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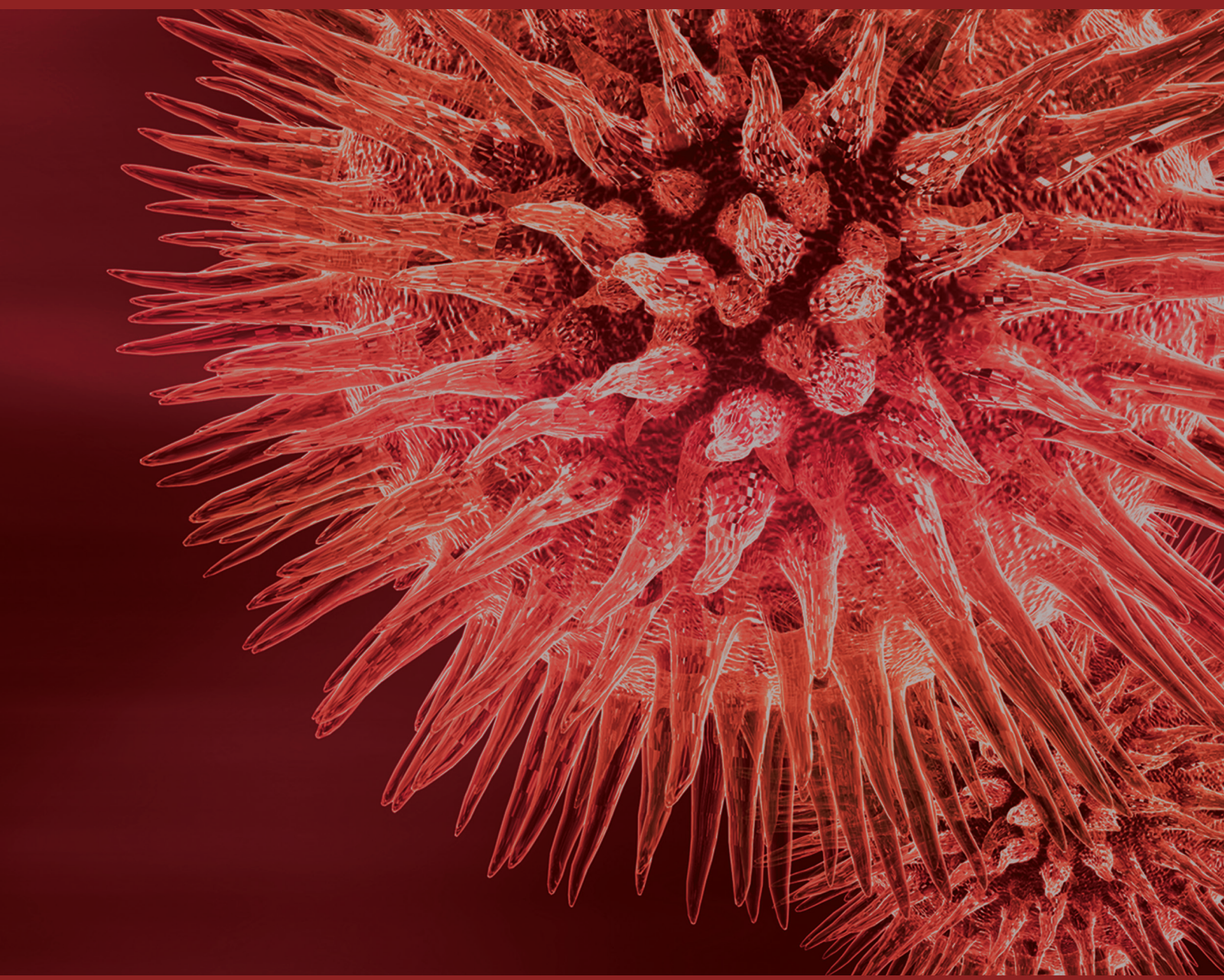
Guest Editors: Mitja Lainscak, Zsolt Molnar, Xavier Monnet, and Gorazd Voga



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Editorial

Cardiovascular Function in Intensive Care Medicine or *Homo Mensura Est*

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Global burden of disease, in terms of both mortality and morbidity, is increasing [1, 2]. Ageing of population and better management of acute conditions are significant contributors, yet there is much more to be done. Also, there are numerous situations in clinical practice where we are left with limited evidence and various degrees of uncertainty regarding how to deliver the best medical practice to our patients. This in particular applies for emergency and intensive care where decisions need to be taken within minutes if not seconds; it is therefore not surprising that practicing physician may take suboptimal ways to handle the clinical challenges [3]. Heart failure serves as a good example and in fact this is only cardiovascular condition with increasing prevalence [4]. By adding various comorbidities to the main disease (e.g., anaemia, chronic obstructive pulmonary disease, chronic kidney disease, and cancer, all potentially with body wasting), you end up with an individual prone to deterioration of one or more components of its health status [5–9]. An additional challenge in acute deterioration of chronic disease is iatrogenic due to complex pharmacological therapy; in its essence, very best incentive for a stable patient can get really cumbersome for patient and a clinician once faced with failing organ functions, a common scenario in emergency and intensive medicine. With changes in pharmacokinetics, pharmacodynamics effects are unpredictable, as may be the drug-drug and in particular drug-disease or drug-disease-drug interactions [10–12]. Adding the immediate-acting drugs we usually use in this setting, we are indeed exploring the limited-evidence land and outcomes are less predictable. This, in fact, reminds us once again that we need to consider every patient as an individual with peculiarities and specific response to disease/acute condition and management we employ. Herein, we need to get back to the basics or to the fact that *Homo mensura est* (*Homo mensura est* stands for man is the measure said by Protagoras (Greek: Πρωταγόρας, c. 490–c. 420 BC)) or, in other words, that medicine is an art [13]. Yet, this coin has two sides: one is the patient whilst the other one is the practicing physician. And both of them are humans, with all pros and cons. Once in hospital due to acute condition or with critical illness, a comprehensive evaluation of cardiovascular system is crucial for reliable assessment of disease severity and management steps. Here, the other side of the coin, namely, the practicing physician, is taking Centre stage. Again, *Homo mensura est* is more true than ever. With all difficulties to assess the cardiovascular function and to take decisions in best of patient interest, one needs to rely on parameters one can reliably assess and interpret. This largely depends on one's training, experience, and confidence with particular monitoring tools or biomarkers [14–16]. Unfortunately, clinical practice tells us, despite all efforts by the clinical community [17, 18], that we do not meet the standards of good clinical practice [19]. Counterintuitively,

the development of less invasive methods for assessment of haemodynamic parameters (that all have limitations in the critically ill) did not change patterns of invasive haemodynamic monitoring. Despite availability, echocardiography remains critically underused for these purposes. The lesson learned from the FENICE study [19] should be considered as an important signal to fine-tune our preclinical and clinical training to optimize patient assessment and management.

In acute conditions, we are indeed left with limited-evidence-based medicine. But are there ways to overcome this? Primarily, we should not have prejudices how to handle our patients. The story of beta-blockers in heart failure might serve as a useful example. Initially these drugs were contraindicated, but in current heart failure guidelines, the largest wealth of evidence for prognostic benefit lies within them. Indeed, we are trying to break some long-lasting taboos of misconception through use of these pharmacological agents in obstructive pulmonary disease and during acute deterioration [20–23]. A similar frontier is sepsis, for example, [24]. In sepsis, a closer cooperation between scientific communities, clinicians, and regulatory agencies is required in order to meet future challenges. Some other communities have already paved the way and it is our mission to follow in their footsteps [25]. This issue tried to address some of these aspects. Indeed, we feel that education aiming to optimize patient assessment and to understand the pathophysiological rationale of our actions is crucial in our striving to improve patient outcome. In clinical practice, various options for haemodynamic assessment should be available. Accurate measurement gives us reliable findings that are the basis for timely diagnosis and therapeutic decisions, tailored to individual patient. We would therefore like to promote this special issue and the two review articles by J. Benes et al. and H. A. Gaspar and S. S. Morhy in particular; furthermore, we would once again like to underline the Protagoras quote *Homo mensura est*. Although generally applicable, the significance in emergency and intensive care medicine may be particularly relevant.

Mitja Lainscak
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Review Article

Fluid Therapy: Double-Edged Sword during Critical Care?

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Fluid therapy is still the mainstay of acute care in patients with shock or cardiovascular compromise. However, our understanding of the critically ill pathophysiology has evolved significantly in recent years. The revelation of the glycocalyx layer and subsequent research has redefined the basics of fluids behavior in the circulation. Using less invasive hemodynamic monitoring tools enables us to assess the cardiovascular function in a dynamic perspective. This allows pinpointing even distinct changes induced by treatment, by postural changes, or by interorgan interactions in real time and enables individualized patient management. Regarding fluids as drugs of any other kind led to the need for precise indication, way of administration, and also assessment of side effects. We possess now the evidence that patient centered outcomes may be altered when incorrect time, dose, or type of fluids are administered. In this review, three major features of fluid therapy are discussed: the prediction of fluid responsiveness, potential harms induced by overzealous fluid administration, and finally the problem of protocol-led treatments and their timing.

1. Introduction

In patients with acute circulatory failure, the primary goal of volume expansion is to increase cardiac output, hence oxygen delivery to the tissues. However, this effect is inconstant [1]: in many instances, fluid administration does not result in any hemodynamic benefits. In such cases, fluids may exert deleterious effects. In this regard, it is now well demonstrated that excessive fluid administration is associated with increased mortality, especially during acute respiratory distress syndrome (ARDS) [2] and in sepsis or septic shock [3, 4]. Whether this association between increased mortality and fluid accumulation is only an epiphenomenon based on illness severity or whether fluids exert harmful effect *per se* has to be further elucidated. However, in reality both features may contribute in part to what makes adequate fluid administration even more important. This is in contrast with the rather benevolent and uncoordinated use of fluids by clinicians worldwide as demonstrated in the recent FENICE trial [5]. In this review, we will focus on three major features of fluid therapy, which can be regarded as a double-edged sword: the prediction of fluid responsiveness, potential harms induced by overzealous fluid administration, and finally the problem of protocol-led treatments and their timing.

2. Predicting Fluid Responsiveness

The risks associated with improper fluid administration led to development of several strategies to assess "fluid responsiveness" before performing volume expansion. Although

conventional parameters of preload have been used for decades for testing fluid responsiveness, their unreliability has been demonstrated by several studies [6]. Therefore, "dynamic" indices have been introduced in order to replace these unreliable "static" markers of preload. These dynamic indices are based on the changes in cardiac output or stroke volume resulting from changes in preload, induced by mechanical ventilation, by postural maneuvers, or by the infusion of small amounts of fluids [7]. In this chapter, we will describe the advantages and drawbacks of these "dynamic" indices of fluid responsiveness and the clinical setting where they may be applicable.

2.1. Static Indices of Cardiac Preload. It is today clearly established that static markers of cardiac preload, such as the central venous pressure or pulmonary artery occlusion pressure, are unable to predict what effect will fluid administration have on cardiac output [6, 8]. The main explanation comes from basic physiology. Indeed, the slope of the cardiac function curve depends on the cardiac systolic function (Figure 1). Since this slope is unknown in a given patient, an absolute value of any "static" measure of preload could correspond to preload dependence and to preload independence. Another explanation for the unreliability of static markers of preload comes from the errors that can occur in their measurements. For instance, the measurement of central venous pressure requires a precise positioning of the pressure transducer with respect to the right atrium. It must also be carefully measured at end-expiration and should take into account the transmission of intrathoracic pressure to the right atrium. Similarly, the pulmonary artery occlusion pressure suffers from many possible errors in its measurement and interpretation [9]. To address shortcomings of these static indices, alternative methods have been developed to predict preload responsiveness. They fit in an overall concept of functional hemodynamic monitoring. They consist in observing some changes in cardiac preload, induced by mechanical ventilation, leg raising, or fluid challenges and in observing the resultant change of cardiac output or stroke volume [10].

2.2. Variations of Stroke Volume Induced by Mechanical Ventilation

2.2.1. Physiological Background. During mechanical ventilation, insufflation increases the intrathoracic pressure, increases the right atrial pressure, and hence decreases the pressure gradient of venous return. If the right ventricle is preload-dependent, this will inevitably reduce the right ventricular outflow. Increase in right ventricular afterload induced by increased lung volume contributes to this reduction of right ventricular outflow during inspiration. As certain time is needed for the transit of blood through the pulmonary vasculature, this will reduce left ventricular preload. During conventional ventilation, this should occur at expiration. If the left ventricle is preload-dependent, the left ventricular stroke volume transiently decreases at expiration. Hence, a cyclic variation of stroke volume under mechanical ventilation indicates preload-dependence of both ventricles [11].

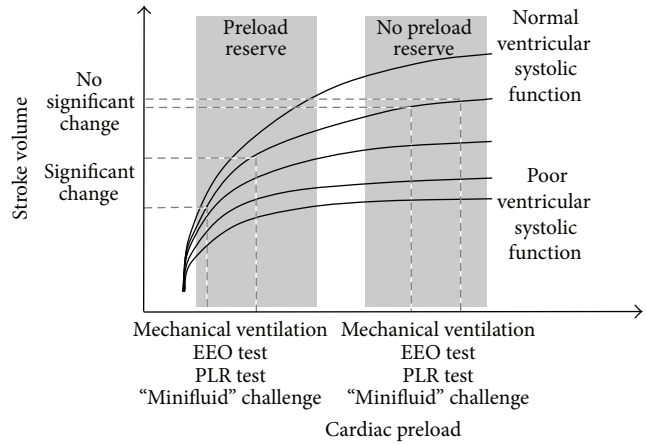

Figure 1: Cardiac function curve. There is a family of cardiac function curves depending on the ventricular contractility. If the ventricles are functioning on the steep part of cardiac function curve, changes in cardiac preload induced by mechanical ventilation, end-expiratory occlusion (EEO), passive leg raising (PLR), or "mini fluid challenge" result in significant changes in stroke volume. This is not the case if the ventricles are functioning on the steep part of cardiac function curve.

2.2.2. How to Assess the Respiratory Variations of Stroke Volume? Several surrogates or estimates of stroke volume have been used in order to quantify these respiratory variations. The first one was the systemic arterial pulse pressure [12], which is proportional to stroke volume. A number of studies have actually demonstrated that pulse pressure variation (PPV) is a reliable indicator of fluid responsiveness, provided that the conditions of its validity are fulfilled. The large number of these studies and a positive meta-analysis [13] contributed to establishment of a large and solid base of evidence for this indicator. Overall, the cut-off above which PPV is considered as significantly associated with fluid responsiveness is around 13%. Of course, as for many tests, this is not a strict cut-off. The farther from 13% the PPV value is, the higher is its diagnostic power.

Alongside PPV, other estimates of stroke volume have been used to predict preload responsiveness through their respiratory variations: stroke volume estimated by pulse contour analysis, blood flow of the left ventricular outflow tract measured by echocardiography, aortic blood flow assessed by esophageal Doppler, and the amplitude of the plethysmography signal recorded by pulse oximetry [1].

2.2.3. Conditions of Validity, Advantages, and Limitations. The respiratory variation of stroke volume as a marker of preload responsiveness is not valid under some conditions. First, in case of spontaneous breathing activity, stroke volume variations relate more to the respiratory irregularity compared to preload dependence [14]. Second, in case of cardiac arrhythmias, the variation of stroke volume within the respiratory cycles is obviously more related to arrhythmia itself than to heart-lung interactions. The third important limitation refers to ARDS [15]. In such cases, low tidal volume and/or low lung compliance [16], which reduces

the transmission of changes in alveolar pressure to the intrathoracic structures, both can diminish the amplitude of the ventilation-induced changes of intravascular pressure. This may result in false negative predictions of fluid responsiveness by PPV. Open chest surgery due to the low ratio of heart rate over respiratory rate [17] (corresponding in fact to respiratory rates at 40 breaths/minute or more) and intra-abdominal hypertension [18] are other circumstances in which PPV is unreliable to predict fluid responsiveness [10]. Overall, the limitations to the use of PPV are much more frequently encountered in the intensive care unit than in the operating theatre [19, 20].

2.2.4. Respiratory Variation of Venae Cavae. Mechanical ventilation could induce some changes in the diameter of venae cavae. Due to their high compliance, the changes are more likely to be observed in case of hypovolemia than in case of normo- or hypervolemia. The respiratory variation of the diameter of the inferior vena cava at the point where it enters the thorax was demonstrated to reliably predict fluid responsiveness [21]. This was also the case for the collapsibility of the superior vena cava [22]. The most important limitation of these methods is that they have only limited predictive value in case of spontaneous breathing activity [23] mainly because of inhomogeneous respiratory efforts. As for PPV, low lung compliance and mechanical ventilation with a low tidal volume should theoretically minimize the effect of ventilation on the vena cava diameter and may thus invalidate the method. By contrast, these methods can be used in case of cardiac arrhythmias. The respiratory variation of the inferior vena cava is simple to measure by transthoracic echocardiography, which represents an important advantage. This could be particularly useful at the early phase of care, when arterial cannulation is yet to be done. The collapsibility of the superior vena cava is much more difficult to measure and requires transesophageal echocardiography. In a patient equipped with an arterial catheter, it is easier to use PPV than the superior vena cava collapsibility.

2.3. The End-Expiratory Occlusion (EEO) Test

2.3.1. Hemodynamic Effects. As stated above, during the mechanical ventilatory cycle cardiac preload is reduced in inspiration. Stopping mechanical ventilation at end-expiration for a few seconds interrupts this cyclic decrease, meaning that end-expiratory occlusion (EEO) induces a transient increase in cardiac preload. This increase allows testing preload dependence. If the right ventricle is preload-dependent, the EEO will lead to an increased right ventricular output. If the duration of EEO is long enough for the transmission of this increased output toward the left cardiac cavities through the pulmonary circulation, left ventricular preload will increase. If the left ventricle is preload-dependent, EEO will eventually provoke an increase in cardiac output (Figure 1). Some studies consistently showed that if cardiac output increases by more than 5% during a 15-second EEO test, volume responsiveness could be predicted with a good reliability [16, 24].

2.3.2. Advantages and Limitations. Beyond its simplicity, an advantage of the EEO test is that it can be used in case of cardiac arrhythmias since it exerts its effects on a period of time (15 sec) that covers several cardiac cycles [24] (Figure 2). The EEO test can be used in patients who are not fully paralyzed and deeply sedated, unless a too marked triggering activity interrupts the 15-second EEO. Another limitation of the EEO test is that it is much easier to assess with a real-time measurement of cardiac output, such as pulse contour analysis [24]. Even if the increase in arterial pulse pressure during EEO is also indicative of fluid responsiveness [24], it requires either printing the arterial pressure curve or displaying the arterial pressure curve with a large scale, what is not allowed by many standard bedside monitors.

The EEO test remains valid whatever the level of positive end-expiratory pressure. One study reported that the prediction of fluid responsiveness by the EEO test was reliable and similar if the positive end-expiratory pressure was either 5 cmH_2O or 13 cmH_2O [25].

2.4. Fluid Challenge.

The most intuitive way to test fluid responsiveness is to administer a small volume of fluid, observe its effects on cardiac output, and expect that a subsequent larger volume expansion will exert similar effects (Figure 1). The question is what should be considered as a "small" volume of fluid. The disadvantage of the "common" fluid challenge is that it consists of infusing 300–500 mL of fluid [26]. This volume is far to be negligible. Indeed, performing the fluid challenge several times a day, as it can be necessary at the early phase of shock, inevitably leads to a significant total volume of fluid that contributes to fluid overload.

A "mini fluid challenge" has been described as an alternative [27]. In an interesting study, the effects of only 100 mL of colloid on stroke volume predicted the response of cardiac output to a 500 mL volume expansion. These changes in stroke volume were estimated by echocardiography [27]. Nevertheless, small amounts of fluid can only induce small changes in stroke volume and cardiac output. Thus, this test requires a very precise technique for measuring cardiac output. Whether echocardiography is precise enough in non-experts' hands is far to be certain. The interest of more precise measurements of cardiac output will likely be investigated.

2.5. The Passive Leg Raising (PLR) Test

2.5.1. Hemodynamic Effects. In a patient lying in the semirecumbent position, elevating the inferior limbs at 45° and lowering the trunk induces a transfer of venous blood from the lower part of the body toward the cardiac cavities. PLR increases right and left cardiac preload and acts like a transient and reversible "self-volume challenge" [28] (Figure 1). The reliability of PLR as a test of preload responsiveness has been demonstrated by several studies. An increase of cardiac output above approximately 10% predicts the response to a subsequent volume expansion with good sensitivity and specificity [29]. A recent meta-analysis of all studies performed with the PLR test confirms its strong reliability [30].

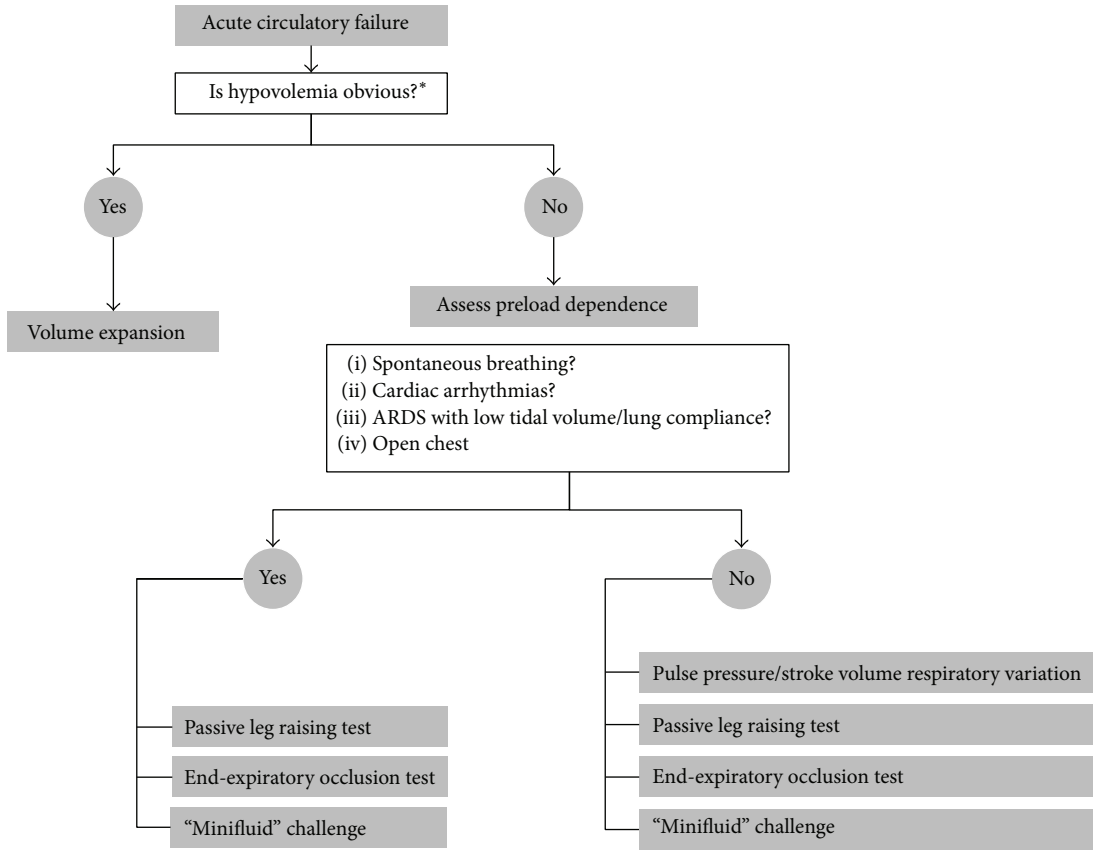

Figure 2: Decision-making algorithm of fluid administration. *Very initial phase of septic shock, when no fluid has been administered yet: in case of haemorrhagic shock or in case of hypovolemic shock due to diarrhoea, vomiting, or ketoacidosis, for instance.

2.5.2. Advantages, Limitations, and Technical Considerations. Since its hemodynamic effects occur over a long period of time, PLR remains valid in case of cardiac arrhythmias and spontaneous breathing activity. The hemodynamic effects of PLR are independent from mechanical ventilation, which explains that the PLR test can be used in some conditions in which PPV is not valid, such as low tidal volume, low lung compliance, and very high respiratory rate (Figure 2). The postural change used for PLR is important to consider. Firstly, the test should start from the semirecumbent and not from the horizontal supine position [33]. Indeed, if it starts from the semirecumbent position, PLR includes the lowering of the trunk, which is associated with a transfer of venous blood from the large splanchnic compartment to the cardiac chambers. It was actually demonstrated that this technique exerts larger hemodynamic effects compared to a horizontal starting position [34]. Secondly, it is important to move the bed of the patient and not the patient itself, because sympathetic stimulations induced by passive hip movement and pain may invalidate the measurement [33]. In this regard, the absence of an increase in heart rate during the PLR test should be checked as it shows that the changes in cardiac output are not related to sympathetic stimulation.

Another important point regards the method that must be used for assessing the PLR-induced hemodynamic changes [33]. Firstly, these effects cannot be assessed by observing the simple arterial pressure. Indeed, it has been demonstrated that the PLR-induced changes in arterial pulse pressure unreliably predict preload responsiveness, with a significant number of false negatives [29]. This is most likely due to the fact that PLR modifies the physiological properties of the arterial tree, thus changing the relationship between arterial pulse pressure and stroke volume. Thus, a technique that directly measures cardiac output is mandatory [33]. Secondly, the effects of PLR must be assessed with a technique providing a real-time measurement of cardiac output. The maximal effect on cardiac output usually occurs within one minute [29]. In some patients with a strong vasodilatation and capillary leak, the effects of PLR progressively vanish over a few minutes. This explains why pulmonary or transpulmonary thermodilution techniques, which take tens of seconds to repeat cold fluid boluses, are not suitable. The PLR method has been tested by esophageal Doppler and the changes in aortic blood flow, with pulse-contour analysis and the changes in cardiac output, cardiac output measured by bioreactance and endotracheal bioimpedance cardiography, subaortic blood velocity measured by echocardiography and ascending aortic velocity measured by suprasternal Doppler [33]. Interestingly, in patients on mechanical ventilation with perfectly regular ventilation, the PLR-induced changes in cardiac output could be simply and noninvasively be estimated by the changes in end-tidal carbon dioxide [35, 36]. This should allow using the PLR test in the absence of any cardiac output monitoring device.

Intra-abdominal hypertension could reduce the validity of the PLR test. It has been suggested that intra-abdominal hypertension could create an obstacle to the transfer of blood from the lower limbs toward the cardiac chambers through the inferior vena cava [37]. One study suggested that the PLR test was not reliable anymore if the intra-abdominal pressure was higher than 16 mmHg [38]. Nevertheless, this study did not measure the intra-abdominal pressure during PLR. Thus, this possible limitation of the PLR test needs further confirmation.

2.6. Using Predictors of Fluid Responsiveness in Practice. The prediction of fluid responsiveness should be considered differently upon the clinical setting. First, one must remember that preload dependence is a physiological condition. Thus, positive predictors of fluid responsiveness should lead to volume expansion only in case of circulatory failure. Second, in case of an obvious hypovolemia, detecting preload dependence is useless since fluid responsiveness is constant. This is the case at the very initial phase of septic shock, when no fluid has been already administered, in case of hemorrhagic shock or in case of hypovolemic shock due to diarrhea, vomiting, or ketoacidosis, for instance.

The operating theatre might be particularly adapted for the respiratory variation of stroke volume or surrogates in anesthetized patients, except if low tidal volumes are used for mechanical ventilation. In addition, such indices can be assessed by means of a simple arterial catheter or by noninvasive hemodynamic monitoring devices, which are suitable for this setting. The EEO test might also be useful, provided that the ventilator allows interrupting ventilation at end-expiration for 15 sec.

In critically ill patients, the frequent presence of cardiac arrhythmias, the low lung compliance and ventilation with low tidal volumes associated with ARDS, and the presence of some spontaneous breathing and of low lung compliance often prevent use of PPV and the related indices. The respiratory variation of vena cava can be used as an alternative in case of cardiac arrhythmias. The EEO and PLR tests are often suitable provided that their conditions of application are fulfilled.

The utility of predictors of fluid responsiveness may also depend upon the context where they are used. In the perioperative setting, prediction of fluid responsiveness might be part of the preemptive, individualized hemodynamic treatment that has been shown to reduce the rate of postoperative complications and the hospital length-of-stay in different categories of surgical patients [39–41]. In the context of intensive care, indicators of preload dependence may be particularly useful to differentiate between fluid responder and nonresponder patients, hence avoiding "underresuscitation" and/or "overresuscitation," both of which are associated with poor prognosis in case of septic shock and ARDS [42].

3. The Risks of Fluid Therapy

Today, we possess clear evidence of how detrimental unjustified and unbalanced fluid administration might be. Similar to several therapeutic interventions, fluid administration is obviously a life-saving intervention in severe hypovolemia and dehydration; however, it can also exert a number of adverse and potentially life-threatening effects (Figure 3). The effects of infusion therapy are determined by discovery of the novel mechanisms in fluid exchange. Thus, a recognition of two new important players, glycocalyx barrier and active water transporters (aquaporins), led to the critique of the Starling concept [43, 44]. The pathophysiological findings of the shift from intravascular to subglycocalyx oncotic pressure resulted in substantial change of our knowledge of the process of vascular fluid transport [45, 46]. Currently, we must realize that fluid distribution within the body of critically ill patients has become as unpredictable as ever. However, understanding these mechanisms during fluid therapy can be helpful to prevent its potential risks and follow the *primum nil nocere* principle.

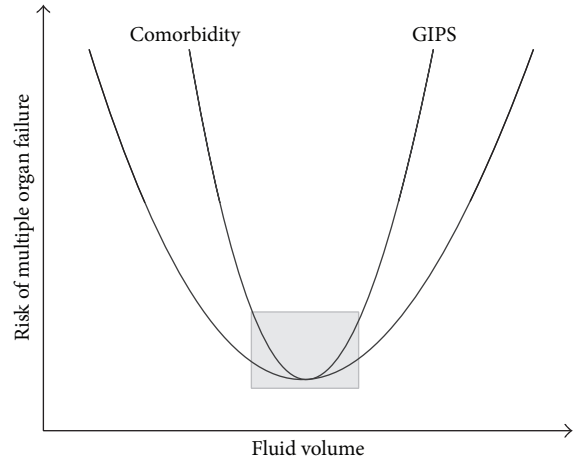

Figure 3: The risks of insufficient and excessive fluid resuscitation. GIPS—global increased permeability syndrome.

3.1. "Third Hit" of Shock. A number of guidelines recommend an aggressive and early "rescue" fluid resuscitation, particularly in severe sepsis, hemorrhagic shock, and necrotizing pancreatitis [47–49]. The body of evidence has shown that fast repletion of fluid deficit in shock using crystalloid and/or colloid solutions within a period of first 3–24 hours after admission prevents the critical decrease of oxygen delivery, attenuates the severity of multiple organ dysfunctions, and reduces the incidence of adverse effects. However, everything has its price. The most common type of dysoxia in ICU, distributive shock, can be associated with delayed "flow" phase global increased permeability syndrome (GIPS) [50]. Under conditions of increased vascular permeability, mainly due to glycocalyx injury and disturbances of lymphatic flow, fluids are leaving vascular bed and expand the interstitium. This scenario results in total weight gain and edema formation, influencing the volumes and interstitial pressure in lungs, splanchnic viscera, and peripheral tissues. An increase of body weight by more than 10% compared with baseline during ICU stay confirms the hyperhydration and may result in secondary and, hence, delayed organ dysfunction—which may be referred to as "third hit" of shock [51, 52].

