Multimodal individualized concept of hemodynamic monitoring

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Purpose of review
To discuss the pathophysiological rationale of advanced hemodynamic monitoring in the critically ill and also to highlight the importance of a multimodal, individualized approach.

Recent findings
There are several clinical studies and animal experiments evaluating, which hemodynamic endpoint should be the best target during fluid management. Recent systematic reviews and meta-analyses also investigated the effects of advanced hemodynamic endpoints targeted hemodynamic management on outcome mainly in high-risk surgical patients. Although most of these studies report positive results, this knowledge does not seem to affect our everyday practice. According to large international surveys, most physicians still rely on inappropriate indices. One of the reasons could be that target values applied in these studies can be misleading in the individual patient. Therefore, we describe the concept of an individualized approach, in which normalizing the components of oxygen delivery are put in the context of the patients' individual response by evaluating components of oxygen consumption, and organ perfusion.

Summary
Advanced hemodynamic monitoring-based management provides a number of benefits, which could be better tailored for the patients' actual needs by putting this into a multimodal, individualized approach.

Keywords
goal-directed therapy, hemodynamic monitoring, oxygen consumption, oxygen delivery

INTRODUCTION

Hemodynamic optimization remains the cornerstone of resuscitation in the critically ill. Early recognition of the patients at risk and the implementation of adequate monitoring guided interventions have profound effects on outcome. Delay or inadequate management will inevitably lead to hypoperfusion, tissue hypoxia and multiple organ failure affecting both outcome and wasting of resources and costs [1]. Therefore, the use of appropriate indices, which are able to detect tissue hypoperfusion and the imbalance between oxygen delivery (DO_2) and oxygen consumption (VO_2) is mandatory for adequate management [2]. Conventional parameters such as heart rate (HR), mean arterial blood pressure, mental status and urine output are important warning signs of inadequate tissue perfusion, but for detailed assessment advanced hemodynamic monitoring is warranted [3]. However, recent clinical studies indicate that there is a considerable gap between the accumulating knowledge about the benefits of advanced hemodynamic monitoring-based optimization and the actual clinical practice. The results of the FENICE trial, in which fluid challenges were evaluated in more than 2000 patients, revealed that the main indicator of administering fluid boluses was hypotension in 57%, and in 43% of cases no hemodynamic variable was used to predict fluid responsiveness [4▪▪]. It is based on strong pathophysiological rationale that detailed assessment of global hemodynamic indices such as cardiac output (*CO*) and derived variables and also the measures of DO_2 and uptake should be taken into account to provide appropriate therapy for these patients [5,6]. Furthermore, in addition to the optimization of global hemodynamic parameters, indicators of tissue perfusion should also be monitored to verify the effectiveness of our interventions [7]. This multimodal approach requires a paradigm shift from the current, often arbitrary or protocolized management, which is often based on predefined

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KEY POINTS

- Advanced hemodynamic monitoring–targeted treatment has several benefits in the critically ill.
- Most physicians still use inappropriate indices in their everyday practice, but treating one single advanced hemodynamic parameter can also be misleading.
- Therefore, in patients at highest risk a multimodal approach, taking the components of oxygen delivery and consumption into account, is mandatory for adequate assessment and treatment.
- Despite its physiological rationale, whether this approach has a significant effect on outcome, will have to be tested in the future.

values of inappropriate indices and may lead us to a better, individualized, patient-centered care. The goal of this review is to highlight the concept of multimodal, individualized hemodynamic management in the context of the pathophysiological background and the results of recent trials.

PHYSIOLOGICAL ISSUES

Tissue oxygenation is determined by the balance between the oxygen transport, oxygen demand and oxygen uptake by the tissues [8]. The main determinants of DO_2 and VO_2 and the indicators of tissue perfusion are depicted in Fig. 1.

