Hemodynamic Monitoring by Double-Indicator Dilution Technique in Patients After Orthotopic Heart Transplantation*

Oliver Goedje, MD; Tobias Seebauer, MS; Markus Peyerl, MS; Ulrich J. Pfeiffer, MD, PhD; and Bruno Reichart, MD, PhD

Study objectives: A transpulmonary thermal-dye dilution (TDD) technique using cold indocyanine green dye was utilized to monitor cardiac index (CI) and preload in patients after heart transplantation. Preload, determined by intrathoracic blood volume index (ITBVI) and global end-diastolic volume index (GEDVI), was compared to central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) and was correlated with stroke volume index (SVI).

Design: Prospective study.

Setting: Cardiac surgery ICU at a university hospital.

Patients: Forty patients (34 men, 6 women) with a mean (± SD) age of 54.4 ± 8.5 years after orthotopic heart transplantation.

Measurements and results: CI and preload measurements were performed with TDD and pulmonary artery catheters in the ICU at 3, 6, 12, 24, 36, 48, and 72 h postoperatively. The femoral artery CI was compared with the pulmonary artery CI. Changes in the ITBVI, GEDVI, CVP, and PAOP were correlated with changes in the SVI. No difference was found between the femoral and pulmonary arterial CIs (r = 0.98 [bias, 0.35 L/min/m²]; p < 0.01). There was no statistically significant correlation between changes in the SVI and changes in CVP (r = −0.23,) and PAOP (r = −0.06). However, the ITBVI (r = 0.65; p < 0.01) and the GEDVI (r = 0.73; p < 0.01) were significantly correlated to changes in the SVI. Changes in the same direction occurred between the SVI and the GEDVI as well as between the SVI and the ITBVI in 76.3% and 71.9% of patients, respectively, while CVP and PAOP also changed in the same direction as SVI in only 35.1% and 36.9% of patients, respectively.

Conclusion: ITBVI and GEDVI are more reliable preload parameters than CVP and PAOP. Even in denervated hearts, ITBVI and GEDVI show significant correlations with SVI. The transpulmonary indicator dilution technique is promising and should be investigated further.

Key words: cardiac filling pressures; cardiac output measurement; cardiac preload; global end-diastolic volume; indicator dilution; intrathoracic blood volume; orthotopic heart transplantation; thermal dye dilution; transpulmonary

Abbreviations: CABG = coronary artery bypass grafting; CI = cardiac index; CIfa = femoral artery cardiac index; CIpa = pulmonary artery cardiac index; CVP = central venous pressure; DST = downslope time; GEDV = global end-diastolic volume; GEDVI = global end-diastolic volume index; HR = heart rate; ICG = indocyanine green; ITBV = intrathoracic blood volume; ITBVI = intrathoracic blood volume index; MTt = mean transit time; PAC = pulmonary artery catheter; PAOP = pulmonary artery occlusion pressure; SVI = stroke volume index; SVRI = systemic vascular resistance index; TDD = transpulmonary thermal-dye dilution

The monitoring of cardiac index (CI) and vascular volume status is crucial to the practice of contemporary critical care medicine. This is particularly true for postoperative cardiac transplant patients, as they are often very sensitive to changes in circulatory conditions. Currently, the pulmonary artery catheter (PAC) represents the most commonly used hemodynamic monitoring tool. However, due to its relatively high degree of invasiveness, the use of the PAC has been criticized.1–5 As an alternative method, a transpulmonary thermal-dye dilution (TDD) technique using cold indocyanine green (ICG) dye has been developed.6 In this technique, CI is measured with the PAC by pulmonary artery thermal dilution, and preload (intravascular volume status) is esti-
imated by the measurement of central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP). TDD offers the possibility of CI determination by arterial instead of pulmonary arterial thermodilution. Additionally, preload is determined by calculating intrathoracic blood volume (ITBV) and global end-diastolic volume (GEDV), the latter consisting of the sum of the end-diastolic volumes of all four chambers of the heart. Several studies have demonstrated that ITBV and GEDV are more sensitive parameters of vascular volume than are CVP and PAOP. In another study, we confirmed these results in cardiac surgery patients undergoing coronary artery bypass grafting (CABG). However, to our knowledge, no information exists on the use of TDD and its derived parameters in patients who have undergone orthotopic heart transplantation. A transplanted heart, and thus a denervated heart, demonstrates different behavior in response to volume changes and pharmacologic interventions. The aim of this study was to assess the TDD method as a tool for hemodynamic monitoring after heart transplantation.

