Measurement of mean systemic filling pressure after severe hemorrhagic shock in swine anesthetized with propofol-based total intravenous anesthesia: implications for vasopressor-free resuscitation

Athanasios Chalkias1,2, Anastasios Koutsovasilis3, Eleni Laou1, Apostolos Papalois4, Theodoros Xanthos5

1Department of Anesthesiology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa; 2Hellenic Society of Cardiopulmonary Resuscitation, Athens; 33rd Department of Internal Medicine, Nikaia General Hospital, Nikaia; 4ELPEN, Experimental-Research Centre, Athens, Greece; 5European University Cyprus, School of Medicine, Nicosia, Cyprus

Background: Mean systemic filling pressure (Pmsf) is a quantitative measurement of a patient’s volume status and represents the tone of the venous reservoir. The aim of this study was to estimate Pmsf after severe hemorrhagic shock and cardiac arrest in swine anesthetized with propofol-based total intravenous anesthesia, as well as to evaluate Pmsf’s association with vasopressor-free resuscitation.

Methods: Ten healthy Landrace/Large-White piglets aged 10–12 weeks with average weight 20 ± 1 kg were used in this study. The protocol was divided into four distinct phases: stabilization, hemorrhagic, cardiac arrest, and resuscitation phases. We measured Pmsf at 5–7.5 seconds after the onset of cardiac arrest and then every 10 seconds until 1 minute postcardiac arrest. During resuscitation, lactated Ringers was infused at a rate that aimed for a mean right atrial pressure of ≤ 4 mm Hg. No vasopressors were used.

Results: The mean volume of blood removed was 860 ± 20 ml (blood loss, ~61%) and the bleeding time was 43.2 ± 2 minutes while all animals developed pulseless electrical activity. Mean Pmsf was 4.09 ± 1.22 mm Hg, and no significant differences in Pmsf were found until 1 minute postcardiac arrest (4.20 ± 0.22 mm Hg at 5–7.5 seconds and 3.72 ± 0.23 mm Hg at 55–57.5 seconds; P = 0.102). All animals achieved return of spontaneous circulation (ROSC), with mean time to ROSC being 6.1 ± 1.7 minutes and mean administered volume being 394 ± 20 ml.

Conclusions: For the first time, Pmsf was estimated after severe hemorrhagic shock. In this study, Pmsf remained stable during the first minute post-arrest. All animals achieved ROSC with goal-directed fluid resuscitation and no vasopressors.

Key Words: anesthesia; hemodynamics; hemorrhagic shock; mean systemic filling pressure; resuscitation

INTRODUCTION

Circulatory shock is one of the commonest causes of death worldwide, occurring in the majority of patients admitted to the intensive care unit [1]. In patients with shock, venous return is maintained by the pressure gradient between the mean systemic filling pressure (Pmsf)
and central venous pressure (CVP) [2]. The Pmsf is a quantitative measurement of the patient’s volume status and represents the tone of the venous reservoir [3].

During hemorrhage, physiological compensation may maintain tissue perfusion [4], but the compensatory response to blood loss and time course for development of shock is largely affected by the individual characteristics of the patient. Adjustments within the venous system are critical for maintaining venous pressure during hemorrhage, and mobilization of unstressed blood volume has been characterized as the predominant and most effective mechanism in preserving venous return and thus cardiac output (CO) [5]. Of note, total intravenous anesthesia (TIVA) is frequently used in patients with hemorrhagic shock due to TIVA’s well-known advantages, such as predictable and rapid recovery, preservation of hypoxic pulmonary vasoconstriction, and reduction in intracerebral pressure [6]. In TIVA, any combination of intravenous hypnotic(s) and opioid(s) can be used; but in practice, propofol-based TIVA (PTIVA), coupled with other agents depending on the patient’s physiological status and the type of procedure, is the most commonly used technique [7].

During the initial stages of acute hemorrhage, venous return, and thus CO is supported by the venous system converting unstressed to stressed blood volumes [5]. However, PTIVA can cause marked reductions in efferent muscle sympathetic nerve activity and plasma catecholamines, reducing systemic vascular resistance (SVR) and aggravating hemodynamics, especially in patients with marginal physiological reserve [6-8]. Although understanding venous return is crucial for optimizing survival rates, the evidence in these patients remains scarce. In this study, we sought to estimate Pmsf after severe hemorrhagic shock and cardiac arrest in swine anesthetized with PTIVA, as well as to study Pmsf’s association with vasopressor-free fluid resuscitation.

