Preload Index: Pulmonary Artery Occlusion Pressure Versus Intrathoracic Blood Volume Monitoring During Lung Transplantation

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In this study, during lung transplantation, we analyzed a conventional preload index, the pulmonary artery occlusion pressure (PAOP), and a new preload index, the intrathoracic blood volume index (ITBVI), derived from the single-indicator transpulmonary dilution technique (PiCCO System), with respect to stroke volume index (SVIpa). We also evaluated the relationships between changes (Δ) in ITBVI and PAOP and ΔSVIpa during lung transplantation. The reproducibility and precision of all cardiac index measurements obtained with the transpulmonary single-indicator dilution technique (Clart) and with the pulmonary artery thermodilution technique (Clpa) were also determined. Measurements were made in 50 patients monitored with a pulmonary artery catheter and with a PiCCO System at six stages throughout the study. Changes in the variables were calculated by subtracting the first from the second measurement (Δ1) and so on (Δ2 to Δ5). The linear correlation between ITBVI and SVIpa was significant (r² = 0.41; P < 0.0001), whereas PAOP poorly correlated with SVIpa (r² = 0.01). Changes in ITBVI correlated with changes in SVIpa (Δ1, r² = 0.50; Δ2, r² = 0.57; Δ3, r² = 0.26; and Δ5, r² = 0.67), whereas PAOP failed. The mean bias between Clart and Clpa was 0.15 l · min⁻¹ · m²⁻¹ (1.37). In conclusion, ITBVI is a valid indicator of cardiac preload and may be superior to PAOP in patients undergoing lung transplantation.

Cardiovascular measurements are often used during anesthesia for lung transplantation (1). Cardiac index (Clpa) is typically measured with the pulmonary artery catheter (PAC) that also allows determination of stroke volume index (SVIpa), central venous pressure (CVP), pulmonary artery (PA) and PA occlusion pressure (PAOP). Some studies show that filling pressures that are assumed to reflect circulating blood volume and cardiac preload have limited usefulness for guiding volume therapy (2–8). During anesthesia for lung transplantation, the mechanical ventilation and the open chest surgery may modify the PAOP with cardiac preload misinterpretation. Currently a newly available system, the PiCCO System (Pulsion Medical System, Munich, Germany), based on the transpulmonary indicator dilution (TPID) technique with the single indicator, provides intermittent Clpa (Clart) assessment, continuous CI measurements by pulse contour analysis, and an estimation of the intrathoracic blood volume (ITBVI) index (ITBVI), which is a valuable index of cardiac preload and a more sensitive indicator of intravascular volume than PAOP (3–8). There is no information on the use of the TPID technique and its derived variables in patients undergoing noncardiac thoracic surgery and lung transplantation. Our hypothesis testing is needed because preload monitoring and fluid and drug management are particularly difficult during lung transplantation procedures when using a conventional pressure index of preload (PAOP).

This study was designed to evaluate the relationship between pressure (PAOP), derived from PAC, and the volume (ITBVI) preload variable, derived from the PiCCO System, with respect to SVIpa. The study also evaluated the relationships between the changes (Δ) in ITBVI and PAOP and ΔSVIpa during lung transplantation. The reproducibility and precision of all Clart and Clpa were also evaluated.
Methods

