Intensive Care Med (2002) 28:947–952
DOI 10.1007/s00134-002-1334-2

C. Pauli
U. Fakler
T. Genz
M. Hennig
H.-P. Lorenz
J. Hess

Cardiac output determination in children: equivalence of the transpulmonary thermodilution method to the direct Fick principle

Received: 15 March 2001
Accepted: 27 July 2001
Published online: 15 June 2002

C. Pauli (✉) · U. Fakler · T. Genz
H.-P. Lorenz · J. Hess
Department of Paediatric Cardiology
and Congenital Heart Disease,
Deutsches Herzzentrum München,
Technische Universität München,
Lazarettstrasse 36,
80636 Munich, Germany
e-mail: pauli@dhm.mhn.de
Tel.: +49-89-12183305
Fax: +49-89-12183333

M. Hennig
Institute of Medical Statistics
and Epidemiology,
Klinikum rechts der Isar,
Technische Universität München,
Germany

Abstract *Objective:* To show the equivalence of the transpulmonary thermodilution method to the direct Fick principle in children. *Design:* Prospective single-centre study. *Setting:* A 16-bed paediatric cardiac ICU and a cardiac catheterisation laboratory at an university affiliated centre for paediatric cardiology and congenital heart disease. *Patients:* We consecutively investigated 18 patients (mean age 12.1± 6.4 years) during cardiac catheterisation and after corrective cardiac operation. *Methods and results:* We prospectively defined limits of equivalence for cardiac index (CI) for both methods of +/–0.25 l/min·m^2. We measured oxygen consumption for determination of CI by Fick as the clinical "gold standard" and performed a set of three transpulmonary thermodilution measurements. The mean CI_{Fick} was 2.88±1.07 l/min·m^2 (range 1.10–4.62 l/min·m^2) and CI_{TPID} was 2.85±1.03 l/min·m^2 (range 1.02–4.49 l/min·m^2). The mean difference between CI_{Fick} and CI_{TPID} was 0.030±0.168 l/min·m^2, and limits of agreement –0.306 to 0.366 l/min·m^2 (90% confidence interval –0.040 to 0.099 l/min·m^2). The regression equation was: $CI_{Fick}=1.0244\times CI_{TPID}-0.040$, $r^2=0.976$, $P<0.0001$. The intraclass coefficient of reliability for three repeated measurements of CI_{TPID} was 0.97, the corresponding lower limit of the 95% confidence interval was 0.94. *Conclusion:* We demonstrated the equivalence of CI measurement by transpulmonary thermodilution and the Fick principle in children. This new method may improve hemodynamic monitoring and management in seriously ill children.

Keywords Cardiac output · Thermodilution · Fick principle · Children · Paediatric intensive care

Introduction

Measurement of cardiac output (CO) is infrequently performed in seriously ill children [1]. Although several methods are available, its use as a routine bedside method is limited. Pulmonary artery catheter thermodilution has major disadvantages due to the risks arising from the use of a pulmonary artery catheter especially in paediatric cardiac patients. Doppler techniques also have their limitations in a postoperative setting in small patients [1, 2]. A recently introduced new method, the transpulmonary indicator dilution method (TPID), is now available for CO determination in children without the need for a pulmonary artery catheter. TPID determines lung water, global end-diastolic volume, and intrathoracic blood volume [3, 4, 5]. Despite the demonstrated accuracy of CO determination with this method [6, 7] the clinical use of this technique in paediatric intensive care has not been implemented widely. The reason might be the remaining doubt regarding accuracy and reliability of this method. We decided to perform a study to ensure the accuracy of cardiac output determination by TPID.

In contrast to the former work by Tibby et al. [7], we prospectively defined limits of equivalence for both

Table 1 Clinical characteristics of patients and results. (*Postop* postoperatively, *cath lab* catheter laboratory, *CAVSD* complete atrioventricular septal defect, *MI* mitral insufficiency, *ASD* atrial septal defect, *IAA* interrupted aortic arch, *LVOTO* left ventricular outflow tract obstruction, *PS* pulmonary valve stenosis, *PV* pulmonary valve, *CoA* coarctation of the aorta, *VSD* ventricular septal defect, *RVOTO* right ventricular outflow tract obstruction, *AS* aortic stenosis, *AI* aortic insufficiency, *AVR* aortic valve replacement, *CCTGA* congenitally corrected transposition of the great arteries, *DORV* double outlet right ventricle, *TGA* transposition of the great arteries, *CMP* cardiomyopathy), *p.H.* pulmonary hypertension

