Assessment of Cardiac Output, Intravascular Volume Status, and Extravascular Lung Water by Transpulmonary Indicator Dilution in Critically Ill Neonates and Infants

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Objective: **To assess cardiac output, intrathoracic blood volume, global end-diastolic volume, and extravascular lung water in critically ill neonates and small infants using transpulmonary indicator dilution.**

Design: **Prospective, observational, clinical study.**

Setting: **Pediatric intensive care unit in a university hospital.**

Participants: **Critically ill neonates and small infants suffering from severe heart failure, respiratory failure, or sepsis (n = 10).**

Interventions: **A total of 194 transpulmonary indicator dilution measurements were done. Global end-diastolic volume, intrathoracic blood volume, and stroke volume were measured and compared with standard hemodynamic parameters during the clinical course and before and after volume loading (16 ± 3.7 mL/kg of 10% albumin solution) in 8 of 10 patients.**

Measurements and Main Results: **A positive correlation was found for stroke volume index versus global end-diastolic volume ($r = 0.76$, $p < 0.001$) and intrathoracic blood volume ($r = 0.56$, $p < 0.001$). In contrast, no correlation was observed for stroke volume index versus central venous pressure. Volume loading resulted in significant increases in stroke volume index ($p < 0.01$), global end-diastolic volume ($p < 0.01$), and intrathoracic blood volume ($p < 0.01$); whereas central venous pressure, heart rate, mean arterial pressure, and extravascular lung water remained unchanged.**

Conclusion: **Transpulmonary indicator dilution enables measurement of cardiac output and intravascular volume status in critically ill neonates and infants at the bedside. The effects of volume loading on cardiac preload and effective change in stroke volume can be monitored by this technique, whereas central venous pressure was not indicative of changes in intravascular volume status.**

KEY WORDS: cardiovascular monitoring, neonates, infants, transpulmonary indicator dilution (TPID)

PHARMACOLOGIC SUPPORT of the circulation and maintenance of an adequate intravascular volume status in critically ill neonates and infants has become increasingly sophisticated. Early surgical intervention in congenital heart disease, successful therapy of sepsis, cardiomyopathy, and myocarditis usually require the use of vasoactive drugs. The administration of vasoactive drugs and the necessity to optimize intravascular volume status require enhanced cardiovascular monitoring techniques to control the effectiveness of therapy. In particular, repetitive measurements of cardiac output (CO) and derived parameters such as vascular resistance are useful in guiding therapy.

Apart from standard monitoring (eg, arterial blood pressure and central venous pressure [CVP]), mainly noninvasive techniques, such as transthoracic or transesophageal echocardiography, are used in neonatal and pediatric intensive care units (ICUs).[1] Echocardiographic estimation of CO in the ICU has several limitations, however, such as technical problems, examiner variability, and costs. Transthoracic echocardiography is *by definition* a noncontinuous measure of cardiac function and filling status and not useful as a trend monitor over hours and days.

Measurement of CO and mixed venous oxygen saturation by pulmonary artery catheterization is done only rarely in neonates and infants because this technique is associated with considerable technical problems in pediatric patients.[2] The catheterization of the pulmonary artery in infants is associated with a high complication rate, such as arrhythmias, thrombosis of the inferior vena cava, valvular lesions, pulmonary infarction, and rupture of a pulmonary artery.[3]

The transpulmonary indicator dilution (TPID) technique is based on central venous injection of the indicator. The site of detection is located in the aorta or the femoral artery, which is routinely used for blood pressure monitoring in infants and neonates. TPID enables bedside assessment of CO and calculation of systemic vascular resistance and compares favorably with Fick-derived CO measurements in infants and children.[4] Analysis of the aortic thermodilution curve enables calculation of global end-diastolic volume (GEDV) and intrathoracic blood volume (ITBV). In adult patients, ITBV and GEDV have been shown to be superior compared with central venous pressure (CVP) and pulmonary artery wedge pressure as indicators for intravascular volume status and cardiac preload.[5-7]

In pediatric patients with the need for continuous arterial pressure monitoring, TPID offers a benefit because there is no need for additional catheters.[8] Limited data are available, however, about the feasibility and usefulness of TPID in neonates and infants weighing <10 kg. In this observational study, TPID was used to assess hemodynamic monitoring in 10 critically ill neonates and small infants. To evaluate the effects of volume loading, the authors studied the effects of volume administra-

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tion on ITBV, GEDV, and CVP and their relationship to changes in stroke volume index.

