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The debate on fluid management and haemodynamic monitoring continues: between Scylla and Charybdis, or faith and evidence…

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We are very excited to present to you this issue of "Anaesthesiology and Intensive Therapy" (AIT) containing the Proceedings of the Fourth International Fluid Academy Days (iFAD) with some excellent reviews from internationally renowned experts in their field!

This 4th iFAD will deliver once more a compact two-day programme on clinical fluid management, a topic that has been neglected for a long time, and haemodynamic monitoring. Although the medical community clearly seems to understand the importance of looking at fluids beyond their role for mere haemodynamic stabilisation, we should treat fluids like any other drug we give to our patients [1, 2]. The side effects of fluids are without doubt more than relevant, and there is increasing evidence that the development of hyperchloremic metabolic acidosis due to the use of unbalanced solutions is not as innocent as previously thought [3–5]. Langer et al. [6] nicely illustrate in their review on the effects of intravenous solutions on acid-base equilibrium that the knowledge of the composition of intravenous fluids, along with the application of simple physicochemical rules best described by Stewart's approach, are pivotal steps towards fully elucidating and predicting alterations of plasma acid-base equilibrium induced by fluid therapy [6].

Fluids have indications and contraindications and indeed potential side-effects, and as such the best fluid is probably the one that has not been given to the patient. As Paracelsus nicely put it, it is the dose that makes the poison, and no less is true when it comes to fluid management in the critically ill: it is all about the type of fluids, the dose, the timing, and the speed of administration.

As a result, the International Fluid Academy (IFA, www.fluid-academy.org) was founded in 2011 to serve as a platform on which to gather experts in the field and to organise meetings, workshops and teaching courses. The IFA is part of iMERiT (the International Medical Education and Research Initiative, a non-profit organisation based in Belgium). The mission statement of the IFA is to foster education, promote research on fluid management and haemodynamic monitoring, and thereby improve survival of the critically ill by bringing together physicians, nurses, and others from throughout the world and from a variety of clinical disciplines.

FLUID MANAGEMENT

The morbidity and mortality associated with poor fluid management is either related to hypovolaemia with convective problems or to hypervolaemia and fluid overload with proven morbidity in different kinds of patients and diseases, due to interstitial oedema-related diffusion problems [7, 8]. This was also the conclusion of a recent meta-analysis published in this issue of AIT [9]. Correct fluid resuscitation is all about finding the balance between Scylla and Charybdis, a story representing the choice that sometimes has to be made between two evils.

In Greek mythology, the sirens Charybdis and Scylla resided in the Sicilian Sea. Homer tells us that because Charybdis had stolen the oxen of Hercules, Zeus struck her with a thunderbolt and changed her into a whirlpool whose vortex swallowed up ships, as a metaphor for the risks of hypovolaemia or under-resuscitation.

Scylla was a supernatural creature, with 12 feet and six heads on long, snaky necks, each head having a triple row of shark-like teeth, while her loins were girt with the heads of baying dogs. From her lair in a cave she devoured whatever ventured within her reach, including six of Odysseus's companions, as a metaphor for the risks of hypervolaemia or fluid overload. In Ovid's Metamorphoses, Books XIII–XIV, she was said to have been originally human in appearance but transformed out of jealousy through the witchcraft of Circe into her fearful shape.

The past two years have been very important with regard to evidence-based medicine in relation to closing, at least for now, the colloid *vs* crystalloid fluid debate that has been going on for decades. But is this really the case?

The publication of the **CHRYSTMAS** study, comparing the use of hydroxyethyl starch (HES 130/0.4 waxy maize) *vs* saline in 196 patients with septic shock marked the start of another series of multicentre studies on fluid management in the critically ill [10]. While CHRYSTMAS showed that less fluid was needed in the HES group (1,370 ± 886 vs 1,709 ± 1,164 mL; $P = 0.02$) to reach haemodynamic stability, no differences were found in mean and cumulative fluid balance over the first four days, and the same was true for renal and coagulation side effects. This was followed by the **6S** trial, a prospective state-of-the-art study, comparing balanced HES (130/0.42 potato) vs Ringer's acetate solution in 798 patients with severe sepsis [1]. Although no differences in median trial fluid volumes (3,000 mL in both arms) were observed, the HES treated patients were more likely to die at day 90 and to require renal replacement therapy (RRT). This study was carefully designed, avoiding HES overdosage, using balanced solutions in both arms, with broad inclusion criteria and many patients exhibiting shock. However, no data was provided on haemodynamic monitoring or if fluids were guided in a protocolised way.

The **CHEST** study concluded the series of large trials including 7,000 general ICU patients randomised to either HES 130/0.4 vs saline [11]. After the first four days, the average amount of study fluids per day was 526 ± 425 mL (HES) *vs* 616 ± 488 mL (NaCl) ($P < 0.001$), while the amount of non-study fluids was 851 ± 675 mL (HES) *vs* 1,115 ± 993 mL (NaCl) ($P < 0.001$), resulting in a net fluid balance of 921 ± 1,069 mL (HES) *vs* 982 ± 1,161 mL (NaCl) ($P = 0.03$). In this issue of AIT, De Hert and De Baerdemaeker give us a deeper insight into the limitations of the above mentioned studies and conclude that colloids should not be abandoned in the operating room [12]. While Hahn believes that crystalloids will do the job during surgery [13], crystalloids have a much better short-term effect on the plasma volume than previously believed. Their efficiency (i.e. the plasma volume expansion divided by the infused volume) is 50–80% as long as an infusion continues, while this fraction increases to 100% when the arterial pressure has dropped. Elimination is very slow during surgery, and amounts to only 10% of that recorded in conscious volunteers. Capillary refill further reduces the need for crystalloid fluid when bleeding occurs. These four factors limit the need for large volumes of crystalloid fluid during surgery.

The publication of these trials however resulted in a *scientific earthquake*. A cascade of reactions began in November 2012 when the German medicines agency, the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), triggered a review on HES solutions by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC had initially recommended, on 13 June 2013, suspending marketing authorisations for infusion solutions containing HES in all patient populations [14]. This was followed by a re-examination request by stakeholders, and on 11 October 2013 PRAC confirmed that HES solutions should no longer be used in patients with sepsis (bacterial infection in the blood) or burn injuries or critically ill patients, because of an increased risk of kidney injury and mortality. HES solutions may, however, continue to be used in patients to treat hypovolaemia (low blood volume) caused by acute blood loss, provided that appropriate measures are taken to reduce potential risks and that additional studies are carried out [15]. On 25 October 2013, the Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh), endorsed the PRAC recommendations [16].

In late 2013, the results of the **CRISTAL** study became available showing that colloids – when given in patients with hypovolaemic shock – are lifesaving (significant reduction in 90-day mortality) [17]. The older gelatins, besides having a shorter half-life, smaller volume effect, and a higher chance of developing anaphylactic reactions than HES, also lack actual scientific proof [18]. Iso-oncotic human albumin had already been shown not to be superior to saline in a general ICU setting many years previously [19], and there is no reason to assume this would be markedly different in a surgical population. There is no evidence for the use of hyperoncotic albumin 20% either, a statement made even stronger after the recent **ALBIOS** trial showed that in patients with severe sepsis, albumin replacement in addition to crystalloids, compared to crystalloids alone, did not improve the rate of survival at 28 and 90 days, although a significant beneficial effect was observed in a post hoc subgroup analysis that included 1,121 patients with septic shock, compared to 660 without septic shock, at the time of enrollment (relative risk with septic shock, 0.87; 95% CI, 0.77 to 0.99; relative risk without septic shock, 1.13; 95% CI, 0.92 to 1.39; $P = 0.03$ for heterogeneity)[20].

The discussion continued with the publication of an open letter by Bellomo et al. to the Executive Director of the EMA concerning the licensing of HES solutions for fluid resuscitation that was co-signed by 76 physicians [21]. They concluded that it seems improbable that the PRAC recommendations: *"that HES solutions should not be used for more than 24 hours and that patients' kidney function should be monitored for at least 90 days"* would guarantee patient safety.

The adverse effects of HES appear to be generic to all HES classes and dose dependent, and as such no safe dose for HES has been defined. The revised PRAC recommen-

dation could mean that many thousands of patients with hypovolaemia and acute blood loss will continue to receive HES, which would expose them to known risks of harm and offer no proven benefit.

The discussion has now reached a higher, almost spiritual, level as this was followed by a counter-statement to the open letter to the Executive Director of the EMA concerning the licensing of HES solutions for fluid resuscitation by Coriat et al. and co-signed by 77 physicians [22].

They said that there is increasing evidence showing that there are relevant differences between the effects of the different products, with the best profile for the latest generation of starches. The authors emphasise that the conduct of further clinical studies would be very useful in gaining more information on the best treatment of surgical and trauma patients.

Ultimately, it should be in everyone's interest to interpret the existing data on medical topics objectively and neutrally, without rushing to premature, far-reaching conclusions, which could confuse physicians and even render future therapy with potentially life-saving drugs impossible.

So it appears that not making a choice is not an option either…

But what about common sense? The majority of physicians are aware of current understanding of the risk-benefit assessment of HES, but how do they take this into account at the bedside? For the time being, while we await new study results, this saga has been halted with the CMDh endorsement by majority of the recommendations of the European Medicines Agency's PRAC, which concluded that HES solutions must no longer be used to treat patients with sepsis (bacterial infection in the blood) or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality.

HAEMODYNAMIC MONITORING

Although the use of less invasive haemodynamic monitoring with either calibrated or uncalibrated techniques is steadily increasing in the intensive care unit (ICU), many questions with regard to their indications and pitfalls remain unanswered [23, 24]. Moreover, other techniques such as microdialysis, bioreactance, bioelectrical impedance analysis (BIA), electrical impedance tomography, and serum biomarkers have become readily available. In this issue of AIT, an interesting review points towards possible indications for BIA (not avoiding limitations and drawbacks) to help assessing fluid status in the critically ill [25].

Haemodynamic monitoring is the foundation upon which to guide fluid management, and while the pulmonary artery catheter (PAC) may have become obsolete after previous negative trials [26–28], doing no monitoring at all is not an option, since clinical examination with estimation of cardiac output (CO) is far from accurate [29]. Non-invasive CO monitoring devices have gained their place in the modern ICU. Calibrated transpulmonary thermodilution techniques (with PiCCO or EV1000) seem most popular in difficult unstable critical care patients with changing conditions of preload, afterload and contractility [30].

The CO is an important haemodynamic parameter that is increasingly being used by ICU physicians to guide fluid therapy, as it is the main determinant of oxygen delivery [31, 32]. Physical examination and vital signs alone often fail to reflect significant derangements in CO, while many of our therapeutic efforts are aimed at increasing CO. Because of the complexity of assessment of clinical variables in septic patients, direct measurement of CO by invasive haemodynamic monitoring is advisable [33]. The main 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! It is disappointing that CO was not included in the revised surviving sepsis campaign guidelines [34]. The question remains however as to whether uncalibrated CO monitors are accurate enough to guide therapy. In other words, not only must they be accurate and precise but they must also keep track of changes [35–42]. When evaluating the role of new CO devices in clinical care, the fundamental question is whether the new device can replace thermodilution CO measurement as a guide to clinical decisions. Although PAC, FloTrac, LiDCO and PiCCO display similar mean CO values, they often trend differently in response to therapy and show different inter-device agreement [38]. In the clinically relevant low CO range (< 5 L min^{-1}), agreement is slightly better. Thus, utility and validation studies using only one CO device may potentially not be extrapolated to equivalency of using another similar device.

Despite the large number of studies evaluating new CO devices, few, if any, answer this fundamental question [43]. There is growing evidence that the pulse contour method (without calibration) may not be the solution providing reliable CO monitoring at the bedside in haemodynamically unstable patients under changing conditions of preload, afterload or contractility [42, 44]. Moreover, recent trials have questioned the use of goal-directed therapy as suggested more than a decade ago by Rivers [45]. Indeed, the **ProCess**, **ARISE** and **SEPSISPAM** studies, including more than 3,700 patients, could not replicate earlier beneficial results [46–48].

A fluid challenge identifies and simultaneously treats volume depletion, while avoiding deleterious consequences of fluid overload through its small volume and targeted

administration [49]. The gold standard in monitoring the response to a fluid challenge is using continuous CO monitoring.

However, a fluid challenge should only be given in a case of suspected fluid responsiveness, as giving fluid boluses until the patient no longer responds increases mortality [50]. Assessment of fluid responsiveness may be even more important than defining cardiac preload because regardless of a low, normal or high preload, the patient may still be fluid-responsive. Cardiac ultrasound is more often being used and can indeed be considered as the gold standard and the 'modern stethoscope' for the intensivist. Antoine Vieillard-Baron and Daniel Lichtenstein, experts in their field, give us their ten best reasons to perform cardiac [51] and lung [52] ultrasound in this issue of AIT.

Organ monitoring techniques can help the clinician to guide treatment; the future of haemodynamic monitoring is already here. Examples include sublingual PCO_2, tissue oxygen saturation, and capillary blood flow measured under the tongue [53]. Such novel monitoring devices may add an extra dimension by allowing real-time assessment of response to therapy, and potentially when to stop. The mechanism of gastro-intestinal injury (related to increased vascular permeability) is widely recognised and accepted in the lung and kidneys, where it is classified as acute lung and kidney injury (ALI/AKI) [54]. The same pathological process occurs in the gut, but this concept is much slower to seep through. However, the role of the gut as the motor of organ dysfunction syndrome cannot be denied and difficulties in assessing gut function should not deter us from recognising that concept [55]. Within this concept, the abdomen may play a central role: pressures in one compartment can easily be transmitted to another compartment causing distant organ dysfunction. This is referred to as polycompartment syndrome and is discussed in this issue of AIT [56]. Compartmental compliance, and most importantly compliance of the abdomen (C_{ab}), may play a key role in understanding organ-organ interactions. The pathophysiology related to increased or decreased C_{ab} is discussed in two reviews on this topic [57, 58].

However, no monitoring device can improve patient-centred outcomes unless it is coupled with a treatment that improves outcome, while a poor protocol may have deleterious effects [59–61]. How should we deal with the inaccuracies and limitations of our monitored parameters? Firstly, we must maximise the information that can be provided by real-time continuous measurement. Secondly, we must beware of protocols, especially those with pre-defined physiological end-points [62–64]. Thirdly, we must adopt a multi-parametric approach when making a potentially critical decision. Finally, we must adopt decision-making strategies that take into account the uncertainty of our measurements and consider the *grey zone* approach [65]. In a situation where fluid overload may be particularly deleterious, higher-than-normal PPV values should serve as an indication for fluid administration.In high-risk patients, the decision about fluid administration should be made within the context of a therapeutic conflict. A therapeutic conflict is a situation where each of the possible therapeutic decisions carries some potential harm [66]. Therapeutic conflicts are the biggest challenge for protocolised haemodynamic management in anaesthetised and critically ill patients. A therapeutic conflict is where our decisions can make the most difference.

We must recognise that all our measurements are a lot less informative and accurate than we may want (or think). Continuity of measurement offers vital insights that may be hidden in the analogue 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'.

RECOMMENDATIONS

What follows is a practical guide in different patient populations [67, 68].

In **sepsis patients**, starches should no longer be used, normal saline is to be avoided, and as an alternative balanced crystalloids are to be the first choice, while hypertonic albumin may have a role to play in the late stage for de-resuscitation.

In **general ICU patients**, HES can be used only a short time after the onset of shock, and its use is limited to acute volume resuscitation (< 24 h) for haemodynamic instability in a case of hypovolaemia and comply with a maximum dose of 50 mL kg^{-1} per day [69]. HES should not be used in acute or chronic renal failure or oliguria not responsive to fluids (6h) and the best alternative is a balanced crystalloid.

In **postoperative hypovolaemic patients**, there may still be a place for HES taking into account the considerations listed above and saline should preferably not be used [4]. In all situations, one needs to use reliable algorithms of fluid responsiveness and predefined haemodynamic endpoints.

So in conclusion, common sense must prevail, and fluids should be regarded like any other drug, with indications and contra-indications and possible adverse effects [70]; fluid requirements change over time; the approach should be targeted and protocol driven; isotonic balanced salt solutions are a pragmatic initial resuscitation fluid in the majority of acutely ill patients; and last but not least, as shown by the **FEAST** trial, fluid boluses should not be given and fluid overload must be avoided at all costs, as illustrated in the **FINNAKI** study and the recent meta-analysis published in this issue of AIT [9, 50, 71, 72].

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