Patient number	Condition	Weight (kg)	CI_{Fick}(l/min·m²)	CI_{TPID}(l/min·m²)	CI_{Fick}–CI_{TPID}(l/min·m²)	Diagnosis
5	Postop	4.3	1.59	1.69	–0.10	Truncus arteriosus repair
10	Cath lab	4.7	1.98	2.23	–0.25	CAVSD repair, severe MI
3	Postop	20.8	4.13	3.96	0.17	ASD repair
11	Cath lab	23.0	3.15	3.30	–0.15	IAA repair, LVOTO
13	Cath lab	25.9	1.88	2.15	–0.27	PS, dilatation of PV
22	Postop	26.6	4.62	4.49	0.13	CoA
18	Postop	27.8	3.78	3.58	0.20	VSD, RVOTO repair
1	Postop	35.0	4.52	4.49	0.03	AS 2°, AI 4°, AVR
7	Cath lab	35.2	2.85	2.56	0.29	TGA, Senning
14	Cath lab	37.3	1.10	1.02	0.08	Hypertrophic CMP
20	Postop	42.0	3.26	3.11	0.15	VSD, AI 4°, repair
2	Cath lab	43.0	2.42	2.30	0.12	Tricuspid atresia, Fontan
19	Postop	48.0	4.38	4.30	0.08	MI 3°
4	Cath lab	49.7	1.49	1.26	0.23	Tricuspid atresia, Fontan
12	Cath lab	53.0	2.70	2.85	–0.15	CCTGA, p.H.
26	Cath lab	70.6	2.72	2.86	–0.14	DORV, RVOTO, Fontan
25	Cath lab	78.0	2.72	2.72	0.00	TGA, LVOTO, Mustard
17	Cath lab	88.0	2.55	2.44	0.11	TGA, Senning

methods and we additionally examined patients during cardiac catheterisation. The evaluation of functional hemodynamics in patients with corrected or palliated cardiac malformations without residual cardiac shunting in the catheter laboratory is time-consuming, mostly because of the repositioning of catheters to obtain blood for calculation according to the Fick method. In these circumstances omitting the Fick method would be beneficial.

Methods

Design

This is a prospective single-centre study to show the equivalence of TPID to the gold-standard Fick principle. In each patient both measurements were performed. After prospectively defining the limits of equivalence with ±0.25 l/min·m² for the CI, a sample size calculation resulted in 18 patients being recruited. An interim analysis was planned after six patients had been examined.

Patients

The study complies with the "Declaration of Helsinki" and was conducted in accordance with the Guidelines for Good Clinical Practice. The research protocol was approved by the local ethics committee and written informed consent was obtained from the patients or their parents.

From 7 July 1998 to 15 April 1999 we consecutively included 20 patients; the investigations were performed according to the protocol (seven patients postoperatively, 13 during cardiac catheterisation).

Two patients were excluded from the evaluation. The reasons for this will be discussed later.

We evaluated 18 mechanically ventilated patients after corrective cardiac surgery (n=7) and during cardiac catheterisation (n=11) without intracardiac shunts. Diagnoses and further information are presented in Table 1.

Protocol and measurements

All patients in the catheter laboratory underwent cardiac catheterisation to delineate the hemodynamic condition for clinical decision-making. The patients received intravenous anaesthesia and were intubated endotracheally to achieve normal pCO_2 values. Mechanical ventilation was volume controlled with a Siemens Servo 900 D ventilator (Siemens-Elema Systems, Solna, Sweden).

Patients investigated postoperatively were sedated with morphine (0.05 mg/kg/dosis) and flunitrazepam (0.02 mg/kg/dosis). The mechanical ventilation mode was volume controlled and pressure regulated with a Siemens Servo 300 ventilator (Siemens-Elema Systems). One patient had a surgically positioned single lumen catheter in the pulmonary artery; the other patients had a 5.5 Fr thermodilution balloon catheter positioned in the pulmonary artery (Arrow, Erding, Germany) via the right internal jugular vein. Intracardiac shunting was excluded by colour-flow Doppler echocardiography.

