The emerging concept of fluid tolerance: A position paper

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A B S T R A C T
Fluid resuscitation is a core component of emergency and critical care medicine. While the focus of clinicians has largely been on detecting patients who would respond to fluid therapy, relatively little work has been done on assessing patients’ tolerance to this therapy. In this article we seek to review the concept of fluid tolerance, propose a working definition, and introduce relevant clinical signals by which physicians can assess fluid tolerance, hopefully becoming a starting point for further research.

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1. Introduction

Fluids are the first-line resuscitation intervention in septic shock [1], aiming at restoring tissue perfusion by effectively increase cardiac output (CO) and oxygen delivery (DO2). However, resuscitation fluids can be considered as a double-edged sword [2], since they have a narrow therapeutic index [3]. On the one hand, insufficient fluid administration can perpetuate hypoperfusion, while excessive administration can determine increased organ dysfunction and morbidity.

Throughout the years, many strategies have been developed to optimize fluid resuscitation, including targeting better resuscitation goals [4,5], restrictive fluid strategies [6], early use of vasopressors [7,8], and guiding fluid administration through systematic fluid responsiveness assessment [9]. However, few strategies have addressed the impact of fluids on the venous side, that may lead to congestion and organ dysfunction. Even though fluid overload has been recently described as a separate entity [10], there is still a knowledge gap in the relationship between acute fluid resuscitation practices [11] and fluid-induced harm. In fact, even in fluid responsive patients, fluid administration could be detrimental, depending on the specific clinical scenario. The emerging concept of fluid tolerance may provide a novel and necessary framework to balance risk and benefits of fluid resuscitation and personalize clinical care.

In this position paper we intend to (1) propose an operational definition for fluid tolerance, (2) explore the relationship between the concepts of fluid responsiveness, fluid overload and fluid tolerance (3) identify the most vulnerable organs to fluid induced harm in a fluid intolerance context and (4) propose some research priorities on this subject.

2. Relevant definitions

Fluid responsiveness (FR) refers to a set of bedside tests that reversibly increase the preload status of the heart, allowing the clinician to assess if this manipulation determines a significant increase in CO [12-14]. Thus, FR assessment allows the administration of fluids only to those patients who will have a higher probability of CO increase. Even though this strategy to guide fluid resuscitation has been endorsed by current guidelines [1,15] and integrated into resuscitation algorithm [16], as a tool to increase flow in the arterial side of the circulation, it remains blind to venous congestion and its impact on organ dysfunction is unconsidered. Also, probably due to an oversimplification of physiology, a positive FR status has evolved into a triggering signal for almost obligatory fluid loading in patients with acute circulatory insufficiency. Under that perspective, attaining a fluid-unresponsiveness status in the resuscitative phase of shock has essentially become a desirable endpoint, neglecting potential side-effects [17].

It is commonly agreed that fluid overload is a state of global body accumulation after fluid resuscitation [3,18,19]. It is a key determinant of weaning failure and is associated with higher morbidity and mortality.
in critically ill patients [20]. Fluid overload has been operationally defined as the increase of > 10% of fluid accumulation, defined by dividing the cumulative fluid balance by the patient’s baseline body weight and multiplying by 100 [10]. However, it is not difficult to see how this definition is too coarse to grasp the full array of consequences, many of them unnoticed to clinicians, of the excess of fluid administration when considering organ and tissue function at a deeper level [19]. On the other hand, as an eminently retrospective diagnosis, it does not allow its timely recognition during the resuscitation period, missing a crucial window of opportunity.

Fluid tolerance, on the other hand, can be defined as the degree to which a patient can tolerate administration of fluids without causation of organ dysfunction. Fluid tolerance comes to fill in the continuum between fluid responsiveness and fluid overload and overcome their inherent limitations (Table 1). It balances the focus from the downstream (i.e., organ perfusion) to upstream (i.e., venous congestion [21]) impact of fluids during the resuscitation phase. This may allow clinicians to potentially modify their strategy and provide a more harmonic resuscitation.