Patients

We obtained approval from the Ethics Committee and written informed consent from 56 patients prior to single- (DLT, n = 14) or double-lung transplantation (DLT, n = 42). Patients were monitored with a lead II/V5 electrocardiogram and a pulse oximeter, and we placed a radial artery catheter to measure systemic arterial blood pressure (MAP) (PCM SpaceLabs, Inc. Redmond, WA). A central venous catheter (trilumen) and a modified 7.5F PAC via an introducer (8.5F; Baxter Edwards Laboratories, Irvine, CA) were placed into the right internal jugular vein with the Seldinger technique and connected to the Vigilance system (Baxter Edwards Laboratories) to obtain CIpa, CVP, PAOP, mean pulmonary arterial pressure, body temperature, continuous cardiac output, and mixed venous oxygen saturation. A 4F thermistor-tipped catheter (Pulsiocath PV2014L; Pulsion Medical System, Munich, Germany) was placed via a 5F introducer (Adam Spence Europe Ltd., Abbeytown, Boyle, CR, Ireland) through the right femoral artery, with the tip in the abdominal aorta, and connected to the PiCCO System (Version 4.1; Pulsion Medical System) for monitoring of arterial pressure, Clart, ITBVI (n.v. 800–1000 mL/m²), and extravascular lung water index (n.v. 4–7 mL/kg) (2). In all patients an epidural catheter was placed (T4-9 space) before anesthesia induction for postoperative pain relief.

Anesthesia and Mechanical Ventilation

After preoxygenation by face mask, anesthesia was induced with propofol (0.5 mg/kg) or midazolam (0.04–0.07 mg/kg). Muscle relaxation was achieved with atracurium besylate (0.4–0.6 mg/kg), cisatracurium besylate (0.15 mg/kg), or vecuronium bromide (0.1–0.2 mg/kg). Analgesia was obtained with alfentanil (7–10 µg/kg) or fentanyl (0.7–1 µg/kg). After the induction of anesthesia, with the tip in the abdominal aorta, and connected to the PiCCO System (Version 4.1; Pulsion Medical System) for monitoring of arterial pressure, Clart, ITBVI (n.v. 800–1000 mL/m²), and extravascular lung water index (n.v. 4–7 mL/kg) (2). In all patients an epidural catheter was placed (T4-9 space) before anesthesia induction for postoperative pain relief.

The PiCCO, which uses only one (cold) indicator, calculates the MTt and the exponential downslope time (DSt) of the thermodilution curve (9). ITBVI and extravascular lung water index were calculated by the mean transit time (DSt) approach, as has been described elsewhere (10).

Cardiopulmonary Monitoring

Clpa measurements were performed by manual injection of 10 mL of saline solution, at room temperature, into the superior vena cava through the atrial port. Three consecutive boluses were injected without regard to the phase of the respiratory cycle, over a 2-min period. To avoid variation between operators, the injection was always performed by the same person. In cases where there was a >10% discrepancy in the CI measurements, then the measurement was repeated five times, and the lowest and highest results were discarded.

All data were obtained while patients were mechanically ventilated. The PAC was palpated before PA stapling to ensure that the catheter was not in the PA of the operative lung, and, if necessary, the PA catheter was withdrawn and repositioned into the nonoperative lung. The zero references for the supine and lateral positions were, respectively, the midaxilla and the right midclavicular line.

PiCCO Monitoring

The CIpa and the volumetric variables were obtained through the TPID technique. The mean of three subsequent CI measurements was used. These measurements were performed by injection of 15 mL of cold saline solution, at a temperature <8°C, via the distal port of the central venous catheter placed in the right internal jugular vein with subsequent detection by the thermistor embedded into the wall of the arterial catheter. CI was calculated with the Stewart-Hamilton principle from the thermodilution curves (9). ITBVI and extravascular lung water index were calculated by the mean transit time (MTt) approach, as has been described elsewhere (10).

The PiCCO, which uses only one (cold) indicator, calculates the MTt and the exponential downslope time (DSt) of the thermodilution curve. The result of the product of COart and MTt is the intrathoracic thermal volume (ITTV), whereas the product of the COart and the DSt is the pulmonary thermal volume.
(PTV). The difference between ITTV and PTV is the global end-diastolic volume (GEDV):

\[ \text{GEDV} = \text{ITTV} - \text{PTV} \ (\text{mL}) \]

or

\[ \text{GEDV} = \text{CO}_{\text{art}} \times (\text{MTt} - \text{DSt}) \ (\text{mL}), \]

which correlates closely with ITBV in experimental studies. By using a structural regression analysis, the mathematical relationship between GEDV and ITBV has been analyzed in a large population. This regression is used to estimate ITBV from GEDV:

\[ \text{ITBV} = a \times \text{GEDV} + b. \]

where \( a \) and \( b \) are two predefined coefficients (respectively, 1.16 and 86 mL/m²).

