Volume assessment in patients with necrotizing pancreatitis: A comparison of intrathoracic blood volume index, central venous pressure, and hematocrit, and their correlation to cardiac index and extravascular lung water index*

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Objective: **Volume depletion and/or increased hematocrit are associated with poor prognosis in necrotizing pancreatitis. Several studies suggest that intrathoracic blood volume index (ITBI) might be superior to central venous pressure (CVP) with regard to preload assessment. Therefore, the aim of our study was to evaluate the predictive value of CVP and hematocrit with regard to ITBI, and to correlate these parameters to cardiac index (CI).**

Design: **Prospective study.**

Setting: **Medical intensive care unit, university hospital.**

Patients and Interventions: **Within 24 hrs of intensive care unit-admission, 96 hemodynamic measurements using the PiCCO system were performed in 24 patients with necrotizing pancreatitis.**

Main Results: **Mean CVP (12.11 ± 5.97 mm Hg; median 11.5 normal: 1–9 mm Hg) was elevated, whereas mean ITBI (822.8 ± 157.0 mL/m^2; median 836 mL/m^2; normal: 850–1000 mL/m^2) was decreased. Fifty-one of 96 ITBI values were decreased (prevalence of hypovolemia of 53%). No CVP value was decreased. Fifty-three CVP measurements were elevated despite simultaneous ITBI levels indicating a normal or decreased preload. Sensitivity, specificity, positive predictive value, and negative predictive value of CVP with regard to volume depletion (ITBI <850 mL/m^2), were 0%, 100%, 0%, and 47%, respectively. An increase in hematocrit (hematocrit >40% [female] or >44% [male]) was found in 11 of 51 measurements with decreased ITBI. Sensitivity, specificity, positive predictive value, and negative predictive value of an increase in hematocrit with regard to volume depletion according to ITBI were 22%, 82%, 58%, and 48%, respectively. ITBI and Δ-ITBI significantly correlated to CI and Δ-CI ($r = .566$, $p < 0.001$; $r = .603$, $p < 0.001$), respectively. CVP and Δ-CVP did not correlate to CI and Δ-CI, respectively. There was a significant correlation between ITBI and extravascular lung water index ($r = .392$; $p < 0.001$), but no correlation between CVP and extravascular lung water index ($r = .074$; $p = 0.473$).**

Conclusions: **Volume depletion according to ITBI was found in more than half the patients. The predictive values of CVP and hematocrit with regard to volume depletion were low. ITBI and its changes significantly correlated to CI and its changes, which was not observed for CVP and Δ-CVP. Therefore, ITBI appears to be more appropriate for volume management in necrotizing pancreatitis than CVP or hematocrit. (Crit Care Med 2008; 36:2348–2354)**

KEY WORDS: necrotizing pancreatitis; resuscitation; hemodynamics; preload; monitoring

Around 15% of patients with acute pancreatitis develop severe/necrotizing pancreatitis (NP) (1, 2). A recent study in technologically advanced intensive care units in the United Kingdom reported a mortality of 43% in patients with NP (3). Recognition and fluid resuscitation of these patients with NP within the first 48 hrs after the onset of symptoms has the potential of improving outcome (1, 4, 5). However, early recognition of the patients at risk of NP is difficult due to the low predictive value of most of the parameters within the first 48 hrs. For example, the Ranson score (6) has the disadvantage of requiring a full 48 hrs-period for its complete evaluation, and the predictive value of the Acute Physiology and Chronic Health Evaluation II score is rather its time course within the first 48 hrs than its level on admission (1, 6, 7).

Recently, two routine laboratory markers have been shown to have high negative predictive values with regard to NP on admission: an elevation of hematocrit (8–10) as well as increased blood glucose levels (11). An elevation of hematocrit ≥44% on admission and at 24 hrs had a negative predictive value for severe pancreatitis of 85% and 96%, respectively. All patients with increased hematocrit on admission and a further increase in hematocrit within the first 24 hrs developed NP (9). However, none of the patients who did not have a further increase in hematocrit developed NP, resulting in a positive predictive value of a further increase in elevated hematocrit within the first 24 hrs after admission of 100% (9). Furthermore, smaller animal and clinical trials have demonstrated the protective effects of early hemodilution (4, 5).

