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LASTING LEGACY IN INTENSIVE CARE MEDICINE

The prediction of fluid responsiveness

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During the cholera epidemics in the nineteenth century, intravenous fluid infusion was observed "to restore the blood to its natural specific gravity and to restore its deficient saline matters" in the blue stage of spasmodic cholera [1]. It then became clear that fluid therapy during shock is aimed at increasing cardiac output (CO), ultimately improving tissue oxygenation. However, during the 1980s, authors measuring the effects of fluid boluses on CO, found that it remained unchanged in roughly 50% of the patients [2]. In fact, they observed at the bedside a physiological reality: the relationship between CO and preload has a variable slope, depending on the preload level and, for a given preload, on ventricular contractility (Fig. 1A). In the 1980s, the concept of predicting fluid responsiveness before infusing fluids arose. For years, the central venous pressure (CVP) and other markers of cardiac preload have been used to guide the decision of administering a fluid bolus (Fig. 1B). Regrettably, many studies then and afterward showed that, on average, these static markers of preload do not indicate the slope of the Frank-Starling curve [3].

Methods to determine fluid responsiveness

The focus then shifted toward avoiding fluid infusion in patients who did not need it while aggressively infusing it to those that did. Instead of the ineffective "static" preload variables (e.g., CVP), a dynamic approach was considered [5] in which cardiac preload was transiently altered by simple maneuvers, and their effect on stroke volume (SV) or any surrogate was assessed. Patients in whom they changed significantly were considered preload responsive (Fig. 1A).

The time-honored method to define volume responsiveness was the fluid challenge, i.e., to rapidly infuse 300–500 mL of fluid and assess if CO increased $\geq$ 15%. However, if repeated in non-responsive subjects, such challenges carry the potential risk to induce volume accumulation for which fluid removal may be later needed [6]. At the same time, the evidence was increasing that a positive fluid balance independently predicted mortality, especially during septic shock [7].

The first method that allows the prediction of fluid responsiveness without infusing a drop of fluid took advantage of heart–lung interactions. The respiratory variations in systolic arterial pressure in ventilated patients had been shown to be related to central blood volume. However, the calculation of the Δup and Δdown parts of this variation during apnea had many drawbacks and did not gain popularity. In 2000, Michard et al. demonstrated that during controlled mechanical ventilation, the respiratory pulse pressure variation (PPV), a reflection of SV variation (SVV), detects fluid responsiveness [8] (Fig. 1B). Subsequently, numerous studies confirmed the validity of PPV, while others described various surrogates for SV, whose respiratory variability predicts fluid responsiveness.

However, the numerous limitations of PPV soon became apparent. Spontaneous breathing, arrhythmias, lower tidal volumes (Vt) used in acute respiratory distress syndrome and low pulmonary compliance, increased intra-abdominal pressure generate false positives and negatives [9], making PPV and SVV unusable in many patients with cardiovascular insufficiency. In 2004, changes in the inferior vena cava diameter were reported to predict fluid responsiveness [10, 11]. Unfortunately, superior and inferior vena cava distensibility share many limitations with PPV, and have limited predictive value [12].

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Fig. 1 *Panel A:* Tests and indices of preload responsiveness. The principle of the dynamic assessment of preload responsiveness is to observe spontaneous or induced changes in cardiac preload, and the resulting change in cardiac output, stroke volume or their surrogates. Some tests or indices use heart–lung interactions in mechanically ventilated patients, while some other mimic a classical fluid challenge. Diagnostic threshold and year of description are indicated. *CO cardiac* output, *PPV* pulse pressure variation. *Panel B:* Chronology of the main findings in the field of fluid responsiveness. *PPV* pulse pressure variation, *SVV* stroke volume variation. *Panel C:* Relationship between fluid responsiveness and fluid tolerance and the risk for fluid accumulation. Fluid tolerance can be defined as the degree to which a patient can tolerate administration of fluids without causation of organ dysfunction, and it fills in the continuum between fluid (un)responsiveness and fluid accumulation and overcomes their inherent limitations. It balances the focus from the downstream (i.e., organ perfusion) to upstream (i.e., venous congestion) impact of fluids during the resuscitation phase [4]. This may allow clinicians to potentially modify their strategy and provide a more personalized and individualized fluid resuscitation and de-resuscitation approach

The passive leg raising (PLR) test was applied to circumvent the limits of PPV. The postural change, which was used for years in patients falling in collapse, transiently transfers blood from the lower extremities and the splanchnic territory (~300 mL), increasing cardiac preload. In 2006, its ability to detect preload responsiveness was demonstrated, including in conditions invalidating PPV [13]. Since then, it has been widely validated.

