

# Personalized Critical Hemodynamic Therapy Concept for Shock Resuscitation

Long-Xiang Su, Da-Wei Liu

Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China

Early goal-directed therapy (EGDT) has been used in clinics as a standard procedure in sepsis resuscitation for a long period. However, the ProCESS, ARISE, and ProMISe trials did not find any benefits from EGDT on sepsis mortality, triggering considerable doubt, and reassessment in the field of intensive care medicine. The heterogeneity of the studied patients, the differences of trial designs and interventions may have led to these disappointing results; however, improving oxygenation and tissue perfusion as early as possible is the core issue at hand. Personalized critical hemodynamic treatment (PCHT) should be proposed and applied for shock cases.

## CLARIFY HEMODYNAMIC THERAPEUTIC TARGETS AND DESTINATIONS FOR SHOCK RESUSCITATION

Targets are the direct results of a specific intervention or clinical practice. Destinations represent the direction of a specific therapeutic strategy or the ultimate outcome for a bundle of therapeutic approaches. Targets control-specific interventions are the basis for completing treatments that will affect the ultimate achievement of the treatment destination. The treatment destination determines the need for specific interventions and thus determines the necessity and direction of specific targets. The therapeutic targets should be established according to the desired destination, and the destination is achieved through the accomplishment of a series of targets.

During shock resuscitation, patients often simultaneously or gradually have pathophysiological changes in blood volume, cardiac function, vascular tone, microcirculation, and may even suffer from cellular hypoxia. In critical hemodynamic therapy (CHT), blood flow is the primary and most important factor, and tissue perfusion is the ultimate goal. Sufficient cardiac output (CO) is the key point for providing blood flow. However, it is often encountered

in clinical practice that shock patients have poor tissue perfusion with satisfied macrocirculation targets due to microcirculation dysfunction. Limited by current monitoring and treatment methods, there are no better methods for microcirculation resuscitation. PCHT provides us with an effective clinical belief that flow-directed resuscitation is the core of shock resuscitation for dealing with both macro and microcirculation. In addition, identifying the etiology and cause of shock and removing it as soon as possible should be the foundation of hemodynamic therapy. For example, septic shock requires the removal and drainage of infected lesions and the immediate use of antibiotics; hypovolemic shock necessitates a blood transfusion; cardiogenic shock requires the amelioration of cardiac function; and obstructive shock necessitates the relief of obstructive factors.

## CRITICAL HEMODYNAMIC MONITORING AND ASSESSMENT

Arterial and central venous catheters are necessary and recommended for critical hemodynamic monitoring, assessment, and treatment. They quickly and accurately provide basic hemodynamic target data, such as central venous pressure (CVP), central venous oxygen saturation (ScvO<sub>2</sub>), venous-to-arterial carbon dioxide difference (Pv-aCO<sub>2</sub>), arterial blood pressure (ABP), pulse pressure variation, and lactate level. Critical care ultrasonography is now recognized and widely used as the preferred initial modality to distinguish and determine

**Address for correspondence:** Prof. Da-Wei Liu, Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China  
E-Mail: dwliu98@163.com