Nevertheless, aggressive volume therapy runs the risk of hyperhydration and pulmonary edema. This underlines the importance of appropriate volume assessment and resuscitation which is acknowledged in several guidelines (1, 2). Most of these guidelines recommend the insertion of a central venous catheter for ini-

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tial parenteral nutrition as well as for preload assessment using central venous pressure (CVP). Traditional preload parameters, such as the cardiac filling pressures, CVP, and pulmonary arterial occlusion pressure, have been shown to be of limited value with regard to preload assessment and "volume responsiveness" (12, 13). In contrast, modern hemodynamic parameters, such as the global end-diastolic volume index, the intrathoracic blood volume index (ITBI), and the variation in stroke volume, and pulse pressure (PPV), have been demonstrated to be superior to pressure-based preload parameters such as CVP and pulmonary arterial occlusion pressure (13, 14). Some of these new parameters can be determined by echocardiography, and can easily be obtained by commercially available monitoring systems such as the PiCCO (Pulsion Medical Systems, Munich, Germany), LiDCO (Cambridge, UK), or FloTrac (Edwards Lite Sciences, Munich, Germany). By including ITBI, global end-diastolic volume index, variation in stroke volume, and pulse pressure, the PiCCO system offers the complete bundle of hemodynamic parameters concerning volumetric preload and "volume responsiveness". In addition, extravascular lung water index (ELWI) as a marker of pulmonary edema can also be determined. Therefore, this hemodynamic tool is promising especially in patients with severe pancreatitis. Amazingly, there are no data on using these parameters in patients with NP. Therefore, it was the aim of our prospective study to evaluate the predictive value of CVP and hematocrit with regard to PiCCO-derived parameters within the first 24 hrs after admission.

Table 1. Patients' characteristics

Gender	
Male	14
Female	10
Age (yrs)	56.7 ± 18.6
Acute Physiology and Chronic Health Evaluation II score	20.4 ± 8.5 (8–34)
Etiology	
Alcohol	6
Biliary	10
Medication	1
Postoperative	1
Unknown	6[a]

[a]Unknown: no evidence of alcoholic, biliary, viral, hyperlipemic, hypercalcemic, drug-induced etiology, or induction of pancreatitis by surgery or endoscopic retrograde cholangio-pancreatography.

MATERIALS AND METHODS

After approval of the institutional ethics review, 24 patients with severe/necrotizing pancreatitis were included prospectively. Severe pancreatitis was assumed in patients with an Acute Physiology and Chronic Health Evaluation II score on admission of at least 8 and/or at least two Ranson-0 h-points and/or an elevation of hematocrit (>44% in men, >40 in women). NP was confirmed in all patients by the presence of necroses in contrast-enhanced CT and/or an elevation of C-reactive protein >15 mg/dL within 1 week after admission. No patient included in the study had to be excluded or was lost to follow-up.

Within 24 hrs after ICU admission, each patient had four hemodynamic measurements (0 hr, 8 hrs, 16 hrs, 24 hrs after admission) using the PiCCO system, resulting in a total of 96 measurements. A 5F thermistor-tipped arterial line (PV2025L20, Pulsiocath, Pulsion Medical Systems) was inserted in the femoral artery and connected to a commercially available hemodynamic monitor (PiCCO Plus; Pulsion Medical Systems).

Based on transpulmonary thermodilution following injection of 15 mL cold saline 0.9% via a conventional central venous catheter, cardiac index (CI), systemic vascular resistance index (SVRI), global end-diastolic volume index, ITBI, and ELWI were determined. Each PiCCO measurement represents the mean of three consecutive thermodilution measurements within 5 mins. In parallel with each hemodynamic measurement, hematocrit was also determined.

End Points. The primary end points were the prevalence of hypo- and hypervolemia according to ITBI (ITBI <850 mL/m^2 and ITBI >1000 mL/m^2, respectively) and the predictive values of CVP (normal: 1–9 mm Hg) and hematocrit (volume depletion assumed in patients with hematocrit >40% [female] or hematocrit >44% [male]) with regard to hypo- and hypervolemia according to ITBI.

Further end points were the correlation of the baseline values of CVP, hematocrit, and ITBI to baseline CI as well as the correlation of Δ-CVP, Δ-hematocrit and Δ-ITBI to Δ-CI with the Δ-values being the difference of these parameters (8, 16, and 24 hrs) and their baseline values (0 hr). Comparisons of Δ-values were calculated for all measurements except where indicated.