MATERIALS AND METHODS

Ethical Approval
All animal procedures performed were approved by the Directorate of Veterinary Services according to the national legislation regarding ethical and experimental procedures. These procedures conformed to the guidelines from Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes or the current National Institutes of Health guidelines. This manuscript adheres to the applicable Animal Research: Reporting of In Vivo Experiments guidelines.

KEY MESSAGES

- In this study, mean systemic filling pressure (Pmsf) was estimated after severe hemorrhagic shock and cardiac arrest in swine anesthetized with propofol-based total intravenous anesthesia (PTIVA).
- Mean Pmsf was 4.09 ± 1.22 mm Hg, while no significant differences in Pmsf were found until 1 minute post-cardiac arrest. All animals achieved return of spontaneous circulation with goal-directed fluid resuscitation and no vasopressors.
- Our findings do not support the early use of vasopressors after hypovolemic cardiac arrest during PTIVA.

Origin and Source of the Animals
This prospective analysis used 10 healthy Landrace/Large-White piglets aged 10–12 weeks with average weight 20 ± 1 kg, all purchased from the same breeder (Validakis, Koropi, Greece). These animals were used for teaching purposes in the Experimental Part of the Postgraduate Study Program “Resuscitation” of the University of Athens, Greece (permit no. 1188/28-2-2014, 4856/15-9-2017).

One week prior to the experiments, the animals were transported to the research facility (Experimental-Research Center Elpen, European Ref Number EL 09 BIO 03) and were acclimatized to laboratory conditions, as previously described [9-11]. The day before the experimentation, the animals were fasted but had free access to water. All animals received anesthetic and surgical procedures in compliance with the Guide for the Care and Use of Laboratory Animals.

Animal Preparation
In brief, the animals were premedicated with intramuscular ketamine hydrochloride (10 mg/kg; Merial, Lyon, France), midazolam (0.5 mg/kg; Roche, Athens, Greece), and atropine sulphate (0.05 mg/kg; Demo, Athens, Greece) [12]. The animals were subsequently transported to the operation research facility, and intravascular access was obtained through the auricular veins. Induction of anesthesia was achieved with an intravenous bolus dose of propofol (2 mg/kg; Diprivan 1% w/v; AstraZeneca, Luton, UK) and fentanyl (2 μg/kg; Janssen Pharmaceuticals, Beerse, Belgium) [9,10]. The same researcher performed the intubation with a size 6.0-mm cuffed endotracheal tube while the animals were breathing spontaneously. The endotracheal tube was secured on the lower jaw, and successful intubation was ascertained by auscultation of both lungs while the piglets were ventilated with a self-inflating bag [10].
The animals were then immobilized in the supine position on the operating table and were volume-control ventilated (tidal volume 10 ml/kg, I:E 1:2, PEEP 0 cm H₂O, and FiO₂ 21%; Siare Alpha-Delta Lung Ventilator, Bologna, Italy), while anesthesia was maintained with 0.1 mg/kg/min propofol infusion, 0.6 μg/kg/min fentanyl, and 20 μg/kg/min cisatracurium. Normocapnia was achieved using continuous monitoring of end-tidal CO₂ (Tonocap TC-200-22-01; Engstrom Division, Instrumentarium Corp., Helsinki, Finland), and the respiratory rate was adjusted to maintain an end-tidal CO₂ of 35–40 mm Hg. Pulse oximetry (SpO₂) was monitored throughout the experiment. Body temperature was monitored by a rectal temperature probe and was maintained between 38.5°C and 39.5°C with a heating blanket.

Electrocardiographic monitoring was performed using leads I, II, III, aVR, aVL, and aVF, which were connected to a monitor (Mennen Medical, Envoy; Papapostolou, Athens, Greece) [12]. The monitor electronically calculated the heart rate. For measurement of aortic pressures, an arterial catheter (model 6523, USCI CR, Bart; Papapostolou, Athens, Greece) was inserted and forwarded into the descending aorta after surgical preparation of the right internal carotid artery. The systolic (SAP) and diastolic (DAP) arterial pressures were recorded, and mean arterial pressure (MAP) was determined by electronic integration of the aortic blood pressure waveform [11]. The left internal jugular vein was also cannulated, and a Swan-Ganz catheter (Opticath 5.5F, 75 cm; Abbott, Lidakis, Athens, Greece) was inserted into the right atrium. Intravascular catheters were attached to pressure transducers that were aligned to the level of the right atrium and were calibrated before their use. This allowed the recording of CVP and arterial pressures.