Oxygen consumption (VO_2) measurement and calculation of CO_{Fick}

Uncuffed tubes were used up to size 6.0, and larger tubes were cuffed. We tolerated an air leak of <5%, calculated as (inspiratory volume – expiratory volume)×100/inspiratory volume. We only accepted inspired oxygen fractions (FiO_2) <0.5. No inhalative anaesthetics were administered. After reaching a stable hemodynamic situation and normal body temperature we measured $\dot{V}O_2$ (Deltatrac II, Datex-Engstroem, Helsinki, Finland) in both sub-

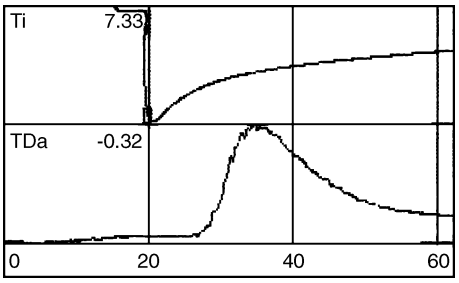

Fig. 1 Representative thermal dilution curve of the transpulmonary indicator dilution (TPID) plotted by the COLD machine; *x-axis* time (s), *y-axis* temperature (°C), *Ti* injection temperature, *TDa* arterial dilution temperature

groups for 10 min and values were averaged. During $\dot{V}O_2$ registration three TPID measurements were performed in the postoperative group. Subsequently arterial and mixed venous blood samples were taken. In the catheter laboratory the TPID measurements were performed immediately after blood sampling when the catheter was pulled back from the pulmonary artery into the inferior caval vein. Oxygen saturation of this single sample was measured three times and then averaged by using a separate standard co-oximeter (OSM 3, Radiometer, Copenhagen, Denmark). Partial oxygen pressures were determined by single measurement using a standard blood gas analyser (AVL 945, AVL List, Graz, Austria). Subsequently, oxygen contents of the arterial and venous blood were calculated. CO_{Fick} was calculated from the Fick equation:

$$CO = VO_2/(CaO_2 - CvO_2)$$
$$\text{where } CaO_2 = (1.36 \times Hb \times SaO_2) + (paO_2 \times 0.003)$$
$$\text{and } CvO_2 = (1.36 \times Hb \times SvO_2) + (pvO_2 \times 0.003)$$

The following abbreviations are used in the equation: Hb haemoglobin concentration (g/l); SaO_2 and SvO_2, arterial and mixed venous oxygen saturation; paO_2 and pvO_2, partial pressures of arterial and mixed venous oxygen (torr).

Transpulmonary indicator dilution

For the determination of cardiac output we used the transpulmonary indicator dilution technique (COLD Z-021, Pulsion Medical Systems). The central venous injected indicator (cold saline solution) is diluted while passing through the right heart, the lungs, the left heart, and the aorta. A thermistor-tipped catheter placed into the aorta detects the thermal dilution curve. These curves are presented on a flat screen in order to control the dilution course. A representative thermal curve is displayed in Fig. 1. Similar to the conventional right heart thermodilution, the COLD system computes the CO using the Stewart-Hamilton method [5].

Patients below a weight of 10 kg body-weight received a 1.3 Fr thermistor (PV2011, Pulsion Medical Systems, Munich, Germany) through a 20 G catheter (Vygon) and in patients with 10 kg body-weight and above a 3 Fr thermodye catheter (PV 2023, Pulsion Medical Systems) was introduced via a 4 Fr catheter (Vygon) in the femoral artery placed in diaphragmatic position.

Three measurements of TPID were performed after the hemodynamic situation was stabilised. We started with 1.5 ml+0.15 ml/kg cold saline solution. We altered the injected volume if necessary to achieve a thermal difference of 0.25 °C minimum in the aortic thermodilution curve. Sources of basal temperature drifts were excluded.

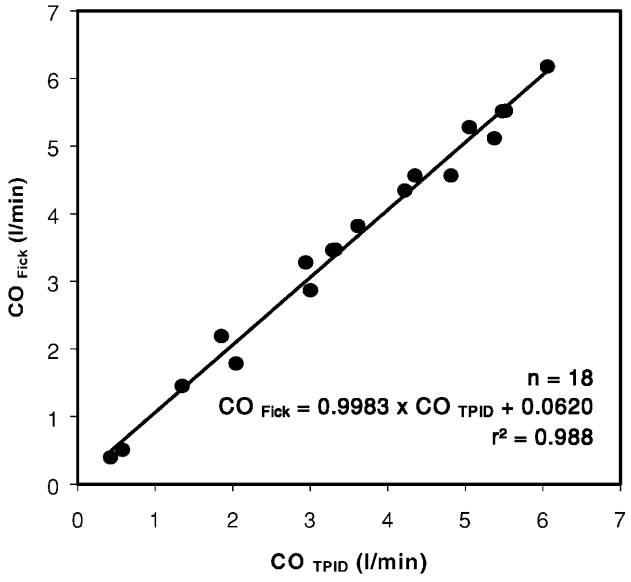

Fig. 2 Linear regression diagram of cardiac output using the Fick principle versus transpulmonary indicator dilution (TPID) for all patients