Following PPV and SVV, other tests then explored the idea of using heart–lung interactions during mechanical ventilation, i.e., manipulating cardiac preload by changing the alveolar pressure and observe the effect on CO. The end-expiratory occlusion test, consisting of temporarily stopping the drop in preload caused by insufflation, was described in 2009 [14]. In 2017, the Vt challenge, a transient increase in Vt from 6 to 8 mL/Kg whose effects are assessed on PPV, was developed to circumvent its limitation in case of low Vt [15]. The respiratory systolic variation test, or the hemodynamic effects of sigh maneuvers are also based on cardiopulmonary interactions.

In 2011, considering potential fluid overload induced by the "classical" fluid challenge, Muller et al. demonstrated that a "mini-fluid challenge," with only 100–150 mL of fluid, also predicts volume responsiveness with less risk for fluid accumulation [16]. It has already been reasonably validated.

Clinical validation

In their initial description and validation, many tests and indices of volume responsiveness were judged relative to precise CO measurements. However, CO monitoring may be difficult to routinely use, and is both expensive and invasive. Subsequent studies focused on using non-invasive CO estimates to monitor heart–lung interaction tests and PLR maneuvers. For example, for the PLR test, many non-invasive monitoring techniques may replace invasive CO measures, such as capnography, plethysmography, bioreactance or simple changes in PPV [9].

Also, the place of the fluid responsiveness prediction has been defined: useless in patients with obvious fluid losses, it is useful in patients at risk of fluid accumulation. Positive fluid responsiveness tests should only lead to fluid infusion if CO is considered too low. This should be assessed on organ function and markers of tissue hypoxia depending on the patient's condition. The decision to administer a fluid bolus must not only be based on the presence of fluid responsiveness, but also the risk of fluid accumulation or thus fluid intolerance (Fig. 1C). It must also be reminded that the ultimate goal of fluid infusion is not to increase CO but to improve tissue oxygenation, which occurs inconstantly even in fluid responders [17]. Finally, the effects of a fluid bolus on CO are transient [18] and fluid responsiveness changes over time [19]. It should therefore be reassessed frequently.

The question is often asked about the relevance of these tests and indices in terms of prognosis. In the perioperative field, protocols guiding fluid loading based on preload responsiveness have shown to reduce complication rates. In critical care, the demonstration is much more difficult, because many factors influence prognosis. However, the implementation of preload responsiveness tests during septic shock has been demonstrated to reduce the total fluid balance [9].

Take-home message

Predicting fluid responsiveness was born from a double observation, namely that fluids are both harmful and inconstantly effective. Assessing fluid responsiveness allows one to avoid the administration of a deleterious treatment to patients who do not need it, and give it when needed [5]. Using these dynamic measures in the most severely ill patients walks the tightrope between aggressive restoration of CO and fluid overload, allowing for truly personalized treatment [20].