The therapeutic algorithm concerning fluid management was based on ITBI and ELWI with a target ITBI of 850 to 1000 mL/m^2 in patients with ELWI <10 mL/kg or 750 to 850 mL/m^2 in patients with ELWI ≥10 mL/kg and/or P_{AO_2}:FIO_2 <250.

Statistics. SPSS Software (Chicago, IL), Spearman correlation.

RESULTS

Patients' Characteristics

Table 1 summarizes the patients' characteristics.

Baseline Hemodynamic Parameters

Table 2 shows the baseline hemodynamic data.

Mean CVP (12.11 ± 5.97 mm Hg; median 11.5 mm Hg) was elevated, whereas mean ITBI (822.8 ± 157.0 mL/m^2; median 836 mL/m^2; normal: 850-1000 mL/m^2) was decreased. Fifty-one of 96 ITBI values were decreased, resulting in a prevalence of hypovolemia of 53% (Fig. 1). By contrast, none of the CVP values were below the lower normal level (Fig. 2; Tables 3 and 4). Fifty-three CVP measurements were elevated, although simultaneous ITBI levels indicated normal or decreased preload. Hypervolemia according to increased ITBI was much less frequent than hypovolemia, found in 13 of 96 measurements (14%).

Predictive Value of CVP With Regard to Hypo- and Hypervolemia

Sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of CVP

Table 2. Baseline hemodynamic data

Parameter	Normal Range	Mean ± SD	Median
CVP	1–9 (mm Hg)	12.11 ± 5.97	11.5
ITBI	850–1000 (mL/m^2)	822.8 ± 157.0	836
CI	3.0–5.0 (L/min/m^2)	4.15 ± 1.08	4.12
SVRI	1700–2400 (Dyne·s/cm^5/m^2)	1734.6 ± 636	1546
ELWI	3.0–7.0 (mL/kg)	6.04 ± 2.08	6
Hematocrit (%)			
Female	≤40	37.7 ± 7.6	34
Male	≤44		

CVP, central venous pressure; ITBI, intrathoracic blood volume index; CI, cardiac index; SVRI, systemic vascular resistance index; ELWI, extravascular lung water index.

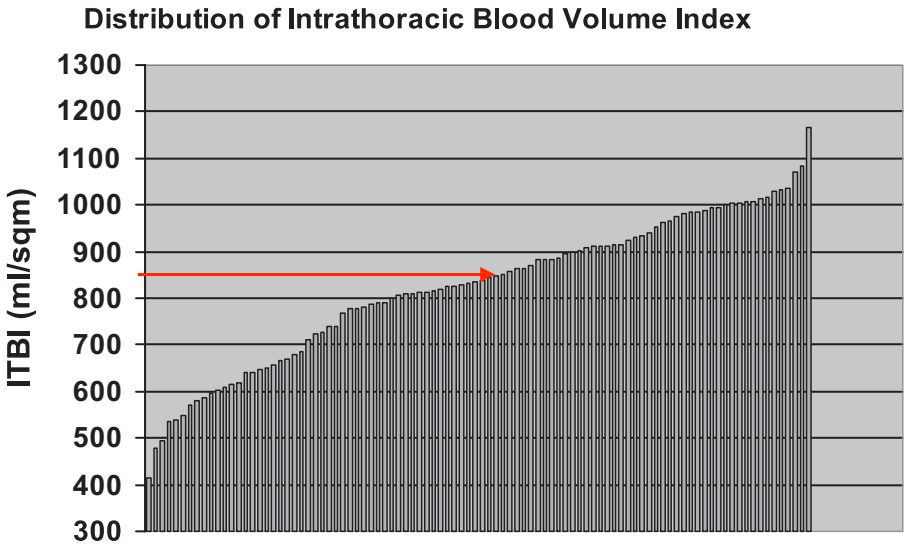

Figure 1. Distribution of intrathoracic blood volume index (*ITBI*) values (normal range: 850–1000 mL/sdqm).

