Impact of large-volume thoracentesis on transpulmonary thermodilution–derived extravascular lung water in medical intensive care unit patients

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Abstract
Purpose: The purpose of this study was to investigate the impact of large-volume thoracentesis (>1000 mL) on transpulmonary thermodilution (TPTD)–derived cardiopulmonary parameters with special regard to extravascular lung water index (EVLWI).

Materials and Methods: Retrospective analysis of a prospectively maintained database including TPTD measurements of patients treated in a medical intensive care unit of a German university hospital between January 2009 and September 2010. Data of 17 patients treated with large-volume thoracentesis were analyzed.

Results: A median of 1350 (25%-75% interquartile range [IQR], 1200-1590) mL of pleural fluid was removed. Extravascular lung water index was statistically significantly higher after thoracentesis compared with baseline (9.0 [IQR, 8.0-13.0] vs 8.0 [IQR, 7.0-13.0] mL/kg) (P = .039). Pulmonary vascular permeability index (PVPI) also increased significantly after thoracentesis (1.7 [IQR, 1.3-2.4] vs 1.4 [IQR, 1.1-2.1]) (P = .019). When determined 2 and 6 hours after thoracentesis, EVLWI and PVPI even further increased. Six hours after removal of pleural fluid, we observed a median EVLWI of 11.0 (IQR, 8.0-15.0) mL/kg (P = .048 compared with baseline) and a median PVPI of 2.0 (IQR, 1.5-2.7) (P = .040 compared with baseline).

Conclusions: Large-volume thoracentesis results in a statistically significant increase in TPTD-derived EVLWI. Because EVLWI was higher after removal of pleural fluid, we conclude that pleural effusions do not take part in single-indicator TPTD as a part of the pulmonary thermovolume and do not increase TPTD-derived EVLWI.

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1. Introduction

Pleural effusions are a common finding in critically ill patients treated in the intensive care unit (ICU) [1].
Both hemodynamic and respiratory function might be compromised by pleural effusions according to data from experimental and clinical studies [2-6]. For treatment of pleural effusions, thoracentesis is a frequently performed procedure.

Single-indicator transpulmonary thermodilution (TPTD) is increasingly used for advanced hemodynamic monitoring in ICU patients. Transpulmonary thermodilution provides parameters reflecting pulmonary hydration (extravascular lung water index [EVLWI]) and pulmonary permeability (pulmonary vascular permeability index [PVPI]) [7-10]. In addition, cardiac function (cardiac index [CI]) and cardiac preload (global end-diastolic volume index [GEDVI]) can be assessed by TPTD [11-14].

Data on the influence of pleural effusions and large-volume thoracentesis on TPTD parameters in medical ICU patients are scarce. Therefore, it was the aim of our study to investigate the impact of large-volume thoracentesis on TPTD-derived hemodynamic and pulmonary parameters in medical ICU patients with special regard to EVLWI.

2. Materials and methods

2.1. Study design, setting, patients, and data extraction

We performed a retrospective analysis of a prospectively maintained TPTD database investigating the effect of large-volume thoracentesis (>1000 mL) on cardiopulmonary parameters in critically ill patients treated in a medical ICU of a German university hospital between January 2009 and September 2010. The study protocol was approved by the institutional review board of our hospital.

We screened the database for patients monitored using TPTD and treated with thoracentesis for pleural effusions. Patients in whom TPTD measurements were recorded directly before and directly after thoracentesis were eligible for study inclusion. Thirty-three thoracenteses with accompanying TPTD data were identified. Thirteen measurements were excluded from the analysis because the amount of pleural fluid removed was less than 1000 mL. In 3 patients, 2 large-volume thoracenteses were recorded each. To avoid repeated measurements within 1 individual, only the first measurement in each patient was included in the study. Therefore, 17 large-volume thoracenteses in 17 patients were included in the final statistical analysis.

