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Short Communication

How to implement the recent Surviving Sepsis Campaign Guidelines at the bedside? A focus on initial fluid resuscitation

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Learning objectives

In order to use the recommendations for the management of patients with sepsis and septic shock as summarized in the Surviving Sepsis Campaign Guidelines (SSCG) one must fully understand the limitations of preload assessment with central venous pressure (CVP). Barometric preload indicators like CVP or the pulmonary artery occlusion pressure (PAOP) can indeed be erroneously increased in situations of increased intrathoracic pressure (ITP) as is seen with high positive end-expiratory pressure (PEEP) application or high intra-abdominal pressure (IAP). Chasing a CVP of 8 to 12 mmHg may lead to under-resuscitation in these situations. On the other hand, a low CVP does not always correspond to fluid responsiveness and may lead to over-resuscitation. When giving fluids during the initial resuscitation phase it is also important to assess fluid responsiveness with either a passive leg raising (PLR) manoeuvre or an end-expiratory occlusion (EEO) test. The use of functional hemodynamics with stroke volume variation (SVV) or pulse pressure variation (PPV) may further help to identify patients that will respond to fluid administration. Furthermore, ongoing fluid resuscitation beyond the first 24 hours guided by CVP may lead to futile fluid loading. In patients that do not transgress spontaneously from the Ebb to Flow phase of shock one should think about (active) de-resuscitation guided by extravascular lung water index (EVLWI) measurements.

Introduction and background

The Surviving Sepsis Campaign (SSC) was launched as a collaboration of three professional organizations at the European Society of Intensive Care Medicine's annual congress in Barcelona in 2002 (www.survivingsepsis.org). Recently the last revision of the Surviving Sepsis Campaign Guidelines have been published (as the third revision since the original publication in 2004)[9—11]. Despite the fact that this initiative is a great step forward in the standardisation of the initial management of patients with sepsis and septic shock, and the authors and co-workers on this project have to be congratulated, some recommendations may have limitations when applied at the bedside. Methods Literature search with regard to the recommendations listed in the SSCG, pragmatic approach with suggestions for improvement of the guidelines and possible pitfalls. The SSCG are based on evidence based medicine and there is no intention to replace the results of randomized controlled trial (RCT) evidence with anecdotes and expert opinion. Some comments and suggestions for improvement will be stated with regard to Early Goal Directed Therapy (EGDT), barometric preload indicators, volumetric preload indicators, fluid responsiveness, fluid balance and cardiac output measurement.

Results and main message

A recent multi-Society Statement clearly states that: "The results of clinical research, pathophysiologic reasoning, and clinical experience represent different kinds of medical knowledge crucial for effective clinical decision making… Each kind of medical knowledge has various strengths and weaknesses when utilized in the care of individual patients… No single source of medical knowledge is sufficient to guide clinical decisions… No kind of medical knowledge always takes precedence over the others." [51]. The importance of this statement at this point and time for Medicine in general cannot be underestimated. The authors believe that: "It reflects the swing of the pendulum away from rigidly adhering to EBM principles and expresses the growing disappointment from RCT's as a guide to clinical decisions." Furthermore "bundling" therapies may

result in unintended effects, particularly if the patient population is not the same as the one originally studied. For example, some sepsis treatments have been studied in sepsis, others in severe sepsis, and others in septic shock, yet we bundle them all together in the SSCG [43].

Early Goal Directed Therapy

It is disappointing to see that even in the third revision of the SSCG the Rivers protocol is still perceived as high-grade evidence [49]. The Rivers single-center study dates from 2001 and has never been repeated and is therefore the only evidence for the effectiveness of the hemodynamic protocol that is now being recommended for all hypotensive and/or hyperlactatemic septic patients, both in and outside the emergency room. These reservations on the Rivers protocol were also raised by others and are based on its perceived physiological flaws (having the same targets of CVP in both arms) and on the possibility that the patients of the Rivers study do not represent all septic patients [46]. As stated in the SSCG: "The strong recommendation for achieving a CVP of 8 to 12 mmHg and an $ScvO_2$ of 70% in the first 6 hours of resuscitation of sepsis-induced tissue hypoperfusion, although deemed desirable, are not yet the standard of care as verified by practice data. The publication of the initial results of the international SSC performance improvement program demonstrated that adherence to CVP and ScvO2 targets for initial resuscitation was low." [16]. Furthermore going through the references of the 2004, 2008 and 2012 SSCG papers there were 135, 341, and 636, respectively in 2004, 2008 and 2012. However, the number of references and the papers referred to themselves, concerning the hemodynamic protocol suggested in the last SSCG have not changed al all between 2008 and 2012. So there maybe is some place for improvement, but do we really have an alternative solution to the CVP?

Barometric preload indicators

As stated above, the CVP and PAOP may be erroneously increased in patients with increased ITP [33]. The latest revision of the SSCG still advocates initial fluid management based on CVP measurements, and suggests reaching a target CVP of 8 to 12 mmHg [11]. However, using pressures to measure preload has been found to be inaccurate time and time again, particularly in patients ventilated with intermittent positive pressure ventilation (IPPV), (auto) PEEP, post cardiac surgery, obesity and those with intra-abdominal hypertension or abdominal compartment syndrome [3, 5, 17, 28, 45]. Although it is re-assuring and noteworthy that the latest SSCG version does mention the effects of increased ITP and IAP on CVP: "In mechanically ventilated patients or those with known preexisting decreased ventricular compliance, a higher target CVP of 12 to 15 mm Hg should be achieved to account for the impediment in filling. Similar consideration may be warranted in circumstances of increased abdominal pressure. Elevated CVP may also be seen with preexisting clinically significant pulmonary artery hypertension, making use of this variable untenable for judging intravascular volume status." Within this respect the compliance of the thorax and the abdomen are key elements in order to explain the index of transmission of a given pressure from one compartment to another: "The use of lung-protective strategies for patients with ARDS… has been widely accepted, but the precise choice of tidal volume… may require adjustment for such factors as the plateau pressure achieved, the level of positive end-expiratory pressure chosen, the compliance of the thoracoabdominal compartment, …" [11]. This lead recently to the recognition of the polycompartment syndrome [30, 31]. Instituting aggressive fluid resuscitation in patients with low CVP values may lead to fluid overload, which may aggravate pulmonary edema, especially in those patients in whom sepsis is associated with acute respiratory distress syndrome (ARDS) and severe pulmonary dysfunction [46]. We therefore disagree with the SSCG statement that: "a low CVP is still a good indicator of someone needing fluid resuscitation". Many patients with a low CVP are nonresponders [37]. As stated before: "The logic of the argument against CVP is that its looking for the coin under the lamp post, but this cliché does not lead to abandonment of this measurement rather to antagonism of other, more sophisticated tools such as the variables obtained with transpulmonary thermodilution."

Volumetric preload indicators

Volumetric estimates of preload status such as global enddiastolic volume index (GEDVI) and right ventricular enddiastolic volume index (RVEDVI) are of significant value in the assessment of traumatically injured patients. This volumetric assessment is especially useful in patients with increased IAP or patients with changing ventricular compliance and elevated ITP in whom traditional intracardiac filling pressure measurements are elevated and difficult to interpret since they are zero-referenced against atmospheric pressure [5, 21, 22, 53]. Reliance on such pressures to guide resuscitation can lead to inappropriate therapeutic decisions, under- or over--resuscitation, and organ failure [28]. Correction of the GEDVI for the corresponding global ejection fraction can further improve its predictive value [25]. One must however take into account that no good normal values exist for GEDVI in different patient populations. The same static volumetric targets, although better than barometric ones may not apply for all patients [35]. A recent meta-analysis showed that baseline values for GEDVI are around 694ml/m2 in surgical and 788ml/m2 in septic patients [12] and thus below the upper limit of normal of 850ml/m2 as was recently used as target for initiating a fluid challenge [52]. We must remember that no single

parameter can change outcome. This can only be achieved by a good protocol [27].

Fluid responsiveness

A significant relationship between values of CVP or PAOP has not been found to identify responders from non-responders. Different techniques are available to assess fluid responsiveness [34]. However there are certain limitations to the use of functional hemodynamic monitoring like SVV or PPV. The patient needs to be in regular sinus rhythm, and the presence of atrial fibrillation or ventricular or supraventricular extra systoles limit their use [33]. The patient also needs to be fully mechanically ventilated without spontaneous breaths and tidal volumes must be above 6ml/kg [8, 48]. The presence of right heart failure and conditions related to increased ITP or IAP will increase the baseline values of the functional hemodynamic parameters making them less reliable unless we define new thresholds [18, 24]. In those situations (or thus in patients with diminished respiratory compliance) other techniques are available in order to assess fluid responsiveness like the use of a PLR or EEO test [4, 39—42]. However the PLR may result in a false negative response in conditions of increased IAP due to diminished venous return [19, 26]. The administration of repeated fluid boluses until the patient is no longer fluid responsiveness cannot be advocated [20, 27, 52].

Fluid balance

As early as 1942, the concept of a dual metabolic response to bodily injury was introduced. In direct response to initial proinflammatory cytokines and stress hormones, the Ebb phase represents a distributive shock characterised by arterial vasodilatation and transcapillary albumin leakage abating plasma oncotic pressure [29, 32]. Arterial underfilling, microcirculatory dysfunction and secondary interstitial edema lead to systemic hypoperfusion and regional impaired tissue use of oxygen. In this early stage of shock adequate fluid therapy comprises goal directed filling to prevent evolution to multiple organ dysfunction syndrome (MODS). Patients with higher severity of illness need more fluids to reach cardiovascular optimization. Therefore, at this point fluid balance may be considered a biomarker of critical illness, as proposed by Bagshaw et al [1]. Patients overcoming shock attain homeostasis of proinflammatory and anti-inflammatory mediators classically within three days. Subsequent hemodynamic stabilization and restoration of plasma oncotic pressure set off the Flow phase with resumption of diuresis and mobilization of extravascular fluid resulting in negative fluid balances. Recent studies showed that conservative late fluid management (CLFM) with 2 consecutive days of negative fluid balance within the first week of stay is a strong and independent predictor of survival [44]. In this context the global increased permeability syndrome (GIPS) has been introduced, characterized by high capillary leak index (CLI, expressed as CRP over albumin ration), excess interstitial fluid and persistent high exrtravascular lung water index (EVLWI), no CLFM achievement and progressing organ failure [6]. GIPS represents a 'third hit' following acute injury with progression to MODS [23]. The dual response to acute inflammatory insult is characterized by a crucial turning point on day 2 to 3. Lower EVLWI and pulmonary vascular permeability indices (PVPI) [15] at day 3 of shock were shown to correlate with better survival. As adverse effects of fluid overload in states of capillary leakage are particularly pronounced in the lungs, monitoring of EVLWI may offer a valuable tool to guide fluid management in the critically ill. It must be stated that EVLWI can never be a trigger to start fluids but it is rather a safety parameter to define the capillary leak and to guide de-resuscitation [27, 36]. In this hypothesis, (change in) EVLWI has a prognostic value as a reflexion of the extent of capillary leakage, rather than as a quantification of lung function impairment by lung water [7]. The proposed Berlin definition for ARDS therefore has no real added value compared to the previous AECC definition [47]. The value of EVLWI in combination with PVPI should "by definition" by part of a future ARDS definition [36].

Cardiac output monitoring

Cardiac output (CO) is the main determinant of oxygen delivery. Physical examination and vital signs alone often fail to reflect significant derangements in CO. However, many of our therapeutic efforts are aimed at increasing the CO. Because of the complexity of assessment of clinical variables in septic patients, direct measurement of CO by invasive hemodynamic monitoring is advisable because it is therefore very useful for proper decision-making in critically ill and high-risk surgical patients [2]. Perioperative optimisation has resulted in better or altered outcomes [13, 14, 38]. The main two reasons to measure CO are the identification of patients who have low (or high) CO values that are not evident clinically or the measurement of the response to diagnostic and therapeutic interventions. Therefore it is time to consider CO as just another vital sign! Based on the available evidence, we cannot agree with the SSCG statement that "The efficacy of these (CO) monitoring techniques to influence clinical outcomes from early sepsis resuscitation remains incomplete and requires further study before endorsement." Continuity of measurement offers vital insights that may be hidden in the analog signals of our monitors. "Physiological Examination" - observing multiple parameters on the monitor in real time - should be considered to be (at least) as important as the classic "Physical Examination" [33, 50].

Take home messages

(1) With regard to EGDT it is not advisable to guide the initial fluid resuscitation based on CVP measurements since they expose the patient to possible over--resuscitation and all the deleterious effects of fluid overload, and in some situations with increased ITP also to under-resuscitation. (2) No single parameter has ever improved survival, only a good protocol or algorithm can. However each patient is unique and as such also merits individualized care. (3) The best fluid is the one that has not been given to the patient, therefore it is advisable not to perform fluid bolus administrations but to use PLR or EEO tests instead. (4) Despite its limitations, functional hemodynamic monitoring can provide further insights towards the identification of fluid responders. (5) In many situations volumetric preload indicators have been proven superior over barometric ones. Taking into account the GEF can further improve the former. (6) CO monitoring should be performed in all septic patients (especially when $ScvO_2$ is low) since this is the only way to make sure that the patient does respond to fluids, as evidenced by a 15% increase in baseline CI. (7) Ongoing fluid resuscitation beyond the initial 24 hours cannot be recommended unless a safety parameter like EVWLI is taken into account to guide de-resuscitation when needed, in those patients that do not transgress spontaneously from Ebb to Flow phase. (8) A future ARDS definition should "by definition" take into account the value of EVLWI in correlation with the PVPI.

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