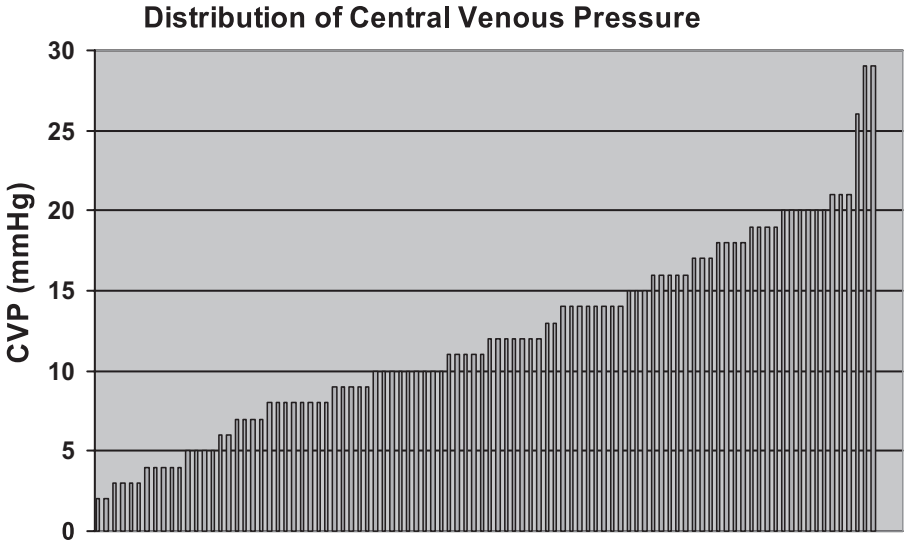

Figure 2. Distribution of central venous pressure (*CVP*) values.

Table 3. Comparison of intrathoracic blood volume index (ITBI) and central venous pressure (CVP)

	ITBI <850 mL/m^2	ITBI 850–1000 mL/m^2	ITBI >1000 mL/m^2
CVP <1 mm Hg	0	0	0
CVP 1–9 mm Hg	19	12	3
CVP >9 mm Hg	32	21	9

with regard to volume depletion (ITBI < 850 mL/m^2) were 0%, 100%, 0%, and 47%, respectively, and with regard to hypervolemia (ITBI >1000 mL/m^2) were 75%, 37%, 14%, and 91%, respectively (Table 4). The accuracy of CVP was 22%. There was no correlation between CVP and ITBI (coefficient of correlation −0.135; $p = 0.189$; Fig. 3).

Table 4. Statistical analysis of the predictive value of central venous pressure with regard to intrathoracic blood volume index

	Hypovolemia	Hypervolemia
Sensitivity (%)	0	75
Specificity (%)	100	37
Positive predictive value (%)	0	14
Negative predictive value (%)	47	91
Accuracy (%)	22	
Prediction of normal range (%)	36	

Predictive Value of Hematocrit

Mean hematocrit was 37.7 ± 7.6% (median 33.95%). An increase in hematocrit was found in 11 of 51 measurements with decreased ITBI. Sensitivity, specificity, PPV, and NPV of an increase in hematocrit with regard to volume depletion according to ITBI were 22%, 82%, 58%, and 48%, respectively.

Hematocrit did not correlate to ITBI ($r = -.044$; $p = 0.668$; Fig. 4). However, it correlated to SVRI ($r = .502$; $p < 0.001$).

Correlation of Baseline and Follow-Up Levels of CI to ITBI and CVP, Respectively

Baseline Values. ITBI significantly correlated to CI ($r = .566$; $p < 0.001$), whereas CVP did not correlate to CI ($r = -.089$; $p = 0.391$) (Fig. 5A and 5B).

There was a significant correlation of the baseline values of ITBI and ELWI ($r = .392$, $p < 0.001$). However, CVP and ELWI did not correlate ($r = .074$; $p = 0.473$).

Follow-Up Values After 8 hrs, 16 hrs, and 24 hrs. Changes in CVP (Δ-CVP) did not correlate to Δ-CI at any of the follow-up time points ($r = .063$, $p = 0.543$ [for all follow-up values]; $r = .080$, $p = 0.709$ after 8 hrs; $r = .078$, $p = 0.717$ after 16 hrs; $r = .025$, $p = 0.909$ after 24 hrs). However, there was a significant positive correlation between Δ-ITBI and Δ-CI in the cumulative analysis of all follow-up values ($r = .603$; $p < 0.001$; Fig. 5C and Fig. 5D) as well as after 8 hrs ($r = .516$; $p = 0.010$), after 16 hrs ($r = .778$; $p < 0.001$), and after 24 hrs ($r = .687$; $p < 0.001$). Δ-ITBI-based volume management resulted in an increase in Δ-CI in 58 of 72 (81%) of comparisons with baseline. Δ-CI was ≥5%, ≥10%, ≥15%, and ≥0.5/min/m^2 in 39 of 72 (54%), 32 of 72 (44%), 27 of 72 (38%), and 33 of 72 (46%) of the measurements.