PATIENTS AND METHODS

After obtaining approval by the institutional review board and informed consent of the parents, 10 critically ill neonates and infants suffering from severe congestive heart failure, severe respiratory failure, or sepsis were included in the study. In addition to routine hemodynamic monitoring (electrocardiogram, CVP, conventional arterial catheter), a 1.3F thermistor catheter or a 4F double-lumen thermistor catheter (PV 2021, PV 2014L08; Pulsion Medizintechnik, Munich, Germany) was introduced into the femoral artery and used for detection of the aortic thermodilution curve, measurement of arterial blood pressure, and blood gas analysis. Of 10 patients, 2 received a combined 3F fiberoptic thermistor catheter (PV 2023; Pulsion Medizintechnik, Munich, Germany) via a 4F introducer sheath (Arrow, Reading, PA). The arterial catheters were placed at the level of the diaphragm, distal from the renal arteries.

Measurements were done using a commercially available device (COLD Z-021 or PiCCO; Pulsion Medizintechnik, Munich, Germany) that enables simultaneous detection of dye and thermodilution curves (COLD Z-021) and calculation of CO and ITBV.[6] The PiCCO system enables continuous monitoring of CO using the pulse contour approach and intermittent measurements of CO, ITBV, and GEDV by single thermodilution.[9]

After initial hemodynamic stabilization, the first set of measurements was done. Measurements were repeated twice daily, before and after volume loading, or if any hemodynamic deterioration occurred. Indicator dilution curves were achieved by triple bolus injections of 3 to 5 mL ice-cooled saline into the superior vena cava. Injections were randomly spread over the respiratory cycle, and CO was calculated from the respective arterial thermodilution curves.[10,11]

Conventionally, ITBV is calculated as the product of CO and the mean transit time of indocyanine green (mtt_{ICG}) between the site of injection (right atrium) and the site of detection (aorta) as previously described in detail.[6,12] The double indicator dilution technique requires a combined fiberoptic-thermistor catheter with a minimal diameter of 3F. In small infants and neonates, the use of a combined fiberoptic-thermistor catheter is not advisable, however, because the catheter may compromise blood flow to the legs and cause ischemia. In 8 patients, an alternative approach was used for the estimation of the ITBV based on single thermodilution.

The intrathoracic thermoaccessible volume (ITTV) can be calculated as the product of mean transit time of the thermal indicator (mtt_{therm}) and CO:[12]

$$ITTV = CO \cdot mtt_{therm} \quad [mL] \tag{1}$$

The pulmonary thermal volume (PTV) is defined as the product of the exponential decay time of the thermal indicator and CO according to equation 2:

$$PTV = CO \cdot dst_{therm} \quad [mL] \tag{2}$$

The exponential decay time (dst_{therm}) can be calculated from the downslope of the arterial thermodilution curve. This method is based on the assumption that for many different mixing chambers in a series connection, the decay of the dilution curve is determined by the largest compartment.[12,13] The difference between ITTV and PTV represents the GEDV of the heart.[14]

$$GEDV = ITTV - PTV \quad [mL] \tag{3}$$

A linear relationship between ITBV and GEDV has been observed in animal and clinical studies. The coefficients of the respective regression lines facilitate calculation of ITBV derived from the thermodilution curve ($ITBV_{TD}$).[14]

$$ITBV_{TD} = a \cdot GEDV + b \quad [mL] \tag{4}$$

$a = 1.16$ and $b = 86$ mL/m^2

Extravascular lung water (EVLW) was measured to estimate the magnitude of pulmonary vascular congestion after left ventricular failure or during volume loading. Similar to ITBV, EVLW can be computed from the dye or thermodilution curves as $EVLW_{mtt}$ (mean transit time) or $EVLW_{Dst}$ (down slope time) based on an empirically derived algorithm.[14]