CO was measured as the product of time-velocity integral of Doppler transaortic flow, the diameter of the aortic valve, and heart rate; SVR was calculated using the formula SVR = (MAP-CVP)/CO × 80, as previously described [10,11]. Coronary perfusion pressure (CPP) was electronically calculated as the difference between minimal DAP and the simultaneously measured right atrial diastolic pressure [12]. Arterial blood gases were measured on a blood-gas analyzer (IRMA SL Blood Analysis System, Part 436301; Diametrics Medical Inc, Roseville, MN, USA; pH, pO₂, pCO₂). Baseline data were collected after allowing each animal to stabilize for a 30-minute period.

Experimental Protocol
The protocol simulated a major hemorrhage scenario and has been previously described [11]. In brief, the protocol was divided into four distinct phases: stabilization, hemorrhagic, cardiac arrest, and resuscitation phases (Figure 1). All animals were treated by the same researchers.

Stabilization phase
After induction of anesthesia and instrumentation for recording of hemodynamic variables, swine were allowed to stabilize for 30 minutes. Once a steady state was achieved, baseline measurements including all variables previously mentioned were obtained.

Hemorrhagic phase
After baseline data collection, acute hemorrhage was induced by repeated removal of 5 ml/kg from the internal jugular vein in less than 5 minutes; total blood volume was estimated as 7% of total body weight. In this phase, data were obtained after completion of blood withdrawal.

Cardiac arrest phase
Cardiac arrest was recognized electrocardiographically and/or confirmed by loss of arterial pulse. Mechanical ventilation and administration of anesthetics were discontinued simulta-
neously with the onset of cardiac arrest.

Resuscitation phase
After the first minute of cardiac arrest and measurement of Pmsf, resuscitation was immediately initiated with ventilation in 100% oxygen and chest compressions at a rate of 100/min (LUCAS; Jolife, Lund, Sweden), while iv infusion of lactated Ringers was started at a rate that aimed for a mean right atrial pressure (RAP) of ≤ 4 mm Hg. No vasopressors were administered during the study period. Successful resuscitation was defined as restoration of spontaneous circulation (ROSC) with a MAP of at least 60 mm Hg for a minimum of 15 minutes. The animals that survived were humanely euthanized by an intravenous overdose of pentobarbital 3 g.

Mean Systemic Filling Pressure
Shortly after cardiac arrest, significant changes in vasomotor tone occur, while the arterial pressure falls and the venous pressure rises until nearly reaching equilibrium [13,14]. This mandates the measurement of Pmsf within the first few seconds after arrest [13,15]. However, the hypotension-induced baroreflex withdrawal maintains an antegrade and pulmonary blood flow that may continue for more than 30–60 seconds [14]. As Pmsf may vary among patients, the maximum flow could be better assessed if the time of arrest is more than 20 seconds [8,16]. Based on these, we initially measured Pmsf using the equilibrium RAP between 5 and 7.5 seconds after the onset of cardiac arrest, before the reflex response had significantly altered the measured plateau pressure [14,17,18]. Then, we continued assessing Pmsf every 10 seconds until 1 minute post-cardiac arrest, provided that the measured plateau pressure had not significantly altered. In our study, Pmsf was measured at six time points (5–7.5, 15–17.5, 25–27.5, 35–37.5, 45–47.5, and 55-57.5 seconds).

**Animal Inclusion Criteria**
As arteries are much less compliant than veins, transfer of the remaining arterial volume sufficient to equalize pressures throughout the vasculature could not significantly increase Pmsf or affect measurements in our study [17]. In this context, a plateau was considered adequate to allow accurate measurement if RAP rose by less than 1 mm Hg over the period from 5 to 7.5 seconds after the onset of cardiac arrest [16]. In our study, all animals had adequate plateau and were included for further analysis.