Patients’ basic characteristics and demographic data as well as data on hemodynamics (including TPTD measurements) and respiratory function were extracted from the patients’ medical records and the TPTD database. Hemodynamic parameters including variables derived from TPTD before thoracentesis and immediately after thoracentesis were analyzed and compared. Transpulmonary thermodilution measurements were additionally available 2 hours after thoracentesis in 13 patients (PVPI in 12 patients). Six hours after removal of pleural fluid, all TPTD data were available in 11 patients. Data on gas exchange (blood gas analysis and fraction of inspired oxygen [FiO2]) were available before and directly after thoracentesis. In 16 patients, these data were additionally available 2 hours after thoracentesis.

2.2. Transpulmonary thermodilution

For determination of EVLWI, PVPI, CI, GEDVI, and systemic vascular resistance index (SVRI), the PiCCO System (Pulsion Medical Systems, Munich, Germany) was used. After injection of the indicator bolus (15 mL of iced 0.9% saline solution) through a central venous catheter, the thermodilution curve was recorded and displayed using a 5F arterial line with a thermistor (Pulsiocath; Pulsion Medical Systems) and a hemodynamic monitor (PiCCOplus or PiCCO2; Pulsion Medical Systems). Each TPTD measurement was performed in triplicate, and the resulting mean values of the hemodynamic parameters were recorded.

2.3. Statistical analysis

For statistical analyses, we used IBM SPSS Statistics 19 (SPSS Inc, Chicago, Illinois). Continuous variables are presented by using median and interquartile range (IQR) (ie, 25%-75% percentile). Categorical data were summarized by absolute frequencies and percentages. To compare the patients’ hemodynamic and respiratory parameters before and after thoracentesis, Wilcoxon test for paired samples was used. In addition, we evaluated the impact of mechanical ventilation on thoracentesis-induced changes in EVLWI using the nonparametric Mann-Whitney U test for these group comparisons. \( P < .05 \) was considered to indicate statistical significance.

3. Results

3.1. Patients’ characteristics

In Table 1, the characteristics of patients included in this study are shown.

3.2. Thoracentesis

In the 17 patients undergoing large-volume thoracentesis, a median of 1350 mL (IQR, 1200-1590 mL) of pleural fluid was removed. Pleural fluids had a median total cell count of 230/μL (IQR, 130-430/μL). The median pleural fluid protein level was 1.42 g/dL (IQR, 1.08-2.19 g/dL).

3.3. Effects of thoracentesis on hemodynamic parameters

After thoracentesis, CI was significantly lower when compared with baseline (4.0 L/min/m² [IQR, 2.7-5.2 L/min/m²] vs 4.7 L/min/m² [IQR, 3.5-5.8 L/min/m²]) (\( P = .039 \)) (Table 2). A
significant decrease in heart rate was observed after thoracentesis compared with the baseline values (96 beats per minute [IQR, 87-104 beats per minute] vs 104 beats per minute [IQR, 89-106 beats per minute]) \( (P = .039) \), whereas stroke volume was not significantly changed by thoracentesis. When measured 2 hours and 6 hours after thoracentesis, CI \( (P = .116 \text{ and } .091, \text{ respectively}) \), stroke volume \( (P = .279 \text{ and } .110, \text{ respectively}) \), and heart rate \( (P = .700 \text{ and } .477, \text{ respectively}) \) were not statistically significantly different compared with the values assessed before thoracentesis.

There was no statistically significant change in central venous pressure (CVP) and TPTD-derived GEDVI or SVRI after thoracentesis (Table 2).

### 3.4. Effects of thoracentesis on gas exchange

As shown in Table 3, median arterial partial pressure of oxygen (\( \text{PaO}_2 \)), \( \text{PaO}_2/\text{FiO}_2 \) ratio, and arterial partial pressure of carbon dioxide (\( \text{PaCO}_2 \)) observed directly after thoracentesis and 2 hours after thoracentesis were not statistically significantly different compared with baseline values obtained before thoracentesis.

### 3.5. Effects of thoracentesis on transpulmonary thermodilution-derived pulmonary parameters

Transpulmonary thermodilution–derived EVLWI was statistically significantly higher after thoracentesis compared with baseline (9.0 mL/kg [IQR, 8.0-13.0 mL/kg] vs 8.0 mL/kg [IQR, 7.0-13.0 mL/kg]) \( (P = .039) \) (Table 4). Pulmonary vascular permeability index increased significantly directly after thoracentesis \( (1.7 \text{ IQR, 1.3-2.4} \text{ vs 1.4 \text{ IQR, 1.1-2.1}}) \ (P = .019) \).

