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Is the shock index correlated with blood loss? An experimental study on a controlled hemorrhagic shock model in piglets

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abstract

Introduction: The quantification of blood loss in a severe trauma patient allows prognostic quantification and the engagement of adapted therapeutic means. The Advanced Trauma Life Support classification of hemorrhagic shock, based in part on hemodynamic parameters, could be improved. The search for reproducible and non-invasive parameters closely correlated with blood depletion is a necessity. An experimental model of controlled hemorrhagic shock allowed us to obtain hemodynamic and echocardiographic measurements during controlled blood spoliatio. The primary aim was to demonstrate the correlation between the Shock Index (SI) and blood depletion volume (BDV) during the hemorrhagic phase of an experimental model of controlled hemorrhagic shock in piglets. The secondary aim was to study the correlations between blood pressure (BP) values and BDV, SI and cardiac output (CO), and pulse pressure (PP) and stroke volume during the same phase.

Methods: We analyzed data from 66 anesthetized and ventilated piglets that underwent blood spoliatio at $2 \text{ mL.kg}^{-1}.\text{min}^{-1}$ until a mean arterial pressure (MAP) of 40 mmHg was achieved. During this bleeding phase, hemodynamic and echocardiographic measurements were performed regularly.

Results: The correlation coefficient between the SI and BDV was 0.70 (CI 95%, [0.64; 0.75]; $p < 0.01$), whereas between MAP and BDV, the correlation coefficient was -0.47 (CI 95%, $[-0.55; -0.38]$; $p < 0.01$). Correlation coefficient between SI and CO and between PP and stroke volume were -0.45 (CI 95%, $[-0.53; -0.37]$, $p < 0.01$) and

0.62 (CI 95%, [0.56; 0.67]; $p < 0.01$), respectively.

Conclusions: In a controlled hemorrhagic shock model in piglets, the correlation between SI and BDV seemed strong.

1. Introduction

Among traumatic deaths, hemorrhagic shock (HS) represents the leading cause of mortality [1,2]. Time is a major prognostic factor in the management of a trauma patient in HS [3], especially in the pre-hospital setting [4]. Approximately 85% of deaths related to HS occur within six hours after hospital admission [5], which imposes the need to develop rapid and efficient management strategies. Damage control resuscitation [6,7], based on early fluid infusion and blood product transfusion with a moderate mean arterial pressure (MAP) objective

[8,9], and damage control surgery, based on rapid surgical management of bleeding [10], have improved the prognoses of patients in hemorrhagic shock [11]. Compensatory physiological mechanisms may initially lead to an underestimation of the severity of a hemorrhage, for which quantification of the volume of blood lost is difficult [12].

The correlation between hemodynamic parameters and blood depletion volume (BDV) needs to be explored to determine simple and reproducible criteria that can predict HS in severe trauma patients (STP). Heart rate (HR) and systolic blood pressure (SBP) are simple and reproducible tools to access and use but not sufficient when used alone; this has led to a controversial Advanced Trauma Life Support (ATLS) classification of HS [13]. Pulse pressure variations (PPVs) are moderately correlated with BDV [14]. The Shock Index (SI), defined by the HR/SBP ratio, has been evaluated as a risk factor for massive hemorrhage in severe

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trauma [15,16]. An increased SI in the management of severe trauma would be a poor prognostic factor [17] and a predictive factor for massive transfusion [18], suggesting an association between this hemodynamic parameter and the extent of hemorrhage.

Our hypothesis was that SI is correlated with BDV. The main aim of our study was to show the correlation between SI and BDV in an experimental model of controlled HS in anesthetized and ventilated piglets.

2. Methods

2.1. Materials

We performed an analysis based on data from four series of experiments performed between 2018 and 2022. The protocol used in this model of controlled HS in piglets was approved (CEEALR-12013 and 9341–2,021,012,709,128,801). The manipulations were performed in a certified laboratory. This animal-based study was conducted according to European Directive 2010/63/EC, which supervises the protection of animals used for scientific purposes.