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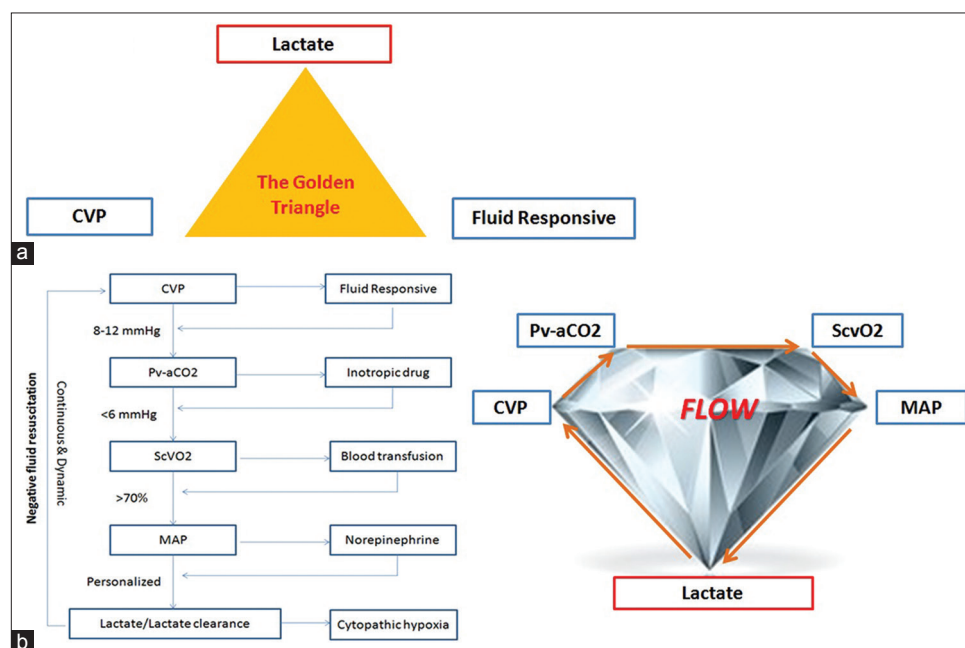
the type of shock, which contributes to immediately identifying etiology. When the initial treatment does not improve the targets for therapeutic destination, advanced critical hemodynamic monitoring, such as transpulmonary thermodilution or pulmonary artery catheterization, is required and should be performed. When all the targets have been achieved, but the destination fails, microcirculation dysfunction, and cytopathic hypoxia should be considered. Orthogonal polarization spectral (OPS) or sidestream dark field (SDF) imaging should be employed to detect changes in sublingual microcirculation. In our previous work, we also found that perfusion index may be a sensitive and noninvasive target reflecting microcirculation.<sup>[1]</sup>

## TARGETS FOR CRITICAL HEMODYNAMIC THERAPY

Increasing blood flow (CO in macro- and micro-circulation) through fluid resuscitation is the first procedure and essential step for shock resuscitation. CVP or the inferior vena cava (IVC)/respiratory variation of the IVC is used to monitor volume status. CVP is a traditional and controversial indicator, but it still has good clinical significance. If CVP is not high enough (8–12 mmHg; 1 mmHg = 0.133 kPa) or the reason for an increase in CVP has not been found or cannot be resolved, a fluid challenge test should be performed to evaluate volume responsiveness. It is especially important to point out that the reasons for high CVP must be considered in conjunction with excessive volume load, cardiac dysfunction, vessel disorder, and pressure factors, which are defined as the elevated CVP (ECVP) principle. Lactate level, CVP, and volume responsiveness appropriately constitute a golden triangle relationship [Figure 1a]. Resuscitation begins from the vertex of the

triangle, using lactate level to determine whether tissue perfusion is satisfactory. If lactate is higher than normal, CVP should be checked, and a crystalloid infused fluid or colloidal solution administered if CVP <8 mmHg. If lactate is higher than the safety range (CVP >12 mmHg), the reasons for the increased CVP should be checked first (e.g., ECVP principle). If there is no other cause of CVP rise or if the cause cannot be immediately removed, then enter the triangle through another vertex of capacity or reactivity. If the fluid responsive test is negative and lactate is still high, continuing fluid resuscitation cannot increase CO. Other methods, such as inotropic drugs, may be used to improve the Frank–Starling curve. Once tissue perfusion has been satisfied, resuscitation successful, and lactate level decreased, a reduction of CVP must be considered, through negative fluid resuscitation.

CO can increase with fluid resuscitation and provide greater oxygen delivery based on the Frank–Starling law. The monitoring of CO provides a direct indication of blood flow, but it often requires invasive methods to obtain. Pv-aCO<sub>2</sub>, which reflects adequate systemic blood flow, can be used to monitor and guide flow instead.<sup>[2]</sup> Some studies have revealed that Pv-aCO<sub>2</sub> can reflect microcirculatory alterations in septic shock but did not correlate with CO.<sup>[3]</sup> Whether Pv-aCO<sub>2</sub> reflects macro- or micro-circulation, more targets should be used to confirm blood flow through critical care ultrasonography or OPS/SDF imaging, such as left ventricular outflow tract velocity time integral (LVOT-VTI), perfused vessel density, proportion of perfused vessels (PPV), microvascular flow index, or even with other advanced critical hemodynamic monitoring technology.



**Figure 1:** The golden triangle (a) and the brightening diamond (b) for personalized critical hemodynamic therapy. CVP: Central venous pressure; CO: Cardiac output; ScvO<sub>2</sub>: Central venous oxygen saturation; Pv-aCO<sub>2</sub>: Venous-to-arterial carbon dioxide difference; MAP: Mean arterial pressure; LVOT-VTI: Left ventricular outflow tract velocity time integral.