**Materials and Methods**

**Patients**

Forty consecutive patients (34 men and 6 women) were studied after orthotopic heart transplantation according to the modified technique of Lower and Shumway. Indications for transplantation were dilated cardiomyopathy (n = 33), ischemic cardiomyopathy (n = 6), and global cardiac failure after aortic valve replacement (n = 1). The mean (± SD) patient age was 54.4 ± 8.5 years (range, 22 to 68 years). Patients with extensive peripheral arterial occlusive disease and patients with a known allergy to ICG dye were excluded from the study. Inclusion criteria were fulfilled with the acceptance to undergo heart transplantation. The study was performed according to the Helsinki and Hong Kong declarations, and informed consent was obtained from all patients prior to the operation.

Following anesthesia induction, a combined 4F thermistor-tipped, fiberoptic catheter (model PV 2024 L; Pulson Medical Systems; Munich, Germany) was advanced into the distal abdominal aorta via a 5F femoral artery sheath (Arrow; Reading, PA). The catheter then was connected to a femoral artery catheter (COLD System; Pulsion Medical Systems). This catheter obviates the need for any additional arterial lines as it also can be used for pressure monitoring and blood sampling. Standard hemodynamic monitoring was achieved by placement of a PAC (Ohmeda; Erlangen, Germany) with its thermistor connected to the femoral artery catheter.

Hemodynamic measurements were made by the injection of a 15-mL, iced 5% dextrose solution with 2.5 mg/mL ICG into the PAC proximal port utilizing an automatic thermodilution injector (model ZI-03; Pulsion Medical Systems). A total of 960 measurements was included for the comparison of CIfa and CIpa by regression analysis and Bland-Altman analysis. To compare the relationship of the preload parameters, ITBV index (ITBVI), GEDV index (GEDVI), PAOP, and CVP, to the stroke volume index (SVI), linear regression analysis and bivariate correlations between the differences of each preload parameter and SVI to the previous measurement result were performed. Measurements were not subjected to analysis if the patient was receiving any inotropic support other than isopren-

**Principles of the Double-Indicator Dilution Measurement**

After injection of the cold ICG solution, the thermal indicator dilution curve was recorded in the pulmonary artery by the thermistor of the PAC. In addition, the thermistor-tipped fiberoptic catheter in the descending aorta recorded the dye indicator dilution curve and the thermal indicator dilution curve.

The determination of flow and volume by this method is based on the simultaneous application of the two indicators; one that is diffusible into the extravascular pulmonary tissue compartment (temperature) and the other that is nondiffusible (dye). Pulmonary arterial CI (CIfa) and femoral artery CI (CIpa) are determined by a standard thermodilution technique. The calculation of intrathoracic volumes is performed by an analysis of the transit times of the indicators derived from the dilution curves that are recorded in the descending aorta.

Mean transit time (MTt) and exponential downslope time (DSt) of the thermal and dye indicators are recorded (Fig 1). By multiplying CIfa with the MTt of each indicator, the volume between the sites of injection and indicator detection can be calculated. The ITBV calculation is based on the dye indicator curve, while the intrathoracic thermal volume is based on the thermal indicator curve. Multiplying the CIfa with the DSt of the thermodilution curve results in the pulmonary thermal volume, which is the largest single mixing volume. GEDV is obtained by subtracting the pulmonary thermal volume from the intrathoracic thermal volume (Fig 2).

**Protocol**

Measurements were performed in the ICU at 3, 6, 12, 24, 36, 48, and 72 h after the operation. Measurements consisted of three consecutive thermal dye dilution determinations with the femoral artery catheter (interval, 6 min) with simultaneous documentation of heart rate (HR), arterial BP, CVP, pulmonary artery pressure, PAOP, and systemic vascular resistance index (SVRI).

**Statistical Analysis**

A total of 960 measurements was included for the comparison of CIfa and CIpa by regression analysis and Bland-Altman analysis. To compare the relationship of the preload parameters, ITBV index (ITBVI), GEDV index (GEDVI), PAOP, and CVP, to the stroke volume index (SVI), linear regression analysis and bivariate correlations between the differences of each preload parameter and SVI to the previous measurement result were performed. Measurements were not subjected to analysis if the patient was receiving any inotropic support other than isoprena-

**Figure 1.** Schematic femoral artery indicator dilution curve explaining MTt and the exponential DSt, which are used for the calculation of volumes by a femoral artery catheter in combination with the thermodilution cardiac output from the dotted area under the curve.
Mean transit time dependent volumes:
\[ \text{CO}_{fa} \times \text{MTT} = \text{needle to needle volume} \]

Intrathoracic blood volume:
\[ \text{ITBV} = \text{CO}_{fa} \times \text{MTT Dye}_{fa} \]

Intrathoracic thermo volume:
\[ \text{ITTV} = \text{CO}_{fa} \times \text{MTT Temp}_{fa} \]