The primary aim of the fluid load is to increase cardiac output and oxygen delivery in patients with compromised oxygen transport. Thus, the dynamic parameters and functional hemodynamic tests can be of great value in determining the clinically effective volume of fluid load. However, in distributive shock associated with severe GIPS targeting "normal" preload and cardiac index can result in life-threatening complications. In severe ARDS, burns, or shock associated with necrotizing pancreatitis even restrictive fluid load can be accompanied by intense fluid accumulation in the tissues, particularly in the lungs, leading to increase in extravascular lung water (EVLW), hypoxemia, and pulmonary edema. This dilemma exerts a "therapeutic conflict" that forces us to modify the goal-directed intervention and consider "permissive hypovolemia" [53]. Without any doubts, this approach can be especially useful in the settings of advanced volumetric and metabolic monitoring.

3.2. Fluid Resuscitation or Accumulation. In the literature, we can find wide range of terms describing fluid therapy in both ICU and perioperative settings including "liberal," "conservative," and "restrictive." In the review of Bundgaard-Nielsen et al. [54] merging results of seven major randomized studies, the volume of intraoperative "liberal" approach ranged from 2750 to 5388 mL, while "restrictive" approach was limited to 998–2740 mL. Therefore, the exact borders of these strategies are rather blurred, requiring individualized goal-directed titration of the fluid in most cases.

In the ICU, an excessive fluid load in the settings of GIPS, systemic inflammatory response syndrome, and multiple organ dysfunction, particularly, in ARDS and acute kidney injury (AKI), can be devastating (Table 1). The RENAL study has shown that negative net fluid balance is an independent predictor of reduced 90-day mortality and increased post-ICU lifespan [55]. In this study, the handling of negative fluid balance significantly decreased the duration of renal replacement therapy and length of ICU stay. Therefore, the goal of "negative fluid balance" should be widely adopted as important part of the delayed goal-directed therapy of critically ill patients. The spontaneous (Deescalation) or triggered ("Evacuation") removal of excessive fluid becomes the link of the modern "chain of ICU survival"—"Rescue-Optimisation-Stabilisation-Deescalation/Evacuation" (ROSD/E, see Section 4.2) [51, 52]. One from the examples for such an approach represents goal-directed ultrafiltration resulting in attenuation of intraabdominal hypertension (guided by intra-abdominal pressure (IAP)), volume overload (guided by global end-diastolic index), and pulmonary edema (guided by EVLW) [56].

During the perioperative period, the liberal fluid therapy is commonly justified by presumption of perioperative dehydration and losses into hypothetical "third space." Current evidence shows that in many patients these factors can hardly be assumed as an important reason for perioperative hemodynamic distress and should not be considered as a prerequisite for the aggressive intraoperative or preoperative fluid load [57]. Thus, in neuraxial anesthesia, vasodilatation caused by arterial hypotension is often treated with extensive fluid load; however, under these conditions the increase in preload does not counteract vasodilation and rarely increases systemic arterial pressure [58, 59]. Furthermore, several studies demonstrated that postoperative weight gain is associated with the risk of severe complications [60]. Along with other perioperative factors (ischemia-reperfusion, cytokine release, hyperoxia, etc.) excessive fluid load may be accompanied by release of atrial natriuretic peptide and the injury of the glycocalyx layer [61]. Moreover, in major abdominal surgery, liberal fluid therapy can pose the risk of increased IAP, respiratory complications, and delayed anastomosis leakage [62].

Therefore, the risks of fluid resuscitation can mainly be related to the following factors:

(1) volume and rate of fluid administration (deliberate or excessive fluid load),

(2) reperfusion phenomenon and microcirculatory recruitment,

(3) fluid-specific complications (AKI for hydroxyethyl starches (HES) or dilutional acidosis for unbalanced crystalloids).

3.3. Choice of Fluid. The choice of type of fluid does probably not primarily affect the clinically important outcomes related to the adverse effects of hyperhydration. However, at later stages the effects of type of fluid become unequivocal. According to the range of the current guidelines the use of albumin and semisynthetic colloids does not carry any obvious benefits over crystalloids and can be harmful in particular subgroups of patients like traumatic brain injury [63]. The risks of acute kidney injury and coagulation disorders related to HES-administration are well recognized in numerous studies [64]. On the other side, some guidelines, for example, European Society of Anesthesiology, comment that, compared with crystalloids, hemodynamic stabilization using isooncotic colloids (albumin, HES) may decrease tissue edema (the quality of evidence, "C") [48]. Indeed, if colloids are leaking from the vascular bed under settings of GIPS and glycocalyx flaking, they can hold the fluid within the interstitium at similar extent like within the intact vasculature.

Initial fluid resuscitation should routinely be started with crystalloid solutions. However, according to Marik [60], hyperhydration with unbalanced crystalloids can result in "Iatrogenic salt water drowning." Beyond the particular problem of hyperhydration, high dose of crystalloids, particularly 0,9% NaCl, increases the net chloride load, resulting in hyperchloremia and hyperchloremic (dilutional) metabolic acidosis. These disturbances were claimed to increase the risk of AKI and mortality [65, 66]. Thus, implementing the protocols of early goal-directed therapy, the use of high doses of unbalanced crystalloids should be avoided. The rational approach might be based on the administration of balanced, "chloride-restricted" crystalloids or, probably, in some situations (like refractory shock and ARDS in the absence of AKI and coagulopathy), on the combination of crystalloids with limited (up to 15 mL/kg) volumes of colloids.

3.4. Chapter Underline. It is important to note that the goal-directed fluid therapy aiming to central venous pressure, as

Table 1: The risks of excessive fluid load.

Settings	Adverse effect	Comment
Perioperative	Hyperchloremia and dilutional acidosis	Can be reduced using anion-balanced crystalloid solutions
	Reduced rate of wound healing	Can be related to the peripheral tissue edema
	Increased risk of anastomosis leakage	Intestinal edema and decreased splanchnic perfusion
	Increased IAP	Intestinal and abdominal wall edema
	Increased risk of respiratory complications	Pulmonary and chest wall edema. Stressfully increased work of breathing
ICU	GIPS and glycocalyx injury	The decrease of subglycocalyx oncotic pressure facilitates the capillary leakage
	Increased IAP/ACS and polycompartment syndrome	Can be associated with polycompartment syndrome resulting in AKI, liver dysfunction, FRC reduction, and ileus
	Deranged oxygenation, pulmonary and chest wall edema, incidence, or increased ARDS severity	EVLWI increase. The fluid load is an independent risk factor of ARDS
	Enteropathy	Gut edema, bacterial translocation, malabsorption, and liver congestion
	Brain edema and increased ICP	Albumin is risky
	Kidney injury	Edema of kidney parenchyma with increase of P_{INT} and decreased GFR
	Myocardial injury	Dilatation, ANP release, and myocardium edema associated with diastolic dysfunction (relaxation) and blockade
	Increased mortality	

IAP: intraabdominal pressure, ICP: intracranial pressure, ACS: abdominal compartment syndrome, GIPS: global increased permeability syndrome, ANP: atrial natriuretic peptide, ARDS: acute respiratory distress syndrome, EVLWI: extravascular lung water index, and GFR: glomerular filtration rate.

Table 2: The risks of increased central venous pressure.

Consequence	Comment
Decreased venous return and cardiac index	CVP is not a reliable characteristic of preload and, when exceeding 8 mmHg, can be an independent predictor of the mortality [31]. The normal CVP value is close to 0. According to Guyton model, both venous return and cardiac output are determined by difference between P_{MS} and CVP. An increase in CVP can result in decrease of CO when it is not associated with concomitant P_{MS} augmentation
Acute kidney injury	Increased CVP is associated with increased renal (subcapsular) (interstitial) pressure resulting in decreased renal blood flow, GFR, and derangement in lymph drainage. CVP is a sole hemodynamic parameter that can independently predict the risk of AKI starting from the values above 4 mmHg! In CVP above 15 mmHg, the risk of sepsis-induced AKI exceeds 80%
Splanchnic congestion/and microcirculatory changes [32]	The microcirculation should be recognized as a low pressure part of circulation due to abrupt decrease in blood pressure on the level of resistive arterioles. Therefore, the critical changes in microcirculation have been demonstrated in CVP > 12 mmHg. Any increase in downstream pressure (CVP) results in microcirculation distress

P_{MS}: mean (systemic) filling pressure, CVP: central venous pressure, and CO: cardiac output.

still required by Surviving Sepsis Campaign [47], in many situations can be dangerous due to number of reasons and should be avoided [31, 32, 60]. The detrimental effects of forced CVP increase can result in numerous complications presented in Table 2. Both insufficient and excessive fluid resuscitation can be detrimental for the organ function and result in deterioration of clinical outcome both in ICU patients and in major surgery. This important clinical dilemma can be resolved using up-to-date advanced methods of hemodynamic and metabolic monitoring and "phasic" approach to fluid management of critically ill patients.

4. Timing and Use of Protocols for Fluid Therapy

4.1. Protocols for Fluid Management. In previous chapters, we have demonstrated several measures to differentiate between patients who would or would not benefit from

Table 3: Four phases of hemodynamic treatment.

	Rescue	Optimization	Stabilization	Deescalation
Treatment goal	Shock reversal/Life salvage	Adequate tissue perfusion	Zero-to-negative daily fluid balance	Fluid accumulation reversal/edema resolution
Time course	Minutes	Hours	Days	Up to weeks
Hemodynamic targets	Autoregulatory thresholds of perfusion pressure	Micro/macrocirculatory blood flow parameters	Weaning of vasopressors with stable hemodynamic conditions	Return to premorbid/chronic values of pressure and flow
Treatment options	Rapid fluid boluses + vasopressors	Repeated fluid challenges + vasopressors + Inotropes	Maintenance fluids + decreasing/chronic vasoactive agents	Diuretics or other means of fluid removal

fluid administration or in fact require fluid removal. Consequences of inadequate or overzealous fluid administration were also discussed. From this point of view, it sounds rational to use strategies enabling individual titration of fluid balance which should be associated with better outcomes in critically ill patients. However, it seems that our praxis is very divergent [5, 67–69]. This may be due to controversies existing in the evidence supporting currently available fluid and/or hemodynamic management protocols. The two recent large multicenter trials ARISE [70] and PROCESS [71] in septic patients showed that protocol-led care (namely, early goal-directed therapy according to Rivers et al. [72]) was comparable to standard "do-what-you-want" treatment in severe sepsis and/or septic shock. The outcomes observed in patients managed using advanced hemodynamic monitoring (with no protocol) were comparable to those without also in other studies [73, 74]. In a recent Chinese study treatment according to transpulmonary thermodilution derived volumetric variables based protocol also showed no measurable benefit [75] although this study received serious criticisms as well [76, 77].

Even in the perioperative setting where numbers of single and multicenter trials have proved significant benefit of advanced hemodynamic monitoring guided management on morbidity, contradictory results have also been published recently. The largest study so far on this topic, the OPTIMISE trial [78], failed to prove its primary outcome of the composite 30-day moderate to major morbidity and mortality. In this last part of this paper we would try to shed some light on this disproportion and offer the reader a rational approach to the use of individualized protocols and hemodynamic monitoring tools.

4.2. Timing of Fluid Interventions (the ROSD/E Concept). It has been established in various scenarios that timing is crucial: immediate commencement of resuscitation and of the time within the target end-points reached is of utmost importance in critical care medicine. As recently pointed out by some most renowned authors [79, 80] four phases are distinguishable in the time course of critical illness: Rescue, Optimization, Stabilization, and Deescalation/Evacuation. In each of these four stages' treatment modalities, goals and monitoring tools will substantially differ (Figure 4, Table 3).

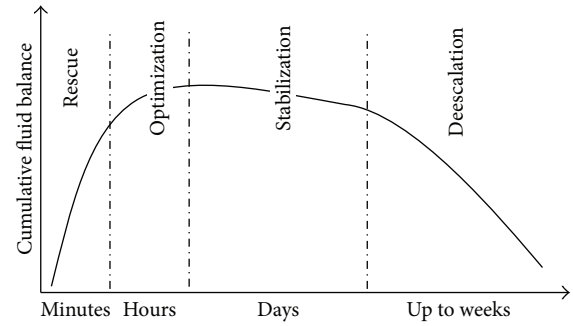

Figure 4: Four phases of hemodynamic treatment in relation to cumulative fluid balance.

4.2.1. Rescue. The Rescue phase encompasses the very first minutes to hours aiming at salvage of the patient. Naturally, only those readily available tools and minimalistic targets may be considered. In some cases, overtreatment may even be associated with harm as, for instance, overresuscitation to higher perfusion pressure with fluids in multiple trauma victims [81]. Evidence is lacking to support the use of protocols in this period. The EGDT/SSC protocol [47], namely, its first part (20 mL/kg bolus and further fluid and vasopressor administration to reach the MAP of 65 mmHg), may be considered as an example of resuscitation for patients with septic shock. However, there are some controversies regarding the predefined amount of fluid bolus, which varies from 20 mL/kg [71] to 40 mL/kg [82], but a single bolus of 1000 mLs has also been used [70]. One can also argue that considering the patients' individual premorbid conditions, higher or lower values of MAP may be more beneficial then what is recommended as a universal target in the guidelines. Reaching the lower autoregulatory threshold of the most vulnerable organs (heart and brain) seems to be the cornerstone. This is reflected in the usually proposed pressure targets: SAP of 80 mmHg (MAP 55 mmHg) in overall young and healthy population of trauma victims and MAP of 65 mmHg in septic patients mostly older with comorbidities. Besides standard pressure measurements, ultrasonography and echocardiography may offer valuable advanced information on heart function, including preload, contractility, and ventricular performance.

4.2.2. Optimization. In the Optimization phase, the therapeutic goal should be to reach the optimal perfusion of peripheral tissue and, according to some authors, to repay the oxygen debt incurred through the previous course of acute illness [83]. It is necessary to emphasize that this phase seems to be time limited. Kern and Shoemaker [84] in their meta-analysis indicated that optimization of tissue perfusion should be done in the time-window of 24 hours after the insult, although physiological rationale suggests limiting oxygen debt for the shortest time possible. Studies trying to reach predefined oxygen delivery targets later failed to improve outcome [85, 86]. This time limit may prompt the use of protocols to assure appropriate care. Fluids, vasopressor, inotropes, and vasodilators are the most commonly used measures to reach optimization goals. Fluids are the mainstay, but in the case of decreased vascular tone vasopressors should be used as early as possible in order to minimize the pathological pooling of blood and help mobilizing the unstressed volume [87]. Providing inotropic support should be reserved for those patients who after optimizing both pre- and afterload still show unsatisfactory heart performance coupled with signs of organ hypoperfusion.

Nevertheless, this pathophysiological rationale based approach is not supported by robust clinical data among critically ill patients, but several studies demonstrated benefit (length of stay and morbidity) in trauma victims [88, 89]. In severe sepsis, recent multicenter trials [70, 71, 75] proved that protocols based on targets with low predictive value for fluid responsiveness and local tissue perfusion (i.e., static parameters, CVP or ITBV, and continuous $ScvO_2$) are comparable to consultant-led treatment alone. Similarly, there is no evidence supporting the early use of advanced hemodynamic monitoring. With widespread use of critical care echocardiography many information on the heart performance may be gathered with the use of a transthoracic probe and with standard monitoring (i.e., arterial pressure curve). More invasive tools of adequate reliability may help to manage difficult patients and also help less experienced physicians to understand the underlying physiology and follow treatment goals. In this view of low evidence, only general recommendation may be derived for the everyday care (Figure 5).

4.2.3. Optimization in the Perioperative Setting. Perioperative goal-directed therapy (pGDT) has a special place in this topic of the protocol-guided therapy in the Optimization phase. In contrast to other critical care scenarios, both time and severity of the insult are well defined. Furthermore, the population of patients undergoing surgery is usually more homogenous from many aspects. Numerous studies and meta-analyses suggested that pGDT reduces the risk of postoperative complications [41, 90]. Still some controversy exists regarding the use of perioperative hemodynamic optimization. First, the rising use of less invasive hemodynamic monitoring devices led to widening of the indication. Nowadays less severe patients and procedures are considered suitable for pGDT as compared to previous years [40]. However, it follows simple logic that in these patients with reduced risks for perioperative complications only limited benefit may be expected. In fact the opposite may be true, as in a fit patient with better cardiopulmonary reserves; optimizing circulating volume to maximize the stroke volume may lead to unnecessary and potentially harmful positive fluid balance and accumulation [91]. Also, targeting the perioperative care to reach global preset values of oxygen delivery lacks advantage of individually tailored care and may be detrimental in some patients [92].

Nevertheless, surgical patients undergoing general anesthesia with controlled mechanical ventilation are ideal candidates for using dynamic predictors of fluid responsiveness (mostly based on heart-lung interactions) to rationalize intraoperative fluid therapy. Using stroke/pulse pressure volume variation or its surrogates was shown to be effective in reaching better outcomes and reducing postoperative complications in a recently published multicenter trial [93] as well as in a large meta-analysis [39]. Despite these promising results, dynamic variables have certain limitations. In a recent study by Cannesson et al., it was found that fluid responsiveness could not be predicted reliably and pressure variation was in the range of 9–13%, also called the "grey zone," which is found in 24% of the cases undergoing surgery [94]. Regarding inotropes, until proved otherwise the use of inotropes should be limited for patients not achieving adequate stroke volume despite satisfactory preload and there are signs of suboptimal global tissue perfusion such as abnormal $ScvO_2$, high lactate, and increased central venous-arterial CO_2-gap. Adequate bedside tools and targets of regional tissue perfusion capable of monitoring microcirculation are, however, still undetermined.

4.2.4. Stabilization and Deescalation/Evacuation. There is limited data regarding protocolized care in Stabilization and Deescalation. Aggressive initial treatment followed by a restrictive approach was demonstrated to be beneficial by Murphy et al. [95]. In ARDS patients FACTT [96] and recent FACTT lite trials [97] demonstrated that restrictive maintenance in stabilization phase was associated with improvement in outcome. It is of vital importance to recognize the right moment to stop the optimization, but unfortunately we possess no evidence based data to elucidate this critical moment. However, conventional indicators, such as the resolution of oliguria, a decrease in lactate levels, and improving $ScvO_2$, can be helpful but may not occur in every patient. However, it is important to acknowledge that none of these indices have a high enough sensitivity on their own to be used as a target in every patient; therefore, the so-called "multimodal" approach, meaning to take all that into account, may be necessary. At any case, if the optimization phase lasts longer than 24 hours after the initial insult, it is not associated with improved outcomes.

Similar to the rather blurred borderline between Optimization and Stabilization phases the optimal moment for the initiation of Deescalation is also unresolved. In many patients the fluid "Deescalation" is a naturally occurring process as a result of the spontaneous healing, during which forcing fluid removal is unnecessary. However, in some cases either the positive fluid balance is too large or the ability of the patient to mobilize the edema is diminished by the disease and active intervention is necessary. For this reason, a "diuretic

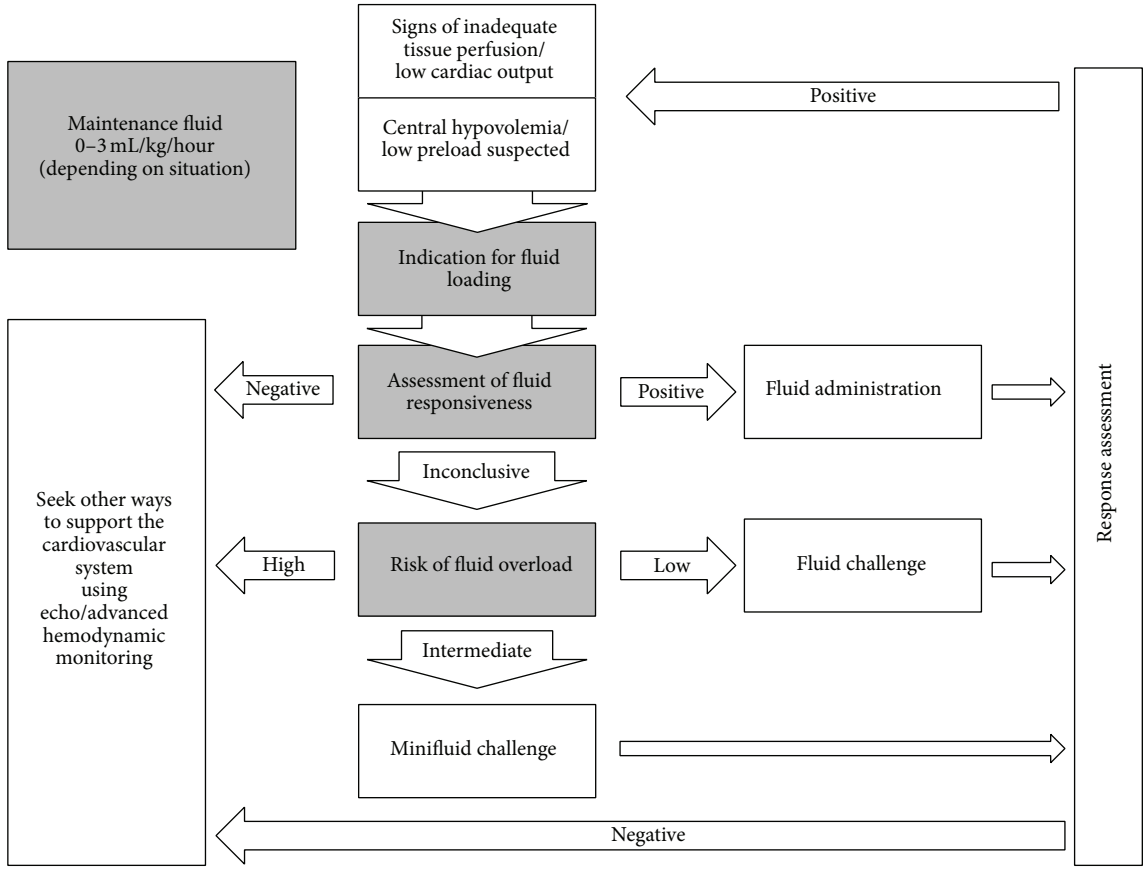

Figure 5: Decision algorithm for fluid loading in optimization phase.

responsiveness test" was recently introduced [98], which may help to identify those patients being able to reach negative fluid balance by receiving diuretics. Achieving negative fluid balance by the combined administration of albumin and furosemide was shown to improve outcomes in a small trial [99] and in a retrospective study [100]. However, in some patients the response for diuretics remains poor. In these cases an active Deescalation by extracorporeal means, also termed "Evacuation," may be considered. Nevertheless, the evidence is too weak to enable us to develop universally applicable protocolized treatment in these patients [101].

4.3. Chapter Underline. Cardiovascular insufficiency due to critical illness is a very heterogeneous entity. As pointed by Vincent et al. [102], patient populations are often defined as syndromes based on gross phenotypic variables (fever, tachycardia) rather than on distinct features of disease origin or chronic conditions. Mixing population of ARDS patients with septic ones may have altered the results of Zhang et al. study [75]. Severe sepsis due to pneumonia needs totally different approach to septic shock of intraabdominal origin in regard of fluid and hemodynamic treatment. These circumstances were probably recognized by an experienced clinician in the control arm of ARISE [70] or PROCESS [71] trials but may be neglected by protocol treatment.

5. Conclusions

Several tools are available today to assess volume responsiveness using dynamic procedures. These tools enable us to administer fluid with the assurance that it will lead to the expected increase in cardiac output. In particular, this should be included into the protocols guiding the hemodynamic treatment in the operating room setting. In the intensive care unit, these tools may be particularly useful in order to refrain from volume expansion that should reduce the risk of overzealous fluid administration. Further studies elucidating the kinetics of glycocalyx injury/regeneration and the role of vascular permeability during the goal-directed, individualized approach to the fluid resuscitation are warranted. The type and volume of the fluid should be thoroughly selected considering the phase of shock, risk of impending organ dysfunction, and individual comorbidity.

Failure to use the time-patient-tool-protocol adequate approach may lead to worse outcomes and false conclusions. Use of protocols without proper individualization will always offer simplistic solution and can never lead to improvement of care in all patients coming from some global population of different disease states and severity. In other words, protocols of care can never replace the well-educated and critically thinking physician, who is able choose the appropriate

diagnostic tools, put all relevant data into context, and tailor treatment to the patients' individualized needs.

Abbreviations

ACS:	Abdominal compartment syndrome
AKI:	Acute kidney injury
ANP:	Atrial natriuretic peptide
ARDS:	Acute respiratory distress syndrome
CO:	Cardiac output
CO_2-gap:	Gap between venous and arterial CO_2 tension
CVP:	Central venous pressure
EEO:	End-expiratory occlusion test
EGDT/SSC:	Early goal-directed therapy/sepsis surviving campaign
EVLW:	Extravascular lung water
FRC:	Functional residual capacity of the lungs
GFR:	Glomerular filtration rate
GIPS:	Global increased permeability syndrome
HES:	Hydroxyethyl starch
IAP:	Intra-abdominal pressure
ICP:	Intracranial pressure
ICU:	Intensive care unit
ITBV:	Intrathoracic blood volume
MAP:	Mean arterial pressure
pGDT:	Perioperative goal-directed therapy
PLR:	Passive leg raising test
P_{MS}:	Mean (systemic) filling pressure
PPV:	Pulse pressure variation
ROSD/E:	Rescue-Optimization-Stabilization-Deescalation/Evacuation
SAP:	Systolic arterial pressure
$ScvO_2$:	Oxygen saturation on vena cava superior.

Conflict of Interests

Jan Benes is advisory board member of the Edwards Lifesciences Inc.; Mikhail Kirov, Zsolt Molnar, and Xavier Monnet are members of the Medical Advisory Board of PULSION Medical Systems (member of the MAQUET-group); the other coauthors (Vsevolod Kuzkov, Gorazd Voga, and Mitja Lainscak) declare not having any competing interests.

Authors' Contribution

Jan Benes, Mikhail Kirov, Vsevolod Kuzkov, and Xavier Monnet were responsible for drafting the paper and revising it critically for important intellectual content; Mitja Lainscak, Zsolt Molnar, and Gorazd Voga participated significantly in the paper preparation and revised it critically for important intellectual content. All authors have read and approved the final paper.

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Review Article

Pressor Response to Noradrenaline in the Setting of Septic Shock: Anything New under the Sun—Dexmedetomidine, Clonidine? A Minireview

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Progress over the last 50 years has led to a decline in mortality from ≈70% to ≈20% in the best series of patients with septic shock. Nevertheless, refractory septic shock still carries a mortality close to 100%. In the best series, the mortality appears related to multiple organ failure linked to comorbidities and/or an intense inflammatory response: shortening the period that the subject is exposed to circulatory instability may further lower mortality. Treatment aims at reestablishing circulation within a "central" compartment (i.e., brain, heart, and lung) but fails to reestablish a disorganized microcirculation or an adequate response to noradrenaline, the most widely used vasopressor. Indeed, steroids, nitric oxide synthase inhibitors, or donors have not achieved overwhelming acceptance in the setting of septic shock. *Counterintuitively*, α_2-adrenoceptor agonists were shown to reduce noradrenaline requirements in two cases of human septic shock. This has been replicated in rat and sheep models of sepsis. In addition, some data show that α_2-adrenoceptor agonists lead to an improvement in the microcirculation. Evidence-based documentation of the effects of alpha-2 agonists is needed in the setting of human septic shock.

1. Introduction

Following immediate resuscitation [1], the clinician treating septic shock faces *different* issues including (a) recoupling the peripheral compartment (i.e., the microcirculation) to the "central" compartment (i.e., brain, heart, and lung) and (b) restoring the pressor response to vasopressors, usually noradrenaline (NA). This minireview addresses these issues in the setting of septic shock, given the surge in interest pertaining to the use of α_2-adrenoceptor agonists in this setting [2, 3].

2. Septic Shock

2.1. Septic Shock. The definition of septic shock includes a systolic blood pressure (SBP) <90 mmHg, after adequate fluid replacement (commonly >30 mL·kg-1 in <6 h) and the need for vasopressor drugs for more than 1 h [4] or for 4 h (minimal requirements of NA >0.05 μg·kg-1·min-1). Earlier series have reported a death toll of ≈70% [5] and recent series still report a high mortality (27% [6], 20% [7], and 16% [8]). Refractory septic shock is defined as a requirement for NA >0.25 μg·kg-1·min-1 (>1 mg·h-1/70 kg) [9] or > 0.5 μg·kg-1·min-1 [10]. Other definitions are (a) worsening circulatory failure despite aggressive use of vasopressors and (b) increasing lactic acidosis despite 6 h of extrarenal replacement therapy (ERRT) [11]. In a study of 51 consecutive patients with septic shock [12], an overall 45% mortality was observed. Sixteen patients presented with refractory septic shock and death (31% of the enrolled patients). The definition of refractory septic shock of this group [12] was no reversal of

shock (i.e., an inability to sustain SBP >90 mmHg for >24 h without NA):

(a) In the refractory septic shock group, the mortality over 48 h was 19%, given the whole 51 patients: ten patients (62% of the patients in refractory septic shock) died within 48 h of circulatory failure. The mortality over 28 d (early circulatory failure and late multiple organ failure) in the refractory septic shock patients was 100%. The NA requirement was ≈2.6 μg-1·kg-1·min-1, that is, ≈11 mg·h-1.

(b) In nonrefractory septic shock, the mortality over 28 d was 20%. The NA requirements were ≈1 μg-1·kg-1·min-1, that is, ≈4 mg·h-1 [12].

2.2. Treatment. The initial treatment for septic shock is volume loading, but the adequacy of volume loading is poorly defined [1]. Presumably, the best index is the collapsibility of the vena cava (superior vena cava [13] or inferior vena cava) or absence of response to passive leg rising. Thus, adequacy of volume load is assessed when little or no change occurs in the diameter of the inferior or superior vena cava or when additional volume loading evokes no additional increase in cardiac output (CO). There is ongoing controversy regarding the balance between the necessity to achieve adequate volemia, during the first 24–72 h, and the necessity to avoid increased lung water by normalizing the net weight gain, as early as possible.

The second line of therapy is the use of vasopressors, usually NA, to achieve a MAP ≥65 mmHg. The dose of NA required varies from ≈1 μg-1·kg-1·min-1 to ≈2.6 μg-1·kg-1·min-1, respectively, in nonrefractory versus refractory septic shock (4 to 11 mg·h-1) [12]. However, the same established group [14] uses NA as high as 50–100 mg·h-1 to treat refractory septic shock. Secondly, setting the MAP ≥65 mmHg may be arbitrary: BP is too low when dealing with patients with preexisting hypertension [15] or with low functional capillary density [16]. Conversely, BP is too high if MAP is the only parameter to be followed (i.e., disregarding the indices of global tissue perfusion such as trends in arterial lactate concentration, mixed venous O_2 saturation or superior vena cava O_2 saturation, and arterial-venous CO_2 gradient). There is also a controversy regarding the time NA treatment is instituted. Most commonly, NA is administered early in sepsis, especially if diastolic BP is low, but early institution of vasopressor treatment before achieving adequate global perfusion is associated with worse outcome [17] suggesting that maldistribution of blood flow may be increased by the liberal use of vasopressor in the setting of septic shock [17]. Therefore, a three-step strategy has been proposed [18]. First, as soon as possible [19], restore volume and peripheral perfusion using iterative monitoring of global tissue perfusion. Second, administer NA to maintain MAP ≥50 mmHg (lower limit of cerebral/coronary autoregulation in normal humans, with a higher MAP if coronary/cerebral perfusion is endangered). Third, optimize kidney perfusion (as an index of single organ perfusion), *after* adequate global perfusion, by increasing the dose of NA [18].

3. Microcirculation

3.1. Uncoupling between the Peripheral and Central Compartments. One of the key problems faced by the intensivist in the setting of septic shock is an "uncoupling" between the macrocirculation ("central compartment": brain, heart, and lung) and the microcirculation. Within this schema, central compartment versus microcirculation, the kidney presents with peculiarities: given the large volume of blood it receives per time unit, the kidney is part of the central circulation. On the other hand, the microcirculation of the kidney is disrupted by sepsis, as any other major central organ: the clinical answer lies in a urine output >0.5 mL·h-1 as an index of adequate microcirculation.

