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EDITORIAL

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Predicting the determinants of volume responsiveness

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Resuscitation from circulatory shock and stabilization of patients following major surgery are important and common problems faced by practicing acute care physicians. In mechanically ventilated patients without significant arrhythmias a pulse pressure variation (PPV) or stroke volume variation (SVV) greater than 15 % is highly predictive of volume responsiveness, defined as greater than 15 % increase in cardiac output (CO) in response to a fluid bolus of 250–500 ml [1, 2]. Similarly, measures of inferior or superior vena caval diameter change during ventilation and the step increase in arterial pressure or CO during transient end-expiratory hold all are also good predictors [3]. Finally, the dynamic change in CO in response to a passive leg raising maneuver is an excellent predictor under most commonly seen clinical scenarios [4]. Although one can easily predict volume responsiveness at the bedside using these and other functional hemodynamic monitoring approaches, none of these parameters explain why a patient is or is not volume responsive.

Cardiovascular state is characterized by performance parameters that encompass cardiac contractility, circulating blood volume, and vascular tone. These, in turn, as originally described by Guyton [5], can be assessed functionally as the effective circulating blood volume, resistance to venous return, and cardiac performance curve. Effective circulating blood volume, which itself is a function of total blood volume, blood flow distribution, and peripheral vasomotor tone, can be approximated as mean systemic pressure (Pms), the upstream pressure driving blood back to the heart from the circulation. That flow, also known as venous return, determines cardiac output, since in steady state conditions the heart must pump all the blood it receives back out and cannot pump any more than it receives. The downstream pressure for venous return is right atrial pressure (Pra). Thus, cardiac output is determined by both this pressure gradient and the resistance to venous return. Maas et al. [6] and Persichini et al. [7] examined at the bedside the effects of changes in norepinephrine infusion rates on cardiovascular state. Both groups showed that both Pms and Pra, their pressure difference (dVR), and the slope of the (Pms − Pra)/CO were altered. Decreasing vasomotor tone not only decreased Pms and dVR but decreased the resistance to venous return, minimizing the expected decline in venous return that would have otherwise occurred if only Pms had decreased. Similarly, increasing vasomotor tone not only increased Pms but also increased the resistance to venous return, minimizing any increase in flow expected by such increased dVR. Importantly, in the Maas et al. study, the ultimate increase or decrease in CO observed in response to the increase in vasomotor tone was the baseline cardiac performance. Thus non-volume-responsive patients decreased their CO, presumably because the increase in arterial pressure-induced left ventricular afterload was a more important determinant of CO than was the increase in Pms. Importantly, in their study, dVR did not increase in the non-responders and

presumably cardiac performance deteriorated in the face of increasing afterload. Thus, the final cardiovascular state created in response to either fluid loading or changes in vasomotor tone is a complex relationship between changes in effective circulating blood volume and cardiac performance.

The classical method for estimating Pms and the resistance to venous return is to measure arterial blood pressure during cardiac arrest. Maas et al. and Persichini et al. used different methods, both based on an estimation of the venous return curve from a beat-to-beat measure of Pra and stroke volume during inspiratory and expiratory holds under positive pressure ventilation [6, 7]. Nevertheless, these later methods are not easy to use in routine practice. If one could assess both effective circulating blood volume and cardiac performance continuously at the bedside then it would be relatively easy to predict a patient's response to specific cardiovascular interventions. Importantly, Parkin and Leaning used a mathematical modeling technique to develop an algorithm for estimating an analogous value of Pms from commonly measured hemodynamic variables without stopping the heart. With this technique, one can accurately and continuously measure Pms, as an analogue construct, referred to as Pmsa [8]. By knowing both Pmsa and Pra, one can define cardiac performance (heart efficiency, Eh) as the ratio dVR/Pms, with a perfect heart having an Eh of 1. Mass et al. [9] reported a poor agreement between Pmsa and Pms but showed that changes in Pmsa could reflect changes in Pms measured by an independent technique. Then Lee et al. [10] subsequently validated, in an animal model, that this dynamic estimate of Pmsa was accurate under conditions of changing intravascular volume and endotoxin-induced changes in vasomotor tone. Finally, using the same algorithm, Cecconi et al. [11] showed that changes in dVR explained the changes in CO seen in postoperative patients in response to fluid bolus challenges.

So can we put these concepts together into a single analysis? The study by Gupta et al. [12] in a recent issue of *Intensive Care Medicine* attempts to do just that. Using the Parkin and Leaning Pmsa and Eh calculations, they described the CO changes of 61 cardiac postsurgical patients in response to 107 fluid boluses. They showed that patients with volume responsiveness, defined by an increase in CO of at least 10 %, were characterized by higher Eh than non-responders. The authors confirmed the results of Cecconi et al. [11] by showing that the increase in CO during volume expansion was accompanied by an increase in dVR that could be evidenced by the mathematical modeling algorithm. Note that this is not surprising since, with this algorithm, Pmsa is computed from CO itself. Furthermore, when traditional measures of cardiac performance, like cardiac power (CPvol), defined as the product of stroke volume and developed pressure divided by Pmsa [13], was also measured, lower CPvol, describing an under-filled heart, predicted volume responsiveness. Nevertheless and again, this result is marred by the fact that CPvol was estimated from CO. Since CO was lower in responders than in non-responders before fluid bolus, the fact that it was also the case for CPvol is not surprising. Thus, the findings of Gupta et al. should be compared with a technique estimating Pms by a method independent of CO measurement. Nevertheless, this new study supports the findings of Mass et al. [6] and is consistent with those of Persichini et al. [7] and Cecconi et al. [11].

So where do we go from here? Is it enough to show that bedside assessments of cardiovascular state can be made, should we incorporate these assessments into routine bedside care, or incorporate such "advanced" analytics only in those difficult to diagnose or manage patients who do not respond as predicted? There really is no right answer. The main interest of assessing venous return in critically ill patients, as illustrated in the study by Gupta et al. [12], is to provide us with a comprehensive understanding of the individual patient's pathophysiology during circulatory failure and its response to treatments. Although knowing that patient responses follow measurable physiological parameters in a predictable fashion may be comforting to the novice clinician and useful to illustrate patient responses during bedside teaching, will it affect patient outcome? If the results of the two recent early goal-directed therapy in sepsis trials are any indication, probably not. Presently, the usefulness of these measures could reside in the province of the difficult to manage patient whose responses behave in an unpredictable fashion or in whom the cardiac and peripheral vascular components of their instability remain unclear but opposite treatments need to be given if the diagnosis is either one or the other. Still, considering the relative ease in continuous bedside measures of Pmsa, Eh, and CPvol, it would be interesting for critical care professionals to be cognizant of the techniques that allow their calculation and how they change in response to disease progression and treatment. The way in which it could modify a patient's evaluation and management is to be defined.

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Conflicts of interest XM is a member of the Medical Advisory Board of Pulsion Medical Systems. MRP is a member of the Medical Advisory Board of LiDCO Ltd, Masimo Inc, received honoraria for lectures from Masimo Inc, and an institutional grant from Edwards LifeSciences.

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