Downslope time dependent volumes:
\[ \text{CO}_{fa} \times \text{DSt} = \text{volume of largest single mixing chamber} \]

Pulmonary thermo volume:
\[ \text{PTV} = \text{CO}_{fa} \times \text{DSt Temp}_{fa} \]

Combinations:

Global end-diastolic volume:
\[ \text{GEDV} = \text{ITTV} - \text{PTV} \]

**RESULTS**

The determination of \( \text{CI}_{fa} \) is required for the calculation of the ITBVI and the GEDVI. To verify the reliability and reproducibility of \( \text{CI}_{fa} \), all simultaneous measurements of \( \text{CI}_{pa} \) and \( \text{CI}_{fa} \) were compared. The regression analysis showed a correlation coefficient of 0.98. The Bland-Altman analysis showed that \( \text{CI}_{fa} \) was greater than its corresponding \( \text{CI}_{pa} \) by a mean difference of 0.35 L/min/m². The limits of agreement (2 SD) ranged from −0.06 to 0.75 L/min/m² (Fig 3).

Table 1 shows the mean values and SDs of 960 single measurements of \( \text{CI}_{pa} \), \( \text{CI}_{fa} \), SVI, ITBVI, GEDVI, CVP, PAOP, HR, and SVRI during the study period. For those parameters dependent on indicator dilution, the mean coefficients of variation are noted. No coefficient of variation exceeded 4.7%. The SVRI did not change significantly during the entire postoperative course.

In Table 2, the coefficients of correlation between changes in GEDVI, ITBVI, PAOP, and CVP and changes in SVI are listed. Changes in the ITBVI \( (r = 0.65) \) and the GEDVI \( (r = 0.73) \) showed statis-
tically significant correlations to changes in the SVI. These relationships also are depicted in the regression analysis for the $\Delta$GEDVI/$\Delta$SVI ratio (Fig 4) and the $\Delta$ITBVI/$\Delta$SVI ratio (Fig 5). No correlation could be found for the $\Delta$PAOP/$\Delta$SVI ratio and $\Delta$CVP/$\Delta$SVI ratio (Fig 6).

A change of GEDVI was accompanied by a change of SVI in the same direction 76.3% of the time (increase, 71.7%; decrease, 78.4%). Changes in the ITBVI showed a similar propensity to move in the same direction as the SVI changes, with overall changes of 71.9% (increase, 65.5%; decrease, 78.4%). However, changes in CVP and PAOP occurred in the same direction as the SVI changes, only at 35.1% (increase, 32%; decrease, 38.8%) and 36.9% (increase, 30.2%; decrease, 38.9%), respectively.

**Discussion**

With the clinical introduction of the PAC in the early 1970s, invasive hemodynamic monitoring in critically ill patients became a routine procedure. In the following 2 decades, the PAC advanced to widespread use in patients undergoing cardiac surgery, particularly following cardiac transplantation. Nevertheless, the safety and efficacy of the PAC have been called into question. The concept of managing intravascular volume status by measuring intravascular pressures such as CVP and PAOP has shown significant unreliability in many clinical investigations, especially during mechanical ventilation. In a study published in 1996, the use of a PAC seemed to increase morbidity and mortality. Other investigations have shown that many physicians who use PACs demonstrated an alarming lack of knowledge concerning technical patterns as well as PAC parameters. PAC monitoring poses additional risks to cardiac transplant patients. PAC is associated with pulmonary artery rupture, with an incidence between 0.03% and 2%, and a mortality rate from 15 to 70%. The risk for this event may be even higher following heart transplantation, as anastomoses of the pulmonary artery and right atrium may be injured during the insertion of the PAC.
The PAC also poses other complications. The risk of infection associated with PAC has been reported to be as high as 16%. In immunocompromised transplant patients, the risk for a catheter-induced infection may be even higher. As a consequence, there is a need for alternatives in hemodynamic monitoring. In this context, the TDD has been shown to have considerable potential; however, there is little information about the usefulness of this technique in patients undergoing cardiac surgery, and to our knowledge, no information about its use in cardiac transplant patients.

Before investigating ITBVI and GEDVI, the underlying measurement of CI by femoral arterial thermodilution has to be validated by a direct comparison to standard pulmonary artery thermodilution. Our results showed a strong correlation between CiFA and CiPA. This excellent correlation has been observed in previous studies as has a slightly higher value measured by CiFA.

The maximum coefficient of variation in the measurement of ITBVI and GEDVI was 4.1% and 4.7%, respectively. As coefficients of variation < 10% are generally accepted in clinical applications, the variabilities of ITBVI and GEDVI determinations proved to be sufficiently low.