**Hemodynamic Targets and Clinical Interventions**

In all patients, lactated Ringer’s solution (5 mL·kg⁻¹·h⁻¹) was infused as baseline volume replacement. Hydroxyethyl starch solution 6% (MW 200/0.5) in 150-mL increasing doses was infused until the volume target (ITBVI between 800 and 1000 mL/m²) was achieved. When fluid challenge failed to obtain a CIpa of >3 L/min, increasing doses of dobutamine (5–10 \( \mu \)g·kg⁻¹·min⁻¹) were administered. In case of hypotension (MAP <60 mm Hg), norepinephrine (0.2–3 \( \mu \)g·kg⁻¹·min⁻¹) or ephedrine (5–10 mg boluses) was administered. IV prostaglandin E1 (20–100 ng·kg⁻¹·min⁻¹) associated with inhaled nitric oxide (10–40 ppm) as a pulmonary vasodilator was administered before or soon after PA clamping. Furosemide (0.3–0.5 mg/kg) and mannitol 18% (0.3 g/kg) were used, when necessary, to obtain a mean urine output of >1 mL·kg⁻¹·h⁻¹.

Twenty percent human albumin (50 mL) was administered according to hypoalbuminemia (2.0 g/dL). Fresh frozen plasma was given if the INR exceeded 1.5. Packed red blood cells were transfused to maintain a hemoglobin value of >9 g/dL. Intraoperative blood loss was recorded by measurement of blood volume in suction devices (cell saver).

**Experimental Procedure**

After the induction of anesthesia and achievement of stable cardiovascular conditions, baseline values of hemodynamic data and intra- and extravascular thoracic volumes were measured. All volumetric and pressure-derived variables were indexed to body-surface area to improve interindividual comparisons. Volumetric and hemodynamic measurements were then obtained at six stages in supine position during DLT:

1. MV: after the induction of anesthesia, with patients mechanically ventilated.
2. CL1: during implantation of the first lung with one-lung ventilation and one-lung perfusion with the contralateral PA cross-clamped.
3. REP1: after reperfusion of the first lung with double-lung ventilation and double-lung perfusion.
4. CL2: during implantation of the second lung with one-lung ventilation and one-lung perfusion of the transplanted lung, with the contralateral PA cross-clamped.
5. REP2: after reperfusion of the second lung with double-lung ventilation and double-lung perfusion.
6. FIN: at the end of surgery.

The four stages during SLT were

1. MV: after the induction of anesthesia, with patients mechanically ventilated in the supine position.
2. CL1: during implantation of the lung with one-lung ventilation and one-lung perfusion with the contralateral PA cross-clamped in the lateral decubitus position.
3. REP1: after graft reperfusion with double-lung ventilation and double-lung perfusion in the lateral decubitus position.
4. FIN: at the end of surgery in the supine position.

Because we performed each set of measurements in a steady-state period—i.e., at least 15 min after a change in dosage of catecholamines, anesthetic infusion rate, or ventilator settings—it can be assumed that relevant changes of myocardial inotropic status or afterload did not occur during the study period. As a consequence, changes of stroke volume must depend on changes of cardiac preload, according to the Frank-Starling law. Therefore, linear regression analysis was applied between changes of preload-dependent left ventricular SVIpa and the corresponding, presumably preload-indicating, variables PAOP and ITBVI.

**Statistical Analysis**

All results are expressed as mean and SD unless indicated otherwise. All hemodynamic and volumetric data obtained were analyzed with analysis of variance for repeated measurements and paired Student’s t-tests with Bonferroni’s post hoc test.