Tissue blood flow is driven by metabolic demand, not by blood pressure (BP). At rest, in the healthy volunteer, this implies that the capillaries are alternatively perfused and then not perfused. In turn, this implies, in the healthy volunteer, that the blood volume needed to operate the whole circulatory system is kept to a minimum because the active part of the circulatory system is also kept to a minimum. By contrast, during exercise, muscle blood flow, under sympathetic restraint, increases 100-fold [20] with maximal capillary perfusion attained in 15 s, compatible with a metabolic demand, restrained by sympathetic activation. Diving mammals are able to store massive loads of lactate at the periphery during diving and recirculate this acid load very quickly, getting ready for the next dive within minutes [21]. Accordingly, elite long-distance runners handle severe lactic acidosis and recirculate this load quickly upon completion of run.

At variance with data gathered in the 1930s, recent results argue against the existence of precapillary sphincters that would allow independent, active control of individual capillaries. Arterioles are enmeshed in a rich plexus of sympathetic nerves and electrical stimulation leads to vasoconstriction spreading along the whole arteriole [22]. The sympathetic nervous system is activated by pressure (cardiac and vasomotor sympathetic baroreflexes), CO_2-H^+-O_2 (chemoreflexes), or metabolism (metaboreflex). The large proximal arteries are controlled primarily by stimulation of α_1-adrenoceptors, whereas small distal arteries are controlled mainly by stimulation of α_2-adrenoceptors [20]. There is evidence that constriction of microvessels mediated by α_2-adrenoceptors may be more sensitive to acidosis, compared with those mediated by α_1-adrenoceptors, but it is unclear if this leads to a better local control of terminal arterioles by metabolic demand [23]. Furthermore, it is unclear how this acidosis-evoked vasodilatation of small arterioles relates to the microcirculatory dysfunction observed during septic shock and massive sympathoactivation. The untested implication is that prolonged tissue hypoxia, or prolonged unloading of arterial baroreceptors, leads to prolonged, metabolically mediated, sympathetic activation. In turn, is this sympathetic activation instrumental in perpetuating tissue hypoxia? Conversely, does sympathetic deactivation alleviate peripheral shunting?

What happens to microvascular flow in to septic shock? This is not crystal clear. However, there is evidence that, in skeletal muscle, there is a large heterogeneity in the flow

rate in capillaries [24]. Given normal BP in a rat model of peritonitis (caecal ligation and perforation) [24], a decrease in continuous blood flow and of normal blood flow was observed, while an increase in stopped flow was observed. The proportion of fast to normal flow increased, possibly due to a convective arterial-venous shunt. The oxygen saturation is lower at the venular end of the capillaries. The increase in oxygen extraction (O_2ER) was directly related to the extent of stopped flow (5 times the O_2ER observed in controls). This corresponded to a *loss of 50% of perfused capillaries*. Taken together, these data indicate a patchy and disperse maldistribution of O_2 during sepsis, as opposed to an inability to utilize O_2 [24], that is, a cytopathic hypoxia [25]. The authors conclude the following: (a) *increasing the delivery of oxygen to supranormal levels may not improve tissue oxygenation if the increased O_2 supply cannot be properly distributed and* (b) *early treatment aimed at restoring uniform distribution of O_2. . .may lead to improve outcomes* [24]. This summarizes the present challenge. The speculation is that some capillaries are vasodilated due to NO excess and thus need NO inhibition. By contrast, flow is stopped in a large proportion of the capillaries: do these stopped capillaries need NO donors? All together this makes the systemic administration of NO inhibitors versus donors a challenge.

In septic humans, a reduced density of perfused sublingual capillaries is observed in nonsurvivors [26], irrespective of a similar circulatory and oxygenation profile observed in survivors versus nonsurvivors. Survival is associated with the increase in small vessel perfusion over the first 24 h but not associated with the overall circulatory and oxygenation variables [27]. Furthermore, there is a strong association between the delay in beginning therapy and outcome, compatible with extensive microcirculatory defects and their consequences, that is, multiple organ failure [19]. Volume load improves microcirculation during early but not late sepsis [28], suggestive of damage to the microcirculation. Additionally, the first bolus of volume loading improves all the indices of microcirculation, with no further improvement with a second bolus [29]: does this imply minimizing volume load during septic shock based on a microcirculatory index? The proportion of perfused vessels is unrelated to the administration of vasopressors [26]. A weak but significant correlation exists between small vessel perfusion, increasing pH and decreasing arterial lactate levels [26], which does not necessarily imply causality. When NA was used to increase BP from 65 to 85 mmHg, *the largest increase in perfused capillary density was observed in patients presenting with the lowest perfused capillary density*, suggestive of a possible effect of BP on functional capillary density: do the sicker patients need a higher BP? By contrast, the patients with the highest baseline perfused capillary density showed a reduction in perfused capillary density [16]. This suggests that individualized titration of NA based on the state of the microcirculation may be beneficial.

Finally, no correlation was observed between the slope of recovery to thenar muscle ischemia and NA requirements [30], although a weak correlation was observed between NA requirement and recovery during ischemia of the thenar muscle [12]. Therefore, NA requirement and the extent of microcirculatory defects are poorly related: "*the alterations in thenar O_2 saturation. . .are more related to the sepsis. . .itself and its severity than to mean arterial pressure and the dose of vasopressor agents*" [30].

4. Pressor Response to Noradrenaline

Reduced pressor responsive to NA is a major challenge for clinicians treating septic patients. The effects of a number of treatments have been studied to determine if they improve the reduced pressor responsiveness to NA in sepsis.

4.1. Nitric Oxide Inhibitors. Based on the assumption of generalized nitric oxide (NO) excess in sepsis and subsequent excessive vasodilation, NO inhibitors have been tested [31]. Briefly (a) in septic patients, NO synthase (NOS) inhibitors (N-monomethyl-L-arginine: L NNMA) increased BP and lowered CO in a dose-dependent manner [32, 33], with a 40% reduction in NA requirements [34], and (b) the changes evoked by L NNMA (inhibition of NO synthase) were reversed by L arginine [33]. However, a large study was stopped because of increased mortality in the group treated with a NOS inhibitor [35]. Studies in an ovine model of hyperdynamic septic shock showed that nonselective NOS inhibition restored BP, but not renal function, and a selective inhibitor of inducible NOS had no effect on BP or renal function [36, 37]. Therefore, NOS inhibitors do not restore, in septic shock, the delicate tuning between active, perfused capillaries and inactive, unperfused capillaries governed by local metabolic demand in the resting healthy volunteer.

Another NO inhibitor, methylene blue (MB), improved the circulatory profile (increased stroke volume and reduced tachycardia) and reduced the NA requirements by 87%, as early as one hour after beginning of administration [38, 39]. A meta-analysis favored the use of MB in hypotensive patients, including septic shock patients (mortality: MB: 16%; control: 23%) [40]. To our knowledge, no further large-scale randomized study has taken up the issue.

4.2. NO Donors. In a nonrandomized study, the NO donor nitroglycerin (NTG) was administered during septic shock (bolus: 0.5 mg; continuous administration: 0.5–4.0 mg·h-1), after volume load (central venous pressure >12 mmHg) and vasopressor administration. A major improvement in the microcirculation was observed, with survival in 7 out of 8 patients [41]. A similar response has also been observed with a NTG patch (12–18 mg every 4 h) [42] and in a randomized study there was evidence that NTG improved perfusion of small vessels in septic patients [43]. Furthermore, the trend in lactate concentrations improved in the NTG group. The study was not conclusive regarding whether NTG reduced the length of stay in the critical care unit, but there was a higher mortality in the NTG group [43]. However, the small size sample and the inclusion of septic patients together with septic shock patients does not allow one to reach a definitive conclusion.

4.3. Hydrocortisone (HSHC). Low dose steroids generated little increase in BP in septic shock patients receiving or not receiving phenylephrine, except when very high doses of phenylephrine were used [44]. HSHC hastened the reversal of septic shock (HSHC: 3.3 days versus placebo; 5.8 days in patients in whom shock was reversed; 76 and 70% in the HSHC and placebo groups, resp.), irrespective of a positive or negative response to corticotropin. However, mortality was unchanged, irrespective of group. A higher incidence of new episodes of sepsis or septic shock was observed in the HSHC group.

4.4. α_2-Adrenoceptor Agonists. As the drugs cited above were not overwhelmingly successful in treating sepsis, our group has examined a novel and *counterintuitive* approach: the use of α_2-adrenoceptor agonists. In two cases [45], treatment with the α_2-adrenoceptor agonist, clonidine (1 μg·kg-1·h-1), in addition to state-of-the-art treatment, reduced NA requirements in (a) a patient presenting with HIV and terminal pulmonary sepsis (−45%) [45] and (b) a neonate presenting with necrotizing enterocolitis (−90%, submitted). In addition, we have documented this reduction in requirement for NA in rat [46] and sheep [47] experimental models of sepsis, using high and low doses, respectively, of the α_2-adrenoceptor agonists, clonidine and dexmedetomidine. Furthermore, the pressor responsiveness to a noncatecholaminergic vasopressor, angiotensin II, was also reduced by clonidine treatment [47].

One possible mechanism [48] for this effect of α_2-adrenoceptor agonists in sepsis is that, during septic shock, as during exercise [49], there is increased sympathetic nerve activity and endogenous plasma catecholamines [50–52] with a downregulation in responsiveness to stimulation of α_1- and β-adrenoceptors, which may result from reduced binding or reduced sensitivity/intracellular coupling. Conversely, the other side of this working hypothesis [48] is that, during rest after exercise, or after lowering plasma catecholamine concentrations with either pharmacologically evoked α_2-adrenoceptor agonists or those occurring spontaneously during recovery from sepsis, the downregulation of α_1-adrenoceptors is converted to upregulation, with an increased pressor response to vasopressors.

Clonidine reduces sympathetic nerve activity to the heart and vasculature by a direct central action, which is its main mechanism of action as an antihypertensive drug [53, 54]. How can this central action of clonidine to reduce BP in hypertensive patients be reconciled with an increased pressor response and lowered NA requirement in patients with sepsis? A recent experimental study indicates that treatment with clonidine reduced renal sympathetic nerve activity from high to normal levels [47]. Together with reductions in sympathetic nerve activity to other organs, this is likely associated with a decrease in plasma catecholamines concentrations and is compatible with our working hypothesis. It remains to be determined whether the maldistribution of capillary perfusion in sepsis [24] is improved by treatment with α_2-adrenoceptor agonists and if so whether this is due to its central sympathetic deactivation or to a direct vascular action.

Given our reports that clonidine reduced the requirement for NA in sepsis [45] and our demonstrations of improved pressor responsiveness in small [46] and large [47] animal models of sepsis, it is essential that evidence-based documentation of the effects of α_2-adrenoceptor agonists in human septic shock is obtained. A concern may be the possible harm to the patient by using an antihypertensive agent during septic shock, indeed a bold and *counterintuitive* move. The answer appears three-fold. First, adequate volume loading before administration of the α_2-adrenoceptor agonist is needed. As the microcirculation corrects slowly (as shown by the changes in arterial lactate, central O_2 saturation, and arterial to venous CO_2 gradient) the most expeditious way would be to optimize the central compartment: little or no collapsibility of the inferior or superior vena cava during ventilation would guarantee no more increase in CO or little response to passive leg rising. Second, the definition of an adequate BP is needed: permissive hypotension [18] (MAP $\geq$ 50 mmHg) versus standard MAP $\geq$65 mmHg [1] versus higher MAP in selected patients [15, 16]. Third, given the very high circulatory-related mortality in refractory septic shock [12], the patients in this category may be administered with a "compassionate" treatment under the Helsinki Declaration ("*where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician's judgment it offers hope of saving life, reestablishing health, or alleviating suffering; where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy*"). The primary end-point will be increased pressor responsiveness to vasopressors. Such a clinical trial should also address whether there are improvements in the microcirculation. For, example, does sympathetic deactivation with an α_2-adrenoceptor agonist reverse the peripheral microcirculatory shut-down and reduce inflammation and multiple organ failure? An end-point on mortality would require a large sample, not compatible with a preliminary trial.

4.5. Clonidine versus Dexmedetomidine. Which alpha-2 agonist is to be selected to head into a preliminary clinical trial? Clonidine has 2 disadvantages and one advantage: (a) a slow onset (3–6 h) when administered slowly and intravenously to evoke no precipitous sympathetic deactivation. In the context of inadequate volemia (§ treatment), precipitous sympathodeactivation will lead to a precipitous fall in BP. *A rigorous proviso should be made to address the issue of an optimized volemia before the initiation of sympathetic deactivation*. When opposed to clonidine, dexmedetomidine will be the drug of choice as its sedative effect is observed after 30–60 min. However, the issue in the setting of septic shock is not to observe a fast onset for sedation, but to observe a putative, increased pressor response to NA, without precipitous fall in BP. As the patient presenting with septic shock is to stay in the CCU for an extended period of time, a faster onset of sedative versus pressor effect will make little pharmacoeconomic difference. Our observations [45]

show that clonidine increases the pressor response to NA within 2-3 h. Nevertheless, a comparison will be needed to address the superiority of any of the two clinically available alpha-2 agonists (b) in healthy volunteers, a long elimination half-life of clonidine (circa 24 h) [55] as opposed to a short elimination half-life for dexmedetomidine (circa 3 h). Any untoward effect will presumably last longer with clonidine. This is not the issue: the point is how to get increased pressor response to NA without inducing a major fall in BP during the *initial* administration of the alpha-2 agonist, and not the possible length of time of such an exaggerated fall. The answer rests with adequate volemia *before* heading to sympathetic deactivation (§ treatment). (c) Clonidine is eliminated via the kidney as opposed to dexmedetomidine eliminated via the liver. Many patients presenting with septic shock require ERRT. Thus, any overdose of clonidine will be easily eliminated. By contrast, dexmedetomidine may not generate an overdose secondary to kidney failure, easing the management. However, administration of dexmedetomidine may become tricky if the patient presents liver failure, as extra-liver replacement therapy is no widely available. Lastly, the key point is the dose of alpha-2 agonist needed to generate sympathetic deactivation, thus increased pressor response: the dose of clonidine we used [45] (1 mcg·kg-1·h-1) needs to be refined to achieve maximal sympathodeactivation with minimal side effects.

5. Conclusion

In healthy volunteers, the microcirculation is constantly shunting blood away from inactive to active territories and vice versa. This fine tuning allows the whole body to be adequately perfused with a blood volume of only 5 L, even in the setting of strenuous exercise. By contrast, in the setting of septic shock, the human organism apparently needs a higher blood volume (or at least reestablishment of adequate blood volume) and a recoupling of the microcirculation with the central compartment. At present, physicians are unable to emulate what humans achieve after long-distance running or diving mammals when they reach the surface, that is, reorganizing a shut-down microcirculation to force O_2 through capillaries and generate a quick wash-out of anaerobic metabolites.

A *different* issue is the pressor response to NA, which defines, when completely blunted, refractory septic shock. Steroids increase the response to phenylephrine, but only when very high doses of phenylephrine are used [44]. NO inhibitors have been withdrawn from trial based on side-effects, possibly related to the dose of drug. Methylene blue has not been assessed in a large double blind trial to handle refractory hypotension in the setting of septic shock. In our studies of α_2-adrenoceptor agonists, we have observed a large (45–90%) reduction in NA requirements in terminal septic shock [45] and in necrotizing enterocolitis. Simultaneously, in our patients [45], peripheral mottling vanished over hours: this suggests that the microcirculation may have been progressively recoupled to the central compartment. We replicated an increase in pressor responsiveness to NA with dexmedetomidine and clonidine in the setting of mild sepsis in rat [46] and sheep [47]. The working hypothesis [45, 48] is that α_2-adrenoceptor agonist mediated sympathetic deactivation lowers the release of endogenous NA, allowing upregulation of vascular α_1-adrenoceptors back towards normal levels. This hypothesis [45, 48] is to be put to the acid test in the setting of human septic shock, preferably refractory. Again, *a rigorous proviso should be made to address the issue of an optimized volemia before the initiation of sympathetic deactivation.*

Abbreviations

BP: Blood pressure
CO: Cardiac output
ERRT: Extrarenal replacement therapy
HSHC: Hemisuccinate of hydrocortisone
MAP: Mean arterial pressure
MB: Methylene blue
NA: Noradrenaline
NO: Nitric oxide
NOS: NO synthase
NTG: Nitroglycerin
O2ER: Oxygen extraction ratio
SBP: Systolic blood pressure.

Conflict of Interests

L. Quintin holds a US patent (8 846 606 B2, September 30, 2014) on *method and drug composition for treating septic shock hypotension*. The other authors declare no conflict of interests.

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Review Article

Haemodynamic Effects of Lung Recruitment Manoeuvres

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Atelectasis caused by lung injury leads to increased intrapulmonary shunt, venous admixture, and hypoxaemia. Lung recruitment manoeuvres aim to quickly reverse this scenario by applying increased airway pressures for a short period of time which meant to open the collapsed alveoli. Although the procedure can improve oxygenation, but due to the heart-lung and right and left ventricle interactions elevated intrathoracic pressures can inflict serious effects on the cardiovascular system. The purpose of this paper is to give an overview on the pathophysiological background of the heart-lung interactions and the best way to monitor these changes during lung recruitment.

1. Introduction

Patients admitted to the intensive care unit are often affected by acute respiratory distress syndrome (ARDS). ARDS is a life-threatening condition precipitated by disorders frequently resulting in critical care admissions like trauma, severe burns, sepsis, pancreatitis, and pneumonia [1]. All of these disorders, either causing direct (pulmonary) or indirect (extrapulmonary) tissue damage, are featured by a systemic inflammatory response. The released cytokines like interleukin- (IL-) 1, IL-6, IL-8, and tumor necrosis factor activate neutrophils in the lung throughout the inflammatory cascade [2]. The activated immune cells excrete injurious substances such as free oxygen radicals and proteolytic enzymes leading to alveolar endothelium and epithelium destruction. The latter pathophysiological mechanism induces impaired permeability in the lung resulting in alveolar immerging by the protein-rich oedema fluid [3]. Surfactant, which has a major role in modulating the surface tension of alveoli, is also washed out. Furthermore, the surfactant production is also decreased due to the dysfunction of type II epithelial cells. As a consequence, pulmonary atelectasis develops due to alveolar collapse [4].

Pulmonary atelectasis is accompanied by arterial hypoxaemia due to increased intrapulmonary shunt [5]. As severe acute hypoxaemia is a potential danger for all vital organs, its resolution is of pivotal importance. There are several interventions, which may help improve oxygenation. In the most severe circumstances, extracorporeal membrane oxygenation [6], high frequency oscillatory ventilation [7], and prone positioning [8] have been shown to reverse persistent hypoxaemia. Some of these interventions require special equipment, demand extra manpower, and may be time consuming to commence. In less severe cases of acute hypoxaemia, especially when this is primarily caused by atelectasis, the collapsed lung areas can be opened up with the help of transient increment in transpulmonary pressure (TP) within a short time, hence decreasing shunt fraction and improving arterial oxygenation [9]. This procedure is called the lung recruitment manoeuvre. It can be accompanied by the titration of the "optimal" PEEP, a process which is called on a broader term the "open lung concept" described by Lachmann in 1992 [10].

Several applications of recruitment manoeuvres have been described so far. Although these may differ in certain details but by-and-large the most common feature is in all of them that they apply peak airway pressures of 40–60 cm H_2O

for a short period of time, usually not exceeding 40–120 seconds [9]. Although survival benefit has not been demonstrated with any of the recruitment manoeuvres, the intervention is frequently administered in atelectasis induced hypoxaemia [11]. It is beyond the scope of this paper to review the available recruitment techniques; therefore we will only concentrate on the heart-lung interactions, haemodynamic effects, and the monitoring alternatives.

The anatomical proximity of the lungs and heart within the chest means that transiently increased intrathoracic pressures have major effect on systemic cardiovascular function. Undesired side effects of the recruitment process mainly arise from the increased airway pressures which can cause overdistension of alveoli in well-ventilated lung areas, marked increase in ventilation-perfusion mismatch, barotrauma, pneumothorax, and new air leak around an existing chest tube [12]. These effects may be even more pronounced in patients with ARDS in whom haemodynamic instability is a common feature [13]. It has strong pathophysiological rationale supported by clinical data that routine ICU monitoring, such as invasive blood pressure and central venous pressure monitoring, may not be adequate to follow haemodynamic changes encountered during lung recruitment [14].

2. Effects on Right Heart and Pulmonary Circulation

Distending lung volume evoked by applied raised airway pressure leads to an increase in TP. TP can be estimated from the difference between alveolar and intrathoracic pressures. The transmission of TP to the pleural space impedes venous return and the filling of the right ventricle. Meanwhile, the increased TP is transposed to vessels interlacing the lung tissue hereby elevating pulmonary vascular resistance (PVR) and right ventricular afterload.

2.1. Systemic Venous Return and Right Ventricle Preload. The increase of intrathoracic pressure compresses the right atrium and caval veins carrying the systemic venous return to the heart. The generated retrograde pressure results in elevation in the central venous pressure (CVP) and could impede right ventricular filling. Due to this mechanism the assessment of cardiac preload by CVP during lung recruitment manoeuvre is misleading, as the transmission of the intrathoracic pressure to the intravascular compartment [14] does not represent the true preload component. Restricted right ventricular preload is a dominant but not solitary mechanism in the fall of the right ventricular ejection fraction.

2.2. Right Ventricular Afterload. Right ventricular afterload represents the resistance, quantified by the pulmonary artery pressure, which the right ventricle should overcome to eject the blood through the pulmonary valve. During the lung recruitment manoeuvre, the interposed TP further increases the area where the intraluminal pressure of the juxta-alveolar capillaries is lower than the intra-alveolar pressure. This results in a significant increase in the pulmonary vascular resistance, parallel to an increase in the pulmonary artery pressure. Thus right ventricular afterload is augmented by transitionally elevated TP.

Hypoxic pulmonary vasoconstriction, which developed to attenuate the ventilation-perfusion mismatch caused by alveolar hypoventilation, is another important determinant of the right ventricular afterload [15]. During significant hypoxaemia, the atelectatic lung regions are served with only marginal circulation. The hypoxic pulmonary vasoconstriction contributes to the overall pulmonary vascular resistance; however there is only limited data about its role and the changes occurring during lung recruitment.

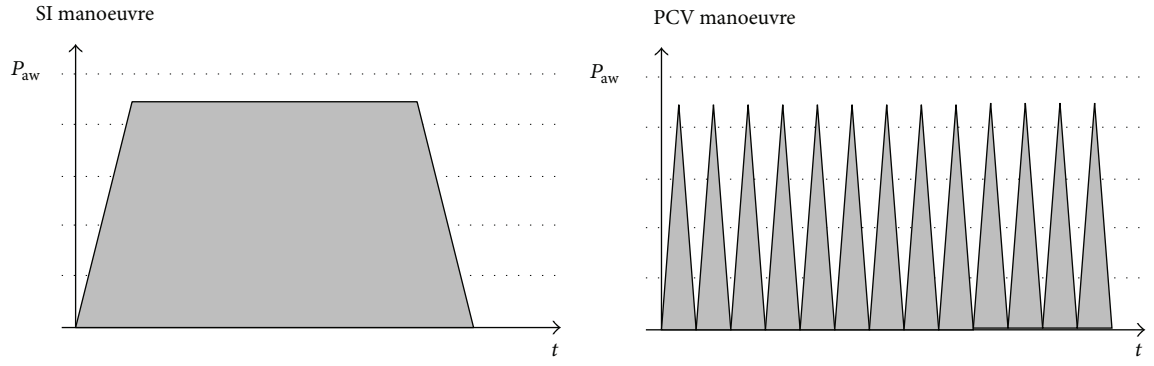
These mechanisms can impair right ventricular function and decrease right ventricular stroke volume. Iannuzzi et al. [16] found that pressure controlled ventilation (PCV) with peak inspiratory pressure of 45 cm H_2O for 2 minutes generated a higher grade of lung opening and resulted in a major and significant increase in PaO_2/FiO_2 ratio compared to sustained inflation (SI) (Figure 1). They found that hypoxic pulmonary vasoconstriction and pulmonary vascular resistance index (PVRI) were also reduced, with smaller degree of hyperinflation in the PCV group (Figure 1).

On the other hand, Reis Miranda et al. could not detect any significant impairment in right heart function comparing conventional mechanical ventilation to the open lung concept in patients after cardiac surgery [17]. This disagreement between the two observations may arise from the different methods applied, especially the different timing of measurements. Whereas Iannuzzi et al. investigated the immediate effects [16], in the other study cardiovascular measurements were taken every 30 minutes for 3 hours [17].

Similar results were reported by Celebi et al. [18] where pulmonary and haemodynamic effects of two different recruitment manoeuvres were investigated in patients after open heart surgery. During the study period, there was no significant change of PVR between the groups, measured after 15 minutes. One may suggest from these observations that the effect of the recruitment manoeuvre on the right ventricular afterload is transient, lasting for seconds only. Relieving high airway pressures after recruitment helps in the normalization of haemodynamic changes in the pulmonary circulation.

Apart from the different methods employed in the studies, controversial results may arise from the different patient inclusion criteria. In the study of Iannuzzi et al., patients with primary ARDS due to hospital acquired bacterial pneumonia were recruited [16], whilst Reis Miranda et al. investigated patients following cardiac surgery without significant lung injury [17]. It has been demonstrated in a murine model of acute lung injury induced by *Escherichia coli* lipopolysaccharide that dynamic inflation applied during lung recruitment produced increased right ventricular pressure and total PVR. It also resulted in sustained inflammation and vascular dysfunction whilst no similar changes were reported in healthy lungs [19].

2.3. Right Ventricular Ejection Fraction. The primary role of the right ventricle is to receive systemic venous blood and to forward it via a high volume and low-pressure system, the pulmonary circulation, to the left heart chambers [20]. Right ventricular ejection fraction is affected by preload,



(a) (b)

	SI manoeuvre	PCV manoeuvre
Lung opening	↑	↑↑↑
PaO_2/FiO_2	↑	↑↑↑
CI	↓↓	↔
PVRI	↑↑	↓↓
RWSVI	↓	↓↓
EI	↑↑	↑

(c)

Figure 1: Pressure-time product (a-b) and main characteristics (c) of sustained inflation (SI) and pressure control ventilation (PCV) recruitment manoeuvres. P_{aw}, airway pressure; t, time; CI, cardiac index; PVRI, pulmonary vascular resistance index; RWSVI, right ventricle stroke work index; EI, eccentricity index.

contractility, and afterload. During the recruitment manoeuvre, the raised intrathoracic and right atrial pressures, as discussed previously, could affect both venous return and afterload significantly [18] (Figures 2 and 3). Both mechanisms can result in impaired right ventricular contractility.

Right ventricular ejection fraction is inversely related to the ventricle's afterload. In the study by Reis Miranda et al. [17], PVRI and right ventricular ejection fraction showed no significant changes following recruitment within the first 3 hours, neither within nor between groups at any measurement points. However, if immediate effects on right ventricular function were investigated, then significant increase in right ventricular stroke work index was reported during the recruitment manoeuvre and 2 minutes following the intervention [21]. These results call for further attention to the immediate effects of the recruitment manoeuvre on right heart function. There is also lack of data, whether it has any clinically relevant long-term effects.

2.4. Ventricular Interdependence. It is important to note that the end-diastolic right ventricular volume has a direct effect on the left ventricle, which holds true *vice versa*. This is called the ventricular diastolic interdependence [22]. The two chambers are coupled within a common pericardial sac and share joint intraventricular septa as a traverse wall. Thus, their volumes are limited by the pericardium; hence any change in the right ventricular end-diastolic volume has an effect on the left ventricular end-diastolic volume (Figure 4).

During sigh recruitment, the right ventricle can have a marked effect on the adjacent heart chamber. When lung recruitment manoeuvre is applied by a sustained inspiration, left ventricular end-diastolic area can be reduced by as much as 45% [23]. PVR is also increasing with the transposed intrathoracic pressure, leading to an acute right ventricular pressure overload with dilation, leftward septal shift, and left ventricular collapse resulting in low cardiac output (CO) and marked systemic haemodynamic changes (Figure 4). These changes are transient and only seen during the manoeuvre, with almost instant normalisation of haemodynamics once the intrathoracic pressure returns to the baseline [16].

There is a special scenario when this interdependence is questioned and this is the postoperative period after cardiac surgery when the pericardial sac is kept open [17]. Theoretically, due to the missing pericardial sac, interaction between the two adjacent ventricles should be impaired and in these patients the diastolic interdependence is not fully present. However, in an animal experiment on dogs, it was found that artificially increasing the pulmonary artery resistance and the right ventricular load had a profound effect on the left ventricular filling dynamics. This was explained by the prolonged relaxation and altered pressure-volume chamber relations [24].

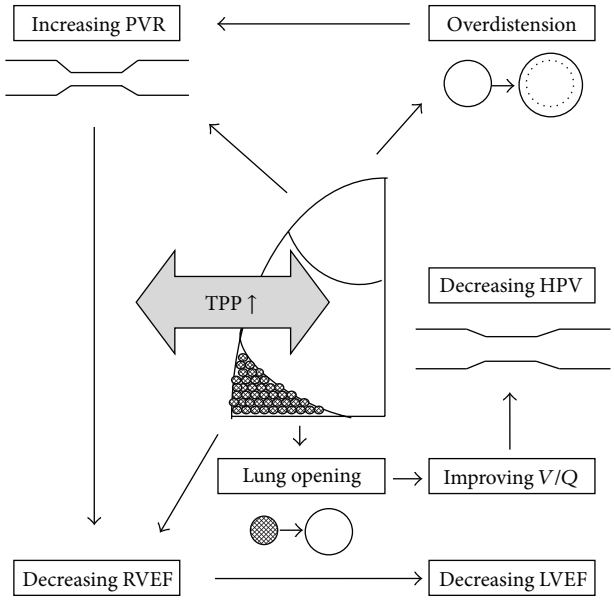


Figure 2: The effects of increased transpulmonary pressure (TPP). PVR, pulmonary vascular resistance; RVEF, right ventricular ejection fraction; LVEF, left ventricular ejection fraction; V/Q, ventilation/perfusion; HPV, hypoxic pulmonary vasoconstriction.

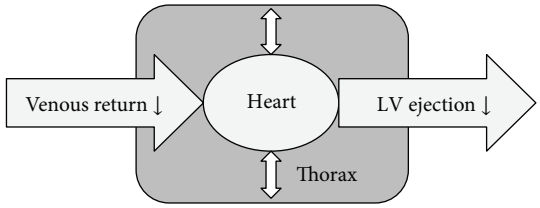


Figure 3: Pressure chamber (heart) in a pressure chamber (thorax). LV ejection; left ventricular ejection.

3. Effects on Left Heart and Systemic Circulation

The cardiopulmonary system is described by Pinsky as a pressure chamber inside a pressure chamber [25]. Any increment in the intrathoracic pressure increases the right atrial pressure and decreases the venous return and the transmural left ventricular systolic pressure, hence attenuating the left ventricular ejection fraction (Figure 3). If haemodynamic changes are solely monitored by mean arterial pressure (MAP) during lung recruitment manoeuvre, one can theoretically miss relevant alterations in the systemic circulation. Recent investigations concluded that simple haemodynamic parameters like MAP or heart rate did not show any significant change during and after various recruitment interventions [17, 21, 26]. However, applying advanced invasive haemodynamic monitoring, relevant changes in the systemic circulation can be observed [14].

3.1. Left Ventricle Preload and Afterload. As described above, ventricular interdependence plays a significant role during lung recruitment manoeuvre in determining the left ventricular preload. The increased TP compresses the right atrium and increases the CVP by the transmission of pressure to the intraluminal compartment of the caval veins. Echocardiographic investigations identify this mechanism as partial cause of the impaired left ventricular preload and consecutive decrease of CO [16].