When the arterial oxygen content and/or *CO* becomes impaired, DO_2 decreases, which is often accompanied by an increase in VO_2 mainly due to the factors listed in Fig. 1 [9,10]. In the early phase of decreasing DO_2, the circulation can compensate to some extent, and VO_2 remains stable. However, beyond a critical point, any further drop in DO_2 will result in a decrease in VO_2. From this point, VO_2 becomes dependent on DO_2, and aerobic metabolism will have to be switched to anaerobic metabolism, leading to low $ScvO_2/SvO_2$, hyperlactatemia, metabolic acidosis and oxygen debt [11].

The principle task of early resuscitation is to regain balance by optimizing the VO_2/DO_2 ratio. However, it is also important to define the endpoints of resuscitation to avoid over-resuscitation. In the case of fluid resuscitation for example, unnecessary administration of fluids will lead to hypervolemia, which increases morbidity and mortality to a similar extent to that of hypovolemia [12,13]. Unjustified blood transfusions also carry the risk of hypervolemia and transmission of infections [14] or allergic reactions [15]. There is evidence that prolonged use of catecholamines is associated with poor outcome [16]. Therefore, it is important to recognize the point when tissue perfusion has normalized, and terminate resuscitation.

INDIVIDUALIZED GOAL-DIRECTED HEMODYNAMIC THERAPY

The multimodal concept in hemodynamic monitoring enables us to appreciate that each patient is different; hence, the so-called normal values, which are more or less appropriate for a given population, may be inadequate for the given patient. Therefore, this concept can be translated into the individualized use of target endpoints to avoid under or over-resuscitation.

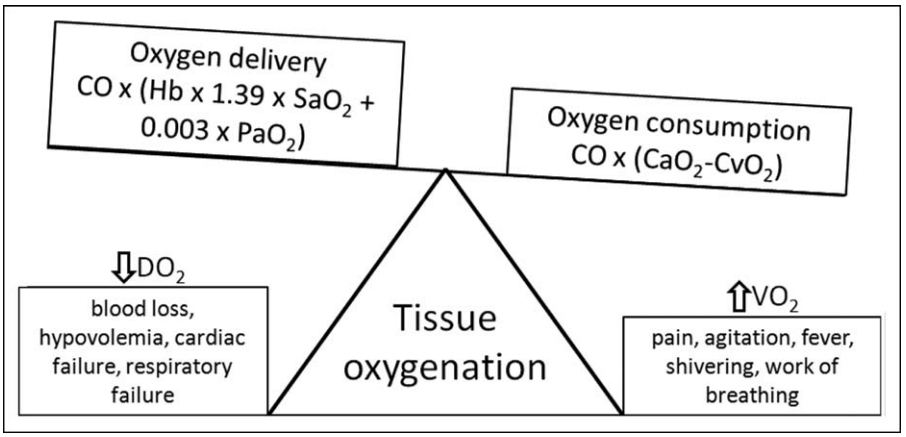

FIGURE 1. Factors affecting oxygen delivery and demand/consumption. CaO_2, arterial oxygen content; CO, cardiac output; CvO_2, venous oxygen content; DO_2, oxygen delivery; Hb, hemoglobin; PaO_2, arterial partial pressure of oxygen; SaO_2, arterial oxygen saturation; VO_2, oxygen consumption. For further explanation, see main text.

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Parameters determining DO_2

Cardiac output and stroke volume as resuscitation endpoints

In two recent experiments, we investigated *CO* and stroke volume (SV) guided hemorrhage and fluid resuscitation in a porcine model [17,18▪]. After baseline measurements, animals were bled until SV index (SVI) dropped by 50%, after which animals were resuscitated in four steps till baseline cardaic index (CI) and SVI values were reached. In the CI-group, SV, global end diastolic volume and central venous oxygen saturation ($ScvO_2$) remained significantly lower, whereas SV variation (SVV), central venous-to-arterial carbon dioxide difference (dCO_2) remained significantly higher by the end of resuscitation as compared with baseline, indicating that fluid resuscitation was inadequate and the normalization of CI was mainly due to the persistently elevated HR, rather than restoration of the circulating blood volume. On the contrary, in the SVI group SVV, $ScvO_2$ and dCO_2 improved significantly or returned to their baseline value by the end of the experiment. Based on these results, it seems that the SVI-based algorithm resulted in better hemodynamic and oxygenation indices as compared with the CI-based approach. This observation certainly has strong pathophysiological rationale, but it should be tested in the clinical setting.