Our primary objective was to show the correlation between SI and BDV in an experimental model of controlled HS in piglets. The secondary objective was to show the correlations between different blood pressure (BP) values and BDV, SI and cardiac output (CO), and pulse pressure (PP) and stroke volume (SV) in this same experimental model.

2.2. Animal preparation

A total of 66 piglets participated in these experimental studies with this model of HS. All animals were prepared according to a previously published and validated protocol [19]. Premedication was performed by intramuscular injection of ketamine 10 mg.kg^{-1} , atropine 0.05 mg.kg^{-1} , and midazolam 10 mg.kg^{-1} . Anesthetic induction was performed by a bolus of propofol (4 mg.kg^{-1}) combined with curarization by cisatracurium (0.25 mg.kg^{-1}) and maintained with propofol $8 \text{ mg.kg}^{-1}.\text{h}^{-1}$. After orotracheal intubation or surgical tracheostomy, the piglets were ventilated with an inspired oxygen fraction of 21%, a tidal volume of 6 or 8 mL.kg^{-1} , and a positive end-expiratory pressure of $5 \text{ cmH}_2\text{O}$. The animals were then conditioned with echo-guided placement of a 7 French triple-lumen central venous line through the internal jugular vein to the right atrium, permitting measurement of central venous pressure and allowing for injection of cold water boluses for transpulmonary thermodilution. One femoral artery was catheterized with a 5 French arterial catheter with an integrated thermistor (PiCCO®Plus; Pulsion Medical Systems, Munich, Germany) that allowed continuous BP monitoring. Finally, the femoral vein was also cannulated by an 8.5 French catheter (Arrow®; Arrow International, Inc., Cleveland, OH, USA) to perform blood withdrawal or fluid filling. These different invasive measurement tools allowed continuous monitoring of BP and HR in particular.

2.3. Experimental protocol and measurement times

As the objective of this study was to assess the evolution of SI in hemorrhage, we only describe the standardized depletion phase of the experimentation. The experiment started at T0 by recording reference hemodynamic data for each animal, including HR and BP values, as well as biological and echocardiographic data. Blood depletion was then initiated via a femoral venous catheter at a rate of $2 \text{ mL.kg}^{-1}.\text{min}^{-1}$ until a mean arterial pressure (MAP) of 40 mmHg was obtained, which defined T1. The same hemodynamic and echocardiographic measurements were performed every 5 mL.kg^{-1} of blood withdrawal, defining T0a, T0b, T0c, etc. At T1, the hemodynamic, biological, and echocardiographic data were measured (Fig. 1).

The SV was calculated by the invasive measurement of CO multiplied by HR. PPVs were calculated based on invasive measurements of SBP and diastolic blood pressure (DBP). Ultrasound measurements were

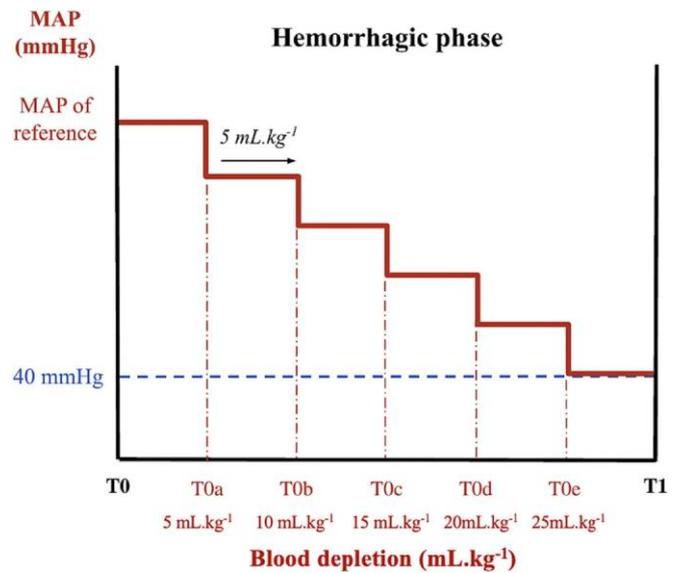


Fig. 1. Experimental protocol with blood depletion at a rate of $2 \text{ mL.kg}^{-1}.\text{min}^{-1}$. MAP = mean arterial pressure.

