Venous-to-arterial carbon dioxide differences and the microcirculation in sepsis

Mui Teng Chua, Win Sen Kuan

Emergency Medicine Department, National University Hospital, Singapore

Correspondence to: Mui Teng Chua. Emergency Medicine Department, National University Hospital, Singapore. Email: mui_teng_chua@nuhs.edu.sg; Win Sen Kuan. Emergency Medicine Department, National University Hospital, Singapore. Email: win_sen_kuan@nuhs.edu.sg.

Submitted Dec 22, 2015. Accepted for publication Dec 24, 2015.
doi: 10.3978/j.issn.2305-5839.2015.12.55
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.12.55

Assessment of the microcirculation has been of particular interest in the management of septic shock for over a decade (1,2). It has garnered more attention in light of conflicting data recently on oxygen-derived parameters in patients with sepsis (3). Microcirculatory dysfunction has been linked to organ failure despite adequate macro-hemodynamic stability (4).The microcirculatory perfusion is regulated by the myogenic, metabolic and neurohumoral systems, which in turn affect the arteriolar tone, driving pressure, capillary patency and hemorheology (4). In septic states, perfusion pressure and deformability of cells are reduced, and arteriolar constriction ensues; the end-result is shunting of blood, bypassing essential areas of capillary exchange (5). These changes debilitate the microcirculation and impede tissue oxygenation, resulting in impaired organ functions. Moreover, with stasis in the capillary bed and inflammatory factors released from injured cells that cannot be cleared due to deficient flow, the microcirculation becomes a nidus for continued bacterial growth and persistent insult, sustaining the toxemia and acidemia.

It has been shown that timely aggressive interventions and treatment with early improvements in organ functions increases the probability of survival (6,7). However, improvement in global hemodynamics, such as mean arterial pressures and central venous oxygen saturations ($ScvO_2$) do not always translate to improved perfusion in the microcirculation (8). Assessment of the microcirculation, through indices such as the microvascular flow index, heterogeneity index and proportion of perfused vessels have been found to be lower in septic patients compared to healthy volunteers, with more marked abnormalities among patients with severe sepsis (9). Sophisticated and novel imaging techniques including the sidestream dark-field imaging and nailfold videocapillaroscopy can allow for direct visualization of the microcirculation at the bedside (1). In spite of that, the use of such imaging techniques requires the availability of expertise and special equipment, which may not be readily accessible in the clinical setting and in acute resuscitation. Furthermore, more trials are required to determine the applicability of these modalities in clinical evaluation and in how it can guide resuscitation goals.

More commonly, biochemical tests such as serum lactate concentration and blood gas levels are performed in routine practice as attempts to evaluate the microcirculation. Actual correlation of these parameters with the microcirculation is fraught with numerous confounders (10). The early goal directed therapy by Rivers and colleagues incorporated measurements of $ScvO_2$ as part of the resuscitation goals (7). However, normal $ScvO_2$ may not be a good indicator of adequate tissue oxygenation as low $ScvO_2$ is neither a common nor consistent finding among critically ill patients (11). In addition, $ScvO_2$ levels may not correlate well with the true value of mixed venous oxygen saturation (SvO_2) (12). The potential of measuring CO_2 as a marker of adequacy of resuscitation has been of growing interest in view of its greater solubility in blood compared to O_2 and hence allowing it to diffuse out to the venous effluent despite the low perfusion state from capillary bed shunting (13). An increase in arteriovenous difference in pCO_2 (normal difference less than 6 mmHg) has been found to reliably reflect tissue hypoxia (14). Conversely, a lower difference has been associated with a higher cardiac index and better lactate clearance (15-17).

Ospina-Tascón and colleagues performed a study that

included 75 patients from a mixed intensive care unit with septic shock to evaluate the adequacy of mixed venous-arterial carbon dioxide difference (Pv-aCO$_2$) in assessing the microcirculatory perfusion during the early stages of resuscitation (18). Data obtained from a sidestream dark-field imaging device to evaluate the sublingual microcirculatory images was correlated with Pv-aCO$_2$. The authors found good agreement between changes in Pv-aCO$_2$ and changes in proportion of perfused vessels (R^2=0.42, P<0.001) at 0 and 6 h (determined by time of pulmonary artery catheter insertion), reflecting the potential of measuring Pv-aCO$_2$ during resuscitation as a surrogate for adequacy of perfusion in the microcirculation. Apart from the changes in proportion of perfused vessels, changes in Pv-aCO$_2$ were also significantly associated with changes in functional capillary density and heterogeneity index. Hence, changes in Pv-aCO$_2$ could potentially provide a good reflection of the state of the tissue perfusion without direct imaging of the microcirculation. Patients with a Pv-aCO$_2$ of more than 6 mmHg despite a normal ScvO$_2$ remain inadequately resuscitated and further interventions such as continued fluid resuscitation or inotropes should be considered to improve tissue perfusion (15).

In the study by Ospina-Tascón and colleagues, Pv-aCO$_2$ did not correlate with cardiac output (R^2=0.01, P=0.45). This finding contrasted with previous experimental models, which showed that Pv-aCO$_2$ is inversely related to cardiac index (17,19,20). The results of this study support the evidence that Pv-aCO$_2$ is related to blood flow variations rather than cardiac output alone (21). Nonetheless, knowledge of the cardiac index in septic patients provides clinicians with an idea of the stroke volume index and guides decision making to optimize cardiac function. It is likely that data from Pv-aCO$_2$ will be complementary to macro-hemodynamic parameters in the global management of patients with septic shock.