During the study period, volume loading was applied 15 times to 8 patients. Volume challenges were performed if clinically deemed necessary. In all cases, stroke volume, ITBV, and GEDV were low, and there was no clinical contraindication for a volume challenge. Indicator dilution measurements were done before and after the end of volume loading. Vasoactive medication and mechanical ventilation remained unchanged within this interval. Heart rate (HR), mean arterial pressure (MAP), CVP, hemoglobin, and arterial oxygen saturation were assessed by standard methods. Normalized CO and stroke volume index (SVI) were calculated using standard equations. Mean values of 3 consecutive measurements were used for further evaluation. For statistical analysis, paired Student *t*-test and regression analysis were used; p values < 0.05 were considered to be significant.

RESULTS

Patient characteristics, individual monitoring technique, and initial outcome are presented in Table 1. Three patients died during their stay in the ICU, 2 from primary cardiac causes and 1 from respiratory failure caused by alveolar proteinosis. A total of 194 sets of measurements (each representing 3 TPID recordings) were done. Mean duration of TPID monitoring was 10.4 days (range, 2 to 22 days); the mean number of measurements in each patient was 19 (range, 5 to 44). The duration of CO, ITBV, GEDV, and EVLW measurements depended on the patient's clinical course. For interindividual comparison, all flow-related or volume-related variables were normalized to body surface area.

In the study patients, mean SVI was 27.8 ± 7.4 mL/m^2, mean GEDV was 405 ± 129 mL/m^2, mean ITBV was 598 ± 198 mL/m^2, mean CVP was 6.9 ± 3.2 mmHg, and mean EVLW was 27.7 ± 16.8 mL/kg. Linear regression analysis of all SVI and GEDV values is shown in Fig 1. The overall Pearson correlation coefficient was $r = 0.76$ ($p < 0.01$,) for SVI versus GEDV. The linear regression coefficients were $r = 0.56$ ($p < 0.01$) for SVI versus ITBV and $r = 0.002$ (not significant) for SVI versus CVP. A good correlation was found for the SVI/GEDV relationship, a fair correlation was found for SVI versus ITBV, and no correlation was found between SVI and CVP.

Volume loading with 10% albumin solution (mean, 16 ± 3.7 mL/kg) was done in 8 patients in whom volumetric variables were indicative of hypovolemia. Volume loading resulted in significant increases in SVI, GEDV, and ITBV; whereas CVP, HR, MAP, and EVLW remained unchanged (Fig 2 and Table 2).

In 1 patient (case 6), the arterial introducer was removed on day 2 after 5 measurements because arterial perfusion of the leg was severely impaired. This complication resolved immediately after removal of the catheter. Apart from this, no catheter-related complications were observed.

Table 1. Patient Characteristics in the ICU

Case	Diagnosis	Age (mo)	Body Weight (kg)	Measurements (n)	Duration (d)	Outcome
1	ARDS	3	4.3	44	22	Survived
2	Sepsis	1	4.7	8	4	Survived
3	Hypoxic heart failure	5	5.5	13	8	Survived
4	Cardiomyopathy	8	6.4	7	4	Died
5	Myocarditis	1	3.8	17	8	Survived
6	Truncus arteriosus communis	11	4.9	5	2	Died
7	Cardiomyopathy	15	8.2	39	17	HTx, Survived
8	Cardiomyopathy	11	8.2	33	13	Survived
9	RSV pneumonia	4	4.5	10	8	Survived
10	Alveolar proteinosis	1	3.9	18	18	Died
Mean ± SD		6.0 ± 5.4	5.4 ± 1.6	19 ± 14	10.4 ± 6.7	

NOTE. Additional measurements by dye dilution were done in patients 3 and 7.
Abbreviations: ARDS, acute respiratory distress syndrome; HTx, heart transplantation; RSV, respiratory syncytial virus.