Left ventricular afterload is defined as the pressure of the wall in the left ventricle during ejection. Following Laplace's law, if there is no significant alteration in the systolic arterial pressure, as seen throughout most of the studies investigating recruitment manoeuvre, left ventricle afterload decreases along with the fall of the transmural pressure of the left ventricle [27]. Measuring these pressure fluctuations requires sophisticated methods at the bedside; therefore correlation between left ventricle afterload and lung recruitment has not been investigated thoroughly in human subjects.

3.2. Cardiac Output and Left Ventricular End-Diastolic Volume. The increased availability of sophisticated continuous CO monitoring using pulse pressure analysis like pulse contour cardiac output (PiCCO), lithium dilution cardiac output (LiDCO), or FloTrac/Vigileo techniques and Doppler cardiac output devices enabled the clinicians to follow alterations in the systemic haemodynamics during each cardiac cycle [28]. Utilising these advanced monitoring techniques, profound and significant decrease in CO was observed during lung recruitment manoeuvres [14, 16, 23]. This decline in left ventricular performance can be explained by interconnected fluctuations within the "chamber in the chamber" system discussed previously [25]. Increased intrathoracic pressure, decreased right ventricular filling, and increased right ventricular outflow impedance with leftward intraventricular septal shift are all precipitating reduced CO (Figure 2). However, rapid recovery of the baseline CO was described when the effects were measured in a temporal study, so the depression is only transient correlating with the temporarily increased TP [29].

The absolute reduction in CO is influenced by the technique of the lung recruitment and also by the nature of the lung injury. As discussed previously, sustained inflation manoeuvre can significantly change left ventricle eccentricity index (Figure 4) indicating a significant reduction in left ventricular end-diastolic volume compared to PCV-recruitment, which was accompanied by a less profound effect.

The importance of the underlying pathology of the lung injury has been emphasised by Lim et al. [29]. They investigated three different types of lung injury models during recruitment: oleic acid injury depicting acute surfactant loss, ventilator-induced lung injury, and finally an injury caused by infection. Animals in all three models underwent a PCV, a sigh, and a PEEP incremental recruitment. Regardless of the way the manoeuvres were executed, a significant but interim drop of CO was observed in each model. However, in the pneumonia model, the CO decreased to a greater extent and the recovery of systemic haemodynamics also showed a moderate pattern as compared to the other two. It is possible that, in septic shock induced inflammatory response,

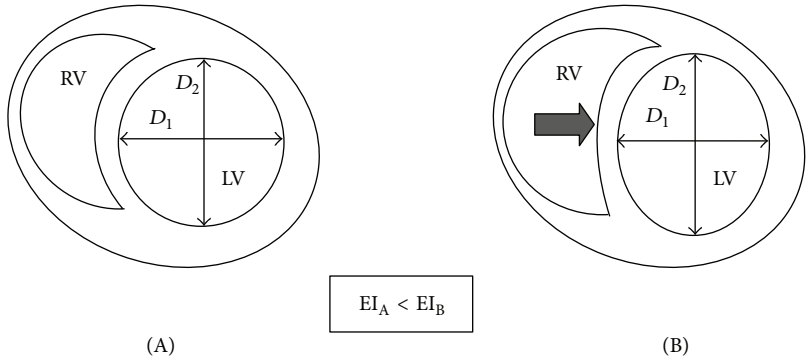


Figure 4: Ventricular interdependence before (A) and during alveolar recruitment manoeuvre (B). D_1, midmitral diameter; D_2, diameter orthogonal to D_1. Eccentricity index (EI) is calculated as D_2/D_1. RV, right ventricle; LV, left ventricle.

a more profound depression of myocardial function and compensatory vasomotor reflexes takes place [30]. Out of the three recruitment techniques, the sigh manoeuvre resulted in the most significant reduction in CO in accordance with previous investigations [16, 29].

One of the available methods to prevent the undesired decrease in CO during lung recruitment is the selective lung opening technique described by Hansen et al. in an elegant animal model [31]. In their experiment, pigs were randomized into two groups of lung recruitment manoeuvres (by applying 40 cm H_2O airway pressure for 30 seconds), either a selective lung recruitment manoeuvre such as using the inner lumen of the bronchial blocker followed by a whole lung recruitment manoeuvre or *vice versa*. Whilst there was no significant difference in the improvement of oxygenation and the end-expiratory lung volume between the two groups, there were no circulatory changes during the selective technique. On the other hand, the whole lung recruitment caused a significant drop in CO and left ventricular end-diastolic volume. This suggests that selective lung recruitment technique might be advantageous in patients with lobar atelectasis prone to haemodynamic instability. However, this new method requires further investigations in humans.

3.3. Alterations in Heart Rate. Along with stroke volume, heart rate is the other determinant of CO. Through the recruitment manoeuvre, one may expect the development of reflex tachycardia along the drop in CO. Many investigations failed to observe such an increase in heart rate; principally no significant alteration of pulse rate was found [14, 16–18, 21, 26]. However, in the investigation of Nielsen et al., the significant reduction in heart rate was suspected as the major component of the declining CO during the sigh manoeuvre [23]. One of the explanations is that the inflated lung tissue can activate vagal tone causing bradycardia [32]. Another assumption is that the sigh manoeuvre may precipitate a similar pattern in intrathoracic pressure as the Valsalva manoeuvre, hence producing reduction in heart rate. As opposed to the previous findings, Lim et al. reported an increased heart rate, perhaps reflecting just a sympathetic response to the lengthy recruitment procedure they used [33].

3.4. The Effect of Volemic State on Left Heart Function. One of the main patient exclusion criteria in the lung recruitment studies is haemodynamic instability and/or signs of intravascular volume depletion [14, 18, 23, 26, 33]. Hypovolaemia can amplify the undesirable haemodynamic effects of lung recruitment manoeuvre as demonstrated by Nielsen et al. [34]. In their animal experiment, the impact of recruitment manoeuvre on central haemodynamics was investigated in pigs with different volemic states. The animals were randomized to a 10-second-long recruitment followed by lung opening lasting 30 seconds by applying 40 cm H_2O airway pressure or *vice versa*, performed under hypo-, normo-, and hypervolemia. Volemic states were controlled either by removing 15% of the estimated blood volume or by infusion of a volume equal to 15% of the estimated blood volume with 3% dextran in Ringer's solution. The study focused on the immediate circulatory effects. They found a significant reduction in left ventricular end-diastolic volume, which could explain the depleted CO during lung recruitment manoeuvre in pigs with acute lung injury. As expected, the impact of this effect was significantly exaggerated by hypovolaemia. On the other hand, hypervolemic conditions prevented the reduction of CO during the extended sigh manoeuvre.

Fougères et al. suggested that some microvessels of the lungs may be collapsed by PEEP and were recruitable by the increased left ventricular preload [35]. In their recent investigation in patients with ARDS, recruitment was accomplished by increasing PEEP for reaching a plateau pressure of 30 cm H_2O. During the manoeuvre, CO was decreased along with increasing right ventricular afterload. Importantly, passive leg raising restored the CO and reduced the PVR. These important observations reinforce the need of appropriate intravascular volume assessment prior to the alveolar opening procedure.

4. Recruitment in Spontaneously Breathing Patients

There is some evidence that patients on continuous positive airway pressure and pressure support ventilation may

benefit from recruitment manoeuvres, resulting in fast and significant improvement in oxygenation [26]. However, there are very few publications in this topic as most studies on recruitment were performed in patients receiving controlled mechanical ventilation. Although it is well known that spontaneous ventilation and spontaneous breathing efforts significantly interfere with heart-lung interactions, apart from routine parameters such as blood pressure and heart rate, we have no detailed haemodynamic information in this patient group. As the changes are markedly different from that observed during controlled ventilation, this can be a potential field for further research.

5. Conclusions

Applying recruitment technique is a simple procedure to perform at the bedside but it is not free of certain risks. Increased airway and intrathoracic pressures can inflict deleterious haemodynamic effects due to the anatomical proximity of the lungs and heart within the thoracic cavity. Therefore, detailed understanding of the physiology and pathophysiology of these changes is necessary to perform lung recruitment safely. The evidence suggests that those patients who are at risk of overt hypovolaemia or whose lung injury is secondary to a primary lung infection, hence developing significant localised inflammatory changes, are more likely to benefit from advanced haemodynamic monitoring by devices that enable continuous and reliable evaluation of cardiac output during lung recruitment so that the treating clinician can maintain circulatory homeostasis.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

The Role of Focused Echocardiography in Pediatric Intensive Care: A Critical Appraisal

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Echocardiography is a key tool for hemodynamic assessment in Intensive Care Units (ICU). Focused echocardiography performed by nonspecialist physicians has a limited scope, and the most relevant parameters assessed by focused echocardiography in Pediatric ICU are left ventricular systolic function, fluid responsiveness, cardiac tamponade and pulmonary hypertension. Proper ability building of pediatric emergency care physicians and intensivists to perform focused echocardiography is feasible and provides improved care of severely ill children and thus should be encouraged.

1. Introduction

Echocardiography is currently considered a key tool for the hemodynamic assessment in Intensive Care Units (ICU), able to identify causes of hemodynamic instability and to quickly guide therapy [1, 2]. Some of its advantages are being a noninvasive method, risk-free, capable of being performed serially and in real time, and analyzed along with clinical data by intensivists.

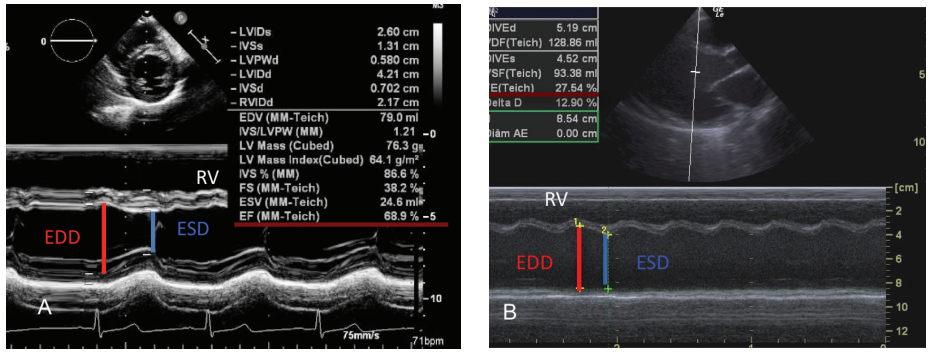
Several studies have demonstrated the positive effect of the use of echocardiography in the management of critically ill patients, changing their treatment in 30%–60% of cases after the test is performed [3–6]. Thus, the recent expert consensuses and reviews on shock point out the importance of echocardiography in the identification of the pathophysiology and categorization of shock as distributive, hypovolemic, obstructive, or cardiogenic [7].

In the pediatric age range, there is an important limitation of noninvasive devices for hemodynamic monitoring, and this makes the use of echocardiography even more promising. An interesting review on hemodynamic monitoring suggests using focused echocardiography with the monitoring devices already routinely used to assess the hemodynamic status of critically ill children [8].

When compared to the full echocardiography, the purpose of the focused echocardiography is the early identification of limited hemodynamics changes thus expediting clinical decisions regarding treatment [9, 10].

Although there is no consensus on the ideal training format for capacity building of nonechocardiographers in focused echocardiography, different training programs for physicians from different areas (anesthetists, internists, intensivists, surgeons, and pediatricians) to perform specific echocardiographic assessments have been published [5, 11–21]. In a previous study, we demonstrated that pediatricians specialized in Emergency or Intensive Care are able to perform focused echocardiography with a good concordance when compared to experienced echocardiographers, after 10 hours of theoretical sessions and 24 real-time training exams performed under supervision [22].

The most relevant parameters assessed by focused echocardiography in pediatrics are left ventricular systolic function, volemia/response to fluid resuscitation, pericardial effusion/cardiac tamponade, and right ventricular systolic function and pulmonary hypertension.



(a) (b)

Figure 1: Calculation of left ventricular fractional shortening by the M mode. (a) Parasternal short-axis view in a patient with normal ejection fraction. (b) Parasternal long-axis view in a patient with viral myocarditis and cardiogenic shock, with reduced ejection fraction. EDD: left ventricle end-diastolic diameter; ESD: left ventricle end-systolic diameter; RV: right ventricle. FS = EDD − ESD/EDD × 100.

2. Left Ventricular Systolic Function

Previous studies have demonstrated the inaccuracy of physical examination in the assessment of the cardiac function and hemodynamic profile of critically ill patients, even when performed by an experienced physician [23]. The echocardiographic assessment of the left ventricular (LV) function as an extension of physical examination has a proven beneficial effect on the timing to start therapy as well as on its quality. A study conducted in adult patients with congestive heart failure showed a significant improvement in the identification of patients with severe LV dysfunction when the medical assessment was associated with focused echocardiography, and this was the main factor for the identification of this group of patients (OR = 154, $p < 0.001$) [24]. Similar findings were reported in an Intensive Care environment, where the use of echocardiography by the intensivist brought additional information regarding the cardiac function and provided changes in therapy in 37% of the patients assessed [5].

In a Pediatric Intensive Care Unit, Ranjit et al. [6] suggested how the echocardiographic analysis of LV systolic function may be part of a multimodal hemodynamic assessment in association with physical examination and invasive blood pressure monitoring and thus may be incorporated in the medical arsenal to care for children with septic shock. In their study, the authors identified the presence of cardiac dysfunction echocardiographically in 45% of children after the baseline medical approach and demonstrated a favorable outcome in 91.6% of cases when the therapeutic management was guided by multimodal hemodynamic monitoring.

The left ventricular systolic function may be assessed by echocardiography both qualitatively and quantitatively.

2.1. Qualitative Analysis of the LV Systolic Function. The qualitative analysis of the LV systolic function consists of the visual analysis of the examiner in relation to the myocardial contractile function and is the method of choice for the assessment of the LV function by nonechocardiographers [25].

Left ventricular ejection fraction (EF) is estimated visually using multiple echocardiography views: the parasternal long and short views and the apical and the subcostal views. This assessment is made by analyzing the myocardial thickness during systole and the reduction of the ventricular chamber diameter during systole in comparison to diastole provided by the ventricular wall motion during systole. LV function is subjectively classified as normal (EF ≥ 55%), slightly reduced (EF 41%–55%), moderately reduced (EF 31%–40%), and markedly reduced (EF ≤ 30%) [26].

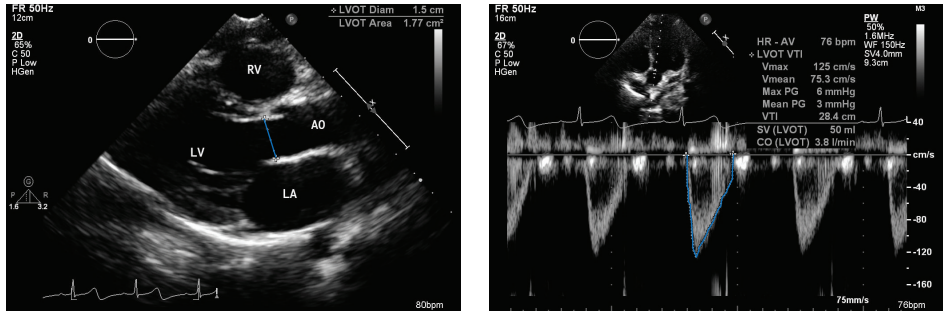
2.2. Quantitative Analysis of the LV Systolic Function. The quantitative analysis of the LV systolic function consists of LV ejection fraction and cardiac output/index measurements. This data aids the physician in choosing between therapeutic options, like fluids and/or inotropic agents.

Ejection fraction may be measured in the M mode or two-dimensional mode. EF calculation in the M mode is the most widely used in clinical practice, especially in pediatric patients, and is derived from the fractional shortening (FS) measurement. Measurements of the LV systolic (ESD) and diastolic diameter (EDD) right below the mitral valve leaflets in the parasternal short- or long-axis views are necessary to obtain the fractional shortening, which is calculated using the formula FS = EDD − ESD/EDD × 100 (Figure 1).

The clinical usefulness of quantitative EF measurements in the management of critically ill patients is broadly accepted both in adult and in pediatric patients [1, 27]; however, it is important to emphasize that this assessment should not be used without also considering patient's preload, cardiac output, and tissue perfusion in order to minimize the improper management of inotropic agents [28]. Studies show that trained nonechocardiographers are able to perform the quantitative analysis of EF even in pediatric patients and that this information may be positively added to the care of hemodynamically unstable pediatric patients [6, 13, 22].

Similar to the qualitative assessment, EF is classified as normal (EF ≥ 55%), slightly reduced (EF 41%–55%), moderately reduced (EF 31%–40%), and markedly reduced (EF ≤ 30%) [26].

The cardiac output (CO) evaluation is not recommended to all shock patients. However, a recent experts consensus was



(a) (b)

Figure 2: Stroke volume (SV) calculation. (a) Measurement of LV outflow tract diameter (LVOTD) using the parasternal long-axis view, and (b) use of pulsed Doppler for the measurement of velocity-time integral (VTI), as obtained in the 5-chamber apical view. Cardiac output (CO) = SV × HR; SV = VTI × LVOT area, where LVOT area = π(LVOT diameter/2)^2.

proposed as evidence level I that the CO measurement should be performed in those patients that are not responding to initial therapy to evaluate the response to fluids or inotropes [28]. As previously cited, it is crucial that the CO assessment is not the only variable used to decide treatment but is indeed added in the preload, left ventricular ejection fraction, and tissue perfusion equation. This concept is supported by a prior trial performed by Vieillard-Baron et al. that demonstrated the existence of patients with low ejection fraction but normal cardiac index, as well as patients with low cardiac index and normal ejection fraction [1]. Hence, inotropic agents should only be given when the compromised ejection fraction is accompanied by inadequate cardiac output and tissue hypoperfusion.

The CO measurement by echocardiography depends on a combination of measurements made in the two-dimensional mode and aortic blood flow study by Doppler. CO is calculated by multiplying the stroke volume (SV) by the heart rate (HR). SV is obtained by measuring the LV outflow tract (LVOT) diameter in the two-dimensional mode (parasternal long-axis view) and the velocity-time integral (VTI) by pulsed Doppler (5-chamber apical view), with SV = VTI × LVOT area, where LVOT area = π(LVOT diameter/2)^2 (Figure 2). The targeted cardiac index in septic children suggested by Surviving Sepsis Campaign is between 3.3 and 6.0 L/min/m^2 [29].

For requiring the use of Doppler, CO measurement may be deemed technically challenging for the nonspecialist physician. Nonetheless, in a previous study conducted in pediatric patients [22], we demonstrated that it is possible to train pediatricians for the analysis of CO, like in a study conducted in adult patients [30], however pioneering in pediatrics. This assessment may provide a new option for hemodynamic monitoring of severely ill children, a population that lacks noninvasive methods for CO measurement.

3. Fluid Responsiveness and Preload Estimation

Fluid resuscitation is part of the initial management of shock. However, aggressive fluid resuscitation may be harmful to some patients and some types of shock [31]. Assessment of the preload and fluid responsiveness is key in the management of critically ill patients and previous pediatric studies demonstrated that only 40–69% of children responded to intravascular volume expansion [32–34]. Clinical assessment and static measurements of filling pressures (central venous pressure and pulmonary wedge pressure) did not predict fluid responsiveness in children, which is consistent with findings in adults [35, 36]. However, in contrast to adults, dynamic variables as pulse pressure variation and stroke volume variation also did not predict fluid responsiveness in children, and that makes this evaluation in pediatric patients even more challenging [36].

The first form of assessing preload and fluid responsiveness by echocardiography is by analyzing the inferior vena cava (IVC) diameter. However, the static measurement of IVC diameter has a poor correlation with the patient's individual response to fluid resuscitation, especially in children in whom the IVC diameter is related to their weight and height [37]. Respiratory changes in IVC diameter are the most frequently used echocardiographic method for the assessment of the fluid responsiveness and consist of the analysis of the IVC diameter change with respiration while under positive pressure ventilation (inspiration and expiration) (Figure 3).

Respiratory changes in IVC by transthoracic echocardiography were established in the clinical practice after two studies conducted in adult patients undergoing mechanical ventilation. These studies showed a strong correlation between respiratory change in IVC and the patient's fluid responsiveness [38, 39]. The authors showed a linear correlation between respiratory changes in IVC and increased CO after fluid loading, where the greater the respiratory change in IVC prior to fluid replacement, the higher the increase in CO after fluid replacement. The index described by Barbier et al. [39], called inferior vena cava distensibility index (dIVC) and calculated using the formula dIVC = $(D_{\max} - D_{\min})/D_{\min} \times 100$, showed the best cutoff value of 18% to discriminate volume-responsive individuals (dIVC > 18%) from non-volume-responsive individuals (dIVC < 18%) with 90% sensitivity and specificity. However, we should note that it was performed in sedated patients with normal sinus rhythm, no spontaneous breathing, and a tidal volume of 10 mL/kg under mechanical

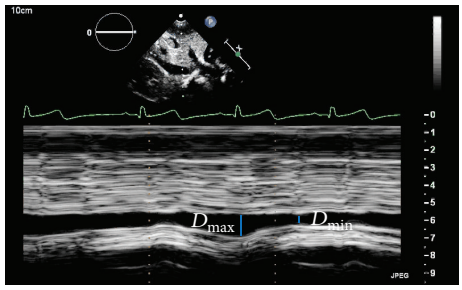


Figure 3: M mode echocardiography from subcostal view in a five-year-old patient in septic shock for urinary tract infection under mechanical ventilation, with sustained hypotension after volume expansion with 60 mL/kg of saline solution. Bedside echocardiography showed significant respiratory changes in IVC diameter, which, along with other clinical and monitoring data, suggested that fluid resuscitation should be maintained. dIVC = 90%, where dIVC = $(D_{max} - D_{min})/D_{min} \times 100$.

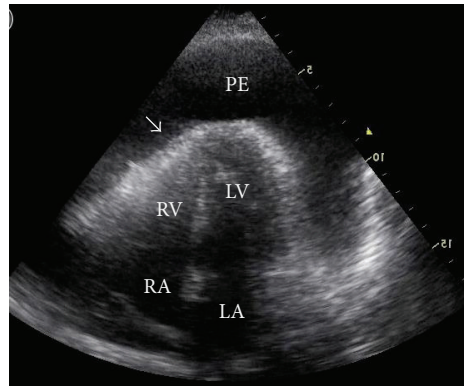


Figure 4: Cardiac tamponade with large pericardial effusion and diastolic collapse of the right ventricle (arrow). LA: left atrium; LV: left ventricle; PE: pericardial effusion. RA: right atrium; RV: right ventricle.

ventilation. For having the advantage of being a noninvasive method that can be performed quickly and serially, the use of dIVC became widespread, but the specific situation in which the study was conducted cannot be disregarded [40]. There are few studies correlating fluid responsiveness with respiratory changes in IVC in pediatric patients and these studies have shown conflicting results; therefore, this is an open field for further investigations [41, 42].

Another means of assessing fluid responsiveness using echocardiography is by analyzing the respiratory change of the aortic peak flow velocity on Doppler during inspiration and expiration in patients under mechanical ventilation. It is calculated as $\Delta V = (V_{peak\ max} - V_{peak\ min})/V_{mean\ peak}$ [43]. The aortic peak flow variation has been correlated with the patient's response to fluid infusion in several previous studies, including at least five studies with pediatric patients, and emerges as a promising form of assessment of fluid responsiveness in children under mechanical ventilation [34, 41, 42, 44, 45].

4. Pericardial Effusion and Cardiac Tamponade

Pericardial effusion (PE) is identified in echocardiography as an echolucent space adjacent to the cardiac structures. It may be diffuse or loculated, more frequently is diffuse and promote a clear separation between the parietal and visceral pericardia [46]. Loculated effusion may be secondary to adherences after cardiac surgery or trauma.

Cardiac tamponade is an emergency situation and its diagnosis is known to be clinical. However, echocardiography may suggest the existence of tamponade physiology, that is, increased intrapericardial pressure precluding the ventricular filling. The major echocardiographic signs that corroborate the clinical diagnosis of cardiac tamponade are systolic collapse of the right atrium and diastolic collapse of the right ventricle, presence of IVC dilatation with no respiratory change, and presence of respiratory change in flow velocities through the heart valves [47–49] (Figure 4).

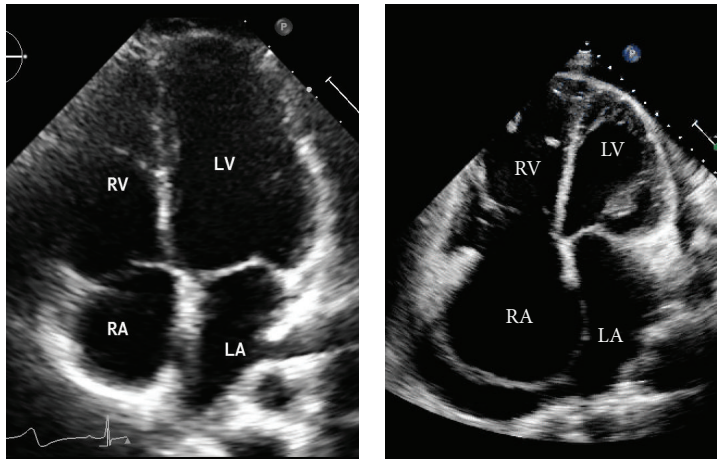
Bedside echocardiography plays an important role in guiding pericardiocentesis. An extensive review from the Mayo Clinic on 1127 patients undergoing echocardiographically guided pericardiocentesis showed that the usual subxiphoid approach had been chosen in only 20% of cases after echocardiographic assessment. In most of the patients, pericardial puncture was performed using transthoracic puncture (apical/parasternal), and this reduced the complication rate of pericardiocentesis from 20% to only 4.7% [50].

5. Right Ventricle and Pulmonary Hypertension

The right ventricular (RV) wall thickness and dimensions should be analyzed using all multiple views, the apical view being the most suitable for this analysis. The RV size is qualitatively analyzed and, in comparison to the LV size, is classified according to the RV and LV ratio as follows: normal, when the RV is smaller than the LV (approximately 60% of the LV size) and the RV apex is lower than the LV; slightly increased, when dilatation is present; however, RV is still smaller than LV; moderately increased, when the RV size is the same as LV; and markedly increased, when RV is larger than LV [46] (Figure 5).

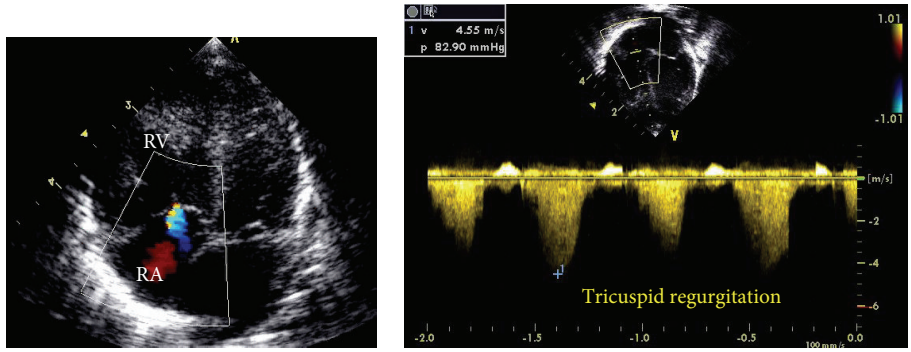
The RV systolic function is assessed by nonechocardiographers only qualitatively, by visual estimation. Just like the assessment of LV function, ventricular wall motion and thickness should be analyzed. The classification of RV function is also similar to the LV's: normal, slightly reduced, moderately reduced or markedly reduced [46].

Echocardiography also allows the estimative of pulmonary artery systolic pressure (PASP) in the presence of tricuspid regurgitation. Using the spectral curve of tricuspid regurgitation obtained by continuous wave Doppler, the pressure difference between RV and RA (gradient pressure) is calculated. The RV-RA gradient pressure added to the RA pressure is equivalent to PASP, when there is no RV outflow tract obstruction (Figure 6).



(a) (b)

Figure 5: (a) Four-chamber apical view demonstrating normal heart. (b) Significant right chambers dilatation with straightened ventricular septum plus small pericardial effusion. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.



(a) (b)

Figure 6: Newborn under invasive mechanical ventilation for hypoxemia in the first day of life. Apical view showing tricuspid regurgitation on color Doppler in blue (a) and on continuous wave Doppler (b). RV-RA gradient of 82 mmHg and the pulmonary artery systolic pressure is estimated at 92 mmHg (RV-RA gradient pressure added to the RA pressure).

Pulmonary hypertension is present in several clinical situations in Pediatric Intensive Care, especially following cardiac surgery and in neonates. This makes its bedside diagnosis by the pediatrician both interesting and useful [51, 52].

6. Conclusion

Bedside echocardiography has become widespread in emergency and Intensive Care Units. It is a useful tool in the diagnosis and treatment of hemodynamic unstable adult and pediatric patients. Adequate training of pediatricians from Emergency and Intensive Care Units to perform focused echocardiography is feasible and provides improved care of severely ill children and thus should be encouraged.

Conflict of Interests

The authors declare that they have no competing interests.

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Research Article

Goal-Directed Resuscitation Aiming Cardiac Index Masks Residual Hypovolemia: An Animal Experiment

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The aim of this study was to compare stroke volume (SVI) to cardiac index (CI) guided resuscitation in a bleeding-resuscitation experiment. Twenty six pigs were randomized and bled in both groups till baseline SVI (T_{bsl}) dropped by 50% (T_0), followed by resuscitation with crystalloid solution until initial SVI or CI was reached (T_4). Similar amount of blood was shed but animals received significantly less fluid in the CI-group as in the SVI-group: median = 900 (interquartile range: 850–1780) versus 1965 (1584–2165) mL, $p = 0.02$, respectively. In the SVI-group all variables returned to their baseline values, but in the CI-group animals remained underresuscitated as indicated by SVI, heart rate (HR) and stroke volume variation (SVV), and central venous oxygen saturation ($S_{cv}O_2$) at T_4 as compared to T_{bsl}: SVI = 23.8 ± 5.9 versus 31.4 ± 4.7 mL, HR: 117 ± 35 versus 89 ± 11/min SVV: 17.4 ± 7.6 versus 11.5 ± 5.3%, and $S_{cv}O_2$: 64.1 ± 11.6 versus 79.2 ± 8.1%, $p < 0.05$, respectively. Our results indicate that CI-based goal-directed resuscitation may result in residual hypovolaemia, as bleeding caused stress induced tachycardia "normalizes" CI, without restoring adequate SVI. As the SVI-guided approach normalized most hemodynamic variables, we recommend using SVI instead of CI as the primary goal of resuscitation during acute bleeding.

1. Introduction

Acute bleeding due to trauma, surgery, or gastrointestinal disorders is a life threatening condition requiring immediate and adequate interventions, of which intravenous fluid therapy is regarded as the first step of resuscitation. Although lifesaving at the time, inadequate fluid resuscitation can lead to hypo- or hyper-perfusion causing the development of multiorgan disorders at a later stage, which then severely affects the outcome of these patients [1, 2]. Therefore, the use of early and efficient therapeutic strategies able to detect and to treat the imbalance between oxygen delivery and consumption is of particular importance in critically ill patients, which has been recognized for decades [3].

Traditional endpoints of resuscitation, such as heart rate, blood pressure, mental status, and urine output can be useful in the initial identification of inadequate perfusion but are limited in their ability to identify ongoing, compensated shock [4]. More detailed assessment of global macrohemodynamic indices such as cardiac output and derived variables, measures of oxygen debt, may be necessary to guide treatment [5, 6].