Furthermore, there was a strong correlation between Δ-SVRI and Δ-CI at all measurement time points ($r = -.488$, $p < 0.016$ after 8 hrs; $r = -.656$, $p < 0.001$ after 16 hrs; $r = -.675$, $p < 0.001$ after 24 hrs; and $r = -.594$, $p < 0.001$ for all follow-up values). Δ-ELWI correlated to Δ-CI after 8 hrs ($r = .414$, $p = 0.044$), 16 hrs ($r = .465$, $p = 0.022$) and for all measurements ($r = .370$, $p < 0.001$).

Additionally there was a weak correlation between Δ-hematocrit and Δ-CI ($r = -.282$, $p = 0.005$) for all measurements.

Despite the absence of a correlation with Δ-CI, Δ-CVP was interestingly correlated to Δ-ELWI ($r = .588$, $p < 0.001$ for all measurements; $r = .539$, $p =$

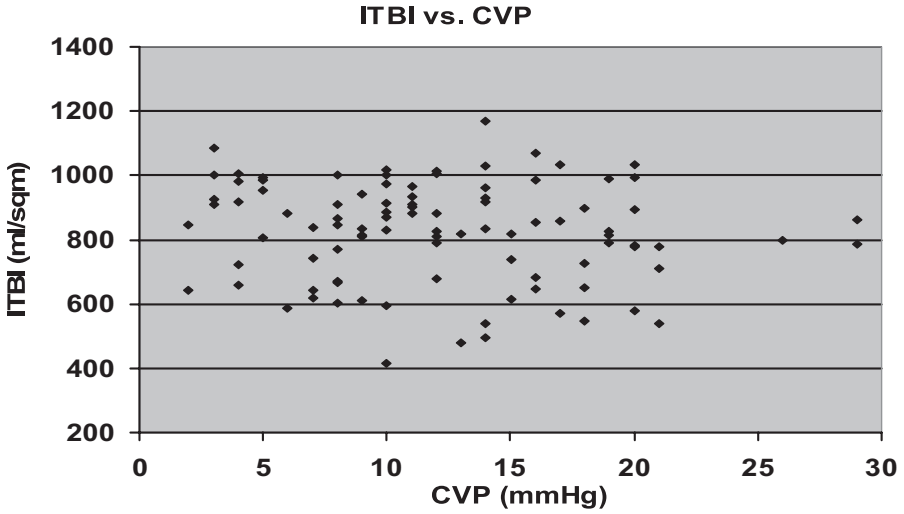

Figure 3. No correlation between intrathoracic blood volume index (*ITBI*) and central venous pressure (*CVP*).

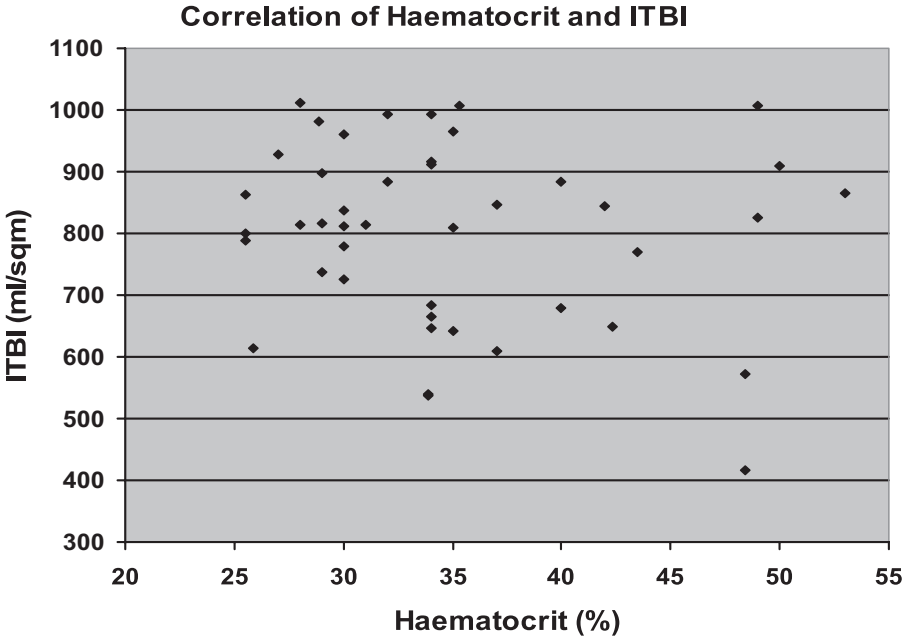

Figure 4. No correlation between hematocrit and intrathoracic blood volume index (*ITBI*).