The use of mixed venous blood in the study by Ospina-Tascón and colleagues requires blood specimens to be obtained from the mixed venous circulation through a pulmonary artery catheter. The insertion of a pulmonary artery catheter requires expertise, is time-consuming and associated with cardiac complications such as dysrhythmias, valve damage and pulmonary infarction (22,23). It is almost exclusively used in the intensive care units. A study by van Beest and colleagues demonstrated strong agreement between central venous-arterial pCO$_2$ difference and mixed venous-arterial pCO$_2$ difference [intraclass coefficient (ICC) =0.70, P<0.001]; likewise an inverse relationship between central venous-arterial pCO$_2$ and cardiac index (21). However, we are unable to draw any conclusions between the results and the microcirculation due to the post-hoc nature and lack of prospective direct microcirculatory assessment in the study. Nevertheless, the appeal of potentially fewer cardiac complications using a central venous catheter compared with a pulmonary artery catheter coupled with wider generalizability to other areas such as emergency departments should prompt further research in this area (24).

In conclusion, the field of research in microcirculation in septic shock is gaining momentum. The vast majority of research in the management of sepsis has been targeting the macrohemodynamics (7,25-28). Although important, it merely completes one piece of the complicated management jigsaw in sepsis and septic shock. Ospina-Tascón and colleagues have demonstrated very interesting and useful correlations between Pv-aCO$_2$ and direct assessments of the microcirculation. Though not yet ready for prime time, future research should focus on the microcirculation earlier in the sepsis continuum, even before septic shock develops, and its applicability beyond the walls of the intensive care units.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by Guest Editor Zhongheng Zhang, MD (Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. De Backer D, Ospina-Tascon G, Salgado D, et al. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. Intensive Care Med 2010;36:1813-25.
2. De Backer D, Creteur J, Preiser JC, et al. Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 2002;166:98-104.
3. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic

shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med 2015;41:1549-60.
4. Ince C. The microcirculation is the motor of sepsis. Crit Care 2005;9 Suppl 4:S13-9.
5. Hinshaw LB. Sepsis/septic shock: participation of the microcirculation: an abbreviated review. Crit Care Med 1996;24:1072-8.
6. Levy MM, Macias WL, Vincent JL, et al. Early changes in organ function predict eventual survival in severe sepsis. Crit Care Med 2005;33:2194-201.
7. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
8. Dubin A, Pozo MO, Casabella CA, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. Crit Care 2009;13:R92.
9. Spanos A, Jhanji S, Vivian-Smith A, et al. Early microvascular changes in sepsis and severe sepsis. Shock 2010;33:387-91.
10. Vernon C, Letourneau JL. Lactic acidosis: recognition, kinetics, and associated prognosis. Crit Care Clin 2010;26:255-83, table of contents.
11. van Beest PA, Hofstra JJ, Schultz MJ, et al. The incidence of low venous oxygen saturation on admission to the intensive care unit: a multi-center observational study in The Netherlands. Crit Care 2008;12:R33.
12. van Beest PA, van Ingen J, Boerma EC, et al. No agreement of mixed venous and central venous saturation in sepsis, independent of sepsis origin. Crit Care 2010;14:R219.
13. Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please "mind the gap"! Intensive Care Med 2013;39:1653-5.
14. Zhang H, Vincent JL. Arteriovenous differences in PCO2 and pH are good indicators of critical hypoperfusion. Am Rev Respir Dis 1993;148:867-71.
15. Vallée F, Vallet B, Mathe O, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? Intensive Care Med 2008;34:2218-25.
16. Bakker J, Vincent JL, Gris P, et al. Veno-arterial carbon dioxide gradient in human septic shock. Chest 1992;101:509-15.
17. Mecher CE, Rackow EC, Astiz ME, et al. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. Crit Care Med 1990;18:585-9.
18. Ospina-Tascón GA, Umaña M, Bermúdez WF, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med 2016;42:211-21.
19. Teboul JL, Mercat A, Lenique F, et al. Value of the venous-arterial PCO2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. Crit Care Med 1998;26:1007-10.
20. Durkin R, Gergits MA, Reed JF 3rd, et al. The relationship between the arteriovenous carbon dioxide gradient and cardiac index. J Crit Care 1993;8:217-21.
21. van Beest PA, Lont MC, Holman ND, et al. Central venous-arterial pCO_2 difference as a tool in resuscitation of septic patients. Intensive Care Med 2013;39:1034-9.
22. Patel C, Laboy V, Venus B, et al. Acute complications of pulmonary artery catheter insertion in critically ill patients. Crit Care Med 1986;14:195-7.
23. Elliott CG, Zimmerman GA, Clemmer TP. Complications of pulmonary artery catheterization in the care of critically ill patients. A prospective study. Chest 1979;76:647-52.
24. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wheeler AP, Bernard GR, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 2006;354:2213-24.
25. ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683-93.
26. ARISE Investigators; ANZICS Clinical Trials Group, Peake SL,et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371:1496-506.
27. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015;372:1301-11.
28. Kuan WS, Ibrahim I, Leong BS, et al. Emergency Department Management of Sepsis Patients: A Randomized, Goal-Oriented, Noninvasive Sepsis Trial. Ann Emerg Med 2015. [Epub ahead of print].

Cite this article as: Chua MT, Kuan WS. Venous-to-arterial carbon dioxide differences and the microcirculation in sepsis. Ann Transl Med 2016;4(3):62. doi: 10.3978/j.issn.2305-5839.2015.12.55