Cardiac output calculated from thermodilution or pulse contour analysis is the most often used end-point during goal-directed therapy [7, 8]. However, there is no consensus on the best or universally accepted parameter as resuscitation target. In a recent animal experiment we described changes in central venous oxygen saturation ($S_{cv}O_2$) and venous-to-arterial carbon dioxide gap (dCO_2) during an experimental stroke volume index- (SVI-) guided bleeding and fluid resuscitation model on porcine. We found that dCO_2 may be a useful hemodynamic endpoint of resuscitation, while $S_{cv}O_2$ is

not strictly a hemodynamic parameter, but rather an indicator of the balance between oxygen delivery and consumption [9]. However, we also noticed that normalizing stroke volume index resulted in higher cardiac index (CI) by the end of resuscitation as compared with baseline, possibly because of the bleeding-induced tachycardia. Hence we hypothesized that normalizing cardiac output only may mask ongoing hypovolemia due to increased heart rate caused by sympathetic response and may result in inadequate fluid resuscitation. Therefore, the objective of the current study was to compare SVI as primary target of fluid resuscitation to CI-based treatment in a bleeding-resuscitation animal model.

2. Materials and Methods

The experiments were performed on the EU Directive 2010/63/EU on the protection of animals used for experimental and other scientific purposes and carried out in strict adherence to the NIH guidelines for the use of experimental animals. The study was approved by the National Scientific Ethical Committee on Animal Experimentation (National Competent Authority), with the license number V./142/2013.

2.1. Animals and Instrumentation. Vietnamese mini-pigs ($n = 27$) underwent a 12-hour fasting preoperatively but with free access to water. Anesthesia was induced by intramuscular injection of a mixture of ketamine (20 mg/kg) and xylazine (2 mg/kg) and maintained with a continuous intravenous infusion of propofol (6 mg/kg/hr iv.), while analgesia was performed with nalbuphine (0.1 mg/kg). The animals' trachea was intubated and the lungs were ventilated mechanically with Dräger Evita XL (Dräger, Lübeck, Germany). The tidal volume was set at 10 mL/kg, and the respiratory rate was adjusted to maintain the end-tidal carbon dioxide and partial pressure of arterial carbon dioxide in the range of 35–45 mmHg. The adequacy of the depth of anesthesia was assessed by monitoring the jaw tone. After induction of anesthesia, the right jugular vein, the left carotid artery, and the right femoral artery were dissected and catheterized using aseptic technique. For invasive hemodynamic monitoring, a transpulmonary thermodilution catheter (PiCCO, PULSION Medical Systems SE, Munich, Germany) was placed in the right femoral artery. Central venous catheter was inserted via the right jugular vein and was positioned by the guidance of intracavital ECG. During the bleeding phase blood was drained from a sheat inserted in the left carotid artery. Animals were kept warm (37 ± 1°C) by an external warming device.

2.2. Hemodynamic Monitoring and Blood Gas Sampling. Cardiac output (CO), global end-diastolic volume index (GEDI), stroke volume (SV), cardiac function index (CFI), index of left ventricular contractility (dPmax), SV variation (SVV), pulse pressure variation (PPV), heart rate (HR), and mean arterial pressure (MAP) were measured by transpulmonary thermodilution and pulse contour analysis at baseline and at the end of each interval. All hemodynamic parameters were indexed for body surface area or bodyweight. Central venous catheter was used for the injection of cold saline boluses for the thermodilution measurements. The average of three measurements following 10 mL bolus injections of ice-cold 0.9% saline was recorded. Central venous pressure (CVP) was measured via central venous catheter at the same times as the other hemodynamic variables.

For blood gas measurements the right femoral artery served as the site for arterial blood gas sampling and the central venous line was used for taking central venous blood gas samples, which were analyzed by cooximetry (Cobas b 221, Roche Ltd., Basel, Switzerland) simultaneously at baseline and at the end of each step. From these parameters the following variables were calculated:

$$\begin{aligned}
&\text{Delivery of oxygen } \left(\mathrm{DO_2}\right) \\
&= \mathrm{CI} * \left(\mathrm{Hb} * 1.34 * \mathrm{SaO_2} + 0.003 * \mathrm{PaO_2}\right), \\
&\text{Oxygen consumption } \left(\mathrm{VO_2}\right) \\
&= \mathrm{CI} \\
&\quad * \left(\mathrm{CaO_2} - \left(\mathrm{Hb} * 1.34 * \mathrm{S_{cv}O_2} + 0.003 * \mathrm{P_{cv}O_2}\right)\right), \\
&\text{Oxygen extraction} = \frac{\mathrm{VO_2}}{\mathrm{DO_2}}.
\end{aligned} \tag{1}$$

2.3. Experimental Protocol. The flowchart of the experiment is summarized in Figure 1. After the instrumentation, animals were allowed to rest for 30 minutes after which baseline (T_{bsl}) hemodynamic, microcirculatory measurements, blood gas analyses, including lactate measurements, and laboratory testing were performed. After these measurements, blood was drained until the stroke volume index dropped by 50% of its baseline value (T_0); then measurements were repeated. At this point the animals were randomized into two groups. In the SVI-group the difference of the $\mathrm{SVI}_{T_{\mathrm{bsl}}} - \mathrm{SVI}_{T_0}$ was divided into four equal target values, which was aimed to reach in 4 steps during fluid resuscitation (T_{1-4}) to reach the initial SVI by T_4. While in the CI-group the difference of the $\mathrm{CI}_{T_{\mathrm{bsl}}} - \mathrm{CI}_{T_0}$ was divided into 4 target values and then the animals were resuscitated in 4 steps in order to reach the $\mathrm{CI}_{T_{\mathrm{bsl}}}$ by T_4. Fluid replacement was carried out with boluses of 200 mL of balanced crystalloid Ringerfundin (B. Braun AG., Melsungen, Germany) over 10 minutes, till the target SVI or CI value was reached. After reaching each step, 20 minutes was allowed for equilibrium; then hemodynamic and blood gas parameters were measured. At the end of the experiment the animals were euthanized with sodium pentobarbital.

2.4. Data Analysis and Statistics. Data are presented as mean ± standard deviations unless indicated otherwise. For testing normal distribution the Kolmogorov-Smirnov test was used. Changes in all parameters throughout the experiment were tested by two-way repeated measures analysis of variance (RM ANOVA) and for the post hoc test Bonferroni test was used. For pairwise comparisons Pearson's correlation was used. The primary end point of the study was the normalization of SVV, as the one of the best indicators of hypo-, normovolemia

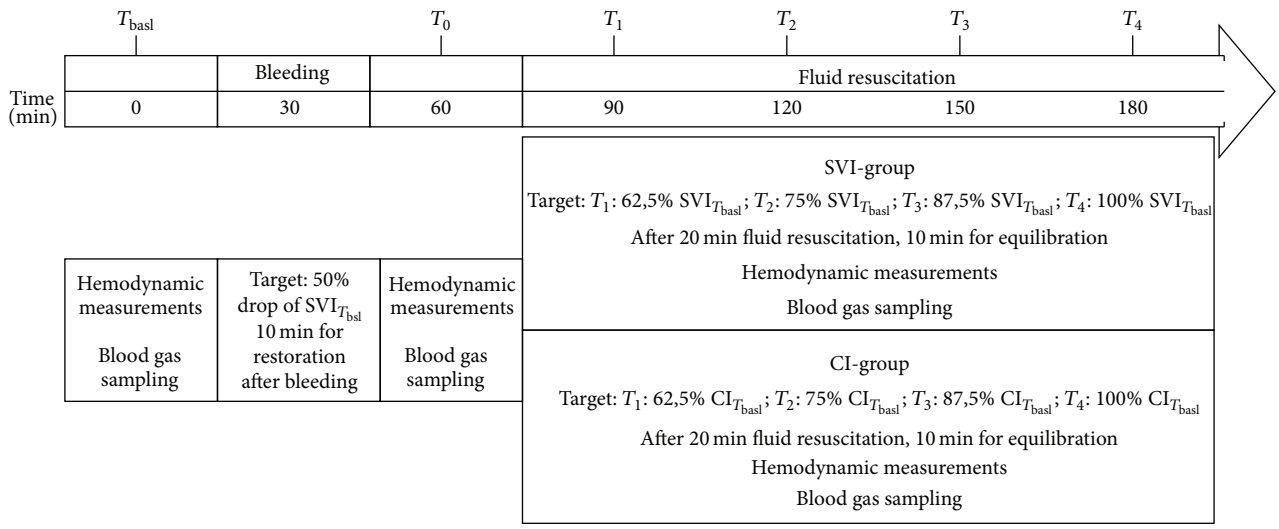

Figure 1: Flow chart. Schematic diagram illustrating the flowchart of the experimental protocol. After baseline measurement, animals were bled until the stroke volume index (SVI) decreased by 50% (T_0); then measurements were repeated and randomized into two group. In the SVI-group the difference of the $SVI_{T_{bsl}} - SVI_{T_0}$ was divided into four equal target values (T_{1-4}), and fluid resuscitated to reach the initial SVI by T_4. In the CI-group the difference of the $CI_{T_{bsl}} - CI_{T_0}$ was divided into 4 target values and then the animals were resuscitated in 4 steps in order to reach the $CI_{T_{bsl}}$ by T_4.

in mechanically ventilated subjects [10]. Based on the results of our previous animal experiment [9] SVV was found to be 12.2 ± 4.3% by the end of resuscitation. Considering that CI-based resuscitation remains inadequate, we regarded a clinically significant difference of 4% (i.e., 12% in the SVI-group and 16% in the CI-group). In order the study to have 80% power to show a difference between the two groups if $\alpha < 0.05$, the required sample size is a minimum of 20 animals (10 in each group). For statistical analysis SPSS version 20.0 for Windows (SPSS, Chicago, IL) was used and $p < 0.05$ was considered statistically significant.

3. Results

All animals survived the experiment, apart from one (CI-group), which had sudden cardiac arrest after induction of anesthesia for unknown reasons. Therefore, the results of 14 animals in the SVI-group and 12 animals in the CI-group were analyzed. Demographics and fluid management data are summarized in Table 1. Animals were of similar weight in both groups. For a 50% decrease of SVI similar blood had to be drained in the two groups. During resuscitation animals in the SVI-group required more fluid in total, and taking into account the volume of crystalloid required to replace a unit of 10 mL blood loss, animals in the SVI-group also received significantly more fluid (Table 1).

3.1. Macrohemodynamics. Hemodynamic parameters were similar at T_{bsl} and goals of 50% reduction in SVI were reached by T_0 in both groups (Table 2). In the SVI-group SVI returned to its baseline value by T_4 and CI was significantly elevated as compared to T_{bsl}. In the CI-group SVI remained significantly lower as compared to T_{bsl}. Mean arterial pressure and heart rate showed a similar pattern in both groups, but in the CI-group heart rate remained significantly higher by T_4 as compared to T_{bsl}, while it normalized in the SVI-group. Mean arterial pressure changed significantly in each group with a similar pattern without significant differences between the groups. There was less change in the CVP throughout the experiment, with a significant increase at T_3 and T_4 only in the SVI-group. Global end-diastolic volume decreased and then increased in both groups, but while it normalized by T_4 in the SVI-group, it remained significantly lower in the CI-group as compared to the SVI-group and as compared to T_{bsl}. Stroke volume variation and PPV also followed a similar pattern, and SVV normalized in the SVI-group but it remained significantly elevated in the CI-group, both as compared to T_{bsl} and between the groups at T_4. Contractility, as indicated by dPmax values did not show any considerable change over time or between the groups.

3.2. Measures of Oxygen Debt. Oxygen delivery followed a similar pattern in both groups, but in the CI-group it remained significantly lower at T_4 as compared to T_{bsl} (Table 3). In the SVI-group there was also a considerable drop by T_4, although it was not significant. This can be explained by the significant and steady decrease in the hemoglobin levels in both groups. Oxygen consumption was more or less stable throughout the experiment, apart from a significant increase during the bleeding phase in both groups. Oxygen extraction changed accordingly with no major difference between the groups. Arterial pH, oxygen partial pressure, and oxygen saturation remained stable and within the normal range throughout.

Table 1: Demographics and fluid therapy.

	SVI-group ($n = 14$)	CI-group ($n = 12$)	p
Weight (kg)	29.00 ± 5.36	27.54 ± 5.46	0.606
BSA (m^2)	0.98 ± 0.09	0.93 ± 0.91	0.390
Shed blood (mL)	485 ± 91	479 ± 101	0.859
Shed blood (mL/m^2)	492 ± 59	508 ± 101	0.719
Total amount of the replaced fluid (mL)	1965 [1584–2165]	900 [850–1780]	0.020*
Required fluid (mL)/unit blood loss (10 mL)	40 ± 12	25 ± 12	0.027*

SVI (stroke volume index), SVI-group; CI (cardiac index), CI-group. Data are presented as mean ± standard deviation or median [interquartile range] as appropriate. * $p < 0.05$.

Table 2: Hemodynamic parameters during hemorrhage and fluid resuscitation.

	Group	T_{bsl}	T_0	T_1	T_2	T_3	T_4
Stroke volume index (mL/m^2)	SVI	27.5 ± 5.4	13.8 ± 2.6*	16.5 ± 2.8*	19.5 ± 3.7*#	23.6 ± 5.1#	28.0 ± 5.0#
	CI	31.4 ± 4.7	14.4 ± 9.0*	18.1 ± 3.6*	19.2 ± 3.6*	23.2 ± 1.3*#	23.8 ± 5.9*#@
Cardiac index ($L/min/m^2$)	SVI	2.6 ± 0.3	1.8 ± 0.3*	2.1 ± 0.4*	2.4 ± 0.3#	2.7 ± 0.4#	2.9 ± 0.4*#
	CI	2.8 ± 0.3	1.7 ± 0.5*	2.1 ± 0.3*	2.4 ± 0.2#	2.6 ± 0.4#	2.7 ± 0.3#
Mean arterial pressure (mmHg)	SVI	116 ± 17	72 ± 17*	75 ± 19*	78 ± 18*	86 ± 17*	92 ± 16*#
	CI	124 ± 12	75 ± 22*	77 ± 18*	80 ± 81*	86 ± 22*	96 ± 20*#
Heart rate (beats/min)	SVI	95 ± 13	133 ± 22*	130 ± 29*	121 ± 21*	111 ± 18#	101 ± 12#
	CI	89 ± 11	139 ± 37*	131 ± 13*	127 ± 28*	121 ± 24*	117 ± 35*
Central venous pressure (mmHg)	SVI	5.9 ± 1.0	4.8 ± 0.7	5.5 ± 1.9	5.6 ± 1.4	6.1 ± 1.2#	6.2 ± 1.3#
	CI	6.0 ± 0.6	4.7 ± 0.8	5.3 ± 0.6	5.6 ± 0.5	6.2 ± 1.5	6.5 ± 0.7
Global end-diastolic volume (mL/m^2)	SVI	308 ± 56	237 ± 61*	243 ± 59*	251 ± 46*	282 ± 58#	298 ± 53#
	CI	312 ± 33	191 ± 56*@	204 ± 32*	211 ± 27*	243 ± 32*#	247 ± 32*#@
Stroke volume variation (%)	SVI	14.7 ± 4.7	22.1 ± 5.5*	22.2 ± 4.9*	18.5 ± 4.6	16.7 ± 5.2#	12.1 ± 3.6#
	CI	11.5 ± 5.3	18.6 ± 5.2*	18.7 ± 3.7*	21.3 ± 4.8	19.3 ± 4.1*	17.4 ± 7.6*@
Pulse pressure variation (%)	SVI	14.2 ± 5.3	24.6 ± 6.9*	23.3 ± 6.7*	19.0 ± 5.8#	16.7 ± 5.2#	13.1 ± 4.1#
	CI	12.2 ± 3.1	25.2 ± 6.7*	22.8 ± 5.4*	19.8 ± 4.5#	17.4 ± 5.8#	16.3 ± 6.7#
Systemic vascular resistance index ($dyn \times s/cm^5/m^2$)	SVI	3261 ± 942	3100 ± 873	2677 ± 734	2442 ± 698*#	2410 ± 466*#	2336 ± 475*#
	CI	3507 ± 597	3191 ± 709	2767 ± 630*	2652 ± 240*	2508 ± 565*	2481 ± 495*#
EVLWI (mL/kg)	SVI	10.1 ± 1.9	10.0 ± 2.2	9.9 ± 1.9	9.0 ± 1.5	9.3 ± 1.6	9.8 ± 1.7
	CI	7.4 ± 1.2@	7.2 ± 0.9@	7.2 ± 1.0@	7.4 ± 1.0	7.5 ± 0.9@	8.2 ± 1.0@
dPmax (mmHg/s)	SVI	561 ± 226	560 ± 344	653 ± 404	682 ± 390	987 ± 269	674 ± 236
	CI	585 ± 87	595 ± 206	579 ± 95	597 ± 137	551 ± 105	639 ± 154

SVI (stroke volume index), SVI-group; CI (cardiac index), CI-group. Data are presented as mean ± standard deviation.
* $p < 0.05$ significantly different from T_{bsl}.
# $p < 0.05$ significantly different from T_0.
@ $p < 0.05$ significantly different between groups.

Central venous oxygen saturation was in the normal range at T_{bsl} in both groups; then there was a significant drop after bleeding, which normalized in the SVI-group but remained significantly lower in the CI-group at T_4 as compared to the SVI-group. The mean decrease in the CI-group from T_{bsl} to T_4 was 15.1% and at T_4 it was 8.8% lower as in the SVI-group. Central venous to arterial CO_2-gap was normal at T_{bsl} in both groups. After bleeding it increased significantly and returned to normal in the SVI-group. In the CI-groups levels also decreased but remained elevated, although they did not reach statistical significance.

Lactate levels were slightly elevated at T_{bsl} in both groups, with significant increase in the SVI-group, which reduced by T_4. In the CI-group significant changes could not be observed, and there was no significant difference between the groups either.

Table 3: Blood gas parameters during hemorrhage and fluid resuscitation.

	Group	T_{bsl}	T_0	T_1	T_2	T_3	T_4
Oxygen delivery index (mL/min/m^2)	SVI	417 ± 64	250 ± 100*	275 ± 71*	291 ± 55*	318 ± 55*	337 ± 81$^\#$
	CI	410 ± 54	271 ± 62*	297 ± 85*	282 ± 47*	278 ± 52*	311 ± 61*
Oxygen consumption (index mL/min/m^2)	SVI	82 ± 27	118 ± 63*	111 ± 19	102 ± 24	98 ± 24	94 ± 23
	CI	71 ± 43	115 ± 48*	111 ± 29	108 ± 21	103 ± 18	99 ± 13
Oxygen extraction (VO_2/DO_2)	SVI	0.20 ± 0.06	0.40 ± 0.11*	0.36 ± 0.06*	0.33 ± 0.11*	0.29 ± 0.09$^{*\#}$	0.27 ± 0.13$^\#$
	CI	0.17 ± 0.09	0.40 ± 0.18*	0.38 ± 0.09*	0.36 ± 0.08*	0.34 ± 0.14*	0.33 ± 0.11*
Arterial pH	SVI	7.48 ± 0.04	7.46 ± 0.07	7.44 ± 0.06	7.41 ± 0.11	7.45 ± 0.04	7.46 ± 0.04
	CI	7.44 ± 0.04	7.43 ± 0.06	7.42 ± 0.05	7.47 ± 0.03	7.42 ± 0.05	7.45 ± 0.05
Partial pressure of oxygen in arterial blood (mmHg)	SVI	94.5 ± 26.5	94.9 ± 27.8	90.1 ± 20.2	94.9 ± 27.1	93.1 ± 27.1	95.5 ± 30.1
	CI	88.3 ± 28.8	89.8 ± 28.8	97.6 ± 30.2	89.2 ± 22.5	93.8 ± 32.6	88.2 ± 27.6
Arterial oxygen saturation (%)	SVI	97.3 ± 1.5	96.7 ± 2.1	96.3 ± 2.0	97.0 ± 1.5	97.0 ± 1.7	96.9 ± 1.8
	CI	95.4 ± 3.6	95.3 ± 5.0	96.1 ± 4.2	98.6 ± 1.5	95.6 ± 4.8	96.0 ± 3.2
Central venous oxygen saturation (%)	SVI	77.4 ± 6.6	57.5 ± 10.8*	60.9 ± 4.8*	64.3 ± 9.2*	68.4 ± 8.6$^{*\#}$	72.9 ± 7.5
	CI	79.2 ± 8.1	56.7 ± 17.0*	58.5 ± 10.6	59.7 ± 8.0	63.0 ± 14.7	64.1 ± 11.6$^{\#@}$
Venous to arterial carbon dioxide gap (mmHg)	SVI	5.7 ± 2.4	10.1 ± 2.6*	8.9 ± 1.7	7.5 ± 2.4	7.2 ± 2.7	5.3 ± 2.3$^\#$
	CI	4.0 ± 3.1	9.9 ± 6.0*	8.8 ± 2.4*	8.5 ± 3.0	8.1 ± 3.1	7.6 ± 4.3
Lactate (mmol/L)	SVI	2.54 ± 1.01	3.97 ± 1.80*	4.72 ± 2.29*	4.37 ± 2.37*	3.90 ± 2.25*	3.26 ± 1.95
	CI	3.32 ± 1.26	4.49 ± 1.83	4.50 ± 2.40	4.32 ± 0.69	4.05 ± 2.52	3.77 ± 2.32
Hemoglobin (g/dL)	SVI	11.6 ± 1.5	10.7 ± 1.5	10.4 ± 1.46*	9.4 ± 1.2$^{*\#}$	8.3 ± 1.5$^{*\#}$	8.1 ± 0.9$^{*\#}$
	CI	11.2 ± 0.7	10.4 ± 1.2	9.5 ± 1.2*	9.2 ± 0.9$^{*\#}$	8.4 ± 0.6$^{*\#}$	8.2 ± 1.5$^{*\#}$

SVI (stroke volume index), SVI-group; CI (cardiac index), CI-group. Data are presented as mean ± standard deviation.
* $p < 0.05$ significantly different from T_{bsl}.
$^\#$ $p < 0.05$ significantly different from T_0.
$^@$ $p < 0.05$ significantly different between groups.

4. Discussion

In this study CI-based resuscitation resulted in residual hypovolemia compared to SVI-based fluid management as indicated by both macro-hemodynamic indices and measures of oxygen debt in a bleeding-resuscitation animal experiment.

4.1. Fluid Resuscitation. Fluid therapy is often regarded as the first line of support in most shock states and this holds especially true for acute bleeding. Fluid infusions directly increase intravascular volume and subsequently improve global and regional perfusion and oxygen delivery. However, this benefit can only occur in patients who are on the ascending limb of the Frank-Starling curve. In patients, who are regarded hypovolemic, only 50% respond to fluid, as defined by a 10–15% increase in stroke volume [11]. Although fluid resuscitation is a potentially lifesaving intervention large volumes can result in severe tissue edema and clinical signs of volume overload. These effects are mainly articulated in encapsulated organs, which have limited capacity to accommodate additional volume without compromising tissue perfusion. There is mounting evidence that both hypovolemia and fluid overload are associated with impaired organ function and increased risk of dying [2, 12, 13]. Therefore, adequate monitoring and defining appropriate resuscitation end points are of pivotal importance. However, according to recent large international surveys physicians apply monitoring and indicate fluid therapy based mainly on parameters, which are unable to predict fluid responsiveness. Several studies showed that mean arterial pressure and static markers of preload such as CVP, pulmonary capillary occlusion pressure have limited value in guiding fluid management; however more than 80% of physicians working in anesthesiology or in critical care still rely mainly on these parameters [14, 15]. Over the last 20 years there were 21 clinical trials published on perioperative goal-directed therapy [16]. In these studies hemodynamic goals showed a great variability. The most frequently used parameters to guide fluid management were CI, SV, SVV, PPV, CVP, MAP, echo-derived dynamic indices, pulmonary artery occlusion pressure, DO_2, and oxygen extraction ratio. This clearly shows that universally accepted hemodynamic target by which fluid therapy should be tailored is missing.

It is important to note that recent milestones of multicenter clinical trials on fluid therapy [17–20] "neglected" this approach to some extent, and in these studies fluid administration was mainly based on the clinicians' "intuition" or inadequate indices rather than appropriate hemodynamic parameters of intravascular blood volume. Nevertheless, one

of the most important messages of these large trials, which is also in accord with the results of recent surveys [14, 15], is that our everyday routine practice should be revised and may be harmful.

The physiological rationale of intravenous fluid administration to a patient is to increase SV, hence DO_2, and also perfusion. In several studies CI was applied as therapeutic goal [21–24], although CO is the product of heart rate and SV; therefore compensatory mechanisms, such as tachycardia, may compensate residual hypovolemia. In the current experiment we found major differences between the SVI- and CI-guided groups. The latter received significantly less fluid in total and also required less fluid to replace every unit of lost blood. These results suggest that simply applying invasive hemodynamics as compared to our daily routine monitoring may not be sufficient, and depending on the parameter we chose to follow, subjects can still remain under- or overresuscitated.

4.2. SVI- versus CI-Guided Goal-Directed Resuscitation: Hemodynamics. During bleeding to restore homeostasis, the sympathetic nervous system becomes activated and releases epinephrine and norepinephrine. As a result, venous return will increase, while on the arterial side norepinephrine-caused vasoconstriction tries to maintain perfusion. Because of this sympathetic activation, heart rate and myocardial contractility will also increase. During resuscitation, our pivotal goal is to restore circulating blood volume by increasing SV to improve oxygen delivery. Recent clinical investigations [25, 26] showed positive effects of SV optimization, and there is frank evidence that PPV and SVV are well-established indicators of fluid responsiveness in mechanically ventilated subjects without cardiac arrhythmias [27]. Therefore in our experiment, SVV was the primary outcome variable as the closest to predict fluid responsiveness, hence hypovolemia. In both groups there was a significant increase after bleeding but values returned to baseline only in the SVI-group. In the CI-group neither dynamic (SVV/PPV) nor static indicators of preload (GEDI) normalized to their baseline values, indicating, that it was not the circulating blood volume, but heart rate compensated CO, which normalized, leaving residual hypovolemia unnoticed.

It is interesting to note that CVP changed to a lesser degree than any other hemodynamic parameter; hence our results provide further evidence of the limitations to CVP as a goal during fluid resuscitation, also described by others [7]. Although mean arterial pressure followed hemodynamic changes to some extent, there was no difference between the groups, indicating that for fine tuning hemodynamics, just as CVP, MAP also has limited value. This is due to the fact that MAP and CI do not correlate with each other [28].

However, "normalizing" global hemodynamics is one thing, but normalizing the balance between oxygen delivery and consumption is another. Therefore, once the macrohemodynamic parameters look physiological, their effect on DO_2/VO_2 should also be assessed.

4.3. SVI- versus CI-Guided Goal-Directed Resuscitation: Oxygen Debt. As it has already been mentioned the primary goal of fluid resuscitation in hypovolemia is to maintain adequate oxygen delivery to the tissues. During bleeding, when oxygen demand/consumption is unchanged (in anesthetized subjects) or increased (in awake subjects), impaired oxygen delivery has to be accompanied by increased oxygen extraction ratio, which can be detected in the changes of $S_{cv}O_2$. Physiological mixed venous oxygen saturation ranges between 68% and 77%, and $S_{cv}O_2$ is considered to be 5% higher [29]. Indeed, in patients under general anesthesia the $S_{cv}O_2$ is often higher than 80%, which is due to the reduced oxygen demand and consumption; hence, higher values should be considered as "normal" [30, 31]. Furthermore, in our previous experiments, $S_{cv}O_2$ showed good correlation with oxygen extraction [32, 33]. Therefore, as interpretation of absolute values may prove difficult in different conditions evaluation of the changes of $S_{cv}O_2$ may be more helpful. In the current experiment we found that $S_{cv}O_2$ improved but remained significantly lower at the end of the experiment as compared to baseline values in both groups. This is most likely due to hemodilution, a feature also found in our previous study [9]. However, in the CI-group $S_{cv}O_2$ remained 15% lower as compared to baseline and more than 10% lower as in the SVI-group, indicating severe oxygen debt. Although interpreting $S_{cv}O_2$ may be difficult when there is problem with extraction typically seen in sepsis, there is international consensus that low levels should be an important warning sign to indicate inadequate DO_2 to meet oxygen demands [34]. In our experiment in the CI-group, we measured lower DO_2, $S_{cv}O_2$ and higher oxygen extraction ratio, indicating that animals resuscitated for CI remained in oxygen debt.

Several authors have reported increased dCO_2 in different low flow states [35–38]. In hypoxemia caused anaerobic metabolism, hydrogen ions are generated by the hydrolysis of adenosine triphosphate to adenosine diphosphate, and by the increased production of lactic acid [36]. These hydrogen ions are buffered by bicarbonate present in the cells, and this process will generate CO_2 production [37]. Arterial $PaCO_2$ is dependent on pulmonary gas exchange, and central venous $PvCO_2$ is dependent on the capability of blood flow to wash out carbon dioxide from the tissues. The Fick principle adapted to carbon dioxide demonstrates the inverse relationship between CO and dCO_2 [39]. Thus, it has been postulated that increased dCO_2 reflects decreased flow. In the current experiment dCO_2 followed the same pattern, what we observed previously, and returned to the baseline value at the end of resuscitation in the SVI-group. In the CI-group, it remained elevated, above the physiological value of 6 mmHg, but this difference did not reach statistical significance. Nevertheless, this tendency gives further evidence that these animals were underresuscitated.

Lactate, the product of anaerobic metabolism, is often referred to as one of the main biochemical targets to be treated during resuscitation [40]. In our experiment, levels were slightly elevated at baseline, possibly due to the relatively long set-up time of the experiment, and there was an increase and then decrease during interventions, but these changes were not as dramatic as one may expect. However, it is important to note, that this experimental model is similar to a "moderate" bleeding event, and animals were resuscitated

within a relatively short period of time. Due to the physiologic relationship between DO_2 and VO_2, namely, due to compensatory mechanisms when there is a drop in DO_2, up to a certain point VO_2 remains stable, in other words independent from DO_2. Therefore, although the VO_2/DO_2 ratio is increasing, but it does not cause and mean cellular hypoxia, hence aerobic metabolism is not disturbed. To conclude, animals during this experiment were heading towards shock; they were in oxygen debt but remained on the flat part of the VO_2/DO_2 curve, not reaching cellular hypoxia and shock, meaning the steep part of the curve. This is also supported by the arterial pH, which remained normal throughout in both groups. In general, this is the rationale and advantage of measuring $S_{cv}O_2$, and for similar reasons SVV or PPV, because we are "one step ahead" of cellular hypoxia and circulatory shock.

4.4. Limitations. One of the limitations of this experiment is that we could not provide data on microcirculation and regional blood flow, which would be interesting to see. Furthermore, these results can only partially be extrapolated for the real clinical settings. Reducing the SVI by 50% is a strictly controlled scenario, rarely happening in the everyday practice. The observation period at the end of the experiment was also short; therefore, long-term effects of SVI or CI-based fluid resuscitation could not be assessed. Another limitation of the model is that bleeding was relatively fast, causing a sympathetic burst, which is a reality in trauma and when major bleeding occurs on the wards, but in the operating room intravascular volume loss and bleeding caused hypovolemia usually occurs over a longer period of time.

5. Conclusion

In this experiment we have shown that SVI-based goal-directed resuscitation of a bleeding subject seems superior to CI-guided resuscitation as indicated by both hemodynamic parameters and measures of oxygen debt returning to baseline in the SVI-group, which was incomplete in the CI-group. However, we would like to emphasize that treating one single parameter during resuscitation is not warranted. It is not one single parameter, but the "hemodynamic puzzle" what we have to solve [41]. Therefore, it is necessary to put hemodynamic variables and measures of VO_2/DO_2 into context in a way that once macro-hemodynamic parameters are "normalized," adequacy of treatment has to be checked by measures of oxygen debt. Measuring SVV or PPV and simple blood gas driven variables such as $S_{cv}O_2$ and dCO_2 are valuable tools to solve this puzzle as quickly as possible.

Conflict of Interests

On behalf of all authors, the corresponding author states that there is no conflict of interests.