The correlations between the variables, as well as correlations between the changes (\( \Delta \)) in these variables, were studied with linear regression analysis. Changes in the variables were calculated by subtracting the first from the second measurement (\( \Delta_1 = \text{CL1} - \text{MV} \)), the second from the third (\( \Delta_2 = \text{REP1} - \text{CL1} \)), the third from the fourth (\( \Delta_3 = \text{CL2} - \text{REP1} \)), the fourth from the fifth (\( \Delta_4 = \text{REP2} - \text{CL2} \)), and, finally,
the fifth from the sixth ($\Delta_5 = \text{FIN} - \text{CL2}$). The relationships between the two different preload variables (PAOP and ITBVI) and the SVIpa were also analyzed at each stage by linear regression.

Clart measurements are required for the calculation of the ITBVI. To verify the reliability and reproducibility of Clart, all simultaneous measurements of Clpa and Clart were compared. Agreement between CI measurements obtained by PAC and PiCCO system was analyzed by using the method suggested by Bland and Altman (11). Bias between the methods was calculated as the mean difference between Clart and Clpa. The upper and lower limits of agreement were calculated as bias ± 2 sd and defined the range containing 95% of the differences between the methods. The precision of the bias analysis and limits of agreement were assessed with 95% confidence intervals.

All statistical analysis was computed by SAS (SAS Institute, Cary, NC) software (for Windows PC, Version 6.01). Statistical significance was considered to be at $P < 0.05$.

**Results**

Fifty-six consecutive patients (28 men and 28 women) receiving 42 DLTs (19 men and 23 women) and 14 SLTs (9 men and 5 women) were enrolled in the study. Six DLT patients who required cardiopulmonary bypass were excluded. Diseases leading to transplantation were cystic fibrosis (36 DLT), bronchiectasis (3 DLT), emphysema (7: 1 DLT and 6 SLT), fibrosis (7: 1 DLT and 6 SLT), and obliterant bronchiolitis (redo) (3: 1 DLT and 2 SLT). The mean age was 27.2 (9) yr and 51.79 (9) yr, respectively, for DLT and SLT. The mean anesthesia time was 617 (111) min for DLT and 436 (124) min for SLT. Hemodynamic and volumetric data are reported in Table 1.

Linear regression analysis revealed a significant correlation between ITBVI and SVIpa ($r^2 = 0.41$, $P < 0.05$).
P < 0.0001) (Fig. 1A), whereas PAOP correlated poorly with SVIpa ($r^2 = -0.01$; not significant) (Fig. 1B). ITBVI changes showed statistically significant correlations with SVIpa changes, apart from $\Delta_3$, whereas PAOP changes failed, as reported in Table 2 and in Figures 2 and 3. Linear regressions between analyzed data per phase are reported in Table 3.

The mean bias between CIart and CIpa was $0.15 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ (2 $\text{sd}$ of differences between methods = $1.37 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) (Fig. 1C).

Mean packed red blood cells, fresh frozen plasma, and human albumin administrations were, for DLT, 6.4 (5.4) U, 19.1 (13) U, and 9.9 (5.1) U, respectively, and for SLT were 1.8 (1.4) U, 6.8 (7.7) U, and 9.0 (2.8) U, respectively. Mean drug administration rates at each stage are reported in Table 1.

**Discussion**

In terms of preload variables, the main findings of this study showed a fairly good correlation between ITBVI and SVIpa, whereas PAOP correlated poorly with SVIpa (Fig. 1). The analysis of the relationships between $\Delta$ITBVI and $\Delta$SVIpa ($\Delta_1, \Delta_2, \Delta_4,$ and $\Delta_5$), as well as the correlation between ITBVI and SVIpa at predefined stages (MV, CL1, CL2, REP1, and FIN) confirmed this correlation (Tables 2 and 3 and Fig. 2). $\Delta$ITBVI $- \Delta$SVIpa did not achieve a significant correlation only at $\Delta_3$ (Tables 2, Fig. 2C). No correlation between PAOP and SVIpa was detected either at predefined stages or at the analysis of $\Delta$PAOP $- \Delta$SVIpa (Tables 2 and 3 and Fig. 3).