performed by a physician with expertise in echocardiography according to the recommendations of the American Society of Echocardiography [20] with a Venue R2.6 (Venue R2.6, GE Medical Systems, Milwaukee, WI, USA), Versana Balance (Versana Balance, GE Medical Systems, Milwaukee, WI, USA), or Vivid S70 (Vivid S70, GE Medical Systems, Milwaukee, WI) device. Measurement of the sub-aortic velocity–time integral (VTI) was performed in a five-cavity apical view with pulsed Doppler. The four-cavity apical view was preferred to measure the E' wave at the lateral mitral annulus using tissue Doppler. Measurements of the minimum and maximum values of the diameter of the inferior vena cava (IVC) were performed in a substernal view. The distensibility of the IVC (dIVC) was calculated according to the formula $dIVC = (IVC_{\text{max}} - IVC_{\text{min}}) / ((IVC_{\text{max}} + IVC_{\text{min}}) / 2)$.

2.4. Statistical analysis

As no studies of SI in this model of HS were available, no sample size calculation was performed. Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as frequencies with percentages. An analysis of variance (ANOVA) was performed to compare the quantitative data between each time point of the experiment. Pearson's correlation coefficients were calculated to assess the relationship between the judgment criteria and blood depletion. The correlation coefficient was interpreted as negligible [0.00; 0.10], weak [0.10; 0.39], moderate [0.40; 0.69], strong [0.70; 0.89], or very strong [0.90; 1.0] [21]. The significance level was set at 5% for all tests. Statistical analysis was performed in R (version 4.0.2, 2017, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Animals and measurement times

Of the 66 piglets included in this data analysis, 52 (79%) were female. The number of piglets included per year was 18 (27%), 17 (26%), 18 (27%), and 13 (20%) in 2018, 2020, 2021, and 2022, respectively. The mean weight was $31 \pm 4 \text{ kg}$. A total of 428 hemodynamic measurements were performed at different times during the hemorrhagic phase of the protocol. The quantitative hemodynamic and echocardiographic data are described in Table 1. The mean BDV of all experiments was $18.10 \pm 10.59 \text{ mL.kg}^{-1}$.

Table 1
Hemodynamic and echographic data at each measurement time of hemorrhagic phase