Statistics

The equivalence between both measurements was investigated by the use of a (1–2 α)-confidence interval for the mean difference between the measurements. As an interim analysis was planned after six patients had been examined, a significance level of α=0.005 for the interim analysis and α=0.048 was used, according to the O'Brien/Flemming approach.

The sample size calculation was based on the following assumptions: α=0.048 (one-sided), equivalence limit for Cardiac Index: 0.25, power: 80%, standard deviation of the difference: 0.405 (using results from internal pilot studies). The calculation was performed using the software NQuery 2.0. If the observed confidence interval of the mean difference in CI was included in the equivalence limits, equivalence was proven. Taking the interim analysis into account, a confidence level of 90.4% was used.

In addition, we performed several explorative analyses, such as linear regression analysis and calculation of coefficients of correlation. To quantify the reproducibility of the TPID measurements for three repeated measurements of CI we used the intraclass correlation coefficient of reliability, including the corresponding one-sided lower limit of the 95% confidence interval. Results are presented as mean±SD unless specified otherwise.

Results

An interim analysis after six patients did not lead to termination of the study. We evaluated 18 patients (11 male, 7 female), mean age 12.1±6.4 years (range 2 months–23.7 years), mean body-weight 39.6±22.7 kg (range 4.3–88 kg), and mean body surface area 1.24±0.52 m^2 (range 0.25–2.07 m^2).

The mean CO_{Fick} was 3.57±1.75 l/min (range 0.40–6.18 l/min) and the mean CO_{TPID} was 3.52± 1.74 l/min (range 0.42–6.06 l/min). The mean difference between CO_{Fick} and CO_{TPID} was 0.06±0.191 l/min, lim-

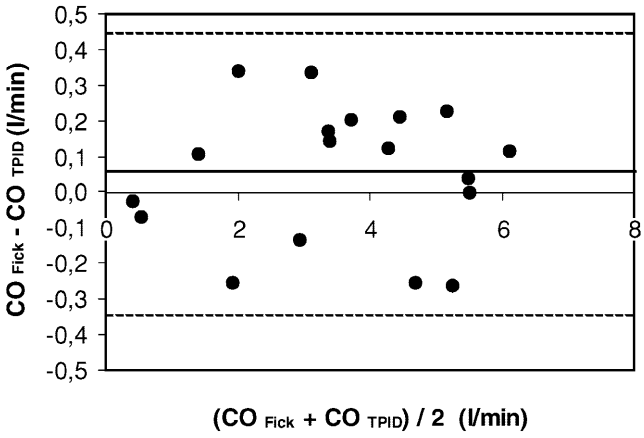

Fig. 3 Bland-Altman plot showing mean difference (0.06 l/min) and limits of agreement (–0.332 to 0.442 l/min) for Fick and TPID derived cardiac output

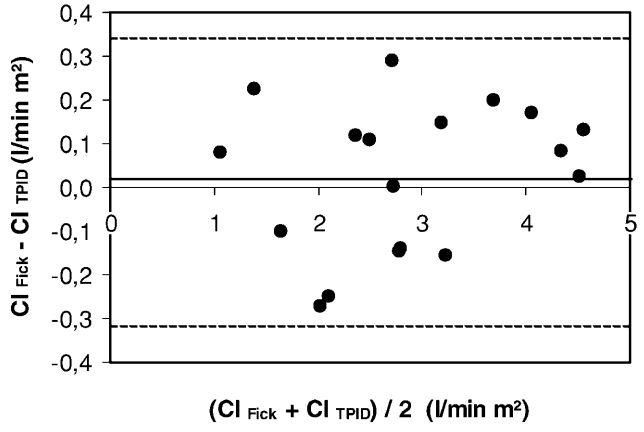

Fig. 4 Bland-Altman plot showing mean difference (0.03 l/min·m^2) and limits of agreement (–0.306 to 0.366 l/min·m^2) for Fick and TPID derived cardiac index

its of agreement –0.322 to 0.442 l/min (90.4% confidence interval –0.024 to 0.135 l/min). The regression equation was: $CO_{Fick}=0.9983\times CO_{TPID}+0.062$, $r^2=0.988$, $P<0.0001$ (Fig. 2). We found an intraclass coefficient of reliability for CO_{TPID} of 0.98 (optimum: 1) (one patient had only two measurements), and the corresponding lower limit of the 95% confidence interval was 0.953.