PAC monitoring represents the current clinical standard during lung transplantation procedure because mean pulmonary arterial pressure monitoring is needed, particularly during cross-clamping of the PA and after graft reperfusion phases. Often in clinical practice, preload is estimated by measuring CVP and PAOP. Because of the high range of PA pressure and the alteration of thoraco-pulmonary compliance and valvular function abnormalities, PAOP has never been described as a reliable preload index in lung transplant recipients. We did not find a correlation between PAOP and SVIpa in our study population, confirming previous reports (2–8). PAOP is influenced by so many factors other than cardiac filling that it is not a reliable estimate of cardiac filling in clinical practice during lung transplantation surgery (1,12–14).

Assessment of cardiac preload is of primary importance in guiding volume therapy and vasoactive drug administration to optimize organ perfusion and avoid fluid overload that can be dangerous and increase the lung edema in these patients. During the past decade, transesophageal echocardiography (TEE) has been used increasingly for the assessment of cardiac preload (15–17). Determination of the end-diastolic area is
a measure of left ventricular filling and correlates well with changes in SVI during volume therapy or graded blood withdrawal in different studies (17,18). TEE has become a common component of the perioperative care of surgical patients for many anesthesiologists. Standards for training are not yet universal, and documentation patterns still fall short of practice guidelines (19). Currently, only 52% of anesthesiologists document patterns still fall short of practice guidelines (19). Currently, only 52% of anesthesiologists (19). Currently, only 52% of anesthesiologists

| Table 2. Coefficient of Correlation for Changes (Δ) of Preload Variables (ITBVI and PAOP) with SVIpa and Level of Significance |
|-----------------|--------|--------|-----------------|--------|--------|
| Δ1              | r²     | P value| Δ2              | r²     | P value|
| ΔITBVI − ΔSVIpa | 0.30   | 0.0002 | ΔITBVI − ΔSVIpa | 0.57   | 0.0001 |
| ΔPAOP − ΔSVIpa  | 0.0001 | NS     | ΔPAOP − ΔSVIpa  | 0.0001 | NS     |
| Δ3              | r²     | P value| Δ4              | r²     | P value|
| ΔITBVI − ΔSVIpa | 0.08   | NS     | ΔITBVI − ΔSVIpa | 0.26   | 0.0003 |
| ΔPAOP − ΔSVIpa  | 0.12   | NS     | ΔPAOP − ΔSVIpa  | 0.04   | NS     |
| Δ5              | r²     | P value|
| ΔITBVI − ΔSVIpa | 0.67   | 0.0001 |
| ΔPAOP − ΔSVIpa  | −0.063 | NS     |

NS = not significant; ITBVI = intrathoracic blood volume index; PAOP = pulmonary artery occlusion pressure; SVIpa = stroke volume index (from pulmonary artery catheter).

In conclusion, ITBVI and PAOP comparison with SVIpa showed that ITBVI seems to be a fair indicator of cardiac preload, and perhaps superior to PAOP, during lung transplantation. Assessment of CIart is a less invasive, valid option for CI during anesthesia for lung transplantation that investigated preload index as ITBVI with the single-indicator thermodilution technique.

Our results are in agreement with previous reports in other fields that showed a fairly good correlation between ITBVI and CI data, which might also have influenced the observed correlation between those variables in our study (22,23). McLuckie and Bihari (22), investigating the relationship between ITBVI and CI, concluded that under euvolemic conditions, increasing CI by increasing inotropic support does not alter ITBVI significantly, thus demonstrating that the two measurements are not mathematically coupled.

