Commentary

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Using the diastolic shock index to determine when to promptly administer vasopressors in patients with septic shock

Running title: Diastolic shock index

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Fluid administration and vasopressor support are widely accepted first-line therapies intended to restore sepsis-induced tissue hypoperfusion. The former assumes that absolute or relative hypovolemia is always present during the early stages of septic shock, while vasopressor support is usually reserved for cases in which the initial fluid loading fails to correct hypotension or when arterial pressure is judged to be insufficient to restore tissue perfusion.\textsuperscript{1} The cardiovascular dysfunction observed during septic shock results from complex interactions among hypovolemia, vasodilation, myocardial dysfunction, altered blood flow distribution, and endothelial and microcirculatory dysfunction.\textsuperscript{2} In addition, imbalances among sympathetic, cholinergic, and anticholinergic inflows may affect inflammatory and immunologic responses beyond their direct effects on the heart and vessel walls. Therefore, different pathophysiological mechanisms determine the progression of circulatory failure, tissue hypoperfusion, and altered cell respiration and metabolism in patients with septic shock. These mechanisms evolve differently over time and vary from patient to patient as the septic shock progresses. Thus, while relative hypovolemia is thought to predominate in the very early phases of septic shock, most patients are not deeply hypovolemic; conversely, their cardiovascular failure is widely marked by a loss of vascular tone. Even though these dissimilar mechanisms produce a common profile characterized by hypotension, tissue hypoperfusion, and elevated lactate levels, the management of septic shock should be based on a personalized approach that includes the following: by administering fluids when hypovolemia predominates and fluid responsiveness is documented; by adjusting vasopressor doses when it is judged that vasoplegia is the preponderant mechanism underlying hypotension, thus limiting unnecessary fluid administration; by adding inodilators when myocardial dysfunction is recognized or when hypoperfusion persists despite appropriate fluid resuscitation and attaining adequate pressure levels; by decreasing vasopressor or inodilator doses when dynamic left ventricular outflow tract obstruction is recognized; and by individualizing the mean arterial pressure (MAP) according to levels established prior to the shock episode. In other words, an initial well-conducted resuscitation should be based on individualized signals of tissue hypoperfusion and macrohemodynamic derangements.

A decrease in vascular tone represents one of the leading mechanisms associated with hypotension and tissue hypoperfusion in septic shock,\textsuperscript{3} and it is fundamentally characterized by a
progressively impaired response from the vascular smooth muscle to endogenous circulating and exogenous vasoconstrictors. Classically, a low diastolic arterial pressure (DAP) has been recognized as an indirect sign of vasodilation, although the in vivo assessment of vascular tone (i.e., during dynamic conditions) is not standardized and has been classically based on indirect measurements of vascular resistances.\textsuperscript{4} Under normal conditions, the DAP is mainly determined by vascular tone, and it remains nearly identical from the center to the periphery (i.e., from the ascending aorta to the peripheral vessels).\textsuperscript{5} In contrast, the systolic arterial pressure (SAP) and consequently the MAP may greatly vary from the aorta to the peripheral vessels as long as peripheral arterial elastance varies. Thus, discrepancies in the SAP and MAP from the center to the periphery are expected during vasodilatory conditions, while DAP values remain virtually identical independently from the site in which they are assessed, even in the presence of severe vasodilation. Nevertheless, the operational definitions of different types of septic shock classically include the reduction of MAP and/or SAP, which acknowledges the pivotal role of both MAP and SAP on organ perfusion, in addition to the clinical prognostic value of sustained low MAP during the shock process. Even though the DAP is not considered when categorizing the severity of septic shock, an evaluation of the DAP could have significant clinical implications, especially when the underlying mechanism of shock is vasodilation (as occurs in septic shock).

If the aortic valve is competent, the DAP reflects (to some extent) the vascular tone. However, the DAP should not be evaluated separately from the heart rate (HR) because acute reductions in arterial pressure and vascular tone are compensated for by increases in sympathetic activity, which ultimately will affect the HR. Remarkably, the DAP is influenced by the duration of the cardiac cycle, the blood volume ejected into the aorta, and the overall arterial compliance.\textsuperscript{6} Thus, under isovolemic conditions and constant arterial compliance, a shortening of diastolic times should result in a higher DAP, while prolonged diastolic times would lead to opposite effects.\textsuperscript{6} Consequently, during pathological conditions, simultaneous and divergent variations in the DAP and HR (i.e., a progressively lower DAP combined with more severe tachycardia) should suggest more severe cardiovascular dysfunction, with shorter diastolic times unable to compensate for a DAP decrease as a consequence of the progressive loss of vascular tone. A recent study evaluated the relationships between HR:DAP ratios (i.e., the diastolic
shock index (DSI) recorded just before or at the start of vasopressor support and the clinical outcomes in patients with septic shock. Three important findings were noted: (1) higher DSI values calculated just before or at the start of vasopressor administration were associated with a gradual increase in the risk of death in patients with septic shock; (2) isolated low DAP or high HR values did not clearly identify such a risk; and (3) nonsurvivors evolved with persistently high DSI values and required higher doses of vasopressors and more resuscitation fluids than survivors. In a similar way, a recent retrospective study showed that DSI and lactate values identified patients who were more likely to require a vasopressor in the context of hypotension and suspected infection. Even though these results are in line with previous reports, the usefulness of DSI in clinical practice has not yet been demonstrated.

A recent observational study suggested that the very early administration of vasopressors in septic shock might be associated with better clinical outcomes. The patients subjected to very early vasopressor use in that cohort received a lower volume of resuscitation fluids, exhibited less net fluid accumulation, and had shorter hypotension times. Similarly, in a recently published study, patients with simultaneous increases in their lactate and DSI levels had a lower 28-day mortality risk when vasopressors were initiated very early. In contrast, others have reported opposite results when vasopressors were introduced very early during the resuscitation process, although it is not clear that this difference indicated an effect of the early start of vasopressors or simply reflected the presence of a more severe disease condition. Regardless of whether the immediate introduction of vasopressors was advantageous, it also remains to be determined which patients would benefit the most from this strategy. Intuitively, more prominent beneficial effects of very early initiation of vasopressors should be observed in cases of more severe vasodilation. In line with this hypothesis, septic patients with higher prevasopressor DSI values had significantly better clinical outcomes when vasopressors were administered early, while such an effect was not evident in those with lower DSI values.

In conclusion, even though hypotension and hyperlactatemia are recognized markers of septic shock, resuscitative interventions should be tailored to each individual because different mechanisms are involved in sepsis-related cardiovascular dysfunction. As there are no unequivocal signals that indicate when vasopressor support should be initiated in hypotensive patients with a suspected infection,
surrogates of severe vasodilation should suggest its immediate requirement; therefore, DSI could be a useful tool for this purpose and should be tested in future clinical trials.

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