Stroke volume variation and pulse pressure variation as resuscitation endpoints

Recently, less invasive devices, like noncalibrated, pulse contour analysis-based technologies have been developed to assess *CO* by an invasive arterial pressure signal. Although these devices are less accurate as compared with thermodilution-based technologies as gold standard, there is some evidence that these methods can adequately show changes and trends in the hemodynamic status of the patient [19]. Pulse pressure variation (PPV) and SVV are well established indicators of fluid responsiveness, and these devices seem like simple and useful alternatives to invasive hemodynamic monitoring in several scenarios [20].

The physiological rationale is the following: mechanical breaths induce heart–lung interactions, first described by Antonio Maria Valsalva, mainly by affecting venous return, hence intermittent positive pressure ventilation can be regarded as a series of Valsalva-maneuvers. PPV and SVV can reflect these changes in venous return if tidal volumes are large enough of ~8–10 ml/kg of ideal bodyweight [21]. In addition to the tidal volume, sinus rhythm and no evidence of right heart failure should also be present to make PPV/SVV interpretation possible [22]. Increasing intrathoracic pressure will impair venous return, and after 2–3 heart cycles this will result in a drop in left ventricular SV, which can be detected by the cyclic changes of PPV and SVV. In cases of normovolemia, the variation is small (<10%), whereas on the contrary, values increase in hypovolemia.

In a recent large multicenter–randomized study, PPV, MAP and CI-trending-based approach reduced postoperative complications in high-risk surgical patients undergoing major abdominal surgery by almost 50% [23]. A subgroup of patients undergoing bowel surgery benefited the most from this intervention. In the treatment group 42% of patients required positive inotropic support, whereas nobody in the control group was administered dobutamine. In another clinical trial goal-directed DO_2-therapy was applied in high-risk surgical patients needing ICU admission after the operation [24▪▪]. Target DO_2 was based on the preoperatively determined individual DO_2 values. In the treatment group after the first hour of optimization, 40% of patients received dobutamine as compared with none in the controls, a very similar result to that of the previous trial [23]. Their main finding was that achievement of preoperative DO_2 soon after major surgery was associated with a reduction in early postoperative morbidity, yet this occurred irrespective of additional postoperative hemodynamic management. This was in part due to the fact that more patients achieved the target DO_2 in the control group (53%) than expected. Their data also suggested that dobutamine use resulted in the development of parasympathetic autonomic dysfunction, which can potentially be harmful. However, in two recent meta-analyses, it was found that patients in the treatment groups received significantly more dobutamine, but morbidity and mortality in general, and also postoperative cardiac complications were significantly reduced when advanced hemodynamic monitoring-based intraoperative management is applied [25,26].

When interpreting the above discussed parameters at the bedside, it is important to bear in mind that being for example fluid responsive as indicated by CI, SVI, SVV or PPV values may not necessarily mean that the patient need fluid administration. The results of these measurements must be put into the context of parameters indicating the patient's oxygen demand and actual consumption.

Parameters reflecting VO_2

Mixed venous and central venous oxygen saturation

Mixed venous oxygen saturation (SvO_2) and its surrogate, $ScvO_2$ are the most commonly used methods

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to assess global oxygen extraction (VO_2/DO_2). $ScvO_2$ is an easily obtained parameter via a central venous catheter already *in situ* in most critically ill patients, and it is often used as a marker of the balance between DO_2 and VO_2. The absolute values of $ScvO_2$ are 5% higher than SvO_2 on average, but changes usually occur in a parallel manner [27]; therefore, $ScvO_2$ is regarded as a surrogate marker in the clinical setting [28–30]. However, recent clinical trials, involving mainly septic patients, were unable to show satisfactory agreement between $ScvO_2$ and SvO_2. This could in part be explained by modifications of blood flow distribution and oxygen extraction by brain and splanchnic tissues [31].