Variable	T0	T0a	T0b	T0c	T0d	T0e	T0f	T0g	T0h	T1	p
HR (bpm)	99 ± 23	103 ± 24	107 ± 28	117 ± 33	130 ± 34	142 ± 39	148 ± 37	181 ± 30	206 ± 24	146 ± 51	<0.01
SBP (mmHg)	97 ± 13	83 ± 15	73 ± 15	73 ± 13	69 ± 14	68 ± 15	66 ± 14	64 ± 12	61 ± 13	49 ± 6	<0.01
MAP (mmHg)	77 ± 12	67 ± 12	59 ± 12	58 ± 11	56 ± 11	54 ± 11	53 ± 12	52 ± 10	48 ± 9	38 ± 3	<0.01
DBP (mmHg)	63 ± 10	54 ± 10	48 ± 11	47 ± 9	46 ± 10	45 ± 9	45 ± 10	44 ± 9	39 ± 7	32 ± 4	<0.01
SI (bpm/mmHg)	1.04 ± 0.33	1.27 ± 0.39	1.52 ± 0.53	1.64 ± 0.47	1.92 ± 0.57	2.17 ± 0.67	2.24 ± 0.63	2.77 ± 0.43	3.34 ± 0.38	3.04 ± 1.08	<0.01
PP (mmHg)	34 ± 8	29 ± 8	25 ± 8	25 ± 6	24 ± 8	23 ± 8	21 ± 5	20 ± 5	22 ± 7	17 ± 5	<0.01
VPP (%)	18.3 ± 6.7	20.8 ± 6.6	23.8 ± 7.6	25.6 ± 8.5	27.9 ± 8.7	27.7 ± 7.5	27.4 ± 6.2	33.0 ± 3.7	31.5 ± 3.1	29.1 ± 8.1	<0.01
E' wave (cm.s ⁻¹)	11.24 ± 3.54	9.61 ± 2.99	8.76 ± 2.48	7.75 ± 2.47	7.06 ± 2.96	6.34 ± 2.43	4.90 ± 2.14	4.09 ± 1.74	5.90 ± 1.79	6.04 ± 2.42	<0.01
VTI (cm)	13.43 ± 3.09	11.68 ± 2.69	10.90 ± 2.20	10.06 ± 2.18	9.50 ± 2.67	8.89 ± 1.89	8.53 ± 2.46	8.18 ± 3.44	9.92 ± 5.39	8.60 ± 2.41	<0.01
dIVC (%)	0.64 ± 0.56	0.72 ± 0.59	0.87 ± 0.75	0.90 ± 0.65	1.08 ± 0.79	1.27 ± 0.80	1.15 ± 0.83	1.15 ± 0.94	0.71 ± 0.90	0.74 ± 0.67	0.05
SV (mL)	34.32 ± 9.33	29.17 ± 8.33	25.37 ± 6.93	23.01 ± 6.38	18.86 ± 5.44	16.61 ± 5.81	14.80 ± 4.61	10.33 ± 2.43	8.49 ± 2.17	14.0 ± 7.0	<0.01
CO (L.min ⁻¹)	3.29 ± 0.90	2.94 ± 0.88	2.64 ± 0.73	2.57 ± 0.63	2.35 ± 0.61	2.25 ± 0.67	2.17 ± 0.70	1.88 ± 0.56	1.75 ± 0.45	1.74 ± 0.41	<0.01

HR = heart rate; SBP = systolic blood pressure; MAP = mean arterial pressure; DBP = diastolic blood pressure; SI = shock index; PP = pulse pressure; VPP = pulse pressure variations; VTI = sub-aortic time-velocity integral; dIVC = distensibility of the inferior vena cava; SV = stroke volume; CO = cardiac output.

3.2. Outcomes

The SI evolution during blood loss is represented in Fig. 2A. The correlation coefficient between the SI and BDV was 0.70 (CI 95%, [0.64; 0.75]; $p < 0.01$). Fig. 2B shows the corresponding linear regression line. The correlation coefficient between the BDV and Δ PP was 0.39 (CI 95% [0.29; 0.48]; $p < 0.01$; Fig. 3A). Regarding the echocardiographic parameters, the correlation coefficient between the BDV and E' wave was -0.50 (CI 95% [-0.57; -0.41]; $p < 0.01$; Fig. 3B). The correlation coefficients between the VTI and BDV and between the dIVC and BDV were -0.38 (CI 95%, [-0.47; -0.28]; $p < 0.01$) and 0.11 (CI 95%, [-0.04; 0.25]; $p = 0.14$), respectively.

The different BP values (MAP, SBP, DBP, and PP) had correlation coefficients with BDV of -0.47 (CI 95%, [-0.55; -0.38]; $p < 0.01$), -0.46 (CI 95%, [-0.54; -0.37]; $p < 0.01$), -0.43 (CI 95%, [-0.51; -0.34], $p < 0.01$), and -0.34 (CI 95%, [-0.45; -0.26]; $p < 0.01$), respectively. Finally, the correlation coefficients between the SI and CO measured by thermodilution and between the PP and SV were -0.45 (CI 95%, [-0.53; -0.37]; $p < 0.01$; Fig. 4A) and 0.62 (CI 95%, [0.56; 0.67]; $p < 0.01$; Fig. 4B), respectively.