Once oxygen delivery can meet the requirements of tissue, ScvO<sub>2</sub> can be applied to judge whether oxygen delivery matches oxygen consumption. Systemic oxygen delivery is determined by CO and arterial oxygen content, and oxygen consumption is determined by hemoglobin level, arterial oxygen saturation, and arterial oxygen partial pressure. In addition, reducing oxygen consumption is also an important approach based on the theories of oxygen delivery and oxygen metabolism and methods for this include the management of body temperature, analgesia, sedation, and others.

Last but not least, different organs have different requirements for perfusion pressure under different hemodynamics, and changes in blood pressure and their relationship with metabolism may be the most important parameters.<sup>[4]</sup> The appropriate ABP should be determined based on tissue perfusion function and the individual patient's specific condition.

## LACTATE CLEARANCE – A PRESENT AND THE BEST DESTINATION OF CRITICAL HEMODYNAMIC THERAPY

Lactate level indicates the presence of anaerobic metabolism. Raised lactate concentrations in blood are an important manifestation of cellular hypoxia, reflecting tissue hypoperfusion. The lactate clearance rate reflects whether tissue hypoperfusion has been improved or if the anaerobic metabolism of tissue cells has been corrected. Jansen *et al.*<sup>[5]</sup> found that in shock patients with lactate levels higher than 3 mmol/L, a decrease in lactate levels by 20% or more within 2 h correlated significantly with a drop in mortality rate. Our previous study confirmed that stepwise lactate kinetics-oriented hemodynamic therapy can reduce mortality in patients with sepsis-associated hyperlactatemia as compared to ScvO<sub>2</sub>-oriented therapy.<sup>[6]</sup> The lactate clearance rate is often the endpoint that needs to be achieved by a series of hemodynamic therapies and is therefore considered to be the best indicator of anaerobic metabolism by far despite that lactate change has hysteresis.<sup>[7]</sup> In addition, raised lactate levels are a well-recognized parameter for a poor prognosis.<sup>[8]</sup> Therefore, the outcome of CHT or a hemodynamic clinical trial should be recommended lactate clearance, not patient survival.

## TRAITS OF CRITICAL HEMODYNAMIC THERAPY – CONTINUOUS AND DYNAMIC

The continuity of hemodynamic therapy ensures more comprehensive and timely access to clinical information. The dynamic approach of hemodynamic therapy enables clinicians to decide proactively and prospectively the direction of the next treatment. Therefore, subsequent treatments need to be adjusted quickly according to sequential targets and the entire dynamic hemodynamic process.<sup>[9]</sup> As there is no specific CO value, no assessment of CO should be performed unless it is combined with tissue perfusion.<sup>[10]</sup> Consequently, we need to find the

patient's best CO, which essentially means a properly adjusted and personalized flow. On the one hand, we need to know which vasoactive medication should be used but yet have no idea which species or dose. Without hemodynamic data, we cannot simply judge whether a drug would work or not. On the other hand, we cannot recognize the damage that occurs over the course of treatment without hemodynamic data. Inappropriate intervention targets aggravate concomitant injury.<sup>[6]</sup> As is the case with inotrope drugs, side effects or potential myocardial injury must be considered when using medication to increase CO. Similarly, excessive resuscitation and fluid overload may also cause organ damage, which requires the attention of clinicians. Therefore, continuous and dynamic hemodynamic monitoring and therapy are traits of CHT. Using real-time hemodynamic data can help move the patient's hemodynamic phenotype to within acceptable limits. In addition, it provides greater clinical significance to static hemodynamic parameters. This dynamic monitoring and evaluation not only guide clinicians on what to do at the moment but also on how to control re-injury during treatment and where to go the next. This contributes to the achievement of PCHT theory.