The main factors, which influence $ScvO_2$, are hemoglobin (Hb), arterial oxygen saturation of Hb, *CO* and VO_2. Theoretically, if three of these factors are kept constant, the value of $ScvO_2$ reflects the changes of the latter. There are multiple physiologic, pathologic and therapeutic factors that influence venous oxygen saturation, such as anemia, hypovolemia, contractility, bleeding, sedation, fever, pain and others [32].

One of the important features of venous saturations is that it can be pathologic both if it is high and when it is low. In a recent large cohort of septic patients in the emergency department, it was found that mortality was 40% in patients admitted with an $ScvO_2$ less than 70% but in patients with an initial $ScvO_2$ of more than 90%, it was almost as high at 34%. The latter was probably due to impaired oxygen utilization [33]. High $ScvO_2$ values may thus represent an inability of the cells to extract oxygen or microcirculatory shunting in sepsis [34]. Therefore, additional measures are necessary to help in evaluating high $ScvO_2$ values, such as for example lactate, central venous to arterial dCO_2, and by applying advanced invasive hemodynamic monitoring.

Lactate

Lactate, the end product on anaerobic metabolism, has been thoroughly investigated over the last decades in critically ill patients. It has good prognostic value in several clinical scenarios such as trauma, sepsis and high-risk surgical patients [35]. Increased lactate production is mainly due to anaerobic metabolism caused by tissue hypoxia. High lactate concentrations are common findings during the management of hemodynamically unstable, bleeding patients [36]. Surgical patients admitted to the ICU with high initial and 24-h lactate levels had higher mortality compared with patients with normal levels [37]. Furthermore, there is mounting evidence that lactate clearance is superior to absolute values and mirrors better the effect of therapy not only in septic, but also in surgical patients. Patients with longer duration of high lactate levels had worse outcome, compared with patients, who responded to resuscitation and had declining lactate levels [38]. These results were further confirmed by trauma victims, wherein patients in whom lactate levels normalized within the first 24 h, the mortality was 10%, as compared with those patients in whom it took 48 h, where mortality was as high as 67% [37]. In a recent experimental hemorrhage and resuscitation model on pigs, we found that considerable changes of lactate level were well beyond the suggested 6-h time frame [17]. Significant increase during and after bleeding and then significant decreases during resuscitation were observed between the observation periods of 20 min. Therefore, it has some rationale to shorten the evaluation time periods that would give a faster signal about the effectiveness of therapy. However, a confounding factor in the interpretation of declining lactate levels during resuscitation could be the diluting effect of the administered fluid. Nevertheless, this should be evaluated in the clinical setting.

Venous-to-arterial CO_2 gap as therapeutic endpoint

Another easily obtainable blood flow related blood gas parameter is the central venous-to-arterial carbon dioxide gap. The phenomenon of increased CO_2 during cardiac arrest [38] and cardiopulmonary resuscitation [39] was first described 30 years ago. As then, several authors have reported increased dCO_2 in different low flow states [40–42]. In oxygen debt caused anaerobic metabolism, hydrogen ions are generated through the hydrolysis of ATP to ADP and increased production of lactic acid [43]. These hydrogen ions are buffered by bicarbonate presented in the cells, and this process will generate CO_2 production [44]. The Fick principle adapted to carbon dioxide demonstrates the inverse relationship between the *CO* and dCO_2 [45], in other words increased levels of dCO_2 reflect low flow states. It has been shown that in sepsis, heart failure and severe hypovolemia, its value can be elevated [46,47].