According to the Frank-Starling relationship, stroke volume depends on the end-diastolic wall tension, which is better estimated by volume than by pressure. Further, there are other agents, such as vasopressors, that can affect intravascular pressures independently of changes in volume. Therefore, estimating the loading conditions of the left ventricle by measuring intravascular pressures (CVP and PAOP) is less desirable than measuring the intravascular volume directly. In daily clinical routine, physicians try to manage the volume status by monitoring changes in CVP, PAOP, and CI during therapeutic measures. However, the relationship between CVP and PAOP and stroke volume is weak, as is shown in Figure 2. This is particularly important in the immediate postcardiac transplantation period in which ischemia and reperfusion injury make the heart extremely sensitive to right heart failure due to fluid overload. Thus, clinicians do not want to volume challenge these patients unnecessarily. In our study, the GEDVI and ITBVI proved to be valuable for cardiac preload determination (Tables 2, 3 and Figs 4, 5), most likely because these parameters include right and left ventricular end-diastolic volumes and, therefore, reflect the overall filling situation of the heart. Compared to ITBVI, GEDVI appears to be slightly more sensitive to preload (Table 2). The reason for this may be that GEDVI only includes right and left heart volumes, while ITBVI also includes pulmonary blood volume.

These results agree with our previous findings in patients following CABG. However, in that study, ITBVI and GEDVI showed a better correlation to SVI (ITBVI, $r = 0.83$; GEDVI, $r = 0.87$). One explanation may be that a normally innervated heart reacts to volume changes in terms of both contractility and HR compared to a transplanted heart, which does not have vagal innervation. Even the missing afferent innervation probably plays a role, as neurohormonal reflexes mediated by atrial filling receptors (ie, the Gauer-Henry reflex) lose their physiologic endocrine impact on cardiac preload.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\Delta$SVI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$GEDVI</td>
<td>0.734</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>$\Delta$ITBVI</td>
<td>0.646</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>$\Delta$PCWP</td>
<td>-0.065</td>
<td>NS</td>
</tr>
<tr>
<td>$\Delta$CVP</td>
<td>-0.23</td>
<td>NS</td>
</tr>
<tr>
<td>$\Delta$HR</td>
<td>-0.04</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS = not significant. See Table 1 for abbreviations not in text.
This results in increased levels of atrial natriuretic peptide, plasma renin, angiotensin II, aldosterone, and vasopressin as well as in hypervolemia.26,27 All patients studied were administered isoprenaline to avoid myocardial architecture dilatation induced by low HRs.28 Nevertheless, we did expect the relationship of GEDVI and ITBVI to SVI to improve, as denervation should simplify the relationship between preload and contractility.

We believe that the ITBVI and GEDVI values shown in Table 1, although normal compared to those of other cardiac surgery patients,21 are too low for this patient population. This conclusion is based on the already mentioned endocrine and neurological alterations and the known enlargement of both atria by the transplantation technique of Lower and Shumway, all of which should result in larger ITBVI and GEDVI volumes.

We did not analyze the measurements at the times when patients were receiving inotropic support, as this would have confounded the relationship between preload and SVI. Nevertheless, volume status monitoring is important in these patients, and ITBVI and GEDVI would be helpful tools to adjust the preload to the optimum.

Further insight into the utility of ITBVI and GEDVI may have been obtained by deliberately manipulating volume status in these patients. However, as mentioned above, performing a volume challenge might be dangerous in this clinical situation. Before doing so, it needs to be shown that the correlation between ITBV/GEDV and cardiac output, which was found in patients after CABG,9 also exists in patients after heart transplantation. As there is a clear difference between healthy, but transplanted and denervated, hearts and hearts with coronary sclerosis, the results from CABG patients may not automatically be transferred.

The lower degree of invasiveness (only a central venous and an arterial line are required for the measurement of GEDVI, ITBVI, SVI, and CI) and the high reliability of TDD reduce the indications for the PAC. From our point of view, the use of a PAC should be limited to patients with diseases in which pulmonary arterial pressure monitoring is essential, such as pulmonary hypertension or postoperative right heart failure. Even in those cases, the combination of TDD with PAC provides additional information related to volume.7,28 We can envision a two-step approach to monitoring in which ITBVI or

**Figure 5.** Regression analysis between changes in ITBVI (ΔITBVI) and SVI (ΔSVI) for all patients and each single patient, respectively.

**Figure 6.** Regression analysis between changes in CVP (ΔCVP) and those in PCWP (ΔPCWP) and SVI (ΔSVI) for all patients. PCWP = pulmonary capillary wedge pressure.
GEDVI are monitored in patients with uncomplicated conditions, while TDD is combined with PAC for monitoring patients with complex problems.

To summarize, we suggest that the arterial double-indicator dilution technique offers several advantages over pulmonary thermodilution, even in the difficult postoperative management of patients who have undergone heart transplantation.

References