When determined 2 and 6 hours after thoracentesis, EVLWI and PVPI even further increased (Table 4). Six hours after removal of pleural fluid, median EVLWI was 11.0 mL/kg (IQR, 8.0-15.0 mL/kg) \( (P = .048 \text{ compared with baseline}) \).

There was a statistically significant difference in EVLWI changes between patients on mechanical ventilation and patients without mechanical ventilation when comparing EVLWI values at baseline and EVLWI values obtained 6 hours after thoracentesis \( (2.0 \text{ mL/kg IQR, 1.0-3.0 mL/kg} \text{ vs 0.0 mL/kg IQR, 0.0-0.0 mL/kg}) \ (P = .009) \). However, the differences in EVLWI values measured before thoracentesis and directly after thoracentesis as well as measured 2 hours after thoracentesis were not statistically significantly different between these patients \( (P = .277 \text{ and } .534, \text{ respectively}) \).

### 4. Discussion

We performed a study evaluating the impact of large-volume thoracentesis on TPTD-derived hemodynamic parameters in medical ICU patients.

The main finding of our analysis is that large-volume thoracentesis results in a statistically significant increase in TPTD-derived EVLWI and PVPI.
In critical care, EVLWI is increasingly used to quantify pulmonary volume status. Transpulmonary thermodilution–derived EVLWI has been shown to correlate with gravimetric measurement of lung water in an experimental setting [7] and with postmortem lung weight in humans [9]. Regarding pulmonary function, it has been demonstrated that EVLWI correlates with markers of acute lung injury in critically ill patients [15]. Moreover, results of an animal study showed that even small increases in extravascular lung water (EVLW) can be accurately detected by EVLWI obtained using TPTD [8]. Because it has been demonstrated that EVLWI can predict acute lung injury [16], it has been suggested to use EVLWI as a definition criterion for acute lung injury [17].

When discussing the impact of pleural effusions on TPTD-derived EVLWI, several considerations have to be taken into account.

Simplified, calculation of EVLWI using TPTD is based on the loss of thermal indicator when the bolus passes the pulmonary circulation [18,19].

Rather based on expert opinion than on systematic data, it has been proposed that pleural fluid might contribute to the dilution of the indicator bolus by being part of the pulmonary thermovolume [20]. If pleural effusions were to be traversed by the cold indicator bolus and, therefore, would participate in TPTD by increasing the pulmonary thermovolume, increased EVLWI values would be observed in patients with pleural effusions, and a decrease in EVLWI should result when pleural fluid is removed by thoracentesis.

However, our data clearly demonstrate that EVLWI values are not higher when pleural effusions are present. This finding might be explained as follows: for measurement of EVLWI using single-indicator TPTD, a thermal indicator bolus (cold saline solution) is injected in the superior vena cava through a central venous catheter [19]. The bolus rapidly passes the right heart, the pulmonary circulation, and the left heart and subsequently reaches the site of distal temperature measurement (ie, arterial catheter with thermistor in the abdominal aorta). Calculation of EVLW (ie, fluid outside of the pulmonary vasculature in the lung tissue or alveoli) is based on the loss of the thermal indicator during its transit of the pulmonary circulation [18,19]. From a theoretical point of view, it seems unlikely that fluid in the pleural space can relevantly contribute to the dilution of the thermoincicator bolus rapidly passing the pulmonary circulation because of the physical distance between fluid in the pleural cavity and the pulmonary vasculature (in contrast to fluid in the lung interstitium or alveolar fluid directly surrounding the vascular system).

In our study, EVLWI even increased statistically significantly after removal of pleural effusions by large-volume thoracentesis. Different explanations can be proposed for this observation.

