z, Preisman S, Keidan I, Livingstone D, Perel A. Pulse pressure and stroke volume variations during severe haemorrhage in ventilated dogs. *Br J Anaesth*. 2005;94:721–726.
7. Nouira S, Elatrous S, Dimassi S, Besbes L, Boukef R, Mohamed B, Abroug F. Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. *Crit Care Med*. 2005;33:2339–2343.
8. Renner J, Meybohm P, Hanss R, Gruenewald M, Scholz J, Bein B. Effects of norepinephrine on dynamic variables of fluid responsiveness during hemorrhage and after resuscitation in a pediatric porcine model. *Paediatr Anaesth*. 2009;19:688–694.
9. Schadt JC, Ludbrook J. Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. *Am J Physiol*. 1991;260:H305–H318.
10. Birkhahn RH, Gaeta TJ, Terry D, Bove JJ, Tloczkowski J. Shock index in diagnosing early acute hypovolemia. *Am J Emerg Med*. 2005;23:323–326.
11. Campbell R, Ardagh MW, Than M. Validation of the pulse rate over pressure evaluation index as a detector of early occult hemorrhage: a prospective observational study. *J Trauma Acute Care Surg*. 2012;73:286–288.

12. Liu N, Chazot T, Hamada S, Landais A, Boichut N, Dussaussoy C, Trillat B, Beydon L, Samain E, Sessler DI, et al. Closed-loop coadministration of propofol and remifentanil guided by bispectral index: a randomized multicenter study. *Anesth Analg*. 2011;112:546–557.
13. Siegel LC, Hennessy MM, Pearl RG. Delayed time response of the continuous cardiac output pulmonary artery catheter. *Anesth Analg*. 1996; 83:1173–1177.
14. Chemla D, Hebert JL, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. *Am J Physiol*. 1998;274:H500–H505.
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 Respir Crit Care Med*. 2000;162:134–138.
16. Gouvea G, Gouvea FG. Measurement of systolic pressure variation on a Datex AS/3 monitor. *Anesth Analg*. 2005;100:1864.
17. Latham RD, Westerhof N, Sipkema P, Rubal BJ, Reuderink P, Murgo JP. Regional wave travel and reflections along the human aorta: a study with six simultaneous micromanometric pressures. *Circulation*. 1985;72: 1257–1269.
18. Poon CS. Analysis of linear and mildly nonlinear relationships using pooled subject data. *J Appl Physiol*. 1988;64:854–859.
19. Stetz CW, Miller RG, Kelly GE, Raffin TA. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. *Am Rev Respir Dis*. 1982;126:1001–1004.
20. Dark P, Little R, Nirmalan M, Purdy J. Systemic arterial pressure wave reflections during acute hemorrhage. *Crit Care Med*. 2006;34:1497–1505.
21. Dart AM, Kingwell BA. Pulse pressure—a review of mechanisms and clinical relevance. *J Am Coll Cardiol*. 2001;37:975–984.
22. Cavus E, Meybohm P, Doerges V, Hugo HH, Steinfath M, Nordstroem J, Scholz J, Bein B. Cerebral effects of three resuscitation protocols in uncontrolled haemorrhagic shock: a randomised controlled experimental study. *Resuscitation*. 2009;80:567–572.
23. Papaioannou TG, Protogerou A, Papamichael C, Mathioulakis D, Tsangaris S, Karatzis E, Toumanidis S, Zakopoulos N, Lekakis J. Experimental and clinical study of the combined effect of arterial stiffness and heart rate on pulse pressure: differences between central and peripheral arteries. *Clin Exp Pharmacol Physiol*. 2005;32:210–217.
24. Albaladejo P, Copie X, Boutouyrie P, Laloux B, Declere AD, Smulyan H, Benetos A. Heart rate, arterial stiffness, and wave reflections in paced patients. *Hypertension*. 2001;38:949–952.
25. Pestel GJ, Hiltebrand LB, Fukui K, Cohen D, Hager H, Kurz AM. Assessing intravascular volume by difference in pulse pressure in pigs submitted to graded hemorrhage. *Shock*. 2006;26:391–395.
26. Dalibon N, Schlumberger S, Saada M, Fischler M, Riou B. Haemodynamic assessment of hypovolaemia under general anaesthesia in pigs submitted to graded haemorrhage and retransfusion. *Br J Anaesth*. 1999;82:97–103.
27. Gelman S, Mushlin PS. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. *Anesthesiology*. 2004;100: 434–439.
28. Wiggers HC, Ingraham RC. Hemorrhagic Shock: definition And Criteria For Its Diagnosis. *J Clin Invest*. 1946;25:30–36.
29. Majde JA. Animal models for hemorrhage and resuscitation research. *J Trauma*. 2003;54:S100–S105.
30. Li T, Zhu Y, Fang Y, Liu L. Determination of the optimal mean arterial pressure for postbleeding resuscitation after hemorrhagic shock in rats. *Anesthesiology*. 2012;116:103–112.
31. Shafer SL. Shock values. *Anesthesiology*. 2004;101:567–568.
32. Howard RS, Finneran JJ, Ridgway SH. Bispectral index monitoring of unihemispheric effects in dolphins. *Anesth Analg*. 2006;103:626–632.
33. Martin-Cancho MF, Lima JR, Luis L, Crisostomo V, Ezquerra LJ, Carrasco MS, Uson-Gargallo J. Bispectral index, spectral edge frequency 95%, and median frequency recorded for various concentrations of isoflurane and sevoflurane in pigs. *Am J Vet Res*. 2003;64:866–873.
34. Johnson KB, Egan TD, Kern SE, White JL, McJames SW, Syroid N, Whiddon D, Church T. The influence of hemorrhagic shock on propofol: a pharmacokinetic and pharmacodynamic analysis. *Anesthesiology*. 2003; 99:409–420.
35. Kurita T, Uraoka M, Morita K, Sato S. Influence of progressive hemorrhage and subsequent cardiopulmonary resuscitation on the bispectral index during isoflurane anesthesia in a swine model. *J Trauma Acute Care Surg*. 2012;72:1614–1619.
36. Bajorat J, Hofmockel R, Vagts DA, Janda M, Pohl B, Beck C, Noeldge-Schomburg G. Comparison of invasive and less-invasive techniques of cardiac output measurement under different haemodynamic conditions in a pig model. *Eur J Anaesthesiol*. 2006;23:23–30.
37. Piehl MD, Manning JE, McCurdy SL, Rhue TS, Kocis KC, Cairns CB, Cairns BA. Pulse contour cardiac output analysis in a piglet model of severe hemorrhagic shock. *Crit Care Med*. 2008;36:1189–1195.
38. Bein B, Meybohm P, Cavus E, Renner J, Tonner PH, Steinfath M, Scholz J, Doerges V. The reliability of pulse contour-derived cardiac output during hemorrhage and after vasopressor administration. *Anesth Analg*. 2007; 105:107–113.
39. Lakhal K, Ehrmann S, Runge I, Legras A, Dequin PF, Mercier E, Wolff M, Regnier B, Boulain T. Tracking hypotension and dynamic changes in arterial blood pressure with brachial cuff measurements. *Anesth Analg*. 2009;109:494–501.
40. Collange O, Charton A, Greib N, Joshi GP, Schaeffer R, Diemunsch PA. Correlation between arterial and capillary lactate measurements in a porcine hemorrhagic shock model. *J Trauma*. 2010;68:32–34.

