Venous-to-arterial CO_2 differences and the quest for bedside point-of-care monitoring to assess the microcirculation during shock

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Abstract: The microcirculation is the anatomical location of perfusion and substrate exchange, and its functional impairment is of paramount importance during the state of shock. The difference in venous-to-arterial carbon dioxide partial pressures (Pv-aCO_2) has recently been reported to correlate with microcirculatory dysfunction during early septic shock with greater fidelity than global hemodynamic parameters. This makes it a potential candidate as a point-of-care test in goal directed therapy that aims to restore microcirculatory function in an emergency clinical context. This early work needs to be explored further, and a better understanding of Pv-aCO_2 during the resuscitation and subsequent patient progression is required. The quest for an ideal bedside point-of-care test for microcirculatory behavior is ongoing, and is likely to consist of a combination of non-invasive sublingual microcirculatory monitoring and biochemical tests that reflect tissue perfusion. These tools have the potential to provide more accurate and clinically relevant data with regards to the microcirculation that more conventional resuscitative monitoring such as blood pressure, cardiac output, and serum lactate.

Keywords: Microcirculation; oxygen; carbon dioxide; sepsis; shock

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Introduction

We read the article "Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock?" (1) with great interest. In their original article, Ospina-Tascón and colleagues test the hypothesis that the difference between mixed-venous and arterial carbon dioxide partial pressures (Pv-aCO_2) may be used as a surrogate marker for the functional adequacy of the microcirculatory flow during septic shock. Such a hypothesis is made in the context of a current understanding that microcirculatory behavior is more predictive of outcomes following septic shock than the more conventional global hemodynamic parameters such as mean arterial pressure and cardiac index (2). At present it may be relatively simpler to collect blood samples and calculate the Pv-aCO_2 than to undertake bedside monitoring of the microcirculation (especially in an emergency scenario). Pv-aCO_2 results are also more immediate than many other methods of monitoring the microcirculation, such as sidestream dark field (SDF) videomicroscopy, which currently requires lengthy offline analysis to produce results. This means that the authors' research question has far-reaching implications for those interested in monitoring microcirculatory behavior in real-time during shock.

The authors tested their hypothesis by comparing standard microcirculatory parameters (3) taken from bedside sublingual SDF imaging with Pv-aCO_2 measurements at the same two time points (at PAC placement—average of 3 h after first hypotensive episode—and then at 6 h subsequently). This study was conducted prospectively over 15 months at a relatively large South American University Hospital intensive care unit (ICU), and included

75 patients with septic shock who had a pulmonary artery catheter (PAC) placed for hemodynamic monitoring. The authors divided the patients into three predefined Pv-aCO_2 categories for analysis (<6.0, 6.0–9.9, and ≥10 mmHg), a decision they attribute to previous observations (4). Their findings elegantly demonstrate that Pv-aCO_2 is strongly associated with microcirculatory function but poorly associated with systemic hemodynamic variables such as mean arterial pressure and cardiac output. Such findings are in keeping with the current concept that microcirculatory parameters are more predictive of tissue oxygenation in a shock state than traditional global parameters (5-7).

Point-of-care is the future: but how?

Part of the rationale for Ospina-Tascón and colleagues' work is the quest to find a simple and effective way of monitoring the microcirculation without having to use traditional bedside monitoring devices such as sublingual SDF, or the newer incident dark field (IDF) imaging (8). This is particularly important because despite recent technological advances, SDF or IDF videomicroscopy are not yet capable of producing immediate objective microcirculatory measurements at the bedside. Instead, the clinician must take the video clips away and meticulously grade them for quality, before using specialized computer software to laboriously and systematically extract the desired parameters from the images. Indeed some video clips may be discarded completely if their quality assessment is not satisfactory. Such a process can be lengthy, and also takes place away from the patient in place and time. Mainstream reporting of microcirculatory parameters are therefore currently confined to research rather than in the clinical capacity. In their argument Ospina-Tascón and colleagues cite a review article written by the senior author (9) which advocates a future in which a goal directed approach to resuscitation may be guided by bedside monitoring, but that none yet exists. In their article, they propose that perhaps Pv-aCO_2 may have a place in the tracking of microcirculatory flow during shock.

We believe that optimism is warranted when it comes to the future of point-of-care microcirculatory monitoring. Recent international efforts have demonstrated that there is good inter-rater reliability and diagnostic accuracy between subjective evaluation and offline analysis of microcirculatory parameters (10). Furthermore real-time qualitative assessment of the microcirculation at the bedside is feasible, and compares well to offline analysis (11). It is therefore feasible (and perhaps even highly likely) that in the near future bedside microcirculatory monitoring may allow for real-time assessment of the microcirculation by trained clinicians either in a continuous manner, or at any desired time-points. Although we agree that Pv-aCO_2 is likely to be a useful adjunct to the understanding of the greater clinical picture, traditional microcirculatory monitoring techniques have an advantage in that the can characterize flow, density, and heterogeneity, giving a greater breadth of targets for goal directed therapy. A disadvantage of Pv-aCO_2 as presented by Ospina-Tascón and colleagues is that it is only defined in three categories: a trichotomy of 'normal', 'abnormal', and 'even worse', which may limit may its clinical and diagnostic utility. Furthermore although the cut-off between 'normal' and 'abnormal' may be considered as 6 mmHg (12), the justification for the higher threshold of 10 mmHg for the worst group is uncertain and is not mentioned in the earlier work they cite (4). We agree with the authors' acknowledgement that if Pv-aCO_2 is to be used in the manner suggested then it would require more detailed examination and validation.