First, large pleural effusions compress lung parenchyma, thus causing atelectasis. In atelectatic lung regions, perfusion (ie, pulmonary blood flow) is reduced secondary according to the Euler-Liljestrand mechanism [21]. Reduced blood flow results in reduced blood volume taking part in TPTD in these lung regions. Therefore, the increase in EVLWI after removal of large amounts of pleural fluid might be owing to the fact that the atelectatic lung regions can expand after decompression by large-volume thoracentesis (like a sponge reexpanding after compression). After that decompression, pulmonary blood flow can increase secondary in these lung regions. The increase in pulmonary thermovolume taking part in TPTD might result in increased EVLWI values after large-volume thoracentesis.

Second, additional fluid extravasation could be induced by reperfusion of lung regions formerly compressed by pleural fluid. Extravasation of fluid after removal of pleural effusions.

### Table 3: Effects of thoracentesis on gas exchange

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before thoracentesis</th>
<th>After thoracentesis</th>
<th>P compared with baseline</th>
<th>2 h after thoracentesis</th>
<th>P compared with baseline</th>
<th>6 h after thoracentesis</th>
<th>P compared with baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂, mm Hg</td>
<td>78.9 (76.2-85.0)</td>
<td>92.3 (77.0-96.5)</td>
<td>.136</td>
<td>81.5 (68.0-93.0)</td>
<td>.959</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FIO₂ ratio</td>
<td>210.5 (194.3-280.8)</td>
<td>236.5 (203.2-302.5)</td>
<td>.287</td>
<td>226.9 (180.7-277.0)</td>
<td>.756</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>41.2 (34.2-57.9)</td>
<td>37.7 (33.5-53.4)</td>
<td>.352</td>
<td>39.5 (32.2-51.1)</td>
<td>.979</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as median and IQR (25%-75% percentile). To compare baseline respiratory parameters with parameters after thoracentesis and 2 hours after thoracentesis, Wilcoxon test for paired samples was used.

### Table 4: Effects of thoracentesis on TPTD-derived pulmonary parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before thoracentesis</th>
<th>After thoracentesis</th>
<th>P compared with baseline</th>
<th>2 h after thoracentesis</th>
<th>P compared with baseline</th>
<th>6 h after thoracentesis</th>
<th>P compared with baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVLWI, mL/kg</td>
<td>8.0 (7.0-13.0)</td>
<td>9.0 (8.0-13.0)</td>
<td>.039*</td>
<td>9.0 (8.0-14.0)</td>
<td>.026*</td>
<td>11.0 (8.0-15.0)</td>
<td>.048*</td>
</tr>
<tr>
<td>PVI</td>
<td>1.4 (1.1-2.1)</td>
<td>1.7 (1.3-2.4)</td>
<td>.019*</td>
<td>1.8 (1.6-2.7)</td>
<td>.015*</td>
<td>2.0 (1.5-2.7)</td>
<td>.040*</td>
</tr>
</tbody>
</table>

Data are presented as median and IQR (25%-75% percentile). To compare baseline TPTD-derived pulmonary parameters with parameters after thoracentesis and 2 hours after thoracentesis, Wilcoxon test for paired samples was used. Significant changes are indicated by an asterisk.
effusions (so-called reexpansion pulmonary edema) has been described as a rare but potentially fatal complication of large-volume thoracentesis [22-24]. In our study, EVLWI determined directly after thoracentesis slightly but statistically significantly increased compared with baseline (9.0 vs 8.0 mL/kg). However, when assessed 6 hours after thoracentesis, EVLWI further increased to a median of 11.0 mL/kg (which is a markedly elevated value even in critically ill patients). In addition to EVLWI, PVPI also significantly increased after large-volume thoracentesis in our study. Pulmonary vascular permeability index is obtained by dividing EVLW by pulmonary blood volume (PBV) (both obtained using TPTD) [10]. Pulmonary vascular permeability index, therefore, is a marker of pulmonary vascular permeability, that is increased in diseases associated with damage in the lung capillary wall, whereas it is not elevated in hydrostatic pulmonary edema [10]. The finding that EVLWI increased to markedly elevated values after removal of pleural fluid whereas PVPI remained relatively low (ie, below the critical upper threshold of 3 that indicates pulmonary edema associated with capillary leakage in pneumonia or acute respiratory distress syndrome) provides evidence for the presence of postthoracentesis hydrostatic pulmonary edema.

