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Defining the boundaries of preload responsiveness at the bedside

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Sustaining blood flow to the body in disease states without causing untoward effects on the circulation is often a difficult problem, especially when the primary determinants of cardiovascular homeostasis are the reasons for treatment. A fundamental therapeutic option in resuscitating patients in circulatory shock is to infuse fluids with the goal of increasing venous return and thus cardiac filling. However, fluid responsiveness may not be related to deficits in intravascular volume if the cause of circulatory shock is primarily due to cardiac pump failure. If fluid loading is done in heart failure patients, life-threatening acute cor pulmonale or pulmonary edema may rapidly develop. Similarly, vasodilatory states, like severe sepsis, are often associated with expanded intravascular volume despite the fact that most of these patients remain fluid responsive. How then does the bedside pediatrician determine if the critically ill patient is volume responsive and when additional fluids, if infused, will be deleterious? Presently, there are two parallel approaches that can be taken to assess preload responsiveness and the risk of fluid overload: using functional hemodynamic monitoring parameters (1) and volumetric analysis (2), respectively.

Preload responsiveness is defined as a state in which increases in right ventricular (RV) and/or left ventricular (LV) end-diastolic volume (EDV) result in an increase in stroke volume (SV). Under normal conditions most subjects are preload responsive over the normal range of RV and LV EDVs. Alternatively, one can estimate volumetrically global EDV (GEDV) by transpulmonary indicator decay. GEDV is often used as a surrogate for cardiac preload because GEDV includes both RV and LV volumes.

Recent studies in children have validated the robustness of functional hemodynamic monitoring approaches like positive-pressure ventilation-induced variations in arterial pulse

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pressure or LV stroke volume or changes in cardiac output (CO) in response to a passive leg raising maneuver as predictive of volume responsiveness (3). Variations in arterial pulse pressure, SV or CO of greater than 10-15% connote volume responsiveness (4,5). With the advent of simple on-invasive echocardiographic and plethysmographic tools, these parameters are within the reach of most pediatric intensivists. Still, it would be useful to also know the degree to which absolute preload varies, because it is closely linked to total thoracic blood volume and the propensity to develop pulmonary edema. Still, there must be relation between GEDV and fluid loading as CO varies during resuscitation,

Presumably, the transition from preload-responsive to preload-non-responsive during the course of resuscitation reflects dilation of the heart to a point above which increasing EDV no longer results in increasing SV, otherwise referred to as the “flat part” of the SV to EDV (Frank-Starling) relation. Whether the Frank-Starling relation is truly flat or merely reflects the pericardial restraint limiting absolute GEDV is probably less important than knowing at cardiac function has optimal filling. Importantly, how changes in GEDV reflect the potential for edema formation is not known.

Although the Frank-Starling relationship of cardiac output responses to fluid resuscitation is simple in concept, can this physiologic construct be applied at the bedside? Meaning, can one predict maximal GEDV values above which fluid resuscitation should be limited? To address this question directly, de la Oliva et al. in this issue of Pediatric Critical Care Medicine (6) measured not only the changes in SV and CO in a broad series of critically ill pediatric patients, but also calculated GEDV and its change along with the baseline cardiac status of 73 pediatric intensive care unit patients from 7 Spanish University Medical Centers (6). They divided their cohort into three groups: normal cardiovascular status, cardiovascular dysfunction and dilated cardiomyopathy. All patients were instrumented with a transpulmonary (central venous and arterial catheters) arterial pulse contour device (PiCCO₂) that allowed estimates of SV, cardiac output, GEDV, extravascular lung water (EVLW). Furthermore, in a 40-patient subset they measured these parameters pre and post a fluid challenge. Importantly, they found that in young children GEDV values increased as a power-law function of body surface area (BSA). Based on these data, a “normal” pediatric GEDV indexed to BSA (GEDVI) is $488.8 \cdot \text{BSA}^{0.388}$. Thus, the pediatric literature now has a reference GEDV to BSA to apply in future studies. Using this “normal GEDVI (GEDVI_N) as a reference, they divided GEDV from low to high at 0.67, >0.67 but 1.33, >1.33 but 1.51 and >1.51 times GEDVI_N. When the preload responsiveness was then assessed as the SV/GEDV slope for these normalized quartiles they observed the greatest gain (i.e. most fluid responsive) in the lowest quartile (i.e. 0.67 times GEDVI_N) with SV increases be less in the next two higher GEDVI_N quartiles and no increase in SV in the highest quartile independent of whether the patients carried the diagnosis of normal or dysfunctional cardiovascular function. Not surprisingly, no dilated cardiomyopathy patients were in the lowest GEDVI_N quartile, and their absolute SV and increase in SV with volume loading were less than the other patient groups. SV did not increase with volume loading above a GEDVI >1.51 times GEDVI_N. Finally, as GEDVI_N increased, EVLW also increased in all subjects reaching levels consistent with pulmonary edema >1.51 times GEDVI_N. If proven correct in other studies, these data support the clinical practice of limiting fluid resuscitation to only those critically ill patients whose GEDVI is <1.51 times

GEDVI_N and possibly if the risk of pulmonary edema is greater, as in acute lung injury states to a GEDVI less than 1.33 times GEDVI_N.

Thus, recent studies in the pediatric literature (3) have shown that functional hemodynamic monitoring can accurately predict volume responsiveness, increasing preload correlates with increasing lung water and that reference GEDV values exist to predict volume responsiveness and set as limits to fluid resuscitation. The above study is interesting and worthy of considering into the diagnosis and management critically ill pediatric patients. However, like all studies, this one has several limitations that restrict the development of guidelines based on its findings. First, the only intervention studied was a volume challenge, not changes in vasomotor tone or inotropy, both of which can alter the Frank-Starling relationship. Thus, should patients with a GEDVI >1.33 times GEDVI_N be given afterload reduction and/or increased inotropy as their primary therapy? The results of this study do not address this question. Second, in the setting of acute lung injury the relation between GEDVI/GEDVI_N and EVLW is unknown but most likely shifted to a greater gain in EVLW for the same GEDVI. Furthermore, the relation between GEDVI/GEDVI_N and hydrostatic pulmonary capillary pressure, the primary pressure driver of pulmonary edema formation is unknown, but probably non-linear. Thus, measuring GEDVI and referencing it to GEDVI_N may be useful but the safety thresholds it will carry across patient groups may vary widely and needs to be studied. Finally, the measures of GEDV and EVLW require a high degree of invasiveness, including the insertion of both a femoral arterial and central venous catheter and having a transpulmonary thermodilution monitoring device available. Although several FDA-approved devices exist to make these measurements, arterial catheterization in the very young carries its own risks that may offset any benefits caused by closer titration of fluid therapy.

At the end of the day, we are one-step closer to understating cardiovascular physiology at the bedside. Still, we need additional validation studies of these measures in other centers and associated with more diverse patient groups (e.g. trauma, sepsis) and complex interventions (e.g. fluids plus inotropes). But perhaps most importantly the field is in desperate need of clinical trials of rational treatment approaches that use these measures in their decision algorithms, either to stratify therapies or as starting and stopping rules, and then see if by a closer titration of appropriate fluid resuscitation patient centered outcomes improve.

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