DISCUSSION

TPID was used to perform serial measurements of CO, volumetric variables of cardiac preload, and EVLW in critically ill infants and neonates. These results suggest that GEDV and ITBV reflect changes in cardiac preload, whereas CVP does not. The authors observed that GEDV and ITBV increased after volume loading, which was accompanied by an increase in SVI, whereas CVP, MAP, and HR did not.

In principle, TPID offers important additional information compared with standard monitoring because simultaneous measurement of CO, cardiac preload (ITBV, GEDV), and EVLW are easily available at the bedside.[6,15,16] The assessment of CO by aortic thermodilution has been shown to be valid and reliable in children and adults. Previously, 2 studies were available in which CO measurements by TPID were compared with other techniques in pediatric patients. Tibby et al[4] compared the validity and reliability of transpulmonary thermodilution with the well-established Fick principle of calculating CO. In their study, the techniques favorably compared with each other. More recently, the arterial thermodilution technique was compared with lithium dilution in

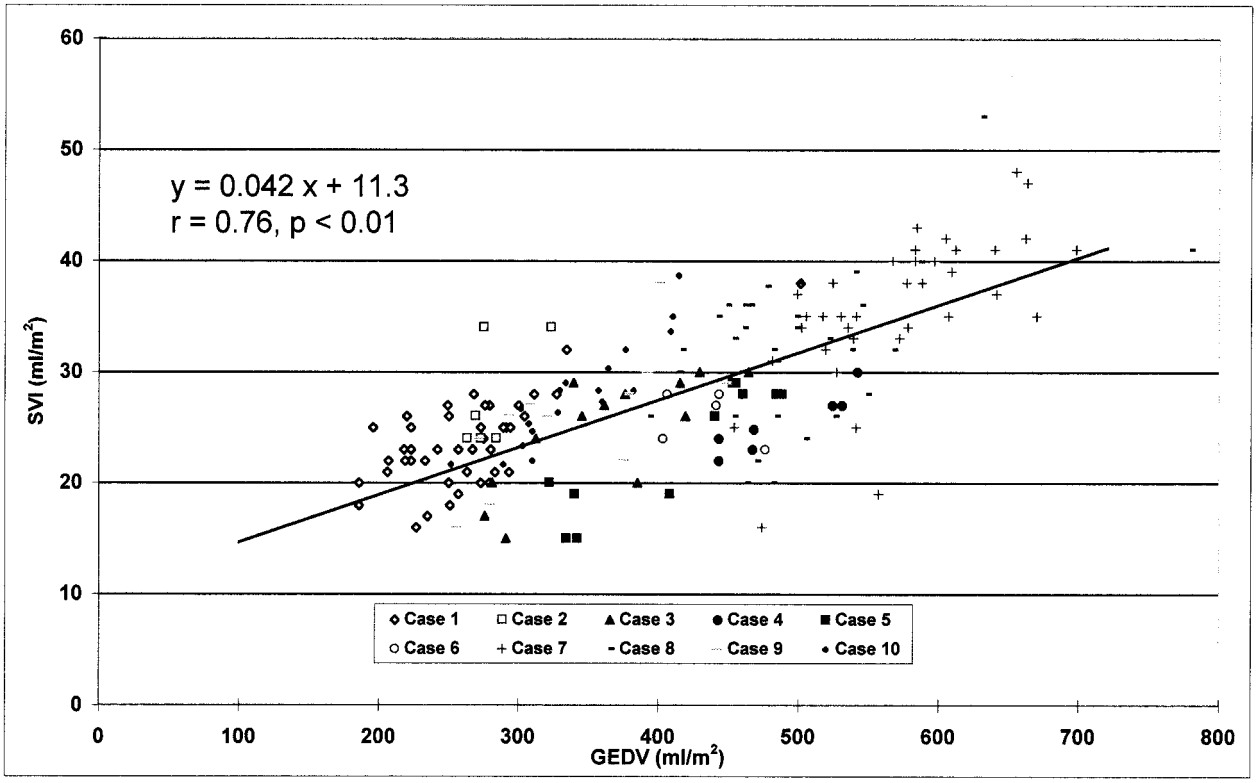

Fig 1. Regression analysis of SVI versus GEDV in 194 TPID measurements. A positive correlation was found between SVI and GEDV ($r = 0.76$, $p < 0.01$).