Our hypothesis that pleural fluid does not take part in thermodilution when determining EVLWI using single-indicator TPTD is in accordance with previous data [9,25,26]. An animal study by Blomqvist et al [25] using a double-indicator dilution technique showed that pleural fluid does not affect EVLW measurements. Moreover, in the autopsy study by Tagami et al [9], the correlation of TPTD-derived EVLW and postmortem lung weight was not dependent on the degree of pleural effusions. There is a previous clinical study evaluating the impact of pleural fluid on EVLWI measurement in 8 critically ill patients [26]. Although the mean amount of pleural fluid removed (765 ± 330 mL) was markedly lower in this previous study by Deeren et al [26] compared with our study, the authors also observed a thoracentesis-induced increase in EVLWI and concluded that “fluid in the pleural space does not contribute to the volume transversed by the thermal indicator” when using TPTD for EVLWI measurement.

Regarding hemodynamics, it has been demonstrated in an animal model that pleural effusions can cause a diastolic collapse of the right ventricle and, therefore, impair right ventricular relaxation in dogs [2]. In humans, there are case reports describing that large pleural effusions might even cause cardiac tamponade or shock [1,3,27,28]. One study in surgical ICU patients monitored using a pulmonary artery catheter demonstrated that thoracentesis resulted in a significant decrease in pulmonary capillary wedge pressure and CVP [29]. In our study, median CI decreased significantly immediately after large-volume thoracentesis. Because stroke volume was not influenced by removal of pleural fluid, this finding was probably owing to the decrease in heart rate. The finding that there was no change in stroke volume after thoracentesis might be owing to the fact that baseline cardiac function (before thoracentesis) was normal in most patients included in our study (median CI, 4.7 L/min/m²) and that cardiac preload (according to TPTD-derived GEDVI values) was relatively high. Because no additional sedating or analgesic drugs were administered for thoracentesis, the decrease in heart rate might reflect that respiratory distress was relieved by removal of pleural fluid.

In general, when using single-indicator (thermal indicator) TPTD for bedside determination of EVLW, several potential limitations of this technique have to be discussed. The accuracy of single-indicator TPTD for the assessment of EVLW has been demonstrated in animal studies comparing TPTD-derived values with values obtained using gravimetry (criterion standard technique) [7,19,30] and in an autopsy study comparing premortem TPTD-derived EVLWI with postmortem lung weight [9]. However, there is still a debate about the underlying theoretical assumptions of this technique for EVLW determination [20]. Extravascular lung water is calculated by the following formula: EVLW = intrathoracic thermal volume (ITTV) – intrathoracic blood volume (ITBV) [19,31]. In contrast to double-indicator thermodilution methods, single-indicator TPTD does not measure but calculates ITBV based on a formula using global end-diastolic volume (GEDV): ITBV = (1.25 * GEDV) – 28.4 mL [19,31]. Although this constant relationship between GEDV and ITBV has clearly been demonstrated by Sakka et al [31], the accuracy of the assessment of EVLW based on the calculation of ITBV has been questioned [20]. In addition, it has been shown that different pathophysiologic conditions associated with decreased pulmonary vascular perfusion can alter EVLW measurements using thermodilution techniques [19]. When using TPTD, EVLW might be measured less accurate when pulmonary edema is present [19,32]. Moreover, values of EVLW are difficult to interpret in patients after lung resection, with aortic aneurysms or with intracardiac shunts [19,31,33].

4.1. Limitations of the study

When interpreting the results of our analysis, several limitations of the study have to be mentioned. This was a retrospective pilot study in a limited number of critically ill patients treated in a medical ICU. Therefore, the findings regarding the large-volume thoracentesis–induced changes in TPTD-derived parameters need to be confirmed in much larger and more heterogenous collectives of patients.

5. Conclusions

In summary, large-volume thoracentesis resulted in a statistically significant increase in TPTD-derived EVLWI and PVPI. Because EVLWI was higher after removal of pleural fluid, we conclude that pleural effusions do not take part in single-indicator TPTD as a part of the pulmonary
thermovolume. The impact of large-volume thoracentesis on TPTD-derived hemodynamic parameters needs to be further evaluated in larger clinical trials.

References