The limitations of the single-thermodilution technique are similar to those of the double-indicator technique. Volume will be overestimated in the presence of large aortic aneurysm or catheters placed too far peripherally (i.e., in the radial or bronchial artery) because of a prolonged MTt. Furthermore, intracardiac shunts may limit the use of this technique.

The investigation of preload data was completed with the measurements of Clart that have been validated by a direct comparison to standard CIpa. Our results showed a close agreement between Clart and CIpa, supporting other authors’ findings (24,25). The level of agreement and precision remained constant throughout the study and also during the cross-clamping and reperfusion phases, when surgical heart manipulation and thermal variation occurred.

In conclusion, ITBVI and PAOP comparison with respect to SVIpa showed that ITBVI seems to be a fair indicator of cardiac preload, and perhaps superior to PAOP, during lung transplantation. Assessment of CIart is a less invasive, valid option for CI during anesthesia for lung transplantation that investigated preload index as ITBVI with the single-indicator thermodilution technique.

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Figure 2. Linear regression analysis between stroke volume index (SVI) changes and intrathoracic blood volume index (ITBVI) changes. A, \( y = 11.903x + 7.8414; r^2 = 0.30; P = 0.0002 \); B, \( y = 9.8614x + 62.179; r^2 = 0.57; P < 0.0001 \); C, \( y = 4.8777x - 63.016; r^2 = 0.08 \); not significant); D, \( y = 11.862x + 47.207; r^2 = 0.26; P = 0.0031 \); and E, \( y = 12.856x + 3.8556; r^2 = 0.67; P < 0.0001 \). Thin line = regression line.
Figure 3. Linear regression analysis between stroke volume index (SVI) changes and pulmonary artery occlusion pressure (PAOP) changes. A, $\Delta_1 (y = 0.0029x + 5.295; r^2 = 0.0001; \text{not significant})$; B, $\Delta_2 (y = -0.0061x - 1.833; r^2 = -0.0001; \text{not significant})$; C, $\Delta_3 (y = 0.2907x + 7.7583; r^2 = 0.12; \text{not significant})$; D, $\Delta_4 (y = 0.2204x - 11.113; r^2 = 0.04; \text{not significant})$; E, $\Delta_5 (y = -0.1068x + 0.0103; r^2 = -0.063; \text{not significant})$. Thin line = regression line.
monitoring compared with PAC. Although PAC is helpful during lung transplantation to monitor PA pressure, we conclude that the PiCCO System is a useful tool to provide more information on effective intravascular volume status.

### References


### Table 3. Linear Regression Analysis ($r^2$) Between ITBVI, PAOP Versus SVIpa, and Clart Versus Clpa at Specific Stages During Lung Transplantation

<table>
<thead>
<tr>
<th>Phase</th>
<th>MV</th>
<th>CL1</th>
<th>REP1</th>
<th>CL2a</th>
<th>REP2a</th>
<th>FIN</th>
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<td>n</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>ITBVI/SVIpa</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>36</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>PAOP/SVIpa</td>
<td>0.43*</td>
<td>0.38*</td>
<td>0.29*</td>
<td>0.31*</td>
<td>0.37*</td>
<td></td>
</tr>
<tr>
<td>Clart/Clpa</td>
<td>0.63*</td>
<td>0.58*</td>
<td>0.73*</td>
<td>0.004</td>
<td>0.005</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* MV = after anesthesia induction (during mechanical ventilation); CL1 = during first lung implantation; REP1 = after first lung reperfusion; CL2 = during second lung implantation; REP2 = after reperfusion of the second lung; FIN = at the end of surgery; Clart = cardiac index (pulmonary artery catheter); Clpa = cardiac index (PiCCO); PAOP = pulmonary artery occlusion pressure; ITBVI = intrathoracic blood volume index; SVIpa = stroke volume index (from pulmonary artery catheter).

* Data referred to double-lung transplantation (36 patients).

* $p \leq 0.0001$; † $p < 0.0005$. 

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