0.007 after 8 hrs; $r = .399$, $p = 0.054$ after 16 hrs; and $r = .722$, $p < 0.001$ after 24 hrs).

Furthermore, Δ-CVP was weakly correlated to Δ-hematocrit ($r = -.216$, $p = 0.034$) and Δ-SVRI ($r = -.306$, $p = 0.002$; all measurements).

Outcome

All patients were volume-resuscitated according to PiCCO parameters. ICU mortality was 1 of 24 (4%).

DISCUSSION

Early goal-directed resuscitation is a cornerstone in the treatment of severe sepsis, resulting in a significant reduction in mortality (15). Since severe pancreatitis is a classic etiology of systemic inflammatory response syndrome, the pathophysiology of NP is in many ways very similar to that of sepsis. Activation of the same cascades of mediators as in sepsis—but without an infectious focus—mimics most of the pathomechanisms of sepsis including septic hemodynamics with hyperdynamic circulatory failure, capillary leakage, and intravascular volume depletion. In addition to the same common pathways as sepsis, decreased fluid intake, vomiting, paralytic ileus, (peri-)pancreatic edema, exudation, fluid collections, and fluid loss into the third space (pleural effusions, ascites) contribute to intravascular fluid deficiency in pancreatitis. In these patients, there may be volume deficiency in the intravascular compartment as well as enhanced volume in the interstitial and third space compartments. Therefore, clinical assessment of intravascular volume and preload are particularly difficult in severe pancreatitis. Similar to septic and hypovolemic shock, intravascular volume depletion largely contributes to consecutive organ failures. Recent data suggest a high prognostic value of hemoconcentration and intravascular volume depletion in patients with acute pancreatitis (8–10). Several animal studies have demonstrated beneficial effects of early aggressive volume resuscitation (4,5). Therefore, monitoring of preload and volume resuscitation have become integral parts of the guidelines for managing acute pancreatitis. Most of these guidelines recommend preload assessment using cardiac filling pressures such as CVP and pulmonary artery wedge pressure, regardless of the absence of data proving the beneficial effects using these tools in volume management in severe pancreatitis (1, 2). The concept of "fluid responsiveness" has been established as the gold standard for the evaluation, if a hemodynamic parameter is appropriate, to predict the therapeutic effects of volume therapy. According to this concept, a certain amount of fluid is applied intravenously, and the baseline and follow-up preload parameters are correlated to CI and its changes following fluid application. This requires baseline and follow-up measurements of preload parameters as well as CI. Numerous recent studies have demonstrated that these pressure-based parameters, CVP and pulmonary capillary wedge pressure, are unreliable in the assessment of preload and volume responsiveness (12–14). This might in part be related to confounders of these pressure-based parameters such as intra-abdominal pressure, mechanical ventilation, mediastinal edema, and pleural effusions, all of which result in an increase in intrathoracic pressure and cardiac filling pressure, despite an impairment of venous return (16). Most of these confounders are frequently found in severe pancreatitis. Therefore, from a pathophysiological viewpoint, cardiac filling pressures seem to be particularly inadequate in severe pancreatitis. Nevertheless, to the best of our knowledge, there are no data using modern hemodynamic parameters such as ITBI, global end-diastolic volume index, stroke volume vari-