In the clinical setting, dCO_2 is also a good predictor of outcome. Preoperatively, patients with high dCO_2 had significantly higher mortality compared with patients with normal values (36.4 versus 4.5%) [48]. High-risk surgical patients admitted to ICU postoperatively with high dCO_2 also developed more complications. The cut of value was 5.8 mmHg [49▪▪]. A dCO_2 more than 5 mmHg had 96% sensitivity to predict the occurrence of postoperative complications in patients with normal ($\geq$71%)

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$ScvO_2$ [50]. In critically ill patients, the dCO_2 is in good inverse correlation with the *CO* [41], and it has also been shown to be a good predictor of bad outcome in patients with septic shock [40]. In cases like septic shock, when due to microcirculatory or mitochondrial defects, oxygen uptake is insufficient, $ScvO_2$ can be supranormal. Previous studies have suggested that under such circumstances, the increased value of dCO_2 (>5 mmHg) can help the physician in detecting inadequate flow to the tissues; hence, the complementary use of $ScvO_2$ and dCO_2 is recommended [50–52].

Similarly to what has been noted at end of the paragraph discussing components of DO_2, measures of VO_2 can only be interpreted and understood if we put them in the context of indices of DO_2. However, all of the above discussed parameters reflect the global situation and provide little information of regional, organ-specific perfusion. For this purpose, several methods have been developed to gain information about the microcirculation.

Microcirculation

In addition to the restoration of macrohemodynamic indices, the most important task is to normalize DO_2 within the microcirculation, especially when signs of tissue hypoxia, such as increased lactate, increased dCO_2, low or supranormal $ScvO_2$ and organ failure are present. There is mounting evidence about the microcirculatory derangement in the critically ill mainly in septic shock [53]. Due to the endothelial dysfunction [54], glycocalyx layer degradation [55] and pathological cell–endothelial interactions [56], a condition termed 'microcirculatory shock' can develop, which can be defined as 'the failure of microcirculation to support tissue perfusion and oxygenation, despite normal systemic hemodynamics' [57]. Under physiological circumstances, a dens capillary system forms the microcirculation, with low heterogeneity in perfusion. During severe sepsis, septic shock, there is an increase in the heterogeneity of capillaries, with 'no perfusion' to 'high perfusion' in both space and time [58]. This heterogeneity in perfusion impairs oxygen transport to the tissues and can lead to organ failure [59]. It has significant clinical relevance as among septic patients the proportion of perfused capillaries as well as heterogeneity index predicts mortality [60]. As multiple causes can result microcirculatory dysfunction, there is no single intervention to restore microcirculation, instead different therapeutic possibilities should be individualized on the patients' needs. Early fluid resuscitation could increase the proportion of perfused capillaries and decrease perfusion heterogeneity; however, in the later phases of therapy, fluid replacement can worsen microcirculation by impairing oxygen uptake of the cells [61]. Red blood cell transfusion improved only the severely impaired microcirculation, whereas preserved microcirculation worsened after transfusion [62]. With the use of vasopressors after reaching adequate perfusion pressure, microcirculation was also restored; however, further increase in mean arterial pressure did not improve microcirculation [63]. Positive inotropic agents improved capillary perfusion with a proportional decrease in lactate level in critically ill patients [64].

With the development of imaging techniques, the third generation incident dark field imaging device [Braedius CytoCam (Braedius Medical BV, Bikbergerweg 18, 1272 PM Huizen, The Netherlands)], which is a hand held device with automatic analysis program, the evaluation of the microcirculation may be feasible at the bedside. Therefore, microcirculation-centered therapy may just be on the doorstep of everyday clinical routine. As the pathological background of microcirculatory derangement is multifactorial, an individualized patient-centered resuscitation should be performed, and the effectiveness of therapy should also be evaluated on the level of the microcirculation [65]. Nevertheless, despite the promising experimental and human research data, its usefulness in the daily clinical practice has to be tested in the future.