**Statistical Analysis**
Continuous variables were expressed as mean (standard deviation) and categorical variables as percentages. The normal distribution of each variable was assessed by Kolmogorov-Smirnov’s test. Comparisons of continuous variables among the groups were made using analysis of variance or the Kruskal-Wallis test, as appropriate. Univariate analysis was per-

**Table 1. Peri-arrest parameters of the animals**

| Variable                  | Animal | Animal | Animal | Animal | Animal | Animal | Animal | Animal | Animal | Animal |
|---------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Blood loss (ml)           | 850    | 870    | 860    | 870    | 860    | 870    | 850    | 860    | 850    | 860    |
| Bleeding time (min)       | 43     | 44     | 44     | 44     | 42     | 43     | 43     | 43     | 44     | 42     |
| Cardiac arrest rhythm     | PEA    | PEA    | PEA    | PEA    | PEA    | PEA    | PEA    | PEA    | PEA    | PEA    |
| Time to ROSC (min)        | 6      | 6      | 5      | 6      | 5      | 7      | 6      | 7      | 7      | 6      |
| Administered volume (ml)  | 400    | 390    | 400    | 390    | 400    | 400    | 390    | 400    | 390    | 380    |

PEA: pulseless electrical activity; ROSC: return of spontaneous circulation.
formed for the differences of the different situations in different periods of time. The correlations between Pmsf and all other variables in the study were measured with the Pearson correlation coefficient. All tests were two-tailed and a probability value of P < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Heart rate and MAP progressively increased and decreased, respectively, while anesthesia remained constant until cardiac arrest occurred. The mean volume of blood removed was 860 ± 20 ml (blood loss -61%) and the bleeding time was 43.2 ± 2 minutes, while all animals developed pulseless electrical activity. The peri-arrest parameters in our animals are depicted in Table 1.

The mean Pmsf value was 4.09 ± 1.22 mm Hg (Figure 2), while no significant differences in Pmsf were observed between the six time points (4.20 ± 0.22 mm Hg at 5–7.5 seconds, 3.72 ± 0.23 mm Hg at 55–57.5 seconds, P = 0.102) (Table 2). During the first minute of cardiac arrest, Pmsf was statistically significantly correlated with SAP (r = 0.926, P = 0.008), MAP (r = 0.926, P = 0.007), CVP (r = 0.926, P = 0.008), end-tidal carbon dioxide (r = 0.956, P = 0.004), shock index (r = −0.916, P = 0.010) and modified shock index (r = −0.949, P = 0.004). There was no statistically significant correlation between Pmsf and DAP (r = 0.370, P = 0.446). During the first minute after cardiac arrest, statistically significant changes in CPP (19.32 ± 0.73 mm Hg at 5–7.5 seconds and 17.62 ± 0.66 mm Hg at 55–57.5 seconds; P = 0.046) and SVR (575.5 ± 36.64 dyn·s/cm² at 5–7.5 seconds and 401.5 ± 16.7 dyn·s/cm² at 55–57.5 seconds, P = 0.016) were observed with time.

All animals achieved ROSC with mean time to ROSC being 6.1 ± 1.7 minutes and mean administered volume being 394 ± 20 ml.

DISCUSSION

Hemorrhagic shock is a condition of acute reduction in central blood volume and inadequate tissue perfusion. At the initial stages of hemorrhage (~10%–15%), the secretion of endogenous catecholamines recruits blood from the unstressed compartment, preserving Pmsf and venous return [1,19,20]. At later stages, this mechanism no longer functions and Pmsf decreases proportionally to circulatory volume [20,21]. The venous system plays an important role in hemodynamic stability, and Pmsf provides a quantitative measurement of the intravascular filling status independent of cardiac function [22]. However, little evidence exist regarding the measure-

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### Table 2. Hemodynamic variables during the first minute of cardiac arrest