4. Discussion

4.1. Outcomes

Our main finding was that the correlation between SI and BDV appeared to be highly moderate to strong ($r_{SI-BDV} = 0.70$) in an experimental model of controlled HS. In our study, the correlations between blood loss and widely used parameters such as PPV or even VTI and E' wave obtained by echocardiography were moderate. These results are consistent with previous studies that have evaluated an increased SI as a risk factor for mortality in trauma patients [15-17]. In intensive care units, BP monitoring using an arterial catheter remains the most common approach, whereas it is less frequent in the emergency department. In emergency medicine, and particularly in the pre-hospital setting, only simple, accessible, and non-invasive monitoring tools are widespread. Nevertheless, we must emphasize that patients in pre-hospital are usually breathing spontaneously with negative pressure ventilation, unlike our experimental model of controlled HS where mechanical ventilation with positive pressure ventilation could have a direct influence on correlation between SI and physiological parameters such as CO and PP.

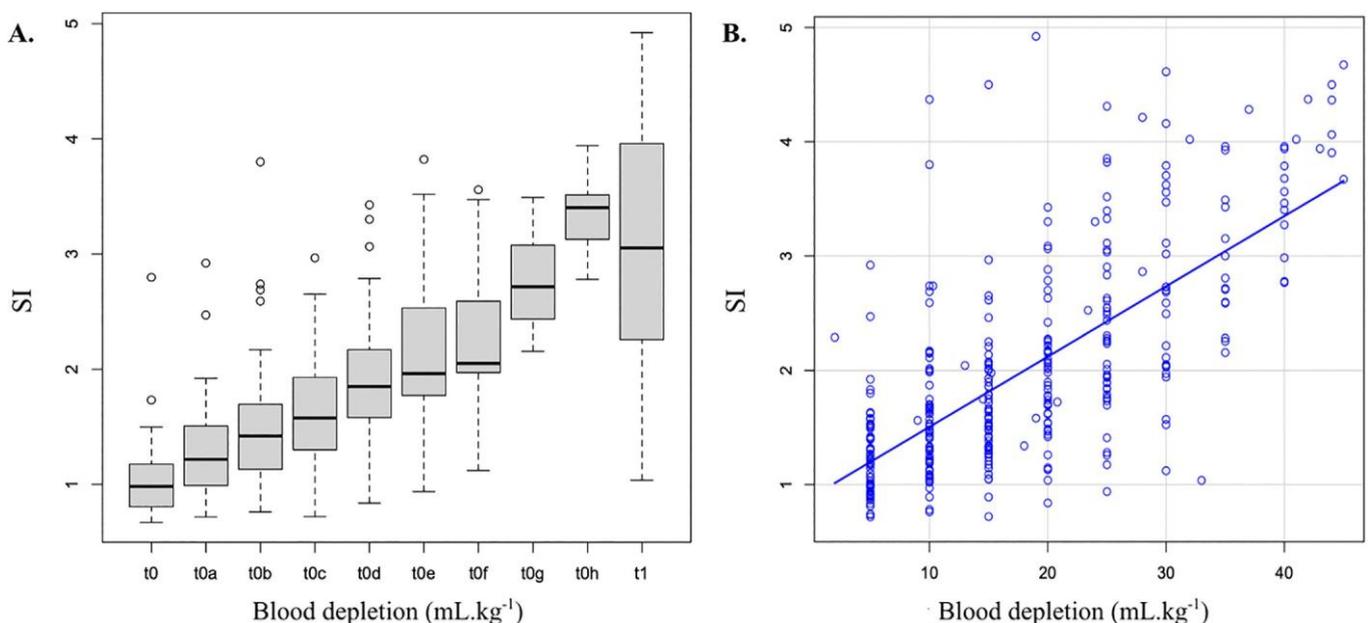


Fig. 2. A. Shock index evolution during hemorrhagic phase. B. Correlation between shock index and blood depletion volume during hemorrhagic phase. SI = shock index.