The multimodal concept: *pros* and *cons*

One of the most important lessons, what we have learned from recent clinical trials, is that one single parameter cannot be used as the only target during resuscitation. Furthermore, 'normal' values or ranges of certain parameters cannot always be applied for the individual patient. Therefore, in patients who do not respond for basic resuscitation and require high vasopressor support; developed acute respiratory distress syndrome as part of multiple organ dysfunction; have threatening renal failure as part of multiple organ dysfunction; and are in septic shock, or suffered major trauma and remain unstable after resuscitation, detailed hemodynamic evaluation-based management is mandatory to guide treatment better and to avoid potential harm that unnecessary therapy can cause. This concept first evaluates the components of DO_2 (Fig. 2). Even if these values are regarded as normal, whether these are adequate for the individual patient at the time of assessment, it has to be tested by the patient's response, which is summarized in the outer circle of the figure. In the case of any imbalance, the factors-affecting VO_2 have to be evaluated, normalized if needed, and patient response to be assessed again.

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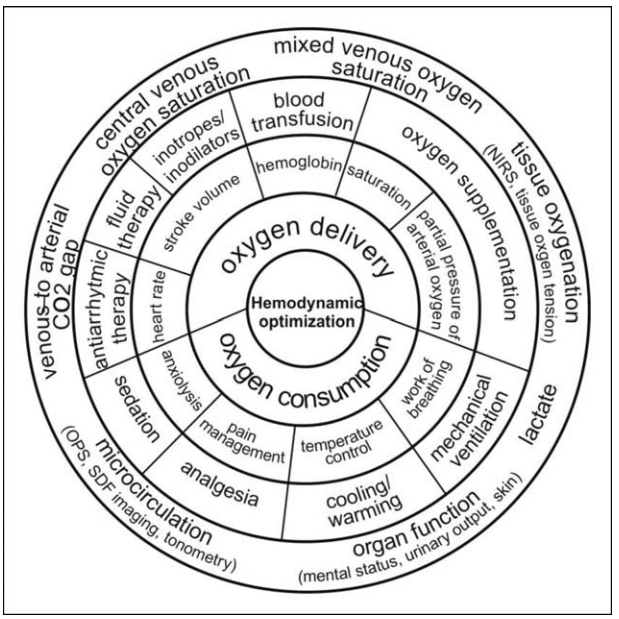

FIGURE 2. The 'hemodynamic disc'. Inner circles: factors affecting and determining oxygen delivery and consumption. Outer circle: parameters, which are affected by changes in oxygen delivery and consumption, which can be assessed at the bedside. For further explanation, see main text.

Unfortunately, these measurements require special devices, invasive catheters; the evaluation can be time-consuming, requires well trained personnel, and it is also costly. Therefore, one cannot apply this strategy for every critically ill patient, and every parameter may not be required in every patient. Careful selection of patients at the highest risk but who would still benefit from this approach, and also the rationalization of the indices required, is therefore mandatory to gain the most out of this management concept.

CONCLUSION

Early and adequate hemodynamic stabilization of the critically ill patients has a significant effect on outcome. Rather than following certain numbers in protocols or algorhythms, a multimodal approach, of assessing hemodynamic variables together with the balance between DO_2 and VO_2, may help to get a detailed picture about the hemodynamic status of our patients and also gives a chance for individualized treatment. One has to appreciate that values applied as treatment endpoints in clinical studies and proved beneficial for the study population may not be adequate for the individual patient. These important results give the frame what we fine tune for the patient's individual needs by putting them in the context of the complex puzzle of physiology. This is what multimodal, individualized hemodynamic support is all about.

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Conflicts of interest

Z.M. receives regular honoraria for being in the Medical Advisory Board of PULSION Maquet, for lectures from Biotest, ThermoFisher Scientific and CytoSorbents. The remaining authors have no conflicting interest.

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