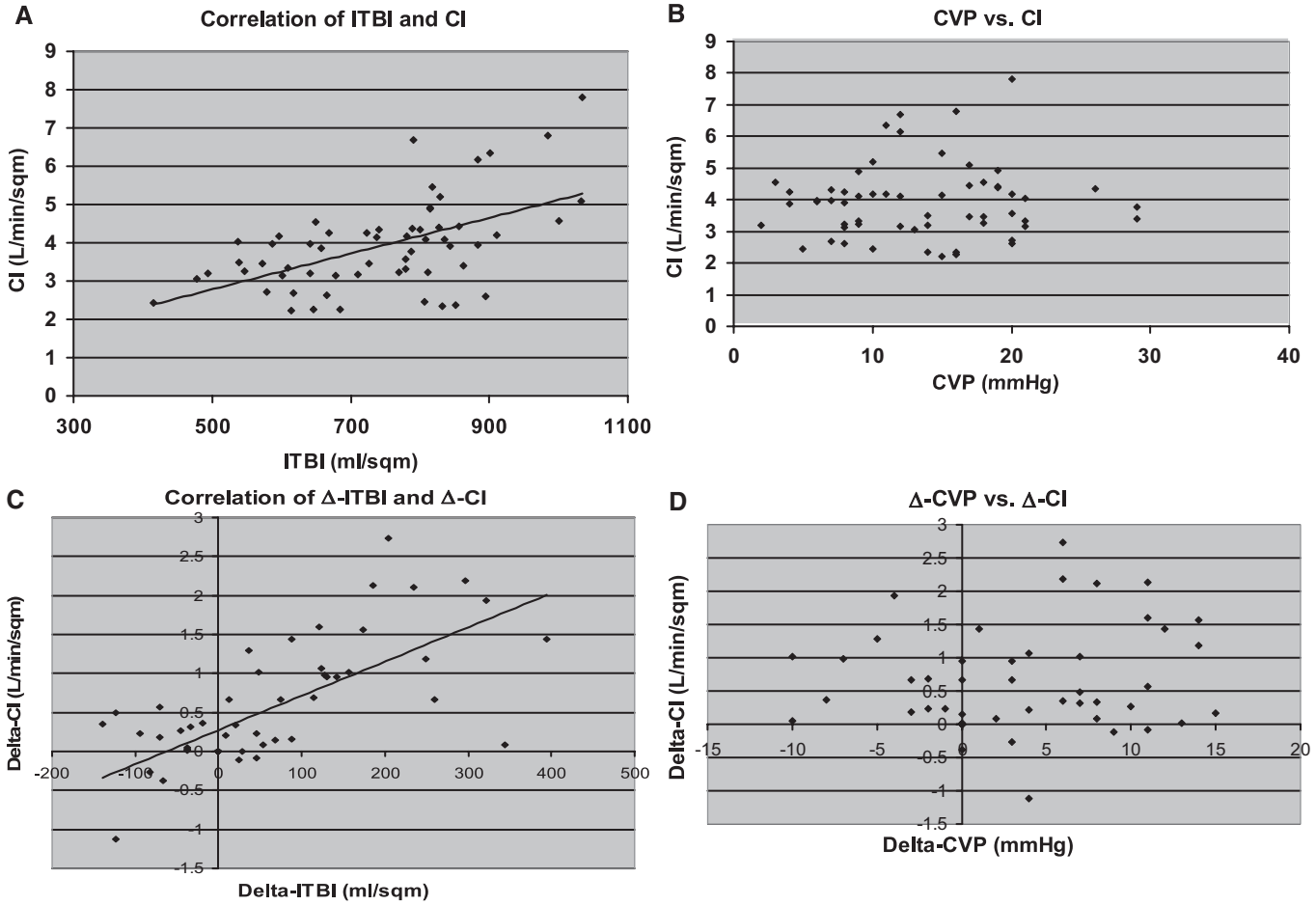

Figure 5. Significant correlations between intrathoracic blood volume index (*ITBI*) and cardiac index (*CI*) (*A*) and between Δ-ITBI and Δ-CI (*C*). No correlation between central venous pressure (CVP) CI (*B*) and no correlation between Δ-CVP and Δ-CI (*D*).

ation, PPV, and ELWI in patients with NP. SVV and PPV, which might be superior even to ITBI and GEDI (14), are only applicable in patients on controlled mechanical ventilation and sinus rhythm. Because most of the patients with severe pancreatitis are spontaneously breathing within the first days after admission, our protocol focused on the volumetric parameters ITBI and ELWI.

As demonstrated in healthy volunteers (13), cardiac surgery patients (14) and several other underlying conditions (12), our data demonstrate that in severe pancreatitis CVP is not appropriate to assess preload or to guide volume resuscitation. There was neither a correlation of baseline CVP to baseline levels to ITBI nor to CI. The same results were found for Δ-CVP with regard to Δ-ITBI and Δ-CI. The predictive values of central venous pressure with regard to hypovolemia and hypervolemia according to ITBI were poor.

This does not necessarily mean that ITBI is the appropriate tool to guide volume resuscitation in these patients. However, the highly significant correlation of ITBI to CI and Δ-ITBI to Δ-CI as well as to ELWI and Δ-ELWI, clearly demonstrates a crucial role of ITBI in the pathophysiology of severe pancreatitis.