## NEGATIVE FLUID RESUSCITATION

For different types of shock, different treatment methods need to be adopted based on the specific causes of low-oxygen delivery. As for the intervention, fluid resuscitation is an important method for increasing blood flow and improving oxygen delivery. However, volume overload due to excess fluid therapy causes numerous adverse effects, especially in critically ill patients.<sup>[11]</sup> Furthermore, pulmonary edema causes lung dysfunction, leading to a decrease in oxygen delivery.<sup>[11]</sup> Therefore, shock resuscitation must be based on the principles of hemodynamic therapy with an improvement in tissue/organ perfusion as its destination, increasing oxygen delivery quantitatively to optimize the therapeutic effect and reducing the incidence of concomitant injury caused by a specific intervention. Sufficient but no higher CO for an individual is to be considered the best CO. Once the tissue perfusion and lactate clearance have been satisfied, CVP must be down-regulated in time to obtain a minimum CVP that matches blood flow, avoiding re-injury during the hemodynamic treatment. A series of clinical trials by our team found that the early realization of a negative fluid balance may be beneficial to patient prognosis.<sup>[12-14]</sup> Practitioners can limit the amount of liquid given, use dehydration, or take other measures to achieve a negative fluid balance when possible e.g. continuous renal replacement therapy (CRRT).

## PERSONALIZED FLOW CHART OF CRITICAL HEMODYNAMIC THERAPY

As tissue perfusion indicators, lactate concentration and lactate clearance are often used as destinations for CHT. Achieving this destination quickly will naturally

improve patient prognosis. To accomplish this goal, a series of target indicators must be employed and achieved. Therefore, specific levels for oxygen, blood flow, and blood pressure are the sequential targets with lactate level as the destination [Figure 1b]. Whether lactate is normal or not is set as the vertex of the diamond. When lactate increases during shock, a fast heart rate and low blood pressure are usually the main clinical manifestations. First, considering volume status, a fluid responsiveness assessment should be performed. Based on Frank–Starling curves, changes in CVP (or ICV) should be evaluated to obtain a certain increase in CO. However, blood flow should continue to be adjusted if it does not satisfy tissue perfusion. According to Pv-aCO<sub>2</sub>, LVOT-VTI, or other indicators, inotropic drugs should be selected, and their relevant drug dose adjusted to further improve the heart function curve. This should be combined with ScvO<sub>2</sub> to determine whether oxygen delivery satisfies tissue perfusion (or further increase hemoglobin, adjust mechanical ventilation, or reduce oxygen consumption). Finally, blood pressure should be set based on the individual patient's specific condition. The entire process is a blood flow-based hemodynamic assessment and treatment. The lactate shown in the figure is the starting point for assessment/resuscitation and the endpoint for the hemodynamic treatment. If this fails, the presence of cytopathic hypoxia should be considered. Each sequential indicator is a target of the resuscitation and treatment process, which is interactive and interdependent, continuous, and dynamic. As soon as the best flow conditions are met, oxygen delivery and oxygen consumption balanced, and lactate drops to normal, it is the time to adjust the blood flow, volume, and pressure to the lowest possible level to meet tissue perfusion (i.e., the lowest CO, CVP, and mean arterial pressure). Negative fluid resuscitation is a necessary and important step. This will help to avoid the occurrence of re-injury during treatment and give a better prognosis. To validate the accuracy of the CHT flowchart, we collected the hemodynamic data of septic shock patients with high lactate levels (>4 mmol/L) between May 2013 and June 2017 at the Department of Critical Care Medicine, Peking Union Medical College Hospital. These patients were divided into three groups after 6 h of resuscitation: EGDT not completed, EGDT completed, and PCHT completed. We found that the groups that completed PCHT and EGDT both had lower ICU mortality than the group that had not completed EGDT (7/111 vs. 3/66, vs. 61/349,  $P = 0.001$ ). Interestingly, the PCHT group had lower lactate and higher lactate clearance levels than both those that had and had not completed EGDT ( $4.9 \pm 3.7$  mmol/L vs.  $4.6 \pm 2.4$  mmol/L vs.  $6.0 \pm 4.9$  mmol/L,  $P = 0.009$ ;  $41.0\% \pm 23.1\%$  vs.  $25.0\% \pm 45.3\%$  vs.  $19.1\% \pm 52.6\%$ ,  $P < 0.001$ ).

In conclusion, guided by the treatment destination, CHT is a continuous process during which a series of treatment methods are applied to achieve the corresponding targets in step by step manner and according to hemodynamic theories. Therefore, PCHT theory has been established. The dynamic assessment and the timely adjustment of the treatment

regimen are necessary based on continuous and dynamic the hemodynamic principles. This flowchart is a closed loop system. Once all targets have been met, and the destination has been achieved, proceed to negative fluid resuscitation as soon as possible. We hope PCHT will get brighter and brighter for the treatment of shock.

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### Conflicts of interest

There are no conflicts of interest.

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