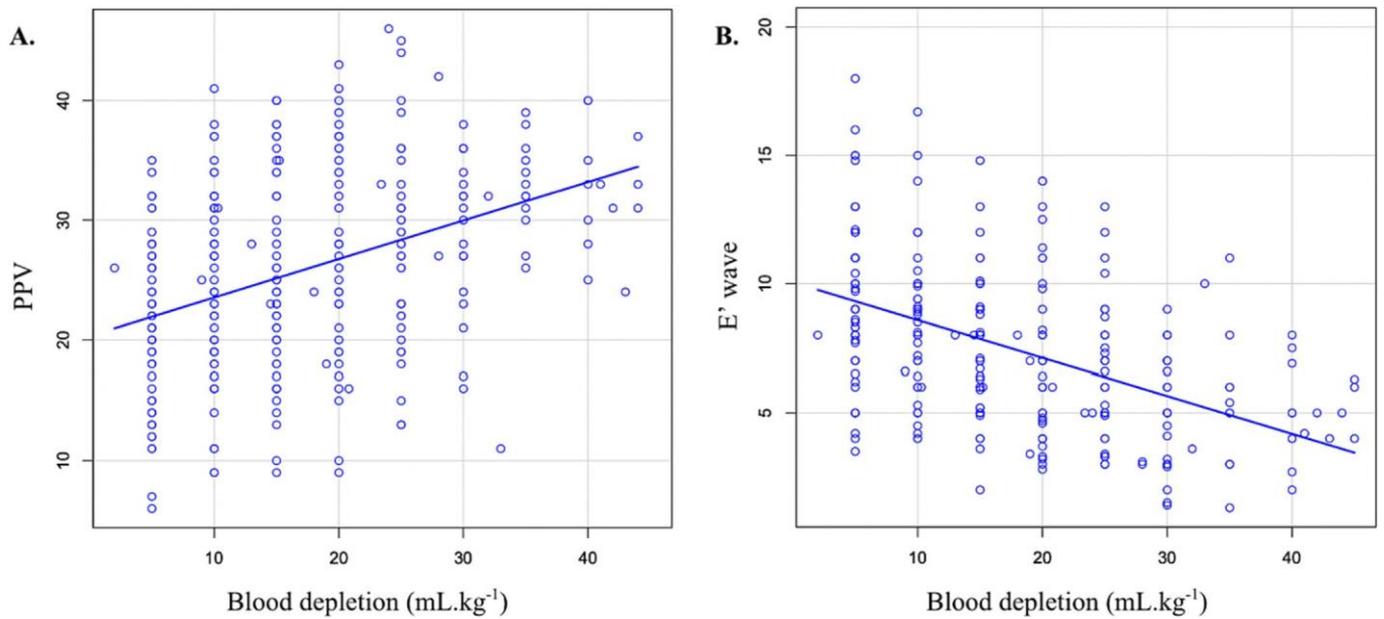


Fig. 3. A. Correlation between pulse pressure variations and blood depletion volume during hemorrhagic phase. B. Correlation between E' wave at the lateral mitral annulus and blood depletion volume during hemorrhagic phase.

PPV = pulse pressure variations.

The SI can be interesting when used alone [22], but it seems even more interesting when combined with other parameters, such as the patient's age and Glasgow coma scale value. The combination of these three parameters could be a better in-hospital death predictor than the Revised Trauma Score or Injury Severity Score [23]. The SI could be of interest in anesthesia medicine when blood depletion during surgery is difficult to assess, as the SI seems to be of significant interest in obstetrical and perioperative medicine to monitor delivery hemorrhage [24]. Quantification of blood loss in the context of severe trauma could also be relevant in the management of blood reserves at the French Blood Establishment. The SI has been evaluated as potentially helpful in decisions about massive transfusion strategies [18]; this finding

is strengthened by the strong correlation between the SI and BDV in our study.