### 2.1. Identifying determinants of fluid tolerance

What determines fluid tolerance? Multiple factors can impact on the ability of each organ to accommodate or handle fluids. Non-modifiable factors include age, comorbidities (i.e. structural heart disease or chronic pulmonary disease), and the severity of the initial circulatory dysfunction, among others. On the other hand, hit-related factors, such as capillary leak, inflammation, endothelial and glycolalynx dysfunction [22-25], and adequacy of the initial resuscitation, are potentially modifiable determinants.

The concept of fluid tolerance tries to encompass the various compartments and organs according to their level of dysfunction-related congestion [21]. While the lung is the most commonly thought of organ in terms of congestion [26-29], it is important to look beyond the left-sided heart and include any area where the effects of inflammation/capillary leak and/or right-heart dysfunction may impact organ function. At the same time, we must agree that it is practically impossible not to see some degree of fluid leakage in the acute phases of resuscitation, probably directly related to the primary hit characteristics and the magnitude of the inflammatory response with the individual phenotypes in play.

The concept implies the ability of different organs and compartments to maintain function without exhibiting evident dysfunction or failure, and that this tolerance to fluids is not the same for all. In general, biomarkers or clinical signs of organ dysfunction appear at a certain level or degree of injury which is unknown for many organs (i.e. liver, gut or kidneys) [3,19,30]. An example is the development of stress biomarkers preceding overt kidney injury [31]. Classic markers of organ dysfunction such as in the SOFA score are somehow late expressions of overt dysfunction [32].

### 2.2. Clinical assessment of fluid tolerance

It is not just fluid overload in net volume terms which matters but, when approaching a patient after resuscitation, it is imperative to look for signs of fluid intolerance. This assessment should be sequential, multimodal and comprehensive since subtle signals will point out to variable degrees of undesirable and deleterious effects of fluid resuscitation. It should include patients’ history, physical examination, radiographic examination and point of care ultrasound (POCUS). The latter is a vast field, particularly cardiovascular ultrasound, and is beyond the scope of this position paper, but will be addressed in a subsequent article.

We propose that the following organ systems are the most likely to suffer from fluid overload and need to be at the forefront of clinicians’ assessment of fluid tolerance. The signs mentioned below are not exhaustive but rather examples of what could be done.

1) **Pulmonary:** oxygen requirements, lung ultrasound (B-lines), pleural effusions, elevated pulmonary capillary wedge pressure or echographic signs of elevated left atrial pressure.

Patients with any form of oxygenation compromise should be thoroughly assessed for pulmonary congestion. Infectious and inflammatory processes will result in a greater degree of pulmonary capillary leakage that is often much below the commonly quoted threshold of 18 mmHg of pulmonary capillary wedge pressure from the heart failure literature [33]. We oppose the practice of performing tracheal intubation and mechanical ventilation to ensure guideline-directed volumes of fluid resuscitation [34].

Assessment should likely combine physical examination which should be focussed on the work of breathing, along with radiographic evidence of substantial pulmonary involvement, echographic signs of pulmonary congestion (pleural effusions, B lines) or of elevated left atrial pressure.

One should probably also estimate the degree of likelihood of progression to the next level of respiratory support. For example, a patient requiring 3 or 4 l of oxygen per minute via nasal cannula may be able to tolerate some fluid before needing to go onto non-invasive ventilation. However, a patient who is already on non-invasive ventilation with a high FiO2 is likely very close to needing tracheal intubation. A certain degree of bedside clinical gestalt needs to be applied here.

