Fluid therapy and perfusional considerations during resuscitation in critically ill patients with intra-abdominal hypertension

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Abstract

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are consistently associated with morbidity and mortality among the critically ill or injured. Thus, avoiding or potentially treating these conditions may improve patient outcomes.

With the aim of improving the outcomes for patients with IAH/ACS, the World Society of the Abdominal Compartment Syndrome recently updated its clinical practice guidelines. In this article, we review the association between a positive fluid balance and outcomes among patients with IAH/ACS and how optimisation of fluid administration and systemic/regional perfusion may potentially lead to improved outcomes among this patient population. Evidence consistently associates secondary IAH with a positive fluid balance. However, despite increased research in the area of non-surgical management of patients with IAH and ACS, evidence supporting this approach is limited. Some evidence exists to support implementing goal-directed resuscitation protocols and restrictive fluid therapy protocols in shocked and recovering critically ill patients with IAH. Data from animal experiments and clinical trials has shown that the early use of vasopressors and inotropic agents is likely to be safe and may help reduce excessive fluid administration, especially in patients with IAH. Studies using furosemide and/or renal replacement therapy to achieve a negative fluid balance in patients with IAH are encouraging. The type of fluid to be administered in patients with IAH remains far from resolved. There is currently insufficient evidence to recommend the use of abdominal perfusion pressure as a resuscitation endpoint in patients with IAH. However, it is important to recognise that IAH either abolishes or increases threshold values for pulse pressure variation and stroke volume variation to predict fluid responsiveness, while the presence of IAH may also result in a false negative passive leg raising test. Correct fluid therapy and perfusional support during resuscitation form the cornerstone of medical management in patients with abdominal hypertension. Controlled studies determining whether the above medical interventions may improve outcomes among those with IAH/ACS are urgently required.

Key words: intra-abdominal hypertension, Abdominal Compartment Syndrome, intra-abdominal pressure, fluid resuscitation, abdominal perfusion, fluid balance
Intra-abdominal hypertension (IAH) constitutes a sustained increase in intra-abdominal pressure (IAP) ≥ 12 mm Hg, while abdominal compartment syndrome (ACS) is defined as a persistent elevation of IAP > 20 mm Hg with new onset of organ failure [1].

As both IAH and ACS are associated with increased morbidity and mortality among critically ill patients [2–5], their medical and/or surgical treatment may improve patient outcomes [6–8].

The World Society of the Abdominal Compartment Syndrome (WSACS, www.wsacs.org) has recently updated its clinical practice guidelines [9]. In principle, this group outlined five medical treatment options for reducing IAP among those with IAH/ACS, or avoiding occurrence of these conditions: 1) improvement of abdominal wall compliance; 2) evacuation of intra-luminal contents; 3) evacuation of abdominal fluid collections; 4) optimising fluid administration; and 5) optimising systemic and regional perfusion.

In this article, we review the association between a positive fluid balance and outcomes among patients with IAH/ACS and how optimisation of fluid administration and systemic/regional perfusion may potentially lead to improved outcomes among this patient population. Medical treatment options to improve IAH/ACS, including improvement of abdominal wall compliance and evacuation of intra-luminal contents and abdominal fluid collections, are not discussed as they have been reviewed elsewhere [10].

METHODS

We searched PubMed, MEDLINE, and EMBASE, using the key terms ‘IAH’, ‘IAH’, ‘ACS’, ‘medical management’, and ‘non-surgical management’, in varying combinations, for articles published in the last three years that reported on a novel approach to the non-surgical management of IAH and ACS.

FLUID BALANCE AND ABDOMINAL HYPERTENSION

FLUID BALANCE AS A ‘BIOMARKER’ OF SICKNESS

Many studies link fluid overload with adverse outcome. For example, in critically ill patients with acute renal failure, a positive fluid balance serves as an independent risk factor for mortality [11].

In a retrospective review of 36 patients with septic shock, the risk of mortality was approximately five times higher among critically ill patients who failed to achieve a negative fluid balance on at least one of the first days after admission compared to those who achieved a negative fluid balance on these days [12]. Importantly, survivors had a lower Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assessment (SOFA) scores than non-survivors. Thus it remains debatable as to whether fluid overload itself causes adverse effects or represents a biomarker of sickness. It may well be that the greater the acute physiological derangement of a critically ill patient, the greater the requirements of initial fluid resuscitation, and that later a negative fluid balance can be achieved.

SECONDARY IAH/ACS IS ASSOCIATED WITH A POSITIVE FLUID BALANCE

Primary IAH/ACS is a condition associated with injury or disease in the abdominopelvic cavity, whereas secondary IAH/ACS occurs as a result of a condition that originates outside the abdomen [1, 9]. Existing evidence suggests that a positive fluid balance is probably the most important risk factor for the development of secondary IAH/ACS [1, 13]. A systematic review of IAH/ACS risk factors by Holodinsky et al. published in 2013 reported that a positive fluid balance was associated with an odds ratio of approximately 5.2 for the development of IAH among mixed populations of adult ICU patients [14]. Furthermore, in a prospective observational study, Daugherty et al. identified 40 critically ill medical patients with a positive fluid balance of ≥ 5 L within a 24 hour period [15]. In this cohort, 85% and 25% had IAH and ACS respectively, which reflects a higher prevalence than previously reported for critically ill medical patients (54% and 4%) [2]. Likewise, in a prospective observational study of 77 patients following major abdominal surgery, IAH was found in 40% [16]. In this study, a positive correlation was also observed between 24 hour fluid balance and daily changes in IAP (R = 0.49, P < 0.001). Interestingly, these patients with IAH exhibited a higher number of systemic inflammatory response syndrome criteria [16].

FLUIDS ARE DRUGS

Critically ill patients may develop a positive fluid balance for several reasons, including: 1) excessive fluid administration during the initial resuscitation phase of a patient who presents with shock [6, 17, 18]; 2) too little fluid removal or mobilisation following the initial resuscitation phase [8, 19]; 3) the type of fluids administered [20–22]; or 4) any combination of the above [23].

In theory, any measure that safely reduces the amount of fluid given without compromising resuscitation may reduce the incidence and severity of IAH/ACS and hence improve outcomes.

Fluids should be seen as drugs with indications, contra-indications and potential beneficial and adverse effects. Therefore, not only the type of fluids, but also dose, timing and speed of administration may influence the ‘pharmacokinetic’ and ‘pharmacologic’ effect of the fluid. It might well be that the best fluid may be the one that has not been given to a patient.

When treating critically ill patients, we need to answer the following questions: 1) when to start fluid administra-
tion/resuscitation and will this benefit the patient?; 2) when to stop fluid administration/resuscitation or is the patient showing signs of adverse effects of fluid administration?; 3) when to start removing fluids from the patient and will this benefit the patient?; and finally 4) when to stop removing fluids from the patient or is the patient showing signs of adverse effects of fluid removal?

ASSOCIATION BETWEEN A NEGATIVE FLUID BALANCE AND OUTCOMES IN PATIENTS WITH IAH

Optimal fluid management might require a biphasic approach tailored to the disease process. In a retrospective analysis of 212 patients with acute lung injury due to septic shock, hospital mortality was lowest for patients achieving both adequate initial fluid resuscitation (initial fluid bolus of > 20 mL kg\(^{-1}\) prior to and achievement of a central venous pressure of > 8 mm Hg within 6 h after starting vasopressors) and restrictive late fluid management (even to negative fluid balance measured on at least two consecutive days) [24]. Mortality was observed to be 18%, 42%, 57%, and 77% if both, the former, the latter, or neither, was achieved (\(P < 0.001\)), respectively [24]. IAP was not measured in this study.

In addition, in a retrospective study of 123 mechanically ventilated patients, Cordemans et al. observed that non-survival was associated with an increased capillary leak index (C-reactive protein divided by serum albumin), not achieving a ‘conservative late fluid management’ (defined as a negative fluid balance on ≥ 2 consecutive days during the first week of intensive care unit (ICU) stay) (odds ratio, OR 9.3, \(P = 0.001\)), not achieving a decrease in extravascular lung water index of ≥ 2 mL kg\(^{-1}\) (OR 7.1, \(P = 0.001\)), and having higher IAP levels in the first week of treatment [19].

HOW MUCH FLUIDS ARE ENOUGH?
AVOIDING EXCESSIVE FLUID RESUSCITATION

IAP values increase in proportion to the amount of fluids administered to critically ill patients (R = 0.79) [21]. In order to reduce the incidence and severity of IAH/ACS, our aim should be to administer fluids swiftly and adequately in order to optimise global and regional blood flow while simultaneously limiting excessive fluid administration.

HOW MUCH FLUIDS SHOULD BE GIVEN TO SEPTIC PATIENTS?

Sepsis is the overwhelming systemic inflammatory response to infection that requires aggressive medical management. Initiating prompt fluid resuscitation during the initial phase is intended to dampen or halt progression of the disease. In a randomised controlled trial (RCT) by Rivers et al., patients with severe sepsis or septic shock who were allocated to receive early goal directed therapy had a reduced mortality compared to a control group [25]. Interestingly, the intervention group received more resuscitation fluid during the first six hours, but less in the following three days.

It might well be that early adequate goal-directed fluid resuscitation of the shocked patient can reduce the total amount of fluid required due to an earlier and/or more complete reversal of the disease, assuming parallel treatment of the underlying disease has also been initiated. However, the recent PROCESS trial comparing early goal directed therapy, protocol-based standard care, and usual care in patients with early septic shock could not confirm these results [26]. Nonetheless, initial fluid received, vasopressor usage and mortality was comparable among the groups [26].

HOW MUCH FLUIDS SHOULD BE GIVEN TO TRAUMA PATIENTS?

Emerging concepts in the management of trauma patients undergoing damage control laparotomy [27], including focused assessment with sonography for trauma, permissive hypotension for those with penetrating injury mechanisms, bedside thrombo-elastography, and the use of higher ratios of high fresh frozen plasma (FFP) to red packed cells in massive transfusion protocols [28], have recently been associated with reduced transfusion requirements and/or improved survival. In a retrospective analysis of 452 patients with blunt trauma requiring massive transfusion, investigators observed that higher ratios of crystalloids relative to red packed cells ( > 1.5:1) were associated with a dose-related increase in the risk of multi-organ failure, acute respiratory distress syndrome, and ACS [22]. These results suggest that excessive amounts of crystalloids may need to be avoided among major trauma patients in order to reduce the incidence of IAH and ACS.

HOW TO TREAT FLUID OVERDOSE?

HOW TO ACHIEVE A NEGATIVE FLUID BALANCE?

Active pursuit of a negative fluid balance has been shown to improve outcomes outside the context of IAH. In a RCT of 1,000 patients with acute lung injury, use of a restrictive fluid administration protocol as opposed to liberal fluid protocols resulted in reduced fluid balances, improved oxygenation, and reduced lengths of mechanical ventilation and ICU stay [29]. In patients with IAH, late restrictive fluid management has also been associated with improved outcome. Cordemans et al. retrospectively compared a late restrictive fluid management protocol versus a standard one in 114 mechanically ventilated patients with acute lung injury, raised extra vascular lung water, and IAH [8]. The restrictive late fluid management protocol (PAL therapy) consisted of adapting positive end-expiratory pressure to the corresponding IAP (positive end-expiratory pressure in cmH\(_2\)O = IAP in mm Hg), followed by administration of hyperoncotic albumin (twice daily 200 mL of 20% to achieve

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albumin levels of 30 g L\(^{-1}\)), and active fluid removal with either furosemide infusion or renal replacement therapy (RRT). One week of restrictive fluid management was associated with reduced cumulative fluid balance and extra-vascular lung water, improved oxygenation, a shorter ICU stay, and improved survival compared to standard fluid management. Although the above findings suggest that late restrictive fluid management may be considered to reduce IAP and potentially improve outcome in patients with IAH, these may have been confounded and therefore further studies are needed.

**PLACE FOR FUROSEMIDE INFUSION OR RENAL REPLACEMENT THERAPY**

There is currently insufficient data to make any specific recommendations in regard to the optimal way to achieve a negative fluid balance in patients with IAH. Mullens et al. studied a treatment regimen incorporating furosemide infusion in 40 patients with acute decompensated heart failure. They found that an improvement in renal function was associated with a decrease in IAP (from 8 mm Hg to 5 mm Hg, \(P < 0.001\)) without any haemodynamic compromise [30].

As in the abovementioned study by Cordemans et al., furosemide infusion has also been successfully applied as part of a treatment combination in non-acute decompensated heart failure patients with IAH [8]. However, the effect of furosemide alone has not been studied in a randomised setting in patients with IAH or ACS. In two retrospective analyses of patients with severe acute pancreatitis, application of RRT was associated with: 1) a negative cumulative fluid balance (approximately \(-1.8\) L vs \(+5.3\) L on day 7, \(P < 0.001\)) [31]; 2) reduced incidence of IAH (31% to 14%, \(P < 0.01\)) and ACS (11% to 4%, \(P = 0.02\)) [32]; 3) reduced surgical requirements (41% to 19%, \(P < 0.001\)) [32]; and 4) a trend towards reduced mortality (12 vs 14%, non-significant) [31].

In a follow up study, Mullens et al. studied nine patients with acute decompensated heart failure who did not respond to the initial medical (mainly furosemide based) treatment. These patients were treated with mechanical fluid removal (using RRT or paracentesis if ascites was present). Average negative fluid balance after 12 hours was 2.5 L and resulted in a marked decrease in IAP (from 13 mm Hg to 7 mm Hg, \(P = 0.001\)) [33].

Kula et al. showed in a case series that RRT with net ultrafiltration decreased IAP [34]. De laet et al. demonstrated similarly that RRT with a mean net fluid loss of 1.9 L in a total of 25 dialysis sessions decreased IAP from 12 to 11 mm Hg (\(P < 0.0001\)) [35]. Finally, Dabrowski et al. recently concluded that continuous RRT to reduce fluid overload in patients with septic shock and acute kidney injury reduces IAP [36].

Albeit the number of patients treated in the aforementioned studies was small and there were only moderate effects of RRT on IAP, they consistently confirm the causal relation between fluid removal and reductions in IAP in patients with fluid overload.

Irrespective of the presence of IAH, early initiation of RRT in critically ill patients with severe acute renal failure was associated with improved hospital survival, reduced RRT duration, and a decreased risk of needing long-term dialysis in two meta-analyses [37, 38] and in a large prospective multicentre observational study [39].

These findings suggest that the use of furosemide in patients with IAH having a preserved urine output and the early use of RRT in patients with IAH and renal failure can be safely applied and probably will reduce IAP levels by reducing cumulative fluid balances. However, efficacy and safety trials are needed before these practices can be recommended.

**HOW TO ASSESS FLUID BALANCE IN PATIENTS WITH IAH?**

In general the fluid balance, and more importantly the presence of fluid overload, in critically ill patients are routinely assessed by calculating the cumulative fluid balance, assessment of peripheral and lung oedema together with additional investigations such as radiological lung images or measuring right and left atrial pressures, extra-vascular lung water and IAP.

Recently introduced bedside whole-body bioimpedance is an easy and practical method to determine body fluid compartments, and has a great potential in critically ill patients for the measurement of adequate fluid administration [40]. The bioimpedance analysis draws on the bio-electrical properties between the wrist and the ankle under the assumption of a steady fluid distribution. By applying low and high frequencies of electrical currents, and using equations incorporating anthropometric data (mainly body mass index affecting resistance to electrical currents), both extra-cellular water and total body water (and indirectly intra-cellular water) can be quantified (low frequency electrical current not penetrating cell membranes) [40]. However, the distribution of total body content strongly affects bioimpedance findings. The same volume of extravascular water may be distributed unequally in different body spaces; this significantly reduces the reliability of whole-body bioimpedance measurement [41]. Moreover, the increase in IAP above 20 mm Hg causes venous visceral congestion and reduces venous outflow increasing femoral venous pressure [42, 43]. This pathology may increase extravascular water content in the limbs disturbing bioimpedance reliability. Dabrowski et al. found a strong correlation between IAP and fluid overload, which was measured using whole-body bioimpedance [36]. A lack of reduction in total body and extravascular water was associated with poor outcome. It is worth noting
that they did not observe IAH higher than 20 mm Hg. Thus whole-body bioimpedance is easy to perform and useful to assess body fluid volumes and may help optimise fluid management and ultimately outcomes in patients with IAH not higher than 20 mm Hg.

**WHAT FLUIDS SHOULD BE USED IN PATIENTS WITH IAH?**

In a retrospective analysis of 48 patients with a major burn injury, Oda et al. found that patients who received hypertonic lactated saline as opposed to compound sodium lactate required less fluid administration volumes to maintain equal urine output (3.1 L vs 5.2 L, \( P < 0.01 \)). This translated into reduced IAP levels (approximately 11 mm Hg vs 23 mm Hg, \( P < 0.05 \)) and incidence of IAH (defined as IAP > 30 cm H\(_2\)O) in the first 24 hours after ICU admission (14% vs 50%, test of significance not provided) \([20]\). However, serum sodium increased from 138 mmol L\(^{-1}\) to 151 mmol L\(^{-1}\) in the hypertonic lactated saline group. Oda et al. \([44]\) used chloride-reduced solutions associated with reduced incidence of acute renal failure and reduced RRT requirements.

In a prospective RCT, 31 patients with major burn injury received either crystalloid or a combined FFP/crystalloids resuscitation to maintain adequate urine output. Combined FFP/crystalloid resuscitation resulted in a smaller IAP increase (peak IAP was 16 vs 32 mm Hg, \( P < 0.006 \)) and reduced amount of total resuscitation fluid required (12.3 L vs 22.1 L, \( P < 0.002 \)) in the first 24 hours of admission to intensive care \([21]\).

In another RCT that included 41 patients with severe acute pancreatitis, patients receiving a 1:3 ratio of starch (6% hydroxyethyl starch 130/0.4) to crystalloids achieved earlier negative fluid balances (2.5 days vs 4.0 days, \( P < 0.05 \)) and developed lower IAP levels (15.3 vs 17.1, significance not provided) compared to patients receiving crystalloids only \([45]\).

The above results suggest that hypertonic fluid, FFP, and starches may potentially reduce the incidence and severity of IAH/ACS. However, among critically ill and septic patients, the use of starches has been associated with: 1) a 1.3-fold decrease in total fluid resuscitation fluid required \([46, 47]\); 2) an increase in blood products requirement \([46, 48]\); 3) an increase in the incidence of renal failure and need for RRT \([46-49]\); and 4) an increase in mortality \([49]\). Albumin, however, was not linked with an adverse outcome (death, time requiring mechanical ventilation, intensive care or RRT) in a large RCT of critically ill patients requiring fluid resuscitation \([50]\). Administration of albumin in mixed populations of critically ill patients with low albumin levels has been associated with improved survival in a meta-analysis \([51]\). In the more recent ALBIOS trial, Caironi et al. did not find albumin replacement in addition to crystalloids alone to improve 28 and 90 day survival in patients with a severe sepsis. However, in a post-hoc analysis, albumin administered to patients with septic shock appeared to improve survival (\( P = 0.03 \)) \([52]\).

As described above, albumin has successfully been applied as a combination therapy (PAL therapy) in patients with IAH and ALI, and this resulted in a decrease in IAP \([8]\). Albumin might be safe in patients with IAH and might be beneficial. However, there have been to date no randomised control trials studying the effect of albumin in patients with IAH/ACS. Thus, evidence is currently insufficient to recommend any specific fluid to be used in patients with, or at risk of, IAH/ACS.

**RESUSCITATION OF THE MICROCIRCULATION**

**OPTIMISATION OF SYSTEMIC/REGIONAL PERFUSION**

Fluid management is largely affected by resuscitation targets \([53]\). Aiming for supranormal oxygen delivery in resuscitation protocols for critically ill patients has not been shown to improve outcomes \([54]\). However, such an approach has been associated with a higher amount of resuscitation fluid administered, which has been linked with a higher incidence of IAH/ACS and death in a retrospective evaluation of trauma patients \([6]\).

**GOAL-DIRECTED RESUSCITATION**

In recent years, there has been a shift from using static preload parameters such as central venous pressure or pulmonary artery occlusion pressure to dynamic parameters such as pulse pressure variation (PPV) and stroke volume variation (SVV) because they constitute more accurate predictors of fluid responsiveness (increase in cardiac output in response to a fluid challenge) in critically ill patients receiving positive pressure ventilation \([55, 56]\).

Several studies have investigated fluid responsiveness in the setting of IAH. Two animal experiments demonstrated that IAH either abolishes or increases threshold values for PPV and SVV to predict fluid responsiveness \([57, 58]\). Therefore, higher thresholds for functional haemodynamic parameters may need to be used among those with IAH to indicate fluid responsiveness \([59]\).

An increase in blood pressure or cardiac output induced by a passive leg raising manoeuvre can often predict fluid responsiveness in critically ill patients \([60]\). In patients with IAH, this test was shown to have a high false negative rate (i.e. low sensitivity) \([61]\), indicating that a patient with IAH might be fluid responsive even without showing haemodynamic response to a passive leg raising manoeuvre. This might be due to inferior vena cava compression and obliteration of the autotransfusion effect of the passive leg raising manoeuvre \([62]\).
Together, these findings imply that IAH blunts the response of parameters that in the absence of IAH can accurately predict fluid responsiveness, which may be due to an IAH-induced increase in right ventricular afterload [63].

**ABDOMINAL PERFUSION PRESSURE**

Similarly to cerebral perfusion pressure [defined as the difference between intracranial and mean arterial pressure (MAP)] [64], abdominal perfusion pressure (APP) is the difference between the MAP and the IAP. As APP may correlate with visceral perfusion [1, 65–67], this measure has been suggested to be used as a resuscitation endpoint in patients with IAH [65].

The largest body of evidence supporting the use of APP derives from retrospective analyses of several different types of critically ill patients, where APP was found to be a greater predictor of mortality than IAP or MAP alone. This relationship has been demonstrated for critically ill surgical patients [68], mixed medical and surgical patients [69], and in patients with septic shock [36, 70], severe acute pancreatitis [71], acute respiratory failure [19], and ruptured abdominal aortic aneurysms [66].

Although APP may have some merits, to date there have been no studies demonstrating that APP is superior to other resuscitation endpoints in patients with IAH (e.g. MAP > 65 mm Hg). Furthermore, aiming for higher blood pressures (i.e. MAP 80 mm Hg when aiming for APP of 50–60 mm Hg in a patient with IAP of 20 mm Hg) carries the inherent risk of additional excessive fluid administration, which might in itself increase the incidence and severity of IAH and ACS. Therefore, there is currently insufficient evidence to recommend use of APP as a resuscitation endpoint in patients with IAH. In addition, the SEPSIS-PIAM trial comparing the outcomes of patients with septic shock who were resuscitated either to a MAP target of 80 to 85 mm Hg or 65 to 70 mm Hg were comparable in terms of 28 and 90 day mortality [72]. Interestingly, fluid management did not differ significantly between the groups.

**VASOACTIVE MEDICATIONS**

IAH is associated with an increased systemic vascular resistance, decreased venous return, reduced cardiac output [63], and diminished intra-abdominal organ perfusion [73]. The question therefore arises as to how vasopressor/inotropic agents affect systemic and abdominal perfusion in patients with IAH. As no vasopressor/inotropic agents have been trialled in patients with IAH, only animal experimental data and clinical data outside the context of IAH currently exists. Thus, the generalisability of the findings of these studies to those with IAH may be questioned.

Noradrenaline is often quoted as having minimal inotropic effects. However, in a septic animal model [74], and in an animal model of IAH [75], noradrenaline was reported to improve cardiac output as well as regional bloodflow to intra-abdominal organs. This agent also increased cardiac output and renal bloodflow (in septic and non-septic conditions). Although noradrenaline may reduce microcirculation to intra-abdominal organs [76], the effect of noradrenaline on the microcirculation (or the relevance of this finding to clinical practice) in patients with IAH or ACS remains largely unknown. Dobutamine appears to be superior compared to dopamine in increasing systemic and regional abdominal bloodflow in animal models [77, 78].

As such, the above animal experimental data suggests that noradrenaline and dobutamine may potentially be safe to use in patients with IAH.

When compared to noradrenaline, vasopressin improved renal blood flow in a septic animal model [79]. In a post-hoc analysis of a multi-centre randomised control trial of vasopressin versus noradrenaline in patients with septic shock (VASST), 106 patients at risk of kidney injury were analysed [80]. Receiving vasopressin as opposed to noradrenaline showed a reduced progression to renal failure/loss (21% vs 40%, \( P = 0.03 \)), a reduced RRT requirement (17% vs 38%, \( P = 0.02 \)), and a reduced mortality (31% vs 55%, \( P = 0.01 \)). One possible explanation for this finding is that vasopressin causes glomerular efferent arteriolar vasoconstriction and thus increases glomerular filtration, as opposed to noradrenaline inducing afferent arteriolar vasoconstriction [80]. However, whether vasopressin has reno-protective properties in patients with IAH and/or ACS has yet to be tested.

In summary, vasoressors/inotropic agents are likely to be safe in patients with IAH. Although these agents may potentially reduce the amount of initial resuscitation fluid and enhance use of a late restrictive fluid management, confirmatory studies are required to validate this suggestion.

**MONITORING REGIONAL PERFUSION**

Changes in femoral venous oxygen saturation [42] or lactate [81] do not correlate with the IAH-induced changes in abdominal perfusion. However, two measurement techniques merit a short discussion: a) the indocyanine green plasma disappearance rate (ICG-PDR); and b) microdialysis of the rectus abdominis muscle.

IAH has been shown to reduce hepatic perfusion [82]. ICG-PDR correlates well with global hepato-splanchnic blood flow [83] and has been demonstrated to be an early indicator of hepatocellular injury [84]. In critically ill patients, ICG-PDR appears to reflect changes in hepatic perfusion associated with IAH [85, 86] and correlates well with IAP and APP [67].

Microdialysis can been used to monitor energy metabolism in severe brain injury [87] and in liver transplantation.
[88]. Raised lactate-to-pyruvate ratio (L/P ratio) and glycerol levels are reliable markers for ischaemia and cell membrane damage respectively [89]. Microdialysis of the rectus abdominis muscle appears to be a reliable method of detecting early organ dysfunction in the setting of IAH in animal experiments [81, 89] and in the clinical setting [90]. Interestingly, changes in L/P ratios in rectus sheath microdialysis appear earlier and are more pronounced than those that occur in the liver, kidney and intestines. Rectus abdominis microdialysis also has the potential to be used at the bedside due to the ease of access.

It appears that ICG-PDR and microdialysis of the rectus abdominis muscle can both detect changes in abdominal perfusion due to IAH. It would be interesting to see these two measurement techniques incorporated in future research projects aiming to improve global and regional resuscitation in patients with IAH.

CONCLUSIONS

A clear association exists between the development of a positive fluid balance and the development/worsening of IAH among critically ill patients.

In observational studies, negative fluid balance seems to be associated with improved outcomes in patients with IAH. Thus, optimal fluid resuscitation for sepsis can best be described as ‘early aggressive, late conservative’, even though specific targets and protocols are not available yet. Although damage control resuscitation, incorporating enhanced plasma-to-RBC ratios, may be the best strategy to avoid IAH/ACS in trauma patients, RCTs are needed before their benefit can be confirmed.

There is very limited data concerning aiming for a negative fluid balance using loop diuretics or RRT among those with, or at high risk of, IAH/ACS. Some case series and small studies have offered positive results, but there is not enough evidence to advocate this approach in routine clinical practice. The presence of IAH alters standard haemodynamic monitoring parameters and alternative targets and thresholds may apply, including those related to fluid responsiveness. The use of vasopressors and/or inotropes (specifically noradrenaline and dobutamine) may be safe and effective in patients with IAH/ACS. Although rectus abdominis muscle sheath microdialysis and ICG-PDR may offer minimally invasive techniques to evaluate splanchnic and hepatic perfusion, their role in the study or treatment of patients with IAH/ACS currently remains largely unknown.

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