The ATLS classification of HS correlates blood loss with different hemodynamic parameters. Up to 30% blood loss (classes III and IV), SBP and PP seem to decrease significantly; meanwhile, HR seems to increase [13]. In our study, MAP appears to be the parameter with the best correlation with BDV, even though it remains moderate ($r_{MAP-BDV} = -0.47$, CI 95%, $[-0.55; -0.38]$) compared with SBP, DBP, and PP. However, PP remains the parameter with the best correlation with SV because it corresponds to the difference in BP between DBP at the end of the diastole and SBP at the peak systole after SV ejection [25]. Our result is consistent since PP seems to benefit, like VTI, from a moderate correlation

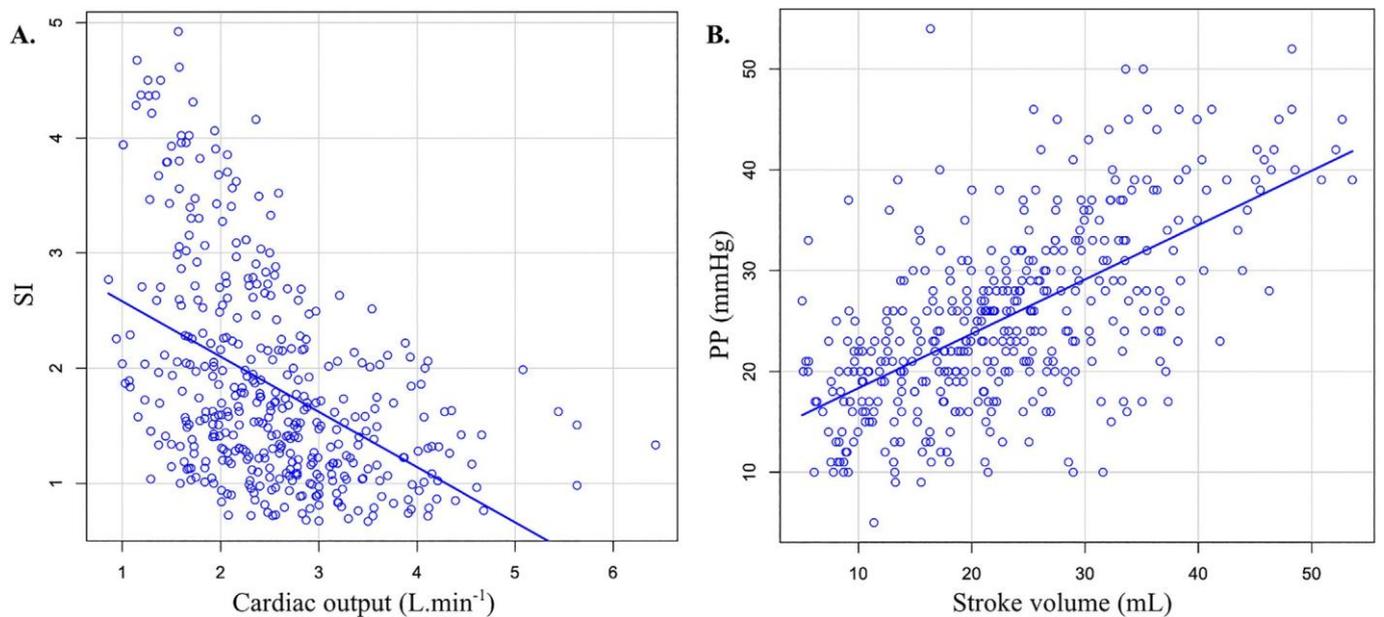


Fig. 4. A. Correlation between shock index and cardiac output measured by thermodilution during hemorrhagic phase. B. Correlation between pulse pressure and stroke volume during hemorrhagic phase.