| Variable       | 5–7.5     | 15–17.5   | 25–27.5   | 35–37.5   | 45–47.5   | 55–57.5   | P-value |
|----------------|-----------|-----------|-----------|-----------|-----------|-----------|---------|
| HR (beats/min) | 135.80 ± 8.42 | 132.32 ± 6.33 | 133.60 ± 5.35 | 133.51 ± 5.15 | 132.64 ± 4.28 | 130.62 ± 2.88 | 0.102   |
| SAP (mm Hg)    | 36.91 ± 1.20  | 35.02 ± 1.91  | 34.33 ± 0.82  | 32.25 ± 0.90  | 31.07 ± 0.55  | 30.29 ± 0.81  | 0.048   |
| DAP (mm Hg)    | 23.52 ± 0.90  | 22.67 ± 1.15  | 23.55 ± 2.52  | 23.13 ± 1.70  | 23.11 ± 1.61  | 23.04 ± 1.30  | 0.223   |
| MAP (mm Hg)    | 27.98 ± 2.10  | 26.82 ± 1.42  | 27.13 ± 1.95  | 26.17 ± 1.40  | 25.80 ± 1.23  | 25.50 ± 1.14  | 0.046   |
| SVR (dyn·s/cm²)| 575.5 ± 36.64 | 534.8 ± 22.11 | 489.5 ± 23.62 | 469.3 ± 21.8  | 429.4 ± 18.6  | 401.5 ± 16.7  | 0.016   |
| CPP (mm Hg)    | 19.32 ± 0.73  | 18.33 ± 0.55  | 18.02 ± 0.57  | 17.82 ± 1.13  | 17.70 ± 0.92  | 17.62 ± 0.66  | 0.046   |
| PP (mm Hg)     | 13.38 ± 0.35  | 12.35 ± 0.88  | 10.78 ± 1.15  | 9.12 ± 1.14  | 7.96 ± 1.42  | 7.25 ± 0.48  | 0.040   |
| SI             | 3.72 ± 0.02  | 3.77 ± 0.05  | 3.92 ± 0.05  | 4.14 ± 0.06  | 4.27 ± 0.04  | 4.31 ± 0.05  | 0.048   |
| MSI            | 4.95 ± 0.04  | 4.92 ± 0.05  | 4.90 ± 0.07  | 5.12 ± 0.03  | 5.15 ± 0.05  | 5.13 ± 0.12  | 0.088   |
| Pmsf           | 4.20 ± 0.22  | 4.11 ± 0.23  | 4.12 ± 0.12  | 3.94 ± 0.22  | 3.93 ± 0.21  | 3.72 ± 0.23  | 0.102   |
| ETCO₂ (mm Hg)  | 12.84 ± 2.13  | 11.44 ± 1.55  | 10.75 ± 0.37  | 10.11 ± 0.35  | 9.96 ± 0.35  | 9.23 ± 0.45  | 0.036   |

Values are presented as mean ± standard deviation.

HR: heart rate; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; CPP: coronary perfusion pressure; PP: pulse pressure; SI: shock index; MSI: modified shock index; Pmsf: mean systemic filling pressure; ETCO₂: end-tidal carbon dioxide.
all animals achieved ROSC with fluid resuscitation only. These findings indicate a significant adaptability of the animals to the major hemorrhagic event that merits further analysis.

Pmsf increases with an increase in blood volume or a decrease in venous compliance. In our animals, the hypovolemic-induced sympathetic stimulation resulted in peripheral vasoconstriction and volume recruitment from the unstressed compartment in an attempt to preserve vital organ perfusion during hemorrhage. The severity of shock (~61% blood loss) implies maximal utilization of the unstressed volume prior to cardiac arrest. After the onset of cardiac arrest, the pressure in the small veins and venules, being the “pivoting point” of the swine cardiovascular system, must not have changed substantially [23]. This pressure is less than the capillary pressure, nearly equal to the portal venous pressure, and greater than the RAP [22]. The non-significant differences in Pmsf between the six time points indicate a preserved vascular tone, which, together with the goal-directed fluid administration (RAP ≤ 4 mm Hg), preserved venous return without the need for an exogenous vasopressor.

Administration of vasopressors in the early stages of hemorrhagic shock remains controversial. Vasopressors are usually used in the presence of life-threatening hypotension and absence of response to fluid therapy or the presence of vasoplegia [24]. Also, administration of anesthetics at any stage of shock may exacerbate hemodynamics; initiation of vasopressor therapy with ongoing volume replacement in order to maintain an adequate tissue perfusion seems rational. However, vasopressor administration in the absence of adequate volume resuscitation may worsen the outcome [25]. Furthermore, a recent post-hoc analysis of a prospective, multicenter, observational study reported that epinephrine administered during in-hospital resuscitation was associated with a lower 7-day survival rate in patients with out-of-hospital cardiac arrest following trauma. The authors suggested that resuscitation without epinephrine in traumatic cardiac arrest should be further studied [26]. Interestingly, our findings indicate that exogenous vasopressors may not always be necessary in severe hemorrhagic shock and/or hypovolemic cardiac arrest and should be carefully titrated during the early stage of resuscitation. Maintaining venous return is crucial; therefore rapid and/or liberal vasopressor and fluid administration may lead to an excessive increase in venous resistance and RAP, respectively, aggravating venous return and CO [1,3,21]. In a porcine model of hemorrhage resuscitation, the slope of RAP exceeded peripheral venous pressure when pulmonary artery occlusion pressure increased to more than 10 mm Hg during volume resuscitation, causing the pressure gradient for venous return to progressively decrease [27]. As even slight changes in blood volume caused by sympathetic activity can have large effects on Pmsf (which is known to increase almost linearly) [28], different resuscitation practices than currently recommended may be needed in order to improve survival rates in hemorrhagic shock or hypovolemic cardiac arrest [6,29-31].

Our results add to the evidence suggesting that changes in Pmsf can be used to assess systemic compliance and guide the choice between fluids or vasopressors [32]. Although Pmsf is not easy to understand, it could be integrated in the future as another monitoring parameter to understand the patient’s condition and to guide personalized physiology-guided resuscitation. According to our findings, an SVR of > 400 dyn-s/cm² may also indicate a preserved arterial tone and no need for exogenous vasopressors. Nevertheless, the optimal dose and time of vasopressor administration in relation to Pmsf or SVR should be further investigated. Of note, new pharmacological agents have shown promising results and may allow the optimization of Pmsf, venous return, and tissue perfusion in hemorrhagic shock and cardiac arrest. Centhaquin, a novel agent under clinical development, was recently evaluated in a Phase II trial and proved highly effective in the resuscitation of hypovolemic shock by increasing MAP and decreasing the volume of administered fluids while maintaining tissue perfusion [32-35].

Furthermore, the potential hemodynamic and organ-protective effects of anesthetics cannot be neglected. Fentanyl attenuates myocardial injury caused by high-dose adrenaline without blunting its hemodynamic effects, protects against myocardial ischemia-reperfusion injury, reduces infarct size, and enhances recovery of cardiac contractile function [36]. Propofol has been reported to improve microcirculatory perfusion and protect against ischemia-reperfusion injury and apoptosis [37]. However, hemorrhagic shock may alter the pharmacology of propofol and increase propofol’s end-organ sensitivity [38]. Also, propofol is 96%–98% protein bound, and changes in unbound propofol between bled and unbled animals have not been reported [39,40]. Two animal studies have reported that lower concentrations are required to achieve a desired drug effect, while partial resuscitation with lactated Ringers solution nearly eliminated the pharmacokinetic changes and attenuated the pharmacodynamic changes of hemorrhagic shock on propofol [41,42]. All these may apply in our animals, in which PTIVA remained constant until the onset of cardiac arrest. Nevertheless, further study is required to assess the protective effects of PTIVA after hypovolemic shock and cardiac arrest.
The authors recognize several limitations in the interpretation of the present findings. First, the study was conducted on apparently healthy pigs without potential comorbidities or associated traumatic injuries. Another limitation is that we measured Pmsf without addressing passive recoil effects, non-steady state effects, or volume transfers between the peripheral and central compartments. Also, we did not assess long-term survival due to the study design. However, our swine model simulates the real hemodynamic events of hemorrhagic shock from the onset of pathophysiological manifestations to cardiac arrest, and our results may add to the understanding of Pmsf complexity in critically ill patients. We believe that the findings of this study are important for the understanding of the physiologic basis of goal-directed treatment and the titration of resuscitation efforts to the patient’s physiologic response [43].

In conclusion, in swine anesthetized with PTIVA, no significant differences in Pmsf were observed between the six time points after severe hemorrhagic shock and cardiac arrest, while all animals achieved ROSC with goal-directed fluid resuscitation and no vasopressors.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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ORCID

Athanasios Chalkias https://orcid.org/0000-0002-7634-4665
Anastasios Koutsovasilis https://orcid.org/0000-0003-4436-6445
Eleni Laou https://orcid.org/0000-0002-4113-3083
Apostolos Papalois https://orcid.org/0000-0001-8339-7426
Theodoros Xanthos https://orcid.org/0000-0003-3670-9305

AUTHOR CONTRIBUTIONS

Conceptualization: AC. Data curation: AC, TX, AP. Formal analysis: AK, EL. Methodology, Project administration, & Visualization: AC, TX. Writing—original draft: AC, TX, EL. Writing—review & editing: all authors.

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