The mean CI_{Fick} was 2.88±1.07 l/min·m^2 (range 1.10–4.62 l/min·m^2) and CI_{TPID} was 2.85±1.03 l/min·m^2 (range 1.02–4.49 l/min·m^2). The mean difference between CI_{Fick} and CI_{TPID} was 0.030±0.168 l/min·m^2, limits of agreement –0.306 to 0.366 l/min·m^2 (90.4% confidence interval –0.040 to 0.099 l/min·m^2). The regression equation was: $CI_{Fick}=1.0244\times CI_{TPID}-0.040$, $r^2=0.976$, $P<0.0001$. The Bland-Altman plots for CO and CI are presented in Figs. 3 and 4.

The mean SD for three repeated measurements of CI_{TPID} was 6.02%. The intraclass coefficient of reliability for three repeated measurements of CI_{TPID} was 0.97 (optimum:1) (one patient had only two measurements), and the corresponding one-sided lower limit of the 95% confidence interval was 0.9433.

The results of the $V.O_2$ measurements, $\dot{V}O_2I$ calculated from CI_{TPID} (reverse Fick), arterial and venous saturations are listed in Table 2. The mean index of $\dot{V}O_2$ was 126.9±29.2 ml/min·m^2 (range 82.2–182.1 ml/min·m^2). The mean $\dot{V}O_2I_{calculated}$ was 125.5±28.7 ml/min·m^2 (range 69.4–174.2 ml/min·m^2). The mean arterial saturation was 97.1±1.6% (range 95–100%). The mean mixed venous saturation was 67.1±10.0% (range 43–78%). No catheter-related complications were found in our patients.

Discussion

In this prospective clinical trial we proved the equivalence of TPID and the Fick principle in infants and chil-

Table 2 Results of measured oxygen consumption ($\dot{V}O_2I$), arterial (SaO_2) and mixed venous (SvO_2) oxygen saturation, reverse $\dot{V}O_2I$, and difference between CI_{Fick}–CI_{TPID}

Patient number	$\dot{V}O_2I$ (ml/min·m^2)	SaO_2 (%)	SvO_2 (%)	Reverse $\dot{V}O_2I$ (ml/min·m^2)	CI_{Fick}–CI_{TPID} (l/min·m^2)
5	137.6	95	43	146.0	–0.10
10	110.0	98	58	124.1	–0.25
3	182.1	96	65	174.2	0.17
11	116.4	100	76	122.4	–0.15
13	106.3	100	65	121.7	–0.27
22	141.5	98	78	137.5	0.13
18	178.2	97	60	168.6	0.20
1	174.6	99	75	173.4	0.03
7	120.9	96	69	108.4	0.29
14	98.0	96	48	89.2	0.08
20	128.2	97	76	122.4	0.15
2	103.5	95	69	98.4	0.12
19	157.1	98	74	147.1	0.08
4	82.2	97	65	69.4	0.23
12	122.5	97	62	129.4	–0.15
26	109.6	97	77	114.4	–0.14
25	109.3	96	75	109.3	0.00
17	106.9	95	72	102.3	0.11

dren after corrective cardiac surgery and during cardiac catheterisation over a wide range of CI values. We found good reliability of three repeated TPID measurements of CI. This confirms observations in adults where coefficients of variation of 7.2% for repeated CI_{TPID} were found [3].

As an independent reference method we used the direct Fick principle as the clinical "gold standard" for determination of CI. This has great clinical importance because monitoring of CI in children now becomes feasible as a routine bedside method without the risks of a pulmonary artery catheter.

Our results are in accordance with the findings of Tibby [7] (CO 0.03±0.48 l/min vs 0.06±0.191 l/min and CI 0.02±0.59 l/min·m^2 vs 0.03±0.168 l/min·m^2). They compared the TPID method with the Fick method in newborns, infants, and children in an ICU setting. Furthermore, we could show the equivalence of TPID and the direct Fick method using measured oxygen consumption in patients during cardiac catheterisation and over a wider range of age in our patients. Consequently, the Fick principle and the anaesthesia required for correct measurement of $\dot{V}O_2$ could be omitted and replaced by TPID in diagnostic procedures in absence of cardiac shunting.