2) **Cardiovascular - lack of fluid responsiveness, D-shaped septum, right to left ventricular (RV:LV) ratio > 1, markers of either systolic or diastolic dysfunction, etc.**

Thanks to the concept of functional hemodynamic monitoring, tightly linked to cardiopulmonary interaction, the assessment of fluid responsiveness has been advocated as an important and essential duty in the early phases of resuscitation. Many tests have been developed and validated for identifying this state [12]. As mentioned above, fluid

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**Table 1**

Key characteristics of fluid responsiveness, fluid tolerance and fluid overload concepts.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluid responsiveness</th>
<th>Fluid tolerance</th>
<th>Fluid overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Increase on cardiac output ≥10% after preload incrementation by manipulation of venous return in a dynamic test context.</td>
<td>Fluid tolerance is the degree to which a patient can tolerate administration of fluids without causation of organ dysfunction.</td>
<td>A state of global body accumulation of fluids after resuscitation with a deleterious impact on organ function.</td>
</tr>
<tr>
<td>When to use</td>
<td>During resuscitation</td>
<td>During resuscitation</td>
<td>After resuscitation</td>
</tr>
<tr>
<td>Adequate use</td>
<td>Increase CO through a fluid challenge in FR+ patients to resolve hypoperfusion</td>
<td>Modify resuscitation strategy (vasopressors, other types of fluids, etc.)</td>
<td>Prompt de-resuscitation</td>
</tr>
<tr>
<td>Inadequate use</td>
<td>Consider fluid responsiveness as a mandatory trigger for fluid administration, irrespective of tissue perfusion status</td>
<td>Assume that fluid intolerance only occurs in fluid unresponsive patients</td>
<td>Inadequate timing or intensity of de-resuscitation</td>
</tr>
<tr>
<td>Limitations</td>
<td>Not assessable in all patients and technical challenges</td>
<td>Theoretical construct, not clinically validated yet</td>
<td>Retrospective diagnosis; still lack of evidence on how to best de-resuscitate</td>
</tr>
</tbody>
</table>

**CO:** cardiac output; **FR+:** fluid responsive.
responsiveness has evolved into a triggering signal or, sometimes, a sort of “license” for fluid loading, with the aim of not falling short from flow and DO2 requirements in patients with acute circulatory insufficiency. Thus, attaining a fluid-unresponsiveness status in the resuscitative phase of shock, as stated earlier, becomes a de-facto endpoint [17]. Nevertheless, from the cardiovascular perspective it is an early sign of fluid intolerance, and perhaps the most unambiguous one. In addition, the status of fluid responsiveness before starting intensive care unit (ICU) based resuscitation may be relevant. Almost 25% of the patients enrolled in a recent randomized controlled trial (RCT) were already FR negative after being admitted to the ICU (after only receiving a median of 24 ml/kg of fluid loading in pre-ICU settings) and were resuscitated by other means with similar target achievement as those FR+ [9].

From a cardiac standpoint, more classic physical examination signs of elevated venous pressures such as a high JVP, peripheral oedema, auscultatory abnormalities such as murmurs and adventitious sounds should all point to limited fluid tolerance. Bedside ultrasound assessment could further refine this and include signs of chronic morphologic abnormalities [35,36], diastolic dysfunction, right or left systolic ventricular failure [37-39], as well as abnormalities in splanchnic venous flow patterns (i.e. venous excess ultrasound score - VExUS [21]). Some of this information could be obtained at the bedside or from recent formal echocardiographic examinations, since chronic abnormalities need to be factored into the tolerance “equation.” Among dynamic tests that may also be predictive of fluid intolerance is the change in CVP after the release of positive pressure ventilation during a spontaneous breathing trial (SBT). A rapid (2 min) raise in CVP has shown to be associated with weaning failure [40]. All in all, the tools, their advantages and pitfalls for a purposeful identification of fluid intolerance are still a matter of research and development.

3) Cerebral - acute injury

Data on how venous congestion might affect the brain are scarce. However, the characteristics of this vital organ located within the non-expandable cranium may make it vulnerable to increases in venous outflow pressure. Some reports in trauma highlighted the impact of abdominal compartment syndrome (ACS) on intracranial hypertension (ICH), and even showed that decompression of the abdomen was associated with a decrease in intracranial pressure [41].

Other studies suggest that venous congestion after cardiac arrest or a positive fluid balance after shock resuscitation may be associated with cognitive dysfunction such as delirium [42]. The association of portal flow pulsatility with cognitive dysfunction in patients undergoing cardiac surgery was recently demonstrated by Benkreira et al. [43].

4) Abdominal – any pathology causing elevated pressure going towards ACS such as pancreatitis, severe ileus, intra-abdominal or retroperitoneal hematomas, bowel edema of any etiology.

Abdominal compartment syndrome and its sequelae have been well described [44,45]. Aggressive fluid resuscitation can exacerbate this, as
has been described in severe pancreatitis, a condition where it has long been considered a mainstay of therapy - a recommendation by the American College of Gastroenterology - despite the lack of evidence supporting it [46-48].

Clinicians should be aware of this in their physical examination and should not hesitate to measure intra-abdominal pressure and manage accordingly, and especially when considering and targeted to appropriate physiological endpoints. The septic patient should not hesitate to measure intra-abdominal pressure and supporting it [46-48].

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Oliguria and creatinine rise are late and easily recognizable markers of renal injury and are actually part of AKI definitions. Nevertheless, overt dysfunction is commonly preceded by a spectrum of early warning signals suggesting the presence of venous congestion-related renal injury, such as ultrasound measurements and stress biomarkers [21,31,49].

Different phenotypes that may arise in clinical practice are illustrated in Fig. 1. The most important to recognize is the one who is fluid responsive, but not fluid tolerant (1C), as this patient will be harmed by a fluid responsiveness-based strategy. It is also important to realize that the phenotypes can change in the course of the patient’s illness. Four clinical examples representing each phenotype are shown in the supplemental digital content 1.

2.3. Areas of uncertainty and future research

We clearly don’t know the precise pathway leading from excess fluid administration to organ dysfunction. Is this initially a microcirculatory problem where a drop in local driving pressure due to an increase in backward venous outflow pressure triggers microcirculatory dysfunction and thus jeopardizes cellular oxygenation? Or rather a venous congestion problem at least in organs such as the kidneys and the liver (more vulnerable to venous congestion), a process that could decrease organ perfusion by increasing organ-specific afterload? Perhaps several mechanisms coexist.

On the other hand, it is obvious that overt organ dysfunction related to fluid intolerance should be preceded by signs of circulatory venous strain that may be signalled by hydraulic parameters in the venous side. Among these, changes in CVP, lung and abdominal ultrasound signs [50,51] and extravascular lung water indexes [29] may have a role, but the exact link between severity of hydraulic and organ dysfunction signals is unknown. Moreover, they provide a set of early warning signals that can be identified during the resuscitation process, conforming a potential window of opportunity for clinicians to develop more rational resuscitation strategies (Fig. 2).

Future studies should aim at answering these and other relevant questions regarding the concept of fluid tolerance. A rich research agenda around this concept can be drawn, including the relationship of fluid tolerance signals with biochemical and clinical outcomes; relationship between fluid tolerance, fluid responsiveness and flow responsiveness; relative weight of organ-specific signals of fluid tolerance on the prediction of outcomes; construction of clinical scoring systems, and finally, assessing the impact of the integration of fluid tolerance on the clinical decision-making process in outcome studies. Thus, integrating these concepts should allow the clinician to tailor the “best hemodynamic suit” for the patient, improving tissue perfusion and avoiding congestion.

3. Conclusion

There is sufficient evidence in the literature to assert that fluid overload and venous congestion contribute to poor clinical outcomes in a
number of clinical scenarios, notably in shock resuscitation. Despite this, the focus of most clinicians today remains squarely on forward flow, meaning cardiac and macrocirculatory parameters, with little or no attention paid towards venous congestion, microcirculation or the relationship to organ function. The novel concept of fluid tolerance may aid clinicians in developing more rational resuscitation strategies, optimizing tissue perfusion while avoiding congestion.

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Appendix A. Supplementary data

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References