Risks and benefits

Although the drawing of blood may seem less invasive and time consuming than sublingual microcirculation monitoring, a pulmonary artery catheter is still required to obtain these mixed samples, and is not without its own complications (13-15). Conversely there have been no reports of complications from sublingual microcirculation monitoring. Furthermore in modern intensive care practice it is unusual to place PAC catheters purely for systemic hemodynamic monitoring in septic shock. Ideally if such blood tests are to be recommended in the monitoring of microcirculatory behavior, they ought to be readily available with minimal risk of complication. If clinical team decides that there is no indication for a PAC then a risk/benefit analysis may perhaps not be deemed favorable for the monitoring of Sv-aCO_2 outside the context of an ethically approved clinical trial.

Central venous CO_2 saturation ($ScvCO_2$) samples may be obtained from a more commonly placed central venous catheter, and may be just as useful in some circumstances as pulmonary artery samples ($SvCO_2$) (16). However, although the utility of $ScvO_2$ was initially considered to be promising for early goal directed therapy (17), such an approach to resuscitation did not seem to be effective in later studies such as the ProCESS trial (18), ARISE study (19), and ProMISe trial (20). Ospina-Tascón and colleagues report

that Pv-aCO_2 is more sensitive than $ScvO_2$ in detecting microcirculatory derangement, and we agree that further investigation is required. Given the experience with $ScvO_2$, caution should be taken in positioning Pv-aCO_2 as the 'new candidate' in the field of tissue perfusion and a potential target for goal directed therapy.

Limitations of a 'snapshot' approach

Values for Pv-aCO_2 at particular time-points may also be limited in utility by their 'snapshot' nature. In order to track the clinical progress of a patient or microcirculatory reaction to particular interventions, repeated blood draws might be required. Furthermore the clinician must decide at which time-points this is best suited. Ospina-Tascón and colleagues have used the arbitrary T0 and T6 time-points, and further evidence is required before these can be considered relevant to clinical practice. This is particularly important when they report a length of stay in the ICU of 6 (interquartile range, 2–10) days. Further work is required to determine the utility of Pv-aCO_2 in detecting and following changes in the microcirculation during the patient's clinical progression. For example it would be interesting to discover what happens to the Pv-aCO_2 beyond the 6-h time point, and whether it 'normalizes' at the same rate as the microcirculation in patients who make a good recovery. Conversely, does it persist, or deviate from the behavior of the microcirculation, and if so, in what manner?

Sublingual microcirculatory monitoring may offer an opportunity for continuous monitoring, as well as monitoring at the time of an intervention, and at regular intervals, without requiring patient's blood. Previous work has demonstrated the feasibility of repeated measurements at short intervals before, during, and after interventions (21,22). We believe that a combined approach may offer the best information to the clinician managing shock in the future by (I) examining the physical behavior of the microcirculation using point-of-care monitoring, and (II) comparing these parameters to the chemical behavior of the microcirculation by means of carbon dioxide partial pressures. Such an approach may be a more sophisticated version of the older, more conventional blood pressure and serum lactate monitoring during resuscitation in common practice.

Other forms of shock?

Of further interest to our group, would be whether the findings of Ospina-Tascón and colleagues can be repeated in the context of hemorrhagic as well as septic shock. These entities are different in many ways, but recent clinical work has shown that similarly dysfunctional microcirculatory behavior may be present following traumatic hemorrhagic shock (23). The ongoing MICROSHOCK study (ClinicalTrials.gov ID: NCT02111109) is also examining immediate microcirculatory derangement after injury and hemorrhagic shock using sublingual IDF technology, but results are not yet available. Of note, the CO_2 gap is also being recorded for these patients, and would provide information with regards to the effects of hemorrhagic shock rather than septic shock. It seems that regardless of the cause of shock, there is a trend towards a greater understanding of the microcirculatory behavior, and a desire for point-of-care, bedside technology in order to direct resuscitation and improve outcomes for patients with these serious pathologies.

Conclusions

The difference between mixed-venous and arterial carbon dioxide partial pressures appears to reflect changes in microcirculatory function and has the potential to make an impact in the search for clinically relevant target for goal directed therapy. Caution and further investigation are both warranted if this is to be translated into clinical practice. Combined with advances in non-invasive sublingual microcirculatory monitoring, point-of-care, bedside, physical and chemical monitoring of the microcirculation may provide a new paradigm for the targeted resuscitation of patients in shock.

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Footnote

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