SI = shock index; PP = pulse pressure.

with SV ($r_{PP-SV} = 0.62$, CI 95%, [0.56; 0.67]). PPVs are also moderately correlated with BDV, confirming the association between SV and BDV [14].

The correlation between SI and CO obtained by the thermodilution system seems moderate ($r_{SI-CO} = -0.45$, CI 95% [-0.53; -0.37]) but still better than with VTI ($r_{VTI-CO} = -0.38$, CI 95%, [-0.47; -0.28]). Echocardiographic evaluation of CO implies VTI and aortic surface measurement, which are often manually performed, implying poor reproducibility. Automatized methods should be developed [26]. In any case, CO assessment remains the gold standard in hypovolemic shock management [27], and an increase of 15% following fluid filling is considered a good response [28]. The CO, directly correlated with the SV by a multiplication by HR, is an indirect estimation of the patient's blood volume. The real challenge is to develop tools for non-invasive estimation of CO from hemodynamic or biological measurements [29] to replace pulmonary artery catheterization, which remains the gold standard but is a highly invasive procedure [30]. Moreover, as CO is associated with peripheral vascular resistance, MAP seems to be preferred to SBP in CO estimation [30-32]. This may explain why the SI does not seem to be an interesting monitoring tool in the assessment of CO. In conclusion, PP seems to be a better tool for CO monitoring than any other BP parameter [33]. It should be noted that we interested in CO rather than cardiac index due to the lack of reproducibility in measuring the body surface area of animals without their sizes, which were not measured.

4.2. Limitations

Our study had some limitations. First, this was an experimental study, and extrapolation of the results to humans must be done with caution. While it seems possible to extrapolate parameter variations to humans, the physiological values are different. For example, the mean SI of piglets in the basal state was >1, whereas a threshold of SI > 0.9 already seems to be a morbidity-mortality factor for the human population [34]. Second, this model of controlled HS differs from the conditions of management of the severe trauma patient since it does not take associated traumatic injuries into account. These tissue injuries alter hemodynamic parameters independently of hemorrhage [35,36]. Third, the piglets were ventilated with a tidal volume of 6 to 8 mL.kg⁻¹, which is different from the recommended tidal volume of 6 mL.kg⁻¹ for all patients [37]. It should be noted that the impact of drugs used for premedication and induction on the physiologic response, especially sympathetic, on hemorrhage was not considered and constitutes a limitation of our study. Finally, SBP was measured invasively. The SI value in assessments of blood depletion when SBP is measured with an oscillometric method will need to be evaluated.

5. Conclusion

In this model of controlled HS in piglets, SI seemed to benefit from a strong correlation with BDV, whereas E' wave correlated moderately and VTI and PPV correlated only poorly. Because SI is an accessible and reproducible monitoring tool, these results should be verified in clinical research and with the use of noninvasive SBP measurement techniques.

Funding

None.

Media summary

Emergency medicine requires reproducible and accessible parameters such as Shock Index for monitoring blood loss in severe trauma patients. This experimental study based on a piglet model of controlled

hemorrhagic shock seems to show a strong correlation coefficient of 0.70 (CI 95%, [0.64;0.75]; $p < 0.01$) between Shock Index and blood loss.

CRediT authorship contribution statement

Thomas Sanchez: Writing – review & editing, Writing – original draft. Fabien Coisy: Data curation. Laura Grau-Mercier: Data curation. Céline Occelli: Data curation. Florian Ajavon: Data curation. Pierre-Géraud Claret: Investigation. Thibaut Markarian: Data curation. Xavier Bobbia: Supervision, Investigation.

Declaration of Competing Interest

XB declares a competing interest as a US teacher for GE (GE. MEDICAL SYSTEMS ULTRASOUND) customers. The other authors state they have no competing interests.

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