Although it is obvious that early goal-directed volume resuscitation is a major target of therapy in severe pancreatitis, the risks of volume overload with pulmonary edema have to be kept in mind. Several recent studies demonstrated a worsening of prognosis and respiratory parameters in parallel to increasing extravascular lung water (17–19). Although, again, there was no correlation between central venous pressure and ELWI, ITBI and Δ-ITBI were highly significantly correlated to ELWI and Δ-ELWI, respectively.

With respect to these data, there remains the question as to what the future role of CVP in hemodynamics in pancreatitis will be. Despite its failure to predict ITBI, CI, and ELWI, we found a correlation between CVP and SVRI ($r = -.247$; $p = 0.015$), and correlations of Δ-CVP with Δ-ELWI ($r = .588$; $p < 0.001$), Δ-hematocrit ($r = -0.216$; $p = 0.034$) and Δ-SVRI ($r = -.306$; $p = 0.002$). These findings suggest a role for CVP in the complex interactions of hemodynamic parameters. However, this role of CVP might be more a rough estimation of whole body fluid content and fluid "trapped precardially" and not immediately available to be transformed to cardiac output (i.e., volume responsiveness). The most important shortcoming of CVP might be its dependency on pressures in other physiologic compartments including the IAP, intrapulmonary and intrathoracic pressures (16,20–22). Therefore, several correction formulas have been proposed resulting in a "corrected CVP" by subtracting 20% to 80% of intra-abdominal pressure (IAP) from CVP (16). Nevertheless, this only corrects one of the confounders of CVP and requires additional measurement of IAP. Therefore, if modern hemodynamic monitoring including ITBI and ELWI is not available,

CVP should be relied on only in less severe cases of pancreatitis, when confounders such as increased IAP, pleural effusions, or mechanical ventilation are less likely. In case of doubt, additional volumetric information should be obtained using transthoracic or transesophageal echocardiography (13). Additionally urinary output and response to passive leg raising should be considered.

The low predictive value of hematocrit in our study might be related to the timing of the study protocol including also patients after completing the Ranson 48-hr criteria. This might have reduced the prognostic value of hematocrit in several patients, because its best predictive capabilities have been demonstrated immediately after admission to the emergency department and not up to 72 hrs later. The problem of time dependency of "pro"gnostic parameters in pancreatitis has been addressed previously (23).

Limitations of the Study

These data were obtained in a limited number of patients with early stage severe pancreatitis using Δ-CI as a hemodynamic surrogate parameter for short-term hemodynamic improvement. Nevertheless, Δ-CI is considered as the hemodynamic gold standard parameter for the assessment of volume responsiveness (12–14,24). Despite the short observation periods of 8 hrs, 16 hrs, and 24 hrs, the absence of an aggressive resuscitation algorithm and a hemodynamic management primarily guided by ITBI and not by CI, this volume management resulted in significant changes of Δ-CI $\geq$10% and Δ-CI $\geq$0.5 L/min/m^2 in 32 of 72 (44%) and 33 of 72 (46%) measurements. This does not necessarily imply that patients with less severe or late-stage pancreatitis must be treated using advanced hemodynamic monitoring. By contrast, in these patients prolonged parenteral feeding using a central venous line should be avoided, and in most of the cases the use of an arterial line is not necessary.

Intra-abdominal pressure (IAP) has recently been shown to be highly predictive of outcome in pancreatitis (25). Therefore, the additional measurement of IAP in our patients might have provided further insight in the complex hemodynamics in severe pancreatitis. Despite the overall favorable outcome related to the severity of pancreatitis/APACHE II, suggesting an improved outcome using PiCCO-guided volume resuscitation, these data have to be confirmed in a randomized controlled study. This study should include monitoring of IAP, as well as markers of macro- and microcirculation such as serum lactate, Scv O_2, indocyanine-green clearance (15,23) and urinary output. The more protracted resolution or prevention of organ failures such as prerenal acute renal failure will require much longer observation than the 24-hr period of our study.

To summarize, this study has shown that CVP is not appropriate for guiding volume resuscitation in severe early-stage pancreatitis. Hematocrit value is a useful predictive tool in the emergency room; however, its role after the commencement of resuscitation remains to be determined. With respect to the particular complexity of hemodynamics in NP, modern hemodynamic monitoring including CI as well as volumetric parameters (global end-diastolic volume index, ITBI, and ELWI) is promising for optimizing the prognosis of these patients with significant mortality.

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