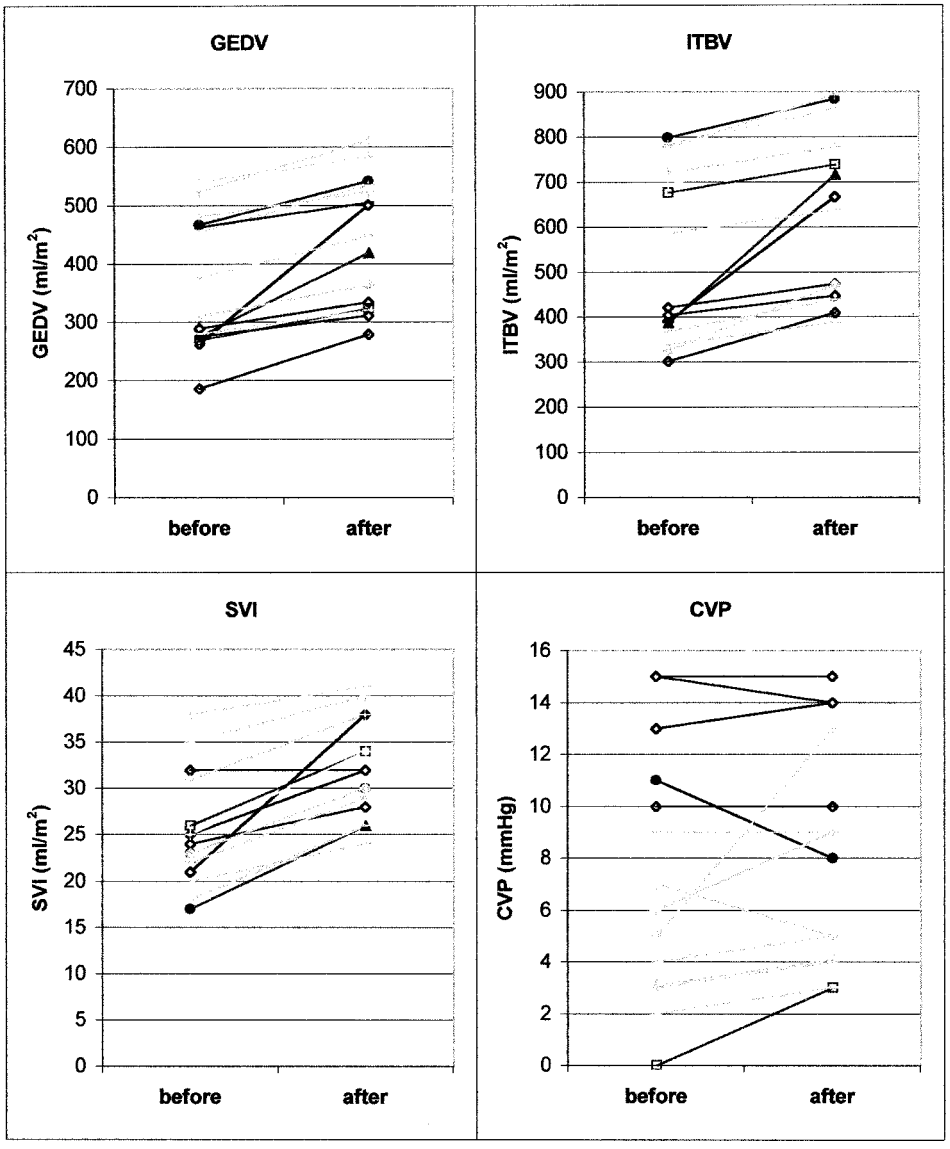

Fig 2. Effects of 15 volume loads (10% albumin solution, means, 16 ± 3.7 mL/kg, in 8 patients) on GEDV (A), ITBV (B), SVI (C), and CVP (D). The administration of the albumin solution resulted in an increase in GEDV and ITBV, whereas CVP remained unchanged. The increases in GEDV and ITBV were accompanied by an increase in SVI, suggesting a positive volume response.

pediatric patients during the recovery period after cardiac surgery.[17] The results suggested a close correlation between the techniques. The TPID technique of measuring CO is an accepted standard with proven validity and reliability.

In small infants and neonates, pulmonary artery catheterization is used infrequently owing to technical reasons. Mainly CVP and clinical signs, such as skin perfusion, urinary output, or presence of edema, are used to assess the intravascular

Table 2. Effects of Volume Loading on Hemodynamics

	CO (L/min/m²)	SVI (mL/m²)	GEDV (mL/m²)	ITBV (mL/m²)	CVP (mmHg)	HR (beat/min)	MAP (mmHg)	EVLW (mL/kg)
Before volume loading	3.2 ± 0.5	25 ± 6	364 ± 117	532 ± 114	7 ± 5	130 ± 26	70 ± 19	29 ± 15
After volume loading	4.3 ± 0.7	32 ± 5	440 ± 121	639 ± 185	8 ± 4	134 ± 23	71 ± 19	27 ± 16
Paired *t*-test	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.01$	NS	NS	NS	NS

Abbreviation: NS, not significant.

volume status. The introduction of transthoracic echocardiography enables assessment of cardiac filling and performance, but measurements of CO are difficult to perform in small infants and neonates because of increased HR and difficult echo conditions, in particular in mechanically ventilated patients.

In the present patients, conventional hemodynamic parameters of volume status and organ perfusion (CVP, HR, MAP) were compared with variables obtained by TPID. A low GEDV and ITBV indicated hypovolemia, which corresponded to a decreased SVI and could not be detected clinically or with standard monitoring (eg, CVP, MAP, and HR). With additional volume loading, significant increases of ITBV and GEDV were observed. Simultaneously, SVI increased, whereas CVP, HR, MAP, EVLW, and clinical signs of pulmonary edema remained unchanged. These data correspond to observations in animal models and clinical studies, which confirmed a good correlation between SVI and ITBV.[18,19] In adult patients during mechanical ventilation, GEDV and ITBV are better indicators of left ventricular preload than CVP and pulmonary artery wedge pressure.[5-7] The latter depend not only on intravascular volume status, but also on vascular tone, myocardial performance, and intrathoracic pressure.[20] No significant correlation between SVI and CVP was observed, whereas linear regression analysis revealed a good correlation between SVI and GEDV and a fair correlation between SVI and ITBV. These data suggest that these parameters could be a superior indicator to control volume requirement in neonates and infants.

The values obtained in the present patients do not represent normal values of these parameters in neonates or small infants; these cannot be derived from the present data. In the present patients, a SVI of >30 mL/m^2 required an ITBV between 600 mL/m^2 and 980 mL/m^2. The mean value was 639 $\pm$ 214 mL/m^2, which is severely decreased compared with the adult standard of 800 to 1,000 mL/m^2.[21,22] Fluid restriction in patients with severely heart failure or adult respiratory distress syndrome may explain low ITBV values in the present patients. It can be hypothesized that normal values in neonates and small infants corrected for body surface area might be lower than in adults. The values obtained in this study are not normal values for neonates or small infants, however, for the reasons mentioned earlier. The evaluation of pediatric normal values may be difficult because only critically ill neonates and infants with severely impaired hemodynamics are monitored by TPID.