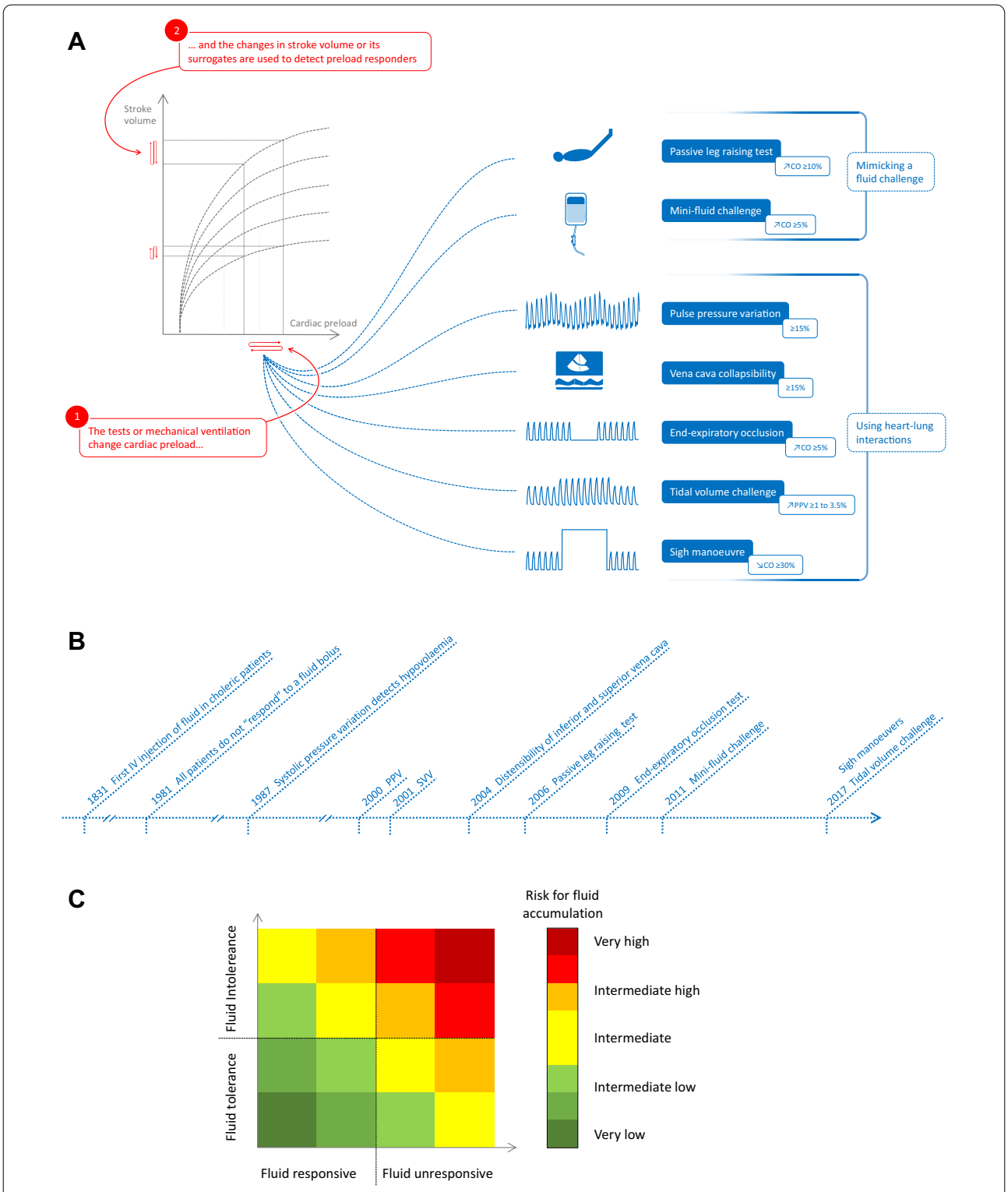

Fig. 1 (See legend on previous page.)

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Declarations

Conflicts of interest
XM is a member of the medical advisory board of Pulsion Medical Systems-Getinge, received limited research grants from Getinge, received honoraria for scientific lectures from Getinge and Baxter. MLNGM is co-founder, past-President and current Treasurer of WSACS (The Abdominal Compartment Society, http://www.wsacs.org). He is member of the medical advisory Board of Pulsion Medical Systems (part of Getinge group), Serenno Medical, Potrero Medical, Sentinel Medical and Baxter. He consults for BBraun, Becton Dickinson, ConvaTec, Spiegelberg, and Holtech Medical, and received speaker's fees from PeerVoice. He holds stock options for Serenno and Potrero. He is co-founder and President of the International Fluid Academy (IFA). The IFA (http://www.fluidacademy.org) is integrated within the not-for-profit charitable organization iMERiT, International Medical Education and Research Initiative, under Belgian law. MRP received NIH and DoD funding, consultant to Baxter Medical and Edwards Lifesciences.

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