Excluded patients

In one patient warm blood was aspirated directly before injection into the line. In combination with a high dead space volume of the injection line this led to a wrong calculation and underestimation of the injection temperature followed by an underestimation of CI using the Stewart-Hamilton method.

The second patient who suffered from aortic coarctation with extensive collateral circulation (unknown before angiography) was not included due to overestimation of CI with the Fick equation caused by minimised desaturation of the collateral vessels and higher mixed venous oxygen saturation. This led to an overestimation of CI calculated by the Fick method.

Measurement of $\dot{V}O_2$ and calculation of CI_{Fick}

We used measured $\dot{V}O_2$ for calculation in the Fick equation. Otherwise, if $\dot{V}O_2$ is estimated this would lead to an unpredictable error in the CI calculation [8]. To minimise the error of $\dot{V}O_2$ measurement we avoided a high fraction of inspired oxygen, air leaks >5%, and the use of anaesthetic gases. The Deltatrac system has already been validated clinically in mechanically ventilated patients [9]. The mean difference and precision of the measured $\dot{V}O_2$ range could be –3.2% (±23%) [10]. For correct measurement of oxygen saturation co-oximetry was used. The results of measured $\dot{V}O_2$ showed a wide range and some values were lower than expected in a similar aged normal population. These objectives can be explained by the underlying diseases of the examined patients. In patients with a "Fontan"-like circulation a low CO is almost invariably present and therefore the oxygen uptake is also low. In patients with a major left-to-right shunt the oxygen consumption is elevated because of the volume overload. Application of the "reverse Fick principle" by calculating $\dot{V}O_2I$ from measured CI_{TPID} shows very similar results and similar distribution to the measured $\dot{V}O_2I$ values, indicating that a major underlying systematic error in $\dot{V}O_2$ determination is not very likely.

Complications

We did not find any catheter-related complications; however, the number of patients included was relatively small. In addition, femoral artery catheterisation in comparison to radial artery catheterisation has been reported to be comparably safe in infants and children, although perfusion-related complications were found to be considerably more frequent in neonates [11].

Conclusion

We were able to demonstrate the equivalence of CO determination by the TPID method and the Fick principle. Cardiac output and derived cardiac index measured by TPID correlates accurately and with high reliability with the Fick method as the clinical "golden standard" of CO estimation in paediatric patients without cardiac shunting. This may improve hemodynamic monitoring and clinical decision-making for rational, guided treatment in critically ill children. In the catheter laboratory it may simplify and shorten dynamic investigations, avoid general anaesthesia, reduce blood sampling, and the dose of radiation.

References

1. Murdoch IA, Marsh MJ, Morrison G (1995) Measurement of cardiac output in children. In: Vincent J.-L. (ed) Yearbook of Intensive Care and Emergency Medicine. Springer, Berlin Heidelberg New York, pp 606–614
2. Notterman DA, Castello FV, Steinberg C, Greenwald BM, O'Loughlin JE, Gold JP (1989) A comparison of thermodilution and pulsed Doppler cardiac output measurement in critically ill children. J Pediatr 115:554–560
3. Godje O, Peyerl M, Seebauer T, Dewald O, Reichart B (1998) Reproducibility of double indicator dilution measurements of intrathoracic blood volume compartments, extravascular lung water, and liver function. Chest 113:1070–1077

4. Lichtwark-Aschoff M, Beale R, Pfeiffer UJ (1996) Central venous pressure, pulmonary artery occlusion pressure, intrathoracic blood volume, and right ventricular end-diastolic volume as indicators of cardiac preload. J Crit Care 11:180–188
5. Pfeiffer UJ, Backus G, Blümel G, Eckart J, Müller P, Winkler P, Zeravik J, Zimmermann GJ (1990) A fiberoptics-based system for integrated monitoring of cardiac output, intrathoracic blood volume, extravascular lung water, O_2 saturation, and a-v differences. In: Lewis FR, Pfeiffer UJ (eds) Fiberoptics in Critical Care Monitoring. Springer, Berlin Heidelberg New York, pp 1–94
6. McLuckie A, Murdoch IA, Marsh MJ, Anderson D (1996) A comparison of pulmonary and femoral artery thermodilution cardiac indices in paediatric intensive care patients. Acta Paediatr 85:336–338
7. Tibby SM, