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Goal-directed fluid resuscitation in acute pancreatitis: shedding light on the penumbra by dynamic markers of preload?

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Introduction

Acute pancreatitis (AP) is a potentially life-threatening disease with increasing incidence in Western countries. Severe AP (SAP) results in mortality of up to 42 % [1–3]. Several recent studies have demonstrated improved early prediction of severity using a new scoring system (bed-side index of severity in acute pancreatitis, BISAP) [4] or single parameters including elevated blood glucose [5], blood urea nitrogen (BUN) [4] and haematocrit [6, 7]. Regarding therapeutic consequences, the association between elevated haematocrit and poor outcome is particularly of interest [6, 7]. These data suggest that impaired macro- and microcirculation with elevated BUN, decreased mean arterial pressure (MAP) and increased lactate [2] are crucial pathomechanisms for the development of SAP promoting pancreatic inflammation,

particularly in parts of the pancreas with critical perfusion called the “penumbra” [3].

Consequently, early goal-directed volume resuscitation is an obvious strategy. Most guidelines recommend “liberal” fluid substitution in AP [1]. However, due to lack of evidence, clear-cut goals and tools to guide resuscitation have not been given. Frequently, fluid management is adjusted according to traditional pressure-based (barometric) markers of preload such as central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP). Particularly for the treatment of AP, this contradicts a substantial amount of evidence. Numerous studies have questioned the usefulness of CVP and PCWP for predicting volume responsiveness [8, 9] because there are several factors that affect these pressures such as ventilation forces, increases in intrathoracic pressure and intraabdominal pressure (IAP) induced by fluid extravasation (pleural effusion, ascites), and impaired gastrointestinal motility. Most of these factors are frequently found in AP, suggesting that CVP and PCWP are particularly inappropriate for fluid management in AP with increased IAP or intraabdominal hypertension (IAH) and risk of polycompartment syndrome [10, 11].

Nevertheless, there is a lack of data on better prediction of volume responsiveness and improved outcome using other haemodynamic monitoring tools in AP. This clearly emphasizes the merits of the study by Trepte et al. [12]. Although volumetric global end-diastolic volume index (GEDVI) and dynamic preload parameters such as stroke volume variation (SVV) and pulse pressure variation (PPV) have become widely available, this is one of the first studies evaluating these tools in AP. So far, only one study has demonstrated a superior association between (changes in) GEDVI and (changes in) cardiac index (CI) compared to CVP [13]. This study resulted in an ongoing multicentre randomized controlled trial (EAGLE) on early goal-directed therapy in AP using a

complex algorithm based on GEDVI, extravascular lung water index and pO_2/FiO_2 [14].

In their experimental study in 34 pigs, Trepte et al. [12] compared a “traditional” algorithm aimed at CVP >12 mmHg and MAP >60 mmHg and an algorithm guided by left-ventricular SVV ($<10\%$), CI (>2.5 l/min/ m^2), and MAP (>60 mmHg). The CVP-based algorithm resulted in an excessive fluid load with $9,988 \pm 2,240$ ml of crystalloids and $4,644 \pm 1,117$ ml of colloids administered within 7 h. This exceeded the resuscitation volumes in the SVV-guided group nearly threefold. CVP-guided aggressive resuscitation resulted in significant decreases in survival, pancreatic oxygen tension and microcirculation compared to the SVV-guided group. Furthermore, extravascular lung water index—a parameter significantly associated with mortality—was significantly higher in the CVP-guided group.

What is the impact of these findings on clinical routine?

Overall this study further emphasizes the importance of goal-directed fluid management in AP as well as the need for appropriate endpoints. As in all controlled studies, differences in outcome might have been due to beneficial effects in the treatment group and/or due to detrimental effects in the controls. A retrospective study [15] demonstrates reduced mortality in case of *early* resuscitation compared to *late* resuscitation. However, excessive hydration with similar fluid volumes, as in the control group of Trepte et al., has been demonstrated to be detrimental in a clinical study [16]: aggressive hydration with 10–15 ml/kg min h (i.e. about 1 L/h for a 70-kg patient) on the day of admission resulted in increased mortality compared to controls with more moderate resuscitation with 5–10 ml/kg min h (30.6 % vs. 10 %). These findings were associated with a significantly higher incidence of abdominal compartment syndrome and sepsis in the high-volume resuscitation group. Nevertheless, general restriction of fluid resuscitation in AP would be the wrong interpretation since the less-hydrated groups with the more favourable outcome received early high-volume resuscitation markedly exceeding the recommendations of most guidelines [16, 17].

However, findings of Trepte et al. have to be analysed with caution because there are several potential differences between this animal study and the clinical setting. Treatment with different algorithms was started immediately after experimental induction of AP. In clinical routine, patients with AP present 12–36 h after the onset of pain [3]. Starting “re”-suscitation before established

fluid loss might explain some of the findings of Trepte et al. In a clinical setting, patients with SAP frequently present with already established dramatic fluid shifts with intravascular hypovolemia, increased haematocrit and IAH. As a consequence of increased IAP, CVP is frequently elevated despite central hypovolemia, which might result rather in fluid restriction when using CVP-based algorithms. With normal mean values for CVP, MAP and CI without catecholamines, aggressive early hydration aimed at “supranormal” CVP might have resulted in detrimental over-hydration in the controls.

Despite some evidence for the usefulness of dynamic preload markers such as SVV and PPV, several shortcomings in the use of these markers particularly for early application in AP have to be kept in mind. The use of SVV indispensably requires *controlled* mechanical ventilation, which is not a realistic scenario in patients with SAP on admission. Furthermore, SVV/PPV are less useful in patients with IAH [18]. Increased IAP is common in SAP and one of the best outcome predictors [19]. Due to dependency of SVV and PPV on tidal volume [20], the ventilator setting used in the study (tidal volume 10 ml/kg, exceeding the current ARDS net recommendations) might have resulted in more liberal initial resuscitation.

What are the implications for future research?

This study is the first providing clear evidence for the use of volumetric and dynamic preload markers in SAP. In view of the complex and prolonged ICU courses in AP, strategies combining volumetric and dynamic parameters (when applicable) with functional tests (passive leg raising, end-expiratory occlusion) and also taking into account IAP and abdominal perfusion pressure may improve outcome of SAP.

Despite a certain complexity, these strategies will be necessary to address different requirements of fluid support during different stages of AP with an early “ebb-phase” and a substantial risk in neglecting the appropriate turning point for initiating the “flow-phase” in patients with persisting capillary leakage and a high risk of fluid overload which is associated with a worse outcome [20–23].

The data of Trepte et al. shed a little light on the penumbra of fluid management in (S)AP. Nevertheless, there is still “more to the picture than meets the eye...”.

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