As a result of the heterogenous study population, regression analysis of individual data emphasizes the need of individual management in each patient. One infant with severe heart failure (case 7), who was scheduled for heart transplantation afterward, required the highest preload to optimize CO (Fig 1). Analogous to the ventricular filling pressure curves of the Frank-Starling equation, similar curves for the volume-derived preload parameters GEDV and ITBV might be expected. The individual regression analysis in some patients suggests a similar bell-shaped curve (cases 1, 3, and 5 [Fig 1]). In most patients, the data points were found in the linear ascending part of the equation, however, most probably as volume restriction was used as a therapeutic principle in these patients with severe heart failure. Fluid restriction is not always advantageous, so additional volume loading was successfully used to optimize the intravascular volume status and CO during the clinical course. With additional volume loading, significant increases in GEDV and ITBV were observed; in contrast, CVP, HR, and MAP remained unchanged. Simultaneously, SVI increased, whereas EVLW remained unchanged or decreased. Because it has been shown clearly in adults that an increase in EVLW during volume loading is an early sign of volume overload,[14] EVLW is also probably useful in guiding fluid therapy in neonates and small infants.

Transpulmonary fluid transport depends on hydrostatic and colloid osmotic pressure differences. Chest radiographs are usually used to estimate pulmonary edema.[23] Kerley B lines as early radiologic signs for pulmonary edema were first noticed when the EVLW, measured by a gravimetrical method, had increased 50% to 80% above normal values.[24] Animal experiments showed that an increase in lung water can be observed by radiograph after a rise by about 35%.[25] Eisenberg et al[26] found that EVLW has diagnostic, prognostic, and therapeutic importance in adult ICU patients regarding volume resuscitation in hypotension or diuretic therapy of pulmonary edema. In the present patients, mean EVLW was 27.7 $\pm$ 16.8 mL/kg, which exceeds normal values obtained in adult patients (8 to 10 mL/kg). EVLW was computed from thermodilution dye curves or single thermodilution curves depending on the type of the catheter (eg, combined fiberoptic-thermistor or single thermistor catheter).[14,27] In 2 patients thermodilution dye–derived and single thermodilution–derived EVLW values were compared with each other, and no significant difference was observed. This finding is in accordance with the results of Sakka et al[14] and Hachenberg et al,[12] who also found no difference between the techniques in septic patients or patients undergoing cardiac surgery. One explanation for the relatively high values obtained in the present patients may be the severity of the underlying disease, which was associated with respiratory failure, cardiac congestion, or both. The highest EVLW values were observed in patients suffering from respiratory failure and systemic sepsis, both known to be associated with capillary leakage and increased fluid shifts into the interstitial space. From these data, however, the authors cannot completely exclude that the algorithm for the calculation of EVLW does not fit for neonates and small infants with a body weight <10 kg. Normal values for EVLW in neonates were not available; however, in single cases a severe increase of 21 mL/kg was observed.[28] In the present study, no significant increase of EVLW after volume loading could be detected. A significant rise in EVLW may limit additional volume loading even in patients with low ITBV or end-diastolic volume.

In conclusion, TPID is a suitable method to monitor CO, cardiac preload, and EVLW status in small infants and neonates. In principle, the TPID technique requires no additional catheters if invasive monitoring of arterial blood pressure for clinical reasons is required. TPID offers the unique feature of simultaneously monitoring flow (eg, CO), cardiac preload (eg, GEDV/ITBV), and pulmonary edema (EVLW) and the response to therapeutic interventions such as volume loading or change in inotropic support. To further validate the technique with respect to clinical outcome, it is necessary to carry out additional studies in neonates and small infants.

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