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Research Article

Monitoring Microcirculatory Blood Flow with a New Sublingual Tonometer in a Porcine Model of Hemorrhagic Shock

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Tissue capnometry may be suitable for the indirect evaluation of regional hypoperfusion. We tested the performance of a new sublingual capillary tonometer in experimental hemorrhage. Thirty-six anesthetized, ventilated mini pigs were divided into sham-operated ($n = 9$) and shock groups ($n = 27$). Hemorrhagic shock was induced by reducing mean arterial pressure (MAP) to 40 mmHg for 60 min, after which fluid resuscitation started aiming to increase MAP to 75% of the baseline value (60–180 min). Sublingual carbon-dioxide partial pressure was measured by tonometry, using a specially coiled silicone rubber tube. Mucosal red blood cell velocity (RBCV) and capillary perfusion rate (CPR) were assessed by orthogonal polarization spectral (OPS) imaging. In the 60 min shock phase a significant drop in cardiac index was accompanied by reduction in sublingual RBCV and CPR and significant increase in the sublingual mucosal-to-arterial PCO_2 gap ($P_{SL}CO_2$ gap), which significantly improved during the 120 min resuscitation phase. There was significant correlation between $P_{SL}CO_2$ gap and sublingual RBCV ($r = -0.65$, $p < 0.0001$), CPR ($r = -0.64$, $p < 0.0001$), central venous oxygen saturation ($r = -0.50$, $p < 0.0001$), and central venous-to-arterial PCO_2 difference ($r = 0.62$, $p < 0.0001$). This new sublingual tonometer may be an appropriate tool for the indirect evaluation of circulatory changes in shock.

1. Introduction

Disturbances of the microcirculation are tightly linked to circulatory failure of different origin; thus evaluation of the microcirculatory status has gained increasing importance in the diagnosis and treatment of critically ill patients. It is recognized that in spite of the normal values of global oxygen delivery regional tissue hypoperfusion may exist, which cannot be detected by conventional monitoring tools [1, 2]. Besides, compensatory mechanisms may lead to the normalization of macrohemodynamic parameters in the early phase of circulatory shock, and silently ongoing microcirculatory insufficiencies can cause cellular hypoxia and metabolic dysfunctions, eventually leading to organ failure [3].

The measurement of the partial pressure of carbon dioxide (PCO_2) in tissues is a potentially feasible technique for the indirect evaluation of the microcirculation [4, 5]. This parameter reflects the adequacy of regional microvascular blood flow, as intramucosal PCO_2 is inversely related to the proportion of well perfused capillaries, and is mainly dependent on tissue perfusion [6, 7]. However, acute increases or decreases in the PCO_2 of the arterial blood (P_aCO_2) result in comparable changes in the tissue PCO_2 [8]; thus it should be interpreted in relation to P_aCO_2. By subtracting P_aCO_2 from the tissue PCO_2, special gap values can be calculated which are more accurate than the mucosal PCO_2 alone, as they are independent of concurrent changes in P_aCO_2. Although there is no consensus on the most sensitive hemodynamic and laboratory parameters indicating the onset of shock, the tissue-to-arterial PCO_2 gap may provide an early and important additional signal of perfusion failure [1, 2, 9]. In addition, the tissue-to-arterial PCO_2 gap values also have prognostic importance [1, 10, 11]; therefore the monitoring of tissue levels of CO_2 may be helpful in titrating therapeutic interventions in critical states [12], or in selecting

patients with compromised physiologic reserve who require expanded hemodynamic monitoring.

Different sites of the gastrointestinal tract are available for the purpose of tissue capnometry and the assessment of the adequacy of mucosal blood flow. As PCO_2 results gained from the stomach and the sublingual regions proved to be interchangeable [6, 13], and the latter is free of some limitations of gastric tonometry, such as interference of gastric acid, enteral feeding, and potential pitfalls of pHi calculation [14], sublingual tonometry may be a useful alternative for measuring mucosal PCO_2. Though promising, this technique is still not available at the bedside because of the lack of a suitable monitoring device; hence clinical and experimental evidence on its efficacy is also missing.

It is generally acknowledged that monitoring of the sublingual microcirculation, the only site of intravital microscopy (IVM) available at the point of care for most critically ill patients, is of particular prognostic value [3]. In our institute a special instrument has been designed and manufactured for the measurement of sublingual PCO_2 (Figure 1), which is a further development of a gastric tonometer [15, 16]. The performance of this new probe was recently tested *in vitro* and also in patients with respiratory disease, and the results showed its suitability for sublingual tonometry [17].

The main goal of the current study was to test this new sublingual probe in a porcine model of hemorrhagic shock and compare its performance to direct microcirculatory measurements with IVM using the orthogonal polarization spectral (OPS) imaging technique. Another aim was to investigate how the capnometry-derived values relate to global indicators of hemodynamic changes during hemorrhage and resuscitation. We also hypothesized that if the same diagnostic end points can be reached, sublingual capnometry could offer a technically simpler, alternative method to monitor sublingual microcirculatory changes noninvasively.

2. Materials and Methods

The experiments were carried out in strict adherence to the National Institute of Health guidelines for the use of experimental animals and the study was approved by the Ethics Committee and the Institutional Animal Care and Use Committee at the University of Szeged. The study was conducted in the research laboratory of the Institute of Surgical Research in a manner that does not inflict unnecessary pain or discomfort upon the animals.

2.1. Animals and Instrumentation. Thirty-six Vietnamese mini pigs of both genders, weighing 16–25 kg, underwent a 24 hr fasting preoperatively with free access to water; the animals were randomly allocated into control (sham-operated, $n = 9$) and hemorrhagic shock groups (shock, $n = 27$). Anesthesia was induced by an intramuscular injection with a mixture of ketamine ($20\,mg\,kg^{-1}$) and xylazine ($2\,mg\,kg^{-1}$) and maintained with a continuous infusion of propofol ($50\,\mu g\,min^{-1}\,kg^{-1}$ iv, $3\,mg\,kg^{-1}\,hr^{-1}$). After endotracheal intubation, the animals were mechanically ventilated with room air (Harvard Apparatus, South Natick, MA, USA).

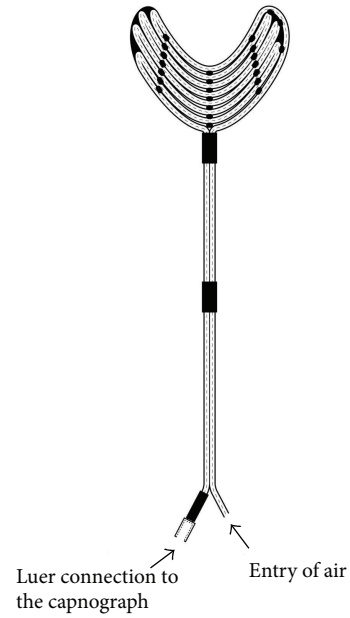

Figure 1: The new capillary tonometer. Illustration of the new sublingual tonometer applied during the examinations.

The tidal volume was set at $9 \pm 2\,mL\,kg^{-1}$, and the respiratory rate was adjusted to maintain the end-tidal partial pressure of carbon dioxide ($EtCO_2$) and P_aCO_2 in the range of 35–45 Torr (4.7–6.0 Pa). The depth of anesthesia was assessed by monitoring the jaw tone regularly. The animals were placed in supine position on a heating pad for maintenance of the body temperature between 36 and 37°C.

For measurement of the sublingual PCO_2 ($P_{SL}CO_2$) the new sublingual capillary tonometer (see below) was placed under the tongue, and a specially designed latex face mask was used to close the oral cavity. Capnography was performed with a Microcap handheld capnograph (Oridion Medical Ltd, Jerusalem, Israel). The sublingual mucosal-to-arterial PCO_2 difference ($P_{SL}CO_2$ gap) was calculated by subtracting $P_{SL}CO_2$ from the simultaneously taken P_aCO_2 values.

For central venous access the left jugular vein was catheterized. A three-lumen central venous catheter (7 F, Edwards Lifesciences LLC, Irvine, USA) was introduced for blood sampling and fluid administration using aseptic surgical technique. The central venous pressure (CVP) was monitored continuously with a computerized data-acquisition system (SPELL Haemosys; Experimetria Ltd., Budapest, Hungary). For hemodynamic measurements a special thermodilution catheter (Pulsiocath, PULSION Medical Systems AG, Munich, Germany) was placed into the left femoral artery. The cardiac output was monitored by transpulmonary thermodilution and continuous pulse contour analysis (PiCCO method). The right carotid artery was also catheterised for bleeding (7 F, PE, Access Technologies, Illinois, USA). The blood gas measurements were carried out by taking arterial and central venous blood samples simultaneously according to the study protocol, which were then analyzed by cooximetry with a blood gas analyzer (Cobas b221, Roche, Austria). Simplified oxygen extraction

rate (O_2ER) was calculated according to the standard formula from arterial (SaO_2) and central venous oxygen saturations ($ScvO_2$): $O_2ER = (SaO_2 - ScvO_2)/SaO_2$. From the central venous and arterial blood gas values the central venous-to-arterial PCO_2 gap ($PcvaCO_2$) was also determined.

For direct evaluation and noninvasive visualization of the sublingual microcirculation the intravital OPS imaging technique (Cytoscan A/R, Cytometrics, Philadelphia, PA, USA) was used. A 10x objective was placed onto the sublingual mucosa, and microscopic images were recorded with an S-VHS video recorder (Panasonic AG-TL 700, Matsushita Electric Ind. Co. Ltd, Osaka, Japan). Quantitative assessment of the microcirculatory parameters was performed offline by frame-to-frame analysis of the videotaped images. Red blood cell velocity (RBCV; $\mu m\,s^{-1}$) changes in the postcapillary venules were determined in three separate fields by means of a computer-assisted image analysis system (IVM Pictron, Budapest, Hungary) [18]. Capillary perfusion rate (CPR; 1/1) was determined as the length of continuously perfused microvessels per total length of capillaries in the observational area. During quantitative assessment of CPR we used a diameter limitation for determination of the microvascular network. Exclusively those vessels were selected for analysis, whose diameters were less than 20 μm. All microcirculatory evaluations were performed by the same investigator.

2.2. Description of the New Tonometric Probe. The new sublingual capillary tonometer (Mediszintech Ltd, Budapest, Hungary) is a specially coiled silicone rubber tube (ID: 1.5 mm, OD: 2.0 mm, and length: 640 mm) with high permeability for gases, which is formed into a multiple V-shape by using a mould and is glued along five lines (Figure 1). To prevent the soft-walled tube from flattening, a polyamide fiber of 0.3 mm thickness is inserted along its full length. Thereby after folding the tube a sufficient gap remains ensuring the free transport of the filling medium. The afferent and deferent parts of the tube are fixed together at their branching. The end of the deferent tube is equipped with a Luer connector. The filling material is room air, which equilibrates quickly with the PCO_2 content of the capillaries in the sublingual mucosa. After the required equilibration time it can be aspirated and measured by capnometry. The duration of the full equilibration of the sublingual probe is about 15 minutes. The PCO_2 of the aspirated gas is measured by infrared spectrophotometry. The results are immediately displayed in units of mmHg.

2.3. Experimental Protocol. The preparation period was followed by a 30 min resting period. After baseline measurements at 0 min (T_0) in the shock group, hemorrhagic shock was induced by bleeding the animals through the right carotid arterial catheter into a heparin ($100\,IU\,mL^{-1}$) containing reservoir. The target mean arterial pressure (MAP) of approximately 40 mmHg was reached in 10–15 min and was kept by repeated bleeding periods until the 60th min of the experiment (T_2). The amount of shed blood was precisely monitored. The average blood loss was about $25\,mL\,kg^{-1}$ 15 min after the onset of hemorrhage, which increased to an average of around $40\,mL\,kg^{-1}$ by the end of bleeding at T_2. This was about 50% of the animals' circulating blood volume. At 60 min (T_2) volume resuscitation with colloid solution (hydroxyethyl starch 130 kDa/0.4, 6% Voluven, Fresenius, Germany) was started. 75% of the starting MAP was reached in 10–15 min. In case of decreasing blood pressure further colloid infusion was given, but the total amount of colloid infusion was maximized in $25\,mL\,kg^{-1}$. This means that the pigs were partially resuscitated and remained hypovolemic in the following period between 60 and 180 min (T_2 and T_6). The reason for choosing this protocol was to enable us to investigate the alterations of different macro- and microcirculatory parameters in two well separated periods: severe shock and moderate hypovolemia. Hemodynamic, arterial, and central venous blood gas measurements and tissue capnometry were repeated and recorded every 30 min for duration of 3 hr (T_0–T_6). Intravital video microscopy was performed at baseline, at 60 (T_2), and at 180 min (T_6) (Figure 2).

Animals in the control group were not submitted to bleeding. They underwent the same operation procedure and received the same instrumentation and monitoring. In this group 0.9% sodium chloride was infused at a rate of $10\,mL\,kg^{-1}\,h^{-1}$ during the experiment. Hemodynamic, blood gas analysis and microcirculatory measurements were performed at the same time points.

2.4. Statistical Analysis. The statistical software package SigmaStat for Windows (Jandel Scientific, Erkrath, Germany) was applied for data analysis. After testing for normality parametric methods were used. Two-way repeated measures analysis of variance (ANOVA) was applied for statistical analysis. For the analysis of differences between the sham-operated and the hemorrhagic shock groups, the time dependent differences from the baseline (T_0) for each group were assessed by Holm-Sidak post hoc test. When we examined the effect of partial resuscitation starting at 60 minutes (T_2), we performed multiple pairwise comparisons of T_3–T_6 results versus T_2 data serving as control. The pairwise comparison of different variables was made with Pearson-correlation. p values < 0.05 were considered statistically significant. The numeric data in the text and values on the figures are given as mean and standard deviations.

3. Results

3.1. Hemorrhagic Shock Phase (T_0 to T_2). Severe shock state was achieved in the animals of the shock group as indicated by marked and significant changes in macrohemodynamics during the first 60 minutes: MAP decreased, heart rate (HR) increased, and cardiac index (CI) and global end-diastolic volume index (GEDVI) decreased significantly (Figures 3(a), 3(b), 3(c), and 3(d)). This change in global hemodynamics was accompanied by a significant drop in base excess (BE) in the shock group (T_0: 6.4 ± 2.1 and T_2: $1.1 \pm 2.8\,mmol\,L^{-1}$ $p < 0.05$), while there was no similar change in the sham group (T_0: 5.6 ± 1.8 and T_2: $5.9 \pm 1.9\,mmol\,L^{-1}$). We detected significant increases both in the $P_{SL}CO_2$ and in the $P_{SL}CO_2$ gap

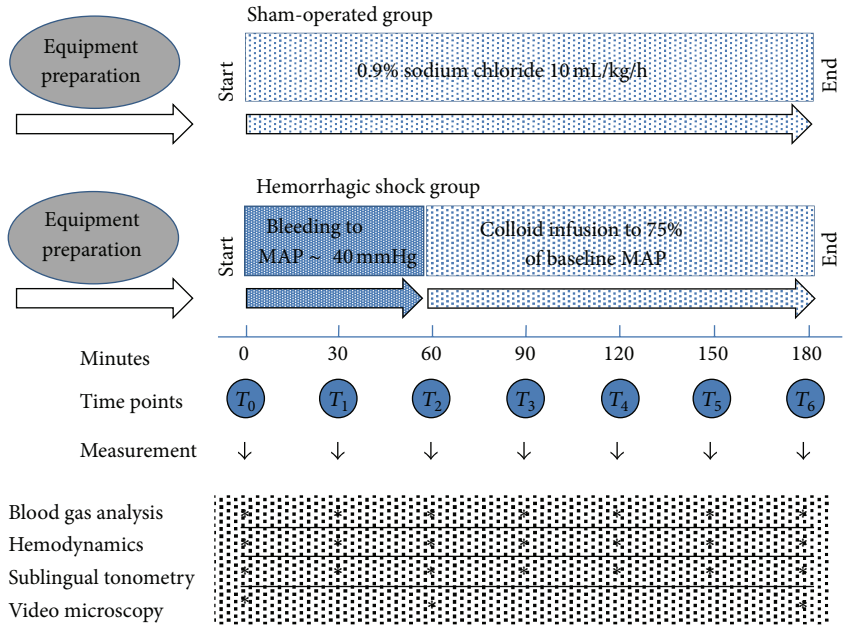

FIGURE 2: Experimental protocol. Flow diagram representing the experimental protocol in both groups of animals. MAP is mean arterial pressure, T_0–T_6 are seven time points of measurements, and $*$ indicates the implementation of different types of measurements.

values (Figures 4(a) and 4(b)). The sublingual postcapillary red blood cell velocity ($RBCV_{SL}$) and the sublingual capillary perfusion rate (CPR_{SL}) decreased significantly (Figures 5(a) and 5(b)). The central venous blood derived variables showed characteristic alterations too: corresponding to the significant increase of the oxygen extraction rate the $ScvO_2$ decreased during bleeding, while the $PcvaCO_2$ increased (Figures 6(a), 6(b), and 6(c)). These changes at 60 minutes were significant compared to the baseline values and differed significantly from the corresponding values of the sham-operated animals.

3.2. Partial Resuscitation Phase (T_2 to T_6). Statistically significant alterations were found regarding MAP, HR, CI, and GEDVI (Figures 3(a), 3(b), 3(c), and 3(d)). The CI increased significantly at T_4, T_5, and T_6 compared to baseline values and at T_4 and T_6 compared to the sham-operated group as well (Figure 3(c)). Improvement in global hemodynamics was also reflected by the significant improvement in BE in the shock group from T_2 to T_6 (1.1 ± 2.8, 3.1 ± 3.4 mmol L^{-1}, $p < 0.05$, resp.), while there was no change in BE in the sham group (5.9 ± 1.9, 6.7 ± 2.9 mmol L^{-1}). The $P_{SL}CO_2$ did not change significantly over time in the sham-operated group. In the shock group there was also a significant improvement during this period, still these values remained elevated as compared to baseline (T_0). Moreover, at T_5 $P_{SL}CO_2$ was significantly higher than in the sham-operated group (Figure 4(a)). Regarding the $P_{SL}CO_2$ gap, it decreased significantly by T_3 as compared to T_2 in the shock group, but it remained significantly higher as compared to T_0 throughout the resuscitation period. In the sham-operated group the $P_{SL}CO_2$ gap showed a slow nonsignificant increase over time. Between T_3 and T_6 there were no significant differences between the sham and shock groups (Figure 4(b)).

Concerning the microcirculatory measurements, both $RBCV_{SL}$ and CPR_{SL} increased significantly in the shock group compared to T_2, but still they remained decreased compared to the baseline values. At 180 min (T_6), there was no difference in $RBCV_{SL}$ between shock and sham-operated groups (Figure 5(a)), while CPR_{SL} in the shock group remained significantly lower than in the sham-operated group (Figure 5(b)).

Samples of the pictures in each phase can be seen as electronically submitted Supplementary Material (see Figure S1 available online at http://dx.doi.org/10.1155/2015/847152).

Fluid resuscitation resulted in a significant decrease of the $PcvaCO_2$ at T_3–T_6 as compared to T_2, but $PcvaCO_2$ changes within the shock group were significant at T_3 compared to T_0 (Figure 6(a)). $ScvO_2$ showed a statistically significant elevation after resuscitation as compared to T_2 but remained significantly lower as compared to the baseline value at T_0 and to the sham-operated group (Figure 6(b)). In case of the oxygen extraction rate significant differences were observed between the sham and shock groups at T_4–T_6 (Figure 6(c)).

3.3. Correlation Analysis. Statistically significant correlation was found between $P_{SL}CO_2$ gap and $RBCV_{SL}$ ($r = -0.648$; $p < 0.0001$) and $P_{SL}CO_2$ gap and CPR_{SL} ($r = -0.644$; $p < 0.0001$) (Figures 7(a) and 7(b)). The $P_{SL}CO_2$ gap also correlated with $ScvO_2$ and $PcvaCO_2$ ($r = -0.504$ and $p < 0.0001$; $r = 0.623$ and $p < 0.0001$, resp.) (Figures 7(c) and 7(d)). A significant but weaker correlation was found between $P_{SL}CO_2$ and $ScvO_2$ ($r = -0.29$; $p < 0.0001$) and $P_{SL}CO_2$ and $PcvaCO_2$ ($r = 0.405$; $p < 0.0001$).

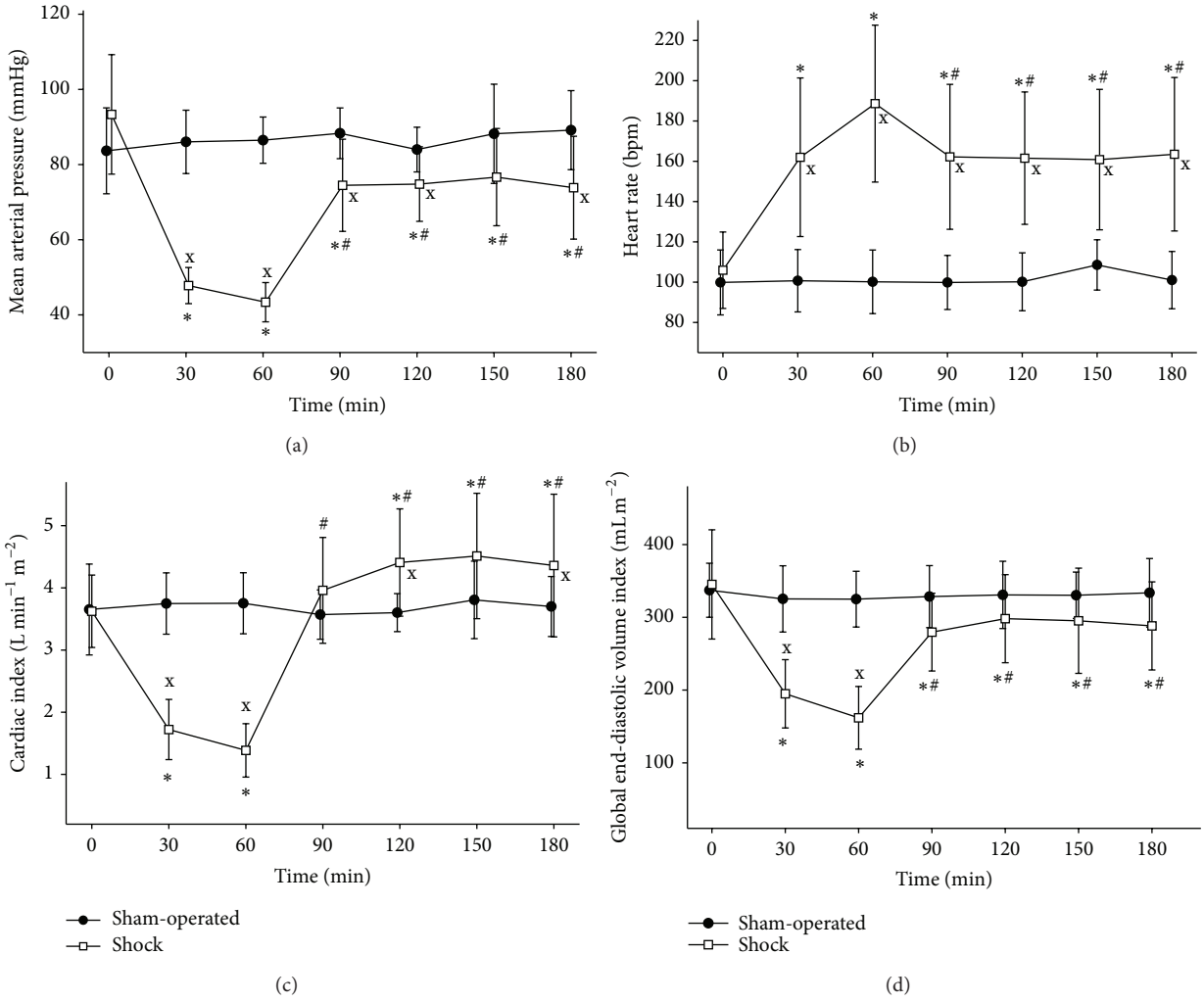

Figure 3: Macrohemodynamic parameters. Changes of macrohemodynamic parameters, mean arterial pressure (a), heart rate (b), cardiac index (c), and global end-diastolic volume index (d). $^{*}p < 0.05$ as compared to 0 min (T_0), $^{\#}p < 0.05$ as compared to 60 min (T_2), and $^{x}p < 0.05$ shock group versus sham-operated group.

4. Discussion

In this study we report on the first *in vivo* application of a new sublingual tonometric device. The major finding of this experiment is that this noninvasive monitor accurately followed the changes in submucosal postcapillary blood flow during bleeding and resuscitation. The measured values showed very good correlation with direct indices of microcirculation as determined by the well-established OPS technique and also with global measures of hypovolemia-caused oxygen debt such as $ScvO_2$ and $PcvaCO_2$.

4.1. Sublingual Capnometry and Microcirculation. There are different methods able to detect the increased concentrations of CO_2 in the periphery. Gastric tonometry is based upon the monitoring of gastric mucosal PCO_2 level; sublingual and buccal capnometry measure mucosal PCO_2 of the proximal gastrointestinal tract [19–21]. Mixed venous-to-arterial or central venous-to-arterial CO_2 partial pressure difference is regarded as markers describing the balance between cardiac output and oxygen consumption by peripheral tissues [22, 23].

The concept of monitoring complementary regional/local perfusion parameters in order to guide or fine-tune resuscitation strategies is rather old and well-established. Historically, one of the first methods was gastric tonometry. However, technical difficulties, long equilibration, and other confounding factors [14] hindered the widespread use of the method, leading to the withdrawal of these devices from the market. In recent years several investigators came to the conclusion that PCO_2 values of the oral mucosa correlate well with gastric mucosal PCO_2 parameters [6, 13, 20, 24]. Although the value of sublingual capnometry in the diagnosis of circulatory failure has been reported previously [20, 25], the method is not available for everyday clinical practice. The monitoring tools used for this purpose in the first experimental and clinical studies were highly sophisticated devices with special PCO_2-electrodes or fiber optic sensors [26]. The device we

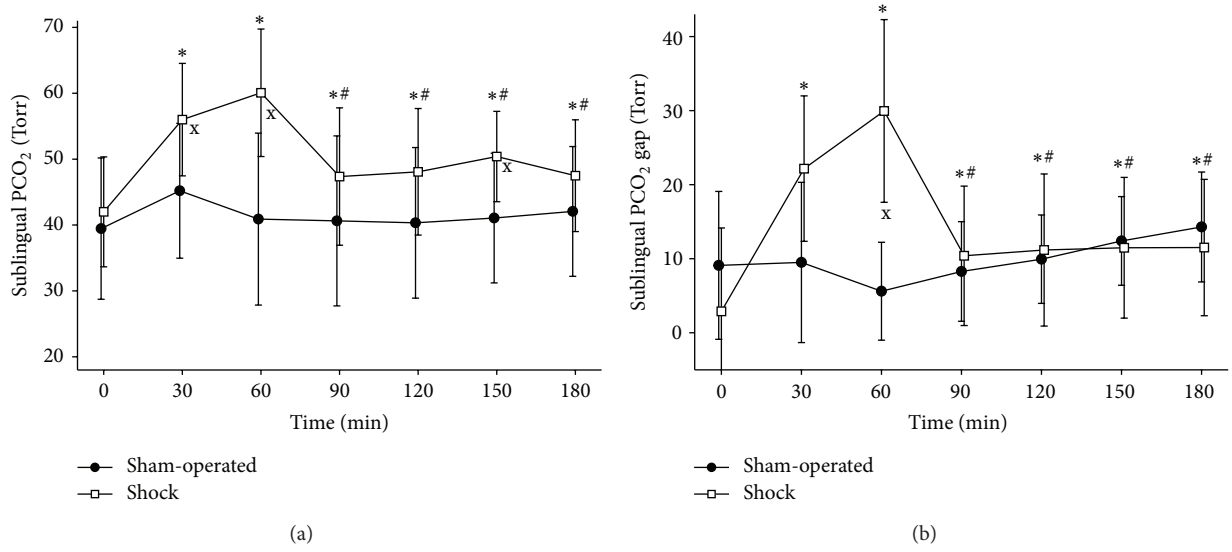

FIGURE 4: Sublingual capnometry. Changes of sublingual tonometric variables measured by the new probe, sublingual PCO_2 (a) and sublingual PCO_2 gap (b). $^{*}p < 0.05$ as compared to 0 min (T_0), $^{\#}p < 0.05$ as compared to 60 min (T_2), and $^{x}p < 0.05$ shock group versus sham-operated group.

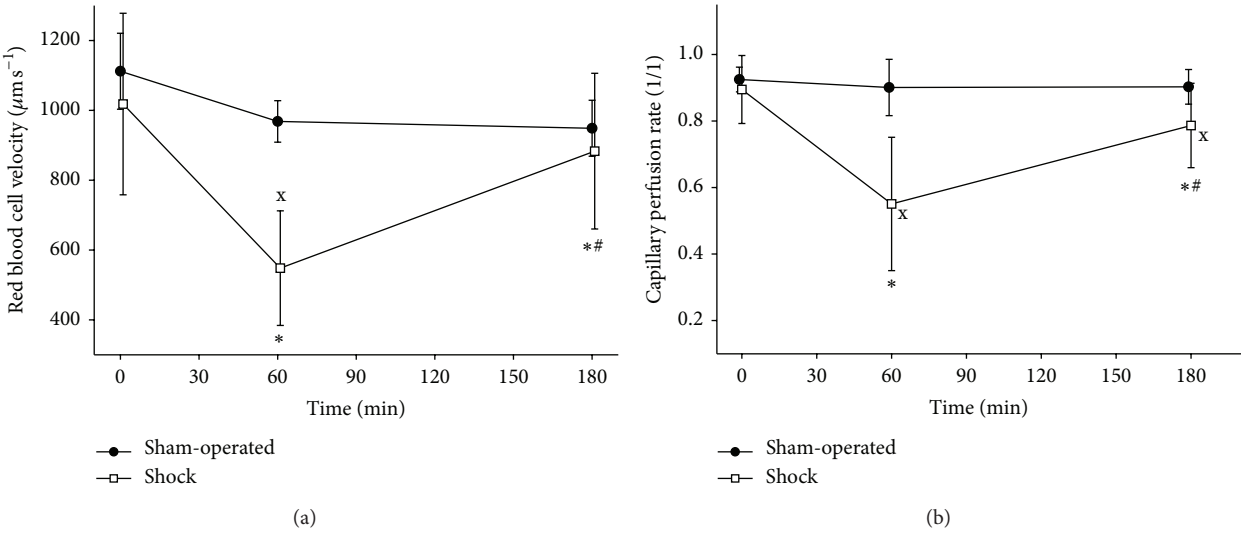

FIGURE 5: Microcirculatory parameters. Changes of microcirculatory parameters measured by orthogonal polarization spectral imaging, red blood cell velocity in postcapillary venules (a) and capillary perfusion rate (b). $^{*}p < 0.05$ as compared to 0 min (T_0), $^{\#}p < 0.05$ as compared to 60 min (T_2), and $^{x}p < 0.05$ shock group versus sham-operated group.

used in the presented experimental protocol proved to be a simple, noninvasive monitor for this purpose.

According to recent studies it was suggested that even the magnitude of blood loss can be estimated by tissue capnometry, and the method may also be useful in guiding fluid resuscitation during hemorrhage. Different authors [27, 28] measured buccal PCO_2 continuously during different severity of hemorrhagic shock in rats and found that tissue PCO_2 monitoring was reliable in the quantitation of acute hemorrhage. Baron et al. [29] measured sublingual PCO_2 in bleeding trauma patients and found similar results. In a porcine model of hemorrhagic shock Xu and colleagues [30] compared different volume replacement protocols based on either sublingual PCO_2 or blood pressure. The animals monitored by sublingual PCO_2 required smaller amount of both crystalloids and transfusion, while the microcirculation, organ functions, and survival were similar in the treatment groups. Although our experiment had different goals, the results give support to both assumptions. Loss of 50% of the circulating blood volume also increased the sublingual PCO_2 by 50%: from $T_0 = 41.6 \pm 8.3$ to $T_2 = 60.1 \pm 9.6$ Torr. On the other hand, sublingual PCO_2 gap increased by 5-fold;

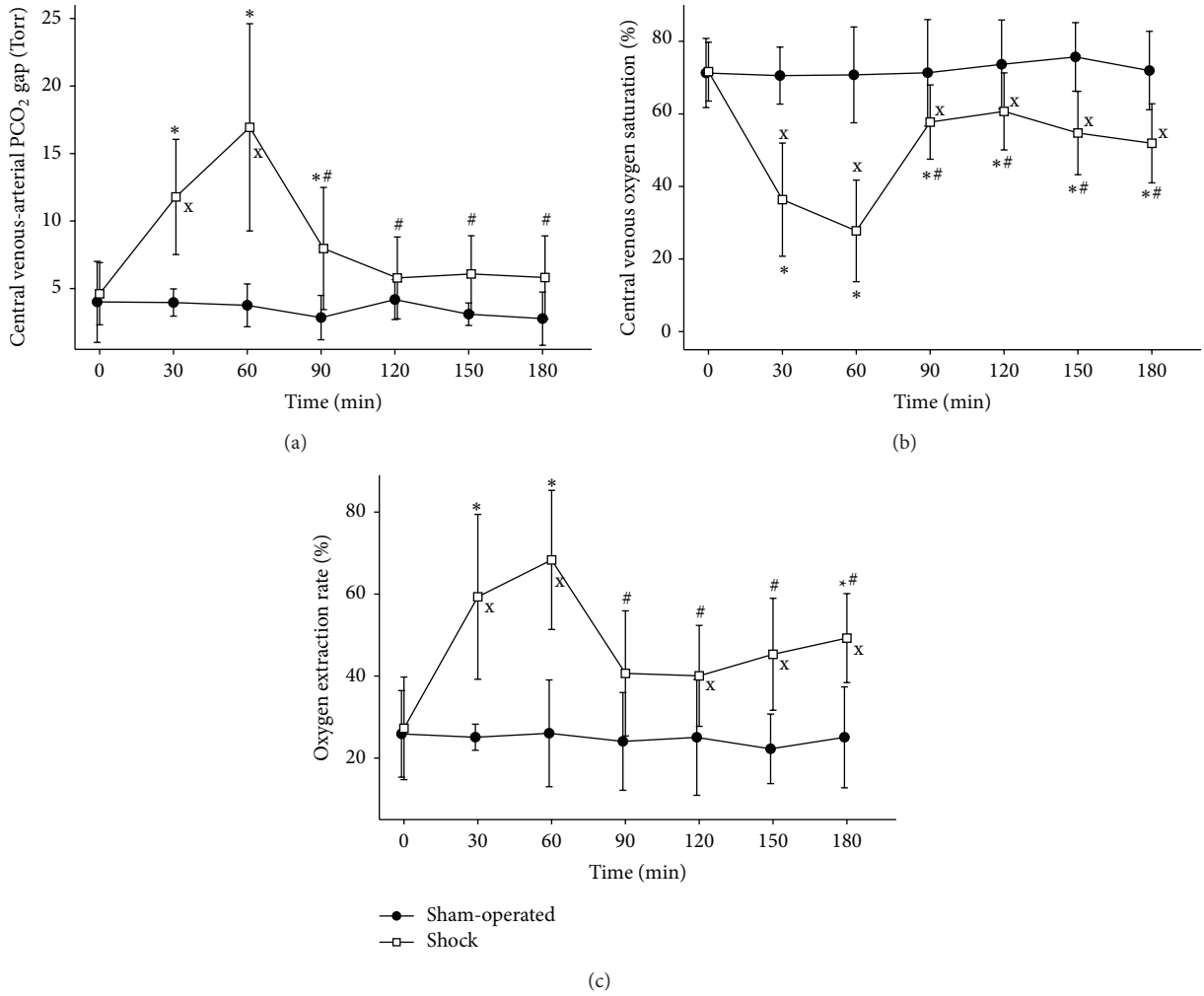

Figure 6: Central venous blood gas derived parameters. Changes of central venous blood derived parameters, central venous-arterial PCO_2 gap (a), central venous oxygen saturation (b), and oxygen extraction rate (c). $^{*}p < 0.05$ as compared to 0 min (T_0), $^{\#}p < 0.05$ as compared to 60 min (T_2), and $^{x}p < 0.05$ shock group versus sham-operated group.

therefore it seems that for this purpose this parameter may be more sensitive than sublingual PCO_2 on its own. We did not observe strong, significant differences in the $P_{SL}CO_2$ and the $P_{SL}CO_2$ gap values between the sham-operated and the shock groups in the partial resuscitation phase, but there were significant changes in the shock group reflecting the hemodynamic changes throughout the experiment. We suggest that it is the kinetics of $P_{SL}CO_2$ rather than the absolute value which deserves attention. This has to be investigated in the future. In general it is important to note that $P_{SL}CO_2$ or $P_{SL}CO_2$ gap has different role and interpretation during "rapid" or "massive" and "slow" bleeding. No one needs additional indicators during massive bleeding with severe hypotension to confirm that the patient is in trouble, and neither is there time for these measurements. Therefore sublingual capnometry may prove its merit during slow bleeding and hypovolemia as one of the potential end points of resuscitation of the microcirculation.

Massive bleeding in our study resulted in severe perfusion abnormalities as indicated by significant deterioration of sublingual CPR and RBCV, which was also reflected by changes of the sublingual $P_{SL}CO_2$ gap. Although the close relationship between the sublingual perfusion and PCO_2 has already been described [6, 31], and investigations on mucosal PCO_2 and the microcirculation of the ileum [32] have been performed in hemorrhagic shock, this is the first study to reveal a correlation between sublingual capnometry and directly measured microcirculatory parameters during hemorrhagic shock.

4.2. Sublingual Capnometry and Global Hemodynamics. Significant changes in MAP, HR, CI, and GEDVI were detected during the shock phase and during partial resuscitation, with the CI being significantly higher by the end of resuscitation as compared with the baseline, possibly because of the sustained tachycardia caused by the bleeding-related stress response. There are several studies showing that hemorrhage-caused hypovolemia is accompanied by sublingual hypoperfusion and/or the increase in $P_{SL}CO_2$ [13, 20, 29]. Nevertheless, it is

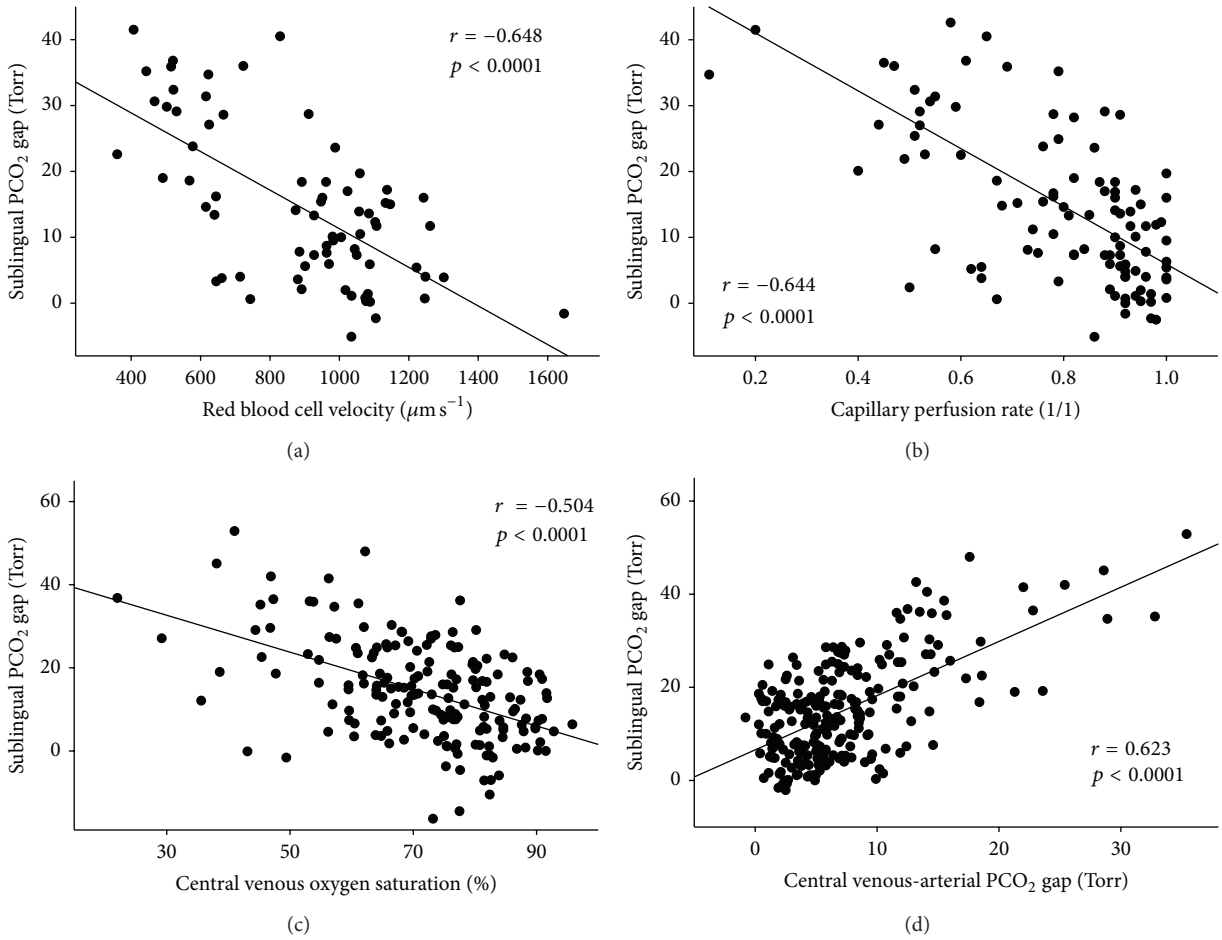

Figure 7: Correlations with sublingual capnometry. Relationships between sublingual mucosal-to-arterial carbon-dioxide partial pressure gap and sublingual red blood cell velocity in postcapillary venules (a), sublingual capillary perfusion rate (b), central venous oxygen saturation (c), and central venous-to-arterial carbon-dioxide partial pressure difference (d).

important to acknowledge that $P_{SL}CO_2$ on its own is a poor indicator of regional circulatory changes, unless it is put in the context of the arterial and/or end-tidal PCO_2. Alternatively, in order to eliminate the influence of global respiratory alterations, minute ventilation should be constant. This may explain why in a laboratory model of progressive hypovolemia caused by lower body negative pressure Chung et al. did not confirm the sensitivity of sublingual capnometry in the early phase of cardiovascular collapse [33]. In our opinion the main limitation of that study is that in their model minute ventilation was not constant (subjects were spontaneously breathing), end-tidal PCO_2 decreased significantly, and they measured $P_{SL}CO_2$ and not $P_{SL}CO_2$ gap. By calculating gap values substantial $P_{SL}CO_2 - P_{ET}CO_2$ gap differences could have been detected. There are other important conceptual differences between their model and the earlier experimental protocols; that is, hypovolaemia was not caused by bleeding, the observation period was only 20 min, and the study population was young, healthy, nonsmoking subjects with presumably good physiologic reserves. Finally, the sublingual microcirculation was not monitored in this study, so the changes of sublingual microvascular perfusion during the experiment remain unknown.

4.3. Sublingual Capnometry and Oxygen Delivery/Consumption. Although the most accurate way to assess cardiac output, oxygen delivery, and consumption is invasive hemodynamic monitoring, it is often unavailable in emergencies. Simple blood gas driven variables such as $ScvO_2$ and $PcvaCO_2$ can help the clinician in defining the need for fluid resuscitation and red blood cell transfusion or may serve as therapeutic targets of goal-directed therapy in high-risk surgical or septic patients [34–36]. In our study $ScvO_2$, O_2ER, and $PcvaCO_2$ showed significant changes during hemorrhagic shock and partial resuscitation. Although in cases of impaired oxygen uptake $ScvO_2$ values can be elevated [5, 37], our hemorrhagic shock-resuscitation model gives further support to the theory that low $ScvO_2$ and high $PcvaCO_2$ indicate hypovolemia and they also correlated well with $P_{SL}CO_2$ gap values. In fact correlation of $ScvO_2$ and $PcvaCO_2$ with $P_{SL}CO_2$ gap was better than with $P_{SL}CO_2$, indicating that the actual condition of the microcirculation is

reflected more precisely by gap values than by absolute values of sublingual PCO_2.

5. Conclusions

This new capillary tonometer may be an appropriate tool for the indirect evaluation of the sublingual microcirculation. There are also some limitations to the use of this method, such as the relatively long equilibration time and the need to draw arterial blood samples to determine the $P_{SL}CO_2$ gap. However, the calculation of gap values is probably not necessary if the alveolar ventilation is considered stable. In our opinion, this device can be best utilized during emergency situations (in the ICU or ER and during major/high-risk surgery), where arterial and central venous catheters are commonly used, and excessive invasiveness should therefore not be a concern.

With these restrictions we concluded that capnometry-derived variables followed the microcirculatory changes and correlated with well-established indices of global hemodynamics in hypovolemia and hemorrhagic shock. Combination of these results with central venous oxygen saturation and central venous-to-arterial carbon-dioxide partial pressure differences may be complementary tools for monitoring and treating hypovolemia and hemorrhagic shock in the clinical setting.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Péter Palágyi and József Kaszaki contributed equally to this work.

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Review Article

Beyond the Limits: Clinical Utility of Novel Cardiac Biomarkers

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Preoperative assessment of cardiovascular risk is essential when it comes to extensive noncardiac surgery procedures. Therefore, accurate and timely diagnosis of myocyte damage is vital. In modern medical practice it is believed that the so-called "multimarker" approach is the most appropriate and most accurate, but new research points out that there are novel biomarkers which could be used independently. Studies that evaluate miRNA, H-FABP, and MR-PAMP give encouraging results. When it comes to miRNA clinical studies show high statistical significance, especially in the case of acute myocardial infarction ($P = 0.001$). Statistical significance of $P = 0.007$ was found in acute coronary syndrome, when H-FABP was measured. Biochemical marker MR-PAMP showed statistical significance of $P < 0.0001$ in most clinical studies.

1. Introduction

Anesthesiologists are daily in contact with patients who are preparing for noncardiac surgery procedures and who are at increased risk to develop cardiovascular complications in perioperative period. The number of these patients is increasing worldwide [1, 2]. Perioperative risk can be estimated based on the severity of existing heart failure, development of recent myocardial infarction, existence of arrhythmias, presence of aortic stenosis, patient's age, type of planned surgery, chronic obstructive pulmonary disease, renal function, previous transient ischemic attack, the general condition of the patient, and so forth [3–6]. Postoperative hypertension, arrhythmia, and heart failure usually occur two days after surgery, while the risk of perioperative myocardial infarction persists during five to six postoperative days [3]. In total, less than 1% of patients develop perioperative myocardial infarction; however about two-thirds of these patients die within 30 postoperative days. Therefore, timely preoperative diagnosis of myocyte damage is vital [1]. Until recently Lee score was used to assess perioperative risk; however European Society of Cardiology (ESC) and European Society of Anaesthesiology (ESA) have proposed a new and comprehensive way to evaluate perioperative cardiac risk [7, 8]. Significant item of this preoperative evaluation and processing of high-risk patients are biomarkers. We have evaluated potential use of miRNA, H-FABP, and MR-PAMP in everyday clinical practice as well as the characteristics which make them stand out as highly promising novel biomarkers.

2. Biomarkers in Clinical Practice

Biological marker or biomarker can be objectively measured and it is an indicator of biological processes [8]. From the definition, ideal biomarker has the following characteristics: a high presence in the heart tissue, an absence in other tissues, an absence in the serum of healthy individuals, quick release for the purpose of early diagnosis, a long half-life for the purpose of late diagnosis, cost-effectiveness, and positive evaluation in clinical trials [9–11]. The search for an ideal cardiac biomarker lasts for almost a century (Table 1).

In modern medicine practice there are numerous biomarkers, those that point to an obvious pathology of cardiomyocytes and those that provide a strong evidence of comorbidity such as acute renal failure and pneumonia [12]. The following biomarkers are currently used: aspartate aminotransferase (AST), lactate dehydrogenase (LDH),

Table 1: Brief history of cardiac biomarkers.

Biomarker	Year of first appearance in literature	One of the first significant references when it comes to myocardial injury
H-FABP	1988	[68]
AST	1954	[69]
LDH	1948	[70]
CK	1954	[71]
HBDH	1963	[72]
CK-MB	1962	[73]
CK-MB mass	1986	[74]
Myoglobin	1941	[75]
TnT	1940	[76]
TnI	1987	[77]
miRNA	2009	[37]
PAMP	2002	[78]

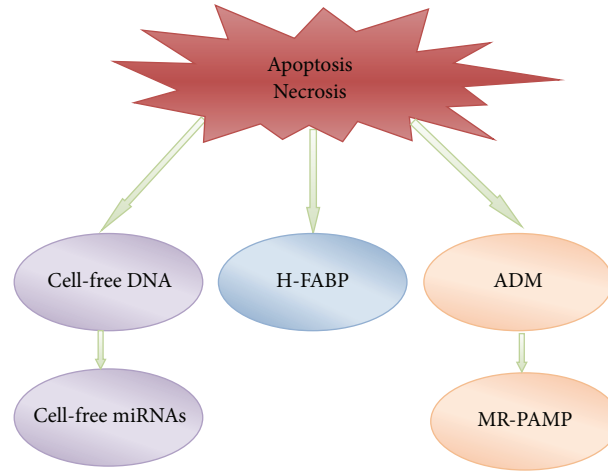

Figure 1: Biomarkers and their precursors in serum after cell apoptosis and necrosis.

creatine kinase (CK), hydroxybutyrate dehydrogenase (HBDH), creatine kinase MB isoenzyme (CK-MB), CK-MB mass, myoglobin, carbonic anhydrase, glycogen phosphorylase BB, troponin T (TnT), and troponin I (TnI) [9, 13]. According to the latest recommendations, biomarkers which determine myocardial ischaemia and damage, inflammation, and left ventricular function are used in the perioperative period. The most popular biomarkers in modern practice are cTnI and cTnT due to higher sensitivity and specificity when compared to other biomarkers. Clinical studies have shown that even a small increase in the concentration of cTnT in the perioperative period indicates myocardial damage and worsens postoperative prognosis and outcome. Preoperative determination of BNP and NT-pro-BNP levels indicates the possibility of developing cardiovascular complications after major noncardiovascular surgeries [8, 13–16]. Biomarkers also have a great role in improving the treatment of heart diseases and monitoring of the effectiveness of the therapy [12]. There is the fact that there are no biomarkers which can be interpreted and included in routine work alone but can only indicate the high-risk patients [8].

It is believed that a multimarker approach is the most appropriate and most accurate and that a new set of biomarkers (currently in the trial phase) is much more accurate and that they could even be used independently [12]. The development and definition of new biomarkers will lead to a faster and more accurate diagnosis of myocardial damage [8, 17]. A large number of studies about new potential biomarkers of myocardial damage such as microRNA (mrRNA), fatty acid-binding protein (FABP), and proadrenomedullin (PAMP) are currently conducted (Figure 1).

3. The Significance of miRNA as a Biomarker

MicroRNA (miRNA) represents a recently discovered class of endogenous, small, noncoding RNA molecules which regulate the expression of approximately 30% of genes in the human genome and are highly stable in the circulation [2, 18–22]. Basic and clinical studies indicate a great importance of miRNA in the regulation of cellular differentiation, growth, proliferation, and apoptosis [23–25]. Besides miRNA, which are specific for the majority of tissues, there are also miRNAs with a tissue-specific expression and they could be useful in practice [19, 26, 27].

These molecules can be transported between the cells in the form of miRNA bound to RISC, Argonaute 2, and Nucleophosmin 1 proteins as well as in the form of miRNA packed in vesicles. It is considered that a free miRNA molecule can be found in blood as a consequence of the release of the cell contents in plasma due to necrosis [26].

The role of miRNA was first studied in the field of oncology, where they were considered to be both oncogenes and tumor suppressors [2, 28]. Earlier studies indicated a great expression of miRNA in the heart cells; however their role has not been completely known until the beginning of the research in 2005 [2, 19]. Research based on miR-155 has indicated that it has a key role in the development of immune disorders, tumors, cardiovascular diseases, viral infections, and so forth [29]. It has later been shown that miRNA molecules are essential for the proper development of cardiovascular system [26]. Some of the miRNAs expressed in the heart tissue are miR-21, miR-29a, miR-129, miR-210, miR-211, miR-320, miR-423, and let-7c. In a completely healthy heart tissue miR-1, miR-16, miR-27b, miR-30d, miR-126, miR-133, miR-143, miR-208, and let-7 families are highly expressed [21].

An aberrant presence of miR-21 in the blood vessel wall after balloon damage has been proved by using microarray and Northern blot analysis as well as qRT PCR method [30]. Several studies made miRNA target molecules in the therapy of atherosclerosis, postangioplastic restenosis, transplantation arteriopathy, and cerebral and heart ischaemia [30–32]. Cipollone et al. have examined 41 miRNAs and discovered

profound differences in the expression of miR-100, miR-127, miR-145, miR-133a, and miR-133b in symptomatic versus asymptomatic plaques [33].

Myocardial hypertrophy represents a great determinant in predicting the mortality and morbidity in cardiovascular diseases [2]. Significant negative effects on the myocardial hypertrophy were obtained by changing the expression of miR-21 by knockdown method, or antisense-mediated depletion method. It can be concluded that miRNA is involved in the process of myocardial hypertrophy and can represent a future target in the therapy of diseases which include myocardial hypertrophy like hypertension, ischaemic heart disease, valvular heart disease, and endocrine diseases [2]. Studies have shown that miR-1, miR-21, miR-133, miR-195, and miR-208 have the most important role in the development of hypertrophy [25].

Lovren et al. have shown that miRNA-145 is highly expressed in the smooth muscle cells of blood vessels and that its overexpression can lead to the development of atherosclerosis [28]. Other miRNAs expressed in the atherosclerosis are miR-126, miR-145, miR-146a, miR-155, and miR-210 [23, 27]. miRNA-145 molecule controls the differentiation of smooth muscle cells and promotes the formation of lesion; miR-126 sends signals about the need to repair endothelium, while miR-155 indicates the presence of proinflammatory macrophages and atherosclerotic lesions [34, 35]. Research about the influence of miRNA on the development of atherosclerosis is a relatively new field so it is considered that the full clinical potential of this molecule in that area is yet to be demonstrated [26, 34].

Patients with arterial coronary disease have decreased levels of miR-126, miR-145, and miR-155 in circulation. Many studies are currently trying to assess the impact of miR-1, miR-133a, miR-133b, miR-208, miR-499, and miR-499-5p on the development of acute myocardial infarction [21]. It has been proved that miR-208b, miR-499, and miR-320a have been significantly elevated in the patients with acute myocardial infarction; however none of them could be used independently in the diagnostics without cTnT or hsTnT [36]. Wang et al. have reported that elevated levels of cardiac-specific miR-208a in plasma may represent a new biomarker for early detection of myocardial damage [37]. Also circulating miR-1, miR-133a, miR-208b, and miR-499 may be useful biomarkers in acute myocardial infarction, but they are not superior to cTnT [38]. However, according to research circulating miR-499 represents a new early biomarker for the identification of perioperative myocardial infarction in cardiac surgery [39].

Atrial fibrillation is associated with reduced levels of miR-1 in atrial tissue and an overexpression of miR-133 and miR-328 [21, 25]. Cardin et al. have concluded that knockdown of the gene miR-21 in atrium suppresses atrial fibrosis and the onset of atrial fibrillation, and therefore miR-21 is an important signaling molecule for the development of this disorder [40]. It is also considered that miR-1 is responsible for the changes in function of many proteins which take over Ca2+, so it is connected with the onset of ventricular fibrillations [21].

It is considered that miRNAs have a significant impact on the development of hypertension, especially through the influence on the renin-angiotensin-aldosterone system. Some of the significant miRNAs for the hypertension onset are miR-181a, miR-663, miR-132, miR-212, miR-143, and miR-145 [21].

The onset of heart failure is connected to miR-122, miR-210, miR-423, miR-5p, miR-499, and miR-622. Research points out to a high specificity of miR-16, miR-27a, miR-101, and miR-150 in predicting the occurrence of left ventricular failure six months after acute myocardial infarction [21]. Circulating miR-423 and miR-5p are considered potential biomarkers of heart failure because they were in correlation with NT-pro-BNP and ejection fraction of the heart [41, 42].

On the other side, miRNA still has a small diagnostic potential when independent of troponin, and test conduction requires too much time [21]. Also there exist difficulties in practice when it comes to measuring absolute levels of miRNA, the lack of standardized protocols, and variations in test performance depending on the laboratory and heparin in the sample represents a significant inhibitor of reactions based on PCR method. Therefore it is crucial to improve methods and standardize protocols before final introduction of this biomarker in practice [43, 44]. However, it is considered that miRNA could represent an important cardiac biomarker in the near future (Table 2).

4. The Significance of H-FABP as a Biomarker

Cytoplasmic FABP represent a family of transport proteins which allow the transport of fatty acids through the membranes. FABP show tissue specificity so there exist liver-type FABP (L-FABP), intestinal-type (I-FABP), brain-type FABP (B-FABP), and heart-type FABP (H-FABP). Expression of H-FABP is also specific for brain tissue while the coexpression of H-FABP and L-FABP is specific for kidney tissue [45]. These biomarkers have found their application in liver rejection and kidney viability assessment, in the diagnosis of inflammatory and ischemic intestinal diseases, in traumatic damage of brain tissue, and in the prevention of muscle damage in those who have intensive physical activity [45].

H-FABP represents a small cytosolic protein that functions as a carrier of long chain fatty acids in cardiomyocytes. It is present in high concentrations in myocardial tissue and is quickly released into the circulation after the damage of the myocardial tissue [46, 47].

When it comes to the patients with chest pain in primary medical care, it is considered that H-FABP is the most specific marker besides a highly sensitive troponin T (hs-cTnT) [48].

This molecule is recommended for the initial diagnosis of myocardial infarction as well as for the evaluation of minimal subclinical myocyte injury [1]. H-FABP has proved to be even more successful than cTnT in research when it comes to the diagnosis of myocardial damage in patients with chronic heart failure [1]. A high diagnostic sensitivity of H-FABP after myocardial damage has been proved, even 93.1% higher than CK-MB and cTnT [25]. Therefore it is considered that detection of positive H-FABP or cTnI indicates the possibility of the onset of myocardial damage [1].

Table 2: Summary of original articles from the literature proving the significance of miRNA as cardiac biomarker.

Authors	Year	Study type	Number of patients	Statistical significance
Raitoharju et al. [32]	2011	Laboratory study	12 atherosclerotic plaques	$P < 0.05$
Li et al. [31]	2011	Clinical study	104 patients with atherosclerosis obliterans	miR-21, miR-130a, miR-27b, let-7f, and miR-210 significantly increased
Cipollone et al. [33]	2011	Laboratory study	53 atherosclerotic plaques	miR-100, miR-127, miR-145, miR-133a, and miR-133b were more expressed in symptomatic versus asymptomatic plaques
Devaux et al. [36]	2015	Clinical study	224 patients with AMI	miR-208b, miR-499, and miR-320a were significantly higher in patients with AMI
Wang et al. [37]	2010	Clinical study	66 patients 33 AMI, 33 non-AMI with chest pain and distress	miR-1, miR-133a, miR-499, and miR-208a in AMI $P < 0.05$
Li et al. [38]	2013	Clinical study	67 patients with AMI	miR-1, miR-133a, miR-208b, and miR-499 in AMI $P < 0.001$
Yao et al. [39]	2014	Clinical study	30 on-pump patients after coronary artery bypass surgery	miR-499, $P = 0.001$; miR-133a, $P = 0.006$; miR-133b, $P = 0.05$

H-FABP represents a highly accurate biomarker for the myocardial tissue damage in acute coronary syndromes and enables detection of minor myocardial tissue damage in the heart failure and unstable angina pectoris [45]. Elevated levels of H-FABP are present in circulation as soon as 2 to 3 hours after the damage and return to normal in 12 to 24 hours after the initial insult [25, 46].

The concentration of myoglobin is much higher in muscle tissue than in myocardial while it is reversed when it comes to H-FABP. Therefore it is considered that H-FABP is more specific biomarker for the assessment of myocardial tissue damage [45]. O'Donoghue et al. have shown that elevated levels of H-FABP are associated with an increased risk of cardiovascular events, onset of heart failure, and death during the first 10 months after the acute coronary syndrome. Moreover, this association is independent of other risk predictors (troponin I, creatinine clearance, patient's history, etc.), age, and sex of the patient [46]. It has been proved that the prognostic significance of H-FABP is highly accurate and it can be successfully interpreted with troponin even in the patients with low and intermediate risk and in the patients with suspected acute coronary syndrome. Studies indicate that H-FABP can be used as a biomarker of myocardial ischemia even in the absence of evident necrosis [49]. H-FABP and TnT are detectable in venous blood of the patients with chronic heart failure with the ongoing myocardial damage. Some of the research show that H-FABP has a higher specificity [47]. H-FABP has shown to be a far more sensitive biomarker when compared to TnT within the first 6 hours after surviving acute heart damage; however, its specificity is reduced after 6 hours [50–53].

It is important to note that not only is H-FABP specific to myocardial tissue, but it is present in skeletal muscle in low concentrations. Most clinicians consider that damage of muscle tissue during the surgery cannot lead to such high levels of H-FABP. However, the damage of kidney tissue during the surgery may result in elevated levels of H-FABP [1]. Also, H-FABP can be elevated in the patients with kidney dysfunction [46].

Further extensive research is necessary in order to evaluate H-FABP as a biomarker of cardiovascular changes and long-term prognosis in the perioperative period (Table 3) [1].

5. Significance of Proadrenomedullin as a Biomarker

Adrenomedullin (ADM) is a peptide which has rapid clearance from the circulation and a short half-life (22 minutes) and is not practical to be used as a routine biomarker. Midregional proadrenomedullin (MR-PAMP) is released in higher concentrations than ADM; it is inactive and has a longer half-life; therefore it represents a suitable substitute [12, 54–56].

Molecule PAMP is secreted from rat cardiomyocytes and there exist specific binding places for PAMP in heart tissue. One of its functions is that it is included in the control of coronary vasculatory tone. The level of PAMP is elevated in the patients with essential hypertension and congestive heart failure [14, 55].

Due to its stability and specificity, MR-PAMP is a significant biomarker for the prediction of heart damage since it basically represents a biomarker of endothelial dysfunction [54, 57]. The level of MR-PAMP is elevated in the patients with heart diseases like congenital heart failure, ischaemic heart disease, and atherosclerosis. It also represents a significant predictor of mortality in these individuals [57]. Smith et al. have shown that MR-PAMP, CRP, and NT-pro-BNP are good predictors of the onset of heart failure and that they are completely independent of the other biomarkers and risk factors [58]. The combination of MR-PAMP and Nt-pro-BNP is suggested for the mortality prediction [59, 60].

It has been examined whether a panel of biomarkers (PCT, MR-PAMP, CT-pro-endothelin-1, CT-pro-arginine

Table 3: Summary of original articles from the literature proving the significance of H-FABP as cardiac biomarker.

Authors	Year	Study type	Number of patients	Statistical significance
Sari et al. [1]	2015	Clinical study	67 patients, 40 with diabetes	$P = 0.01$
O'Donoghue et al. [46]	2006	Clinical study	2287 patients with acute coronary syndrome	Elevated in 332 patients (14.5%)
Niizeki et al. [47]	2007	Clinical study	126 patients with chronic heart failure	$P < 0.001$
Willemsen et al. [48]	2015	Clinical study	202 patients with acute coronary syndrome	AUC 0.79 versus 0.80
Viswanathan et al. [49]	2010	Clinical study	1080 patients with suspected acute coronary syndrome	$P = 0.007$
Ruzgar et al. [50]	2006	Clinical study	40 patients with suspected acute coronary syndrome	$P = 0.014$
Mad et al. [51]	2007	Clinical study	22 patients with AMI 20 with unstable angina and 15 with noncardiac chest pain	$P < 0.05$
Liao et al. [52]	2009	Clinical study	74 patients with AMI	$P < 0.05$
Haltern et al. [53]	2010	Clinical study	97 with acute ischaemic chest pain	$P < 0.05$

Table 4: Summary of original articles from the literature proving the significance of MR-PAMP as cardiac biomarker.

Authors	Year	Study type	Number of patients	Statistical significance
Eggers et al. [57]	2013	Cohort study	1797 patients over 70 years of age	$P < 0.001$
Smith et al. [58]	2010	Cohort study	5187 individuals	Heart failure, $P < 0.03$; atrial fibrillation, $P < 0.001$
Von Haehling et al. [59]	2007	Clinical study	525 patients with chronic heart failure	$P < 0.0001$
Von Haehling et al. [60]	2010	Clinical study	501 patients with chronic heart failure	$P < 0.0001$

vasopressin, and MR-pro-ANP), each separately or using the Acute Physiology and Chronic Health Evaluation IV score, has a greater significance in the prediction of intrahospital mortality. It has been shown that the greatest significance in the first 6 to 18 hours after entering the ICU has MR-PAMP, even in the case when its significance has been compared to the Acute Physiology and Chronic Health Evaluation IV score in elective cardiosurgery [61].

Recently published BACH (Biomarkers in Acute Heart Failure) study pointed out that MR-PAMP has a much greater significance than BNP in the mortality prognosis within 90 days in patients with diagnosed acute heart failure [62, 63]. This supports the superiority of MR-PAMP compared to NT-pro-BNP and BNP in the prediction of mortality within 14 days [62–65].

A comparative analysis of 12 biomarkers showed that NT-pro-BNP, GDF-15, MR-PAMP, cystatin C, and MR-pro-ANP are the strongest predictors of cardiovascular complications in patients with stable angina pectoris, alone and in combination [66].

Elevated levels of MR-PAMP indicate the existence of coronary heart disease, heart failure, left ventricular failure, and complications in the septic patients [54]. Studies indicate the possibility of using MR-PAMP as a prognostic biomarker for subclinical and manifest cardiovascular diseases (Table 4) [67].

6. Conclusion

Preoperative prediction of cardiovascular risk in patients who are preparing for non-cardiac surgery is essential. New protocols have confirmed that biomarkers have a significant role in that. The "multimarker strategy" is highly present in contemporary clinical practice because there are no independent biomarkers which would timely and accurately indicate the cardiomyocyte damage. The task of future studies is to find the "so-called" ideal biomarker, and studies which evaluate miRNA, H-FABP, and MR-PAMP give encouraging results.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

The Impact of Thrombocytopenia on Outcome in Patients with Acute Coronary Syndromes: A Single Center Retrospective Study

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Background. In acute coronary syndromes (ACS), treated by combined antithrombotic therapy and percutaneous coronary interventions (PCI), thrombocytopenia may occur. Our aim was to evaluate predictors and the impact of thrombocytopenia on mortality in high-risk ACS patients. *Methods*. We retrospectively evaluated high-risk ACS patients. Thrombocytopenia was defined as platelet count <140.000/mL or a drop in platelet count of >50% during in-hospital stay. We compared demographic, laboratory, clinical, and mortality data between nonthrombocytopenic and thrombocytopenic ACS patients and evaluated independent predictors of thrombocytopenia. *Results*. In 371 ACS patients, thrombocytopenia was observed in 21.3%. Thrombocytopenic patients were significantly older and, less likely treated by PCIs (72.1% versus 89.7%, $p < 0.001$) and combined antithrombotic therapy, with increased incidence of in-hospital complications and the use of additional treatments, but with increased mortality at 30 days (27.8% versus 10.2%, $p < 0.001$) and 6 months (35.4% versus 13.6%, $p < 0.001$) when compared to nonthrombocytopenic patients. The use of antibiotics, transfusions, insertion of intra-aortic balloon pump (IABP), and prior stroke independently predicted thrombocytopenia. *Conclusions*. Thrombocytopenia, observed in about 20% of high-risk ACS patients, was associated significantly with in-hospital complications and mortality. Predictors of thrombocytopenia were the use of antibiotics, transfusions, insertion of IABP, and prior stroke.

1. Introduction

Acute coronary syndromes (ACS) with (STEMI) or without (NSTEMI) ST-segment elevation are mainly the consequence of acute coronary atherothrombosis [1]. The most effective therapy is percutaneous coronary intervention (PCI), either primary PCI in STEMI or early PCI in high-risk NSTEMI patients, resulting in coronary recanalization and myocardial reperfusion [2, 3].

PCI in STEMI and high-risk NSTEMI patients should be accompanied by combination of antiplatelet and anticoagulant drugs to prevent thrombus formation at the site of coronary intervention [2, 3]. Antiaggregatory effect of antiplatelet drugs together with pronounced anticoagulant effect of heparins, either unfractionated or of low molecular weight, can also lead to increased risk of bleeding and increasing mortality in high-risk ACS patients [1, 4]. Platelet dysfunction can be particularly expressed within the first hours after PCIs, related with the loading doses of antiplatelet agents. If this leads to clinical thrombocytopenia, mortality in ACS patients may exceed 20% [5].

Thrombocytopenia is defined mostly as a decrease of platelet count below referenced lower limit of normal or a drop in platelet count of more than 50% during in-hospital stay [6]. A low platelet count in high-risk ACS patients can be the consequence of different causes. It may be either immunomediated due to heparins, glycoprotein receptor IIb/IIIa (GPIIb/IIIa) inhibitors, or thienopyridines or consumptional, due to PCI or insertion of intra-aortic balloon pump (IABP) or due to acute heart failure [7]. In the GRACE registry, 0.3% of thrombocythemia was heparin-induced (HIT), 0.6% was glycoprotein-associated (GAT), and 0.7% was of other origins [8]. Profound thrombocytopenia (<100.000) was observed in 2.5% of myocardial infarcts after abciximab

and 0.5% after tirofiban treatment combined with PCI and dual oral antiplatelet agents and in 0.6% of patients treated by GPIIb/IIIa inhibitors according to the GRACE registry [8–10]. Clopidogrel-related thrombocytopenia was observed in 1.0% patients after percutaneous stent implantation [11]. After PCI, about 16% of patients developed a moderate to severe decline in platelet count according to De Labriolle et al. [12].

After the use of the direct thrombin inhibitor bivalirudin, in comparison to heparin with GPIIb/IIIa inhibitor, thrombocytopenia developed in 3.7% [13].

Acute heart failure in high-risk ACS patients, as the consequence of myocardial dysfunction due to extensive ischemic necrosis, promotes neurohumoral activation, inflammation, and acute kidney injury. Activation of inflammation in acute heart failure seems an important stimulus for thrombocytopenia due to enhanced platelet clearance by macrophages [14]. Also, hypotension in severe acute heart failure may inhibit production of platelets in the bone marrow [15]. In patients with IABP, thrombocytopenia can develop even in 43–58%, according to one study [16].

In NSTEMI patients, low platelet count was independently associated with female sex, ST-segment depression, PCI, heart failure, systolic blood pressure, heart rate, and so forth, in one cohort [5]. However, De Labriolle et al. demonstrated that thrombocytopenia in coronary patients after PCI was predicted by male gender, age, hypercholesterolemia, acute renal and heart failure, IABP insertion, STEMI, reduced hematocrit, heparin use, and low osmolar contrast agent [12]. Therefore, these studies support a possibility of a multicomponent background for decreased platelet counts [5, 12, 16].

The incidence of thrombocytopenia varies in different trials. In the CRUSADE registry, 13% of NSTEMI patients, in ACUITY trial, only 6.8% of ACS patients, and in the GRACE registry, 1.6% of STEMI or NSTEMI patients developed reduced platelet counts [4, 5, 8].

These registries have found increased risk of mortality if thrombocytopenia was observed in the setting of ACS [4, 5, 8]. In the GRACE registry, thrombocytopenia was associated with up to 21% in-hospital mortality [8]. In ACUITY trial, 30-day and 1-year mortality correlated with severity of thrombocytopenia, being approximately 9% at 30 days and at one year in severe decline in platelet count [4].

Our aim was to evaluate the incidence of thrombocytopenia in every-day clinical practice in high-risk ACS patients, STEMI, and high-risk NSTEMI patients and the impact of low platelet count on treatments, in particular on the use of PCIs, on in-hospital complications (bleeding, reinfarctions, heart failure, and acute renal failure) and mortality (within 30 days and 6 months), and on predictors of thrombocytopenia.

2. Methods

2.1. Study Design. This was a retrospective observational study, approved by the National Medical Ethics Committee of the Republic of Slovenia (number 123/06/10), who waived the need for informed consent because of the retrospective nature of the study. Personal data of all the patients were protected according to the Law on Personal Data Protection.

2.2. Patients and Protocol. We analysed relevant data of patients being admitted to the Medical ICU of the University Clinical Centre of Maribor with acute myocardial infarction as a discharge diagnosis. We obtained a list of 371 consecutive ACS patients through the institutional medical information system, meeting either standard criteria for STEMI or high-risk NSTEMI and recorded their clinical, demographic, and mortality data [2, 3]. As soon as STEMI/NSTEMI was diagnosed by emergency medical services, the patients received antithrombotic therapy at the first medical contact according to the current ESC guidelines (acetylsalicylic acid (ASA), clopidogrel, and heparin i.v.), oxygen to maintain $SatO_2$ 94–98%, morphine with antiemetics, and sublingual nitroglycerin if deemed necessary [2]. In case of pulmonary edema and/or cardiogenic shock, these ACS patients were treated by morphine and/or diuretics and vasopressors and/or were intubated and mechanically ventilated if deemed necessary. All patients in cardiac arrest were resuscitated appropriately and those who had successful cardiopulmonary resuscitation (CPR) for ventricular fibrillation (primary VF-arrest) subsequently underwent angiography with a view of intervention as all STEMI patients [2].

The high-risk NSTEMI patients usually received antithrombotic therapy according to the ESC guidelines after admission to medical ICU if there were no contraindications for their use (ASA, clopidogrel, and unfractionated or low-molecular-weight heparin). Angiography and PCI were performed within the first hours of ICU stay [3]. The first blood samples were usually obtained just before or after the PCI for routine tests. After PCI, either primary (STEMI) or early emergency (NSTEMI), noninvasive monitoring (continuous ECG and pulse oximetry, blood pressure measurements hourly) was initiated for at least the first 24 hours. Standard ECG and basic laboratory parameters had been repeated after intervention, including Troponin I [2, 3].

Within the first few hours after PCI, the patients usually received oxygen by face mask or by nasal prongs, i.v. infusion of fluids to prevent renal injury, and i.v. infusion of an GPIIb/IIIa inhibitor at the discretion of the treating physician to prevent in-stent thrombosis [2, 3]. The GPIIb/IIIa inhibitor was usually discontinued 12 or 24 hours after the PCI according to the current ESC guidelines [2, 3].

Statins, beta blockers, and angiotensin-converting enzyme inhibitors were prescribed after the first 24 hours. Dual antiplatelet therapy (ASA and clopidogrel) in maintenance dose was continued to prevent in-stent thrombosis and progression of ischemia [2, 3].

Standard ECG and laboratory tests were usually repeated on daily basis and an echocardiography at least once during in-hospital stay. Echocardiography and other diagnostic procedures (chest X-ray, coronary angiography) were repeated in suspected complications [2, 3].

Acute myocardial infarction (MI) was diagnosed with the rise and fall of Troponin I in addition to ECG changes with or without Q waves [2, 3].

We registered demographic and clinical data on admission and during in-hospital stay, in-hospital treatments and mortality data (at 30 days and 6 months).

Table 1: Clinical and laboratory data of all ACS patients and nonthrombocytopenic and thrombocytopenic ACS patients.

Clinical and laboratory data (mean ± SD)	All (n = 371)	Nonthrombocytopenic (n = 292)	Thrombocytopenic (n = 79)	p values
Age (years)	64.1 ± 12.7	63.3 ± 12.8	66.8 ± 11.8	0.032
Admission of Troponin I (μg/L)	11.4 ± 23.5	10.6 ± 22.4	14.3 ± 27	ns
Peak Troponin I (μg/L)	41.5 ± 36.2	41.5 ± 35.6	41.3 ± 38.7	ns
Admission CRP (mg/L)	18.9 ± 45.0	16.2 ± 42.3	28.8 ± 53.0	0.030
Peak CRP (mg/L)	78.1 ± 88.1	66.0 ± 82.8	117.6 ± 93.8	<0.001
ICU stay (days)	3.6 ± 4	2.9 ± 2.3	6.0 ± 6.9	ns
In-hospital stay (days)	10.2 ± 22.7	9.6 ± 25.0	12.4 ± 10.5	<0.001

ACS, acute coronary syndrome; SD, standard deviation; CRP, C-reactive protein.

Regarding demographic data, we registered age, gender, comorbidities (arterial hypertension, diabetes, dyslipidemia, prior myocardial infarction, and stroke), and smoking. From laboratory data, we registered platelet count and Troponin I levels on admission and peak levels during the hospital stay.

Among in-hospital treatments, we registered PCIs and the use of antithrombotic therapy (ASA clopidogrel, heparins, and GPIIb/IIIa inhibitors).

In terms of in-hospital complications, we registered acute heart failure, arrhythmias, reinfarctions, bleeding, and acute kidney injury at any time of in-hospital stay. Arrhythmias, registered by continuous ECG monitoring and standard ECG recordings, were defined as atrial or ventricular or conduction disturbances [2].

Heart failure was quantified by the Killip classification as classes II–IV, including patients with pulmonary congestion, pulmonary edema, and cardiogenic shock [2, 3].

Reinfarctions were classified as recurrence of chest pain with new ECG changes and recurrent rise and fall of serum Troponin I [2].

Bleeding was considered major (cerebral or symptomatic bleeding of other locations with a drop in hemoglobin >50 g/L or the need of ≥2 units of blood product transfusions) or minor (symptomatic bleeding with a drop in hemoglobin of 30–50 g/L) or minimal (symptomatic bleeding with a drop in hemoglobin <30 g/L), according to TIMI criteria [2, 3, 17].

Acute kidney injury was defined as an increase of serum creatinine of more than 50% within 48–72 hours, according to Acute Kidney Injury Network (AKIN) criteria [18, 19].

In case of complications, the patients were treated according to professional protocols (e.g., by vasopressors, inotropic agents, mechanical ventilation, intra-aortic balloon pump (IABP), red blood cells transfusions, antibiotics, antiarrhythmic drugs, and pacing) [2, 3].

2.3. Laboratory Tests. Troponin I levels were determined by the immunochemical method (Boehringer, Germany, normal levels < 0.015 μg/L) [20].

C-reactive protein (CRP), a marker of inflammation, was measured by immunochemical method (Siemens Healthcare Diagnostics, Germany; normal levels were <3.0 mg/L).

Platelet count was measured by the Sysmex XE2100 automatic analyser, Kobe, Japan (normal levels 140.000/mL–340.000/mL) [6]. Thrombocytopenia in ACS patients was defined as platelet count <140.000/mL or a drop in platelet count >50% during in-hospital stay, including patients with admission platelet count <140.000/mL [6].

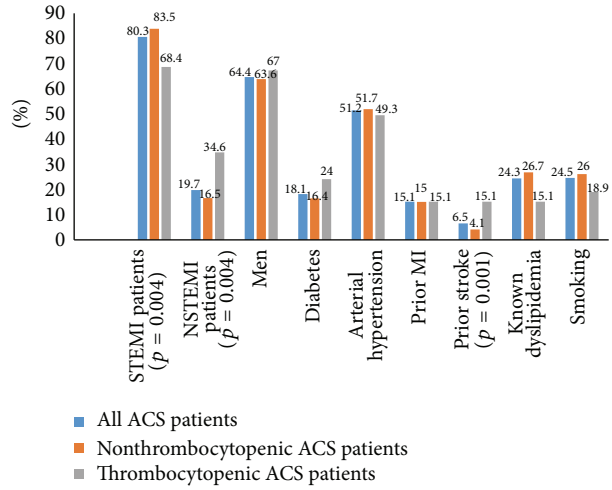

Figure 1: Baseline clinical data in all ACS patients and in nonthrombocytopenic and thrombocytopenic ACS patients. ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; MI, myocardial infarction.

2.4. Statistical Analysis. Statistical analyses were performed using the SPSS statistical package, version 19 (SPSS Inc., Chicago, IL, USA) for Windows. Data were expressed as mean ± standard deviations or percentages. Differences between the groups were tested by the two-sided Student's t-test for mean ± standard deviations and by the chi-square test for percentages. A p value < 0.05 was considered statistically significant. To identify independent predictors of thrombocytopenia, all significant variables of interest gained by univariate analysis were entered in a model of binary logistic regression.

3. Results

Thrombocytopenia was observed in 21.3% of all ACS patients. Baseline characteristics of our ACS patients and differences between nonthrombocytopenic and thrombocytopenic patients are displayed in Table 1 and Figure 1.

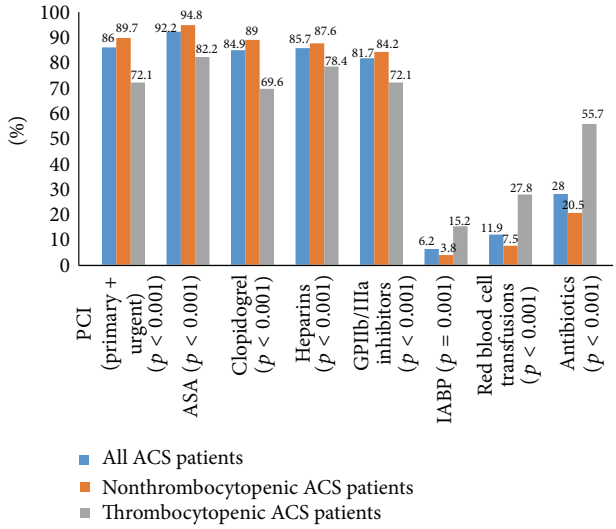

Figure 2: In-hospital treatment of all ACS patients and nonthrombocytopenic and thrombocytopenic ACS patients. ACS, acute coronary syndromes; PCI, percutaneous coronary intervention; ASA, acetylsalicylic acid; GPIIb/IIIa, glycoprotein receptor IIb/IIIa; IABP, intra-aortic balloon pump.

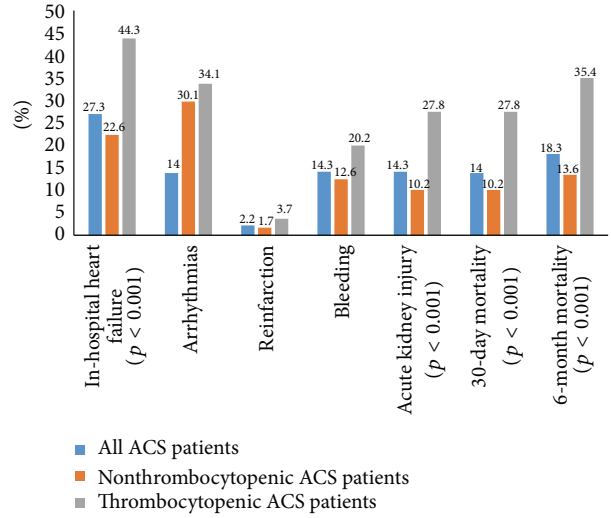

Figure 3: In-hospital complications and mortalities in all ACS patients and thrombocytopenic and nonthrombocytopenic ACS patients. ACS, acute coronary syndromes.

Between the nonthrombocytopenic and thrombocytopenic patients, we observed statistically significant differences in mean age (63.3 ± 12.8 years versus 66.8 ± 11.8 years, $p = 0.032$), mean admission CRP (16.2 ± 42.3 mg/L versus 28.8 ± 53.0 mg/L, $p = 0.030$), and peak CRP levels (66.0 ± 82.8 mg/L versus 117.6 ± 93.8 mg/L, $p < 0.001$), prior stroke (4.1% versus 15.1%, $p = 0.001$), the incidence of STEMI (83.5% versus 68.4%, $p = 0.004$), and NSTEMI (16.5% versus 34.6%, $p = 0.004$) (Figure 1) (Table 1).

Treatments for our ACS patients are presented in Figure 2.

PCIs had been performed significantly less often in thrombocytopenic patients (72.1% versus 89.7%, $p < 0.001$) and antithrombotic therapy was used less frequently than its use in nonthrombocytopenic patients (ASA 82.2% versus 94.8%, $p < 0.001$; clopidogrel 69.6% versus 89%, $p < 0.001$; heparins 78.4% versus 87.6%, $p = 0.024$; GPIIb/IIIa antagonists 72.1% versus 84.2%, $p = 0.027$) (Figure 2).

In-hospital complications and mortality data are presented in Figure 3.

In-hospital complications, such as heart failure, were more frequent in thrombocytopenic patients (44.3% versus 22.6, $p < 0.001$) and acute renal failure (27.8% versus 10.2%, $p < 0.001$) was observed significantly more often (Figure 3), as well as treatment by IABP (15.3% versus 3.8%, $p = 0.001$), red blood cell transfusions (27.8% versus 7.5%, $p < 0.001$), and use of antibiotics (55.7% versus 20.5%, $p < 0.001$) than in the nonthrombocytopenic patients (Figure 2). We observed significant increase in 30-day (27.8% versus 10.2%, $p < 0.001$) and six-month mortality (35.4% versus 13.6%, $p < 0.001$) in thrombocytopenic ACS patients in comparison to those with normal platelet count (Figure 3).

Severe thrombocytopenia (<50.000/mL) was observed only in 3 patients; one of them died within 30 days. Moderate thrombocytopenia (<100.000/mL) was observed in 15 patients. Six of them died within 30 days. Mild thrombocytopenia (platelet count < 140.000/mL and >100.000/mL) was observed in 64 ACS patients. Sixteen of them died within 30 days.

Significant variables of interest gained by univariate analysis were entered in a model of binary logistic regression, which found significant independent predictors of thrombocytopenia during the in-hospital stay as insertion of IABP, prior stroke, the use of antibiotics, and red blood cell transfusion (Table 2).

4. Discussion

In-hospital thrombocytopenia, being mostly mild and transient, was observed in 21.3% of our high-risk ACS patients and was associated with less frequently performed PCIs and with more than 2-fold increased 30-day and six-month mortality. Post-PCI treatments of complications by IABP insertion, red blood cell transfusion, and use of antibiotics as well as prior stroke significantly and independently predicted thrombocytopenia during the in-hospital stay.

Coronary revascularization by PCIs in high-risk ACS patients should be combined with antithrombotics for prevention of coronary reocclusion at the site of coronary intervention [2, 3]. Antithrombotics prevent residual platelet reactivity and thus coronary thrombosis but can trigger thrombocytopenia [7, 8, 12]. Drug-induced thrombocytopenia in a setting of ACS is difficult to affirm as there are no specific tests, except for HIT [7]. In addition, multiple causes for thrombocytopenia coexist, including pharmacological, procedural, and clinical ones such as complications of the acute coronary event [7].

In the ACS setting, there are two main types of drug-induced thrombocytopenia, that is, HIT and GIT, with a different prognosis for each type. Mild and transient decline in platelet count occurring 1–4 days after initiation of therapy

Table 2: Binary logistic regression model to identify independent predictors of thrombocytopenia in ACS patients.

Variables	OR	95% confidence interval	p values
PCIs	2.362	0.695 to 8.033	0.169
ASA treatment	0.633	0.138 to 2.900	0.556
Clopidogrel treatment	1.739	0.543 to 5.577	0.352
Heparin treatment	1.700	0.690 to 4.185	0.249
GPIIb/IIIa inhibitors	0.531	0.185 to 1.528	0.241
Antibiotics	0.405	0.189 to 0.866	0.020
Red blood cell transfusion	0.371	0.143 to 0.963	0.042
Acute heart failure	0.822	0.395 to 1.713	0.601
Acute kidney injury	1.448	0.559 to 3.750	0.446
Stroke	0.292	0.101 to 0.848	0.024
IABP	0.232	0.620 to 0.871	0.030
STEMI	1.388	0.630 to 3.057	0.415
Age	0.995	0.970 to 1.0190	0.671

PCI, percutaneous coronary intervention; ASA, acetylsalicylic acid; GPIIb/IIIa, glycoprotein receptor IIb/IIIa; IABP, intra-aortic balloon pump; STEMI, ST-elevation myocardial infarction; OR, odds ratio.

is common and observed in up to 15% of unfractionated heparin-treated patients. It is not immunomediated and rarely leads to a severe reduction in platelet levels. It mostly resolves spontaneously, despite continuation of unfractionated heparin [7, 8, 12]. The majority of ACS patients in this cohort with reduced platelet count belonged to this type of thrombocytopenia.

In our ACS patients, the reversible small molecular GPIIb/IIIa inhibitor, eptifibatide, was used predominantly and abciximab was used only in individual cases. The time interval from the administration of i.v. eptifibatide to the onset of thrombocytopenia was 48–72 hours, suggesting the possibility of eptifibatide as the cause of thrombocytopenia, but that was not proven as specific tests are lacking [10, 21].

Heparins, either nonfractionated or of low molecular weight, are an important potential cause of immunomediated thrombocytopenia, HIT. In our ACS patients, HIT antibodies were demonstrated only in 1 patient, who was exposed to heparin in prior hospitalization. Thrombocytopenia developed within the first few days of in-hospital stay in the majority of our patients, mostly within the first 5 days in contrast to HIT, which generally occurs between 5 and 10 days [7, 8, 12].

On the other hand, PCIs were performed less often in ACS patients with reduced platelet count; therefore, antithrombotic drugs were also given less frequently to them than to patients with normal platelet counts.

PCIs were not performed in those presenting late with STEMI or those with complex multivessel disease in a setting of either NSTEMI or STEMI, if early death occurred or in those who refused the interventional therapy. Regarding complex multivessel coronary disease, current ESC STEMI guidelines recommend strategy of "culprit vessel only" primary PCI, followed by further elective revascularisation in case of ongoing ischaemia. This can lead to a substantial delay in reperfusion of the myocardium at risk [2]. This problem was in particular evident in STEMI patients with apparently new left bundle branch block. The advantage of complete revascularization at the time of presentation for STEMI patients over "culprit vessel only" strategy was demonstrated by the recent Culprit trial but needs further evaluation [22].

In addition, radial arterial access for PCI has been proven to offer an advantage in ACS setting with increased risk of bleeding by decreasing the risk of vascular complications and mortality within 30 days when compared to femoral arterial access [2].

The main reasons not to use antithrombotic agents were early complications such as early death and renal failure, as well as early CABG. However, PCIs and antithrombotic agents were still used in approximately 70% of our thrombocytopenic ACS patients.

When early coronary revascularization is delayed or abandoned in the setting of ACS, extensive myocardial necrosis develops, which can be followed by severe myocardial dysfunction with subsequent activation of neurohumoral factors and of inflammation to lead to increased platelet consumption and thrombocytopenia. Thus, thrombocytopenia may act as a marker of the acuity and severity of the inflammation in ACS settings. In addition, activated inflammation and neurohumoral system can further impair hemodynamics and contribute to other organ hypoperfusion, including that of the kidneys [2, 3, 7, 12]. In our thrombocytopenic ACS patients, we observed increased incidence of acute heart failure and of kidney injury, increased levels of the inflammatory marker CRP and, finally, increased short- and long-term mortality.

Several trials demonstrated that thrombocytopenia in addition to drug-induced antiplatelet effect in ACS patients was associated with increased risk of bleeding. However, bleeding was not significantly increased in our thrombocytopenic patients, but red blood cells were significantly more often transfused than in the nonthrombocytopenic patients. Red blood cells were transfused in case of major bleeding, but also in case of severe anemia with hemoglobin level < 80 g/L irrespective of etiology to improve oxygen delivery in the setting of coronary ischemia.

No platelets were transfused, what is in accordance with current guidelines, which recommend infusion of platelet rich plasma only in pronounced drop in platelet count (<10.000/mL) in case of active bleeding [2, 3, 7]. We observed a drop in platelet count below 50.000/mL only in 3 patients

(0.8% of all ACS patients) and the platelet count dropped below 100.000/mL only in 15 patients (4% of ACS patients). Other studies observed a drop of platelets below 50.000/mL in approximately 6% of ACS patients, treated by combination of antiplatelet and anticoagulant agents [4, 5].

We observed that even a mild drop in platelet count in high-risk ACS patients was associated with increased mortality and complication rate, what is consistent with the results of other studies [4, 5, 8, 12, 23, 24]. The short- and long-term mortality were twofold increased in our thrombocytopenic ACS patients as compared to those with normal platelet counts. In addition, treatment modalities such as insertion of IABP, use of antibiotics, and blood transfusions predisposed patients to thrombocytopenia even more. Our data confirm that thrombocytopenia in high-risk ACS patients seems to be multifactorial. It may be associated with drug effects such as GPIIa/IIIb inhibitors, heparins, and even clopidogrel, but also procedures such as PCIs and IABP insertion. An important predisposing factor in ACS setting is myocardial pump failure with organ hypoperfusion after delayed percutaneous revascularization, which can be aggravated by activated neurohumoral system and inflammation. Acute kidney injury is an important complication of tissue hypoperfusion, but it can also be induced by contrast agents during PCI [4, 5, 7, 8]. In our ACS patients, acute kidney injury was significantly more frequent in thrombocytopenic patients, in particular, in combination with heart failure [2, 3, 18, 19].

In recent years, novel antiplatelet and anticoagulant drugs have been developed and tested. Their use seems promising in preventing drug-induced thrombocytopenia. Novel ADP-receptor antagonists, like prasugrel and ticagrelor, may also induce thrombocytopenia with earlier onset of action than clopidogrel. It appears prudent to replace the heparin plus GPIIb/IIIa inhibitor regime by one of the novel anticoagulants such as bivalirudin in STEMI or fondaparinux in NSTEMI patients presenting with low platelet counts [2, 25]. This strategy may help to reduce the risk of drug-induced thrombocytopenia to some extent [2, 3, 7].

4.1. Conclusions. Our conclusions are as follows: even mild degree of thrombocytopenia, observed in approximately 20% of high-risk ACS patients, is significantly associated with less often performed PCIs and with several complications, including increased short- and long-term mortality. However, thrombocytopenia was independently predicted by post-PCI procedures, aimed at mastering in-hospital complications. Therefore, early treatment of high-risk ACS patients should focus on early PCI to prevent large ischemic necrosis: particularly in the elderly with comorbidities and in patients with hemodynamic instability or with large anterior infarcts, which can reduce mortality (the higher-risk patients benefit most from early PCI strategies). The use of novel antiplatelets with reversible platelet inhibition (ticagrelor) and antithrombotic drugs with direct thrombin inhibition (bivalirudin) can reduce the risk of drug-induced thrombocytopenias during interventional therapy and should be preferred.

Regarding PCI procedures multivessel coronary interventions at presentation should be performed in case of severe acute heart failure to prevent delays in reperfusion in particular in STEMI setting. To avoid any further bleeding risks, radial vascular approach has the priority if possible.

4.2. Limitation of the Study. Our study is a retrospective observational design with limited number of patients, carrying all the limitations and biases inherent in such studies. However, the data are taken from the "real world" as an observational study and therefore can reflect on the complexity of managing ACS patients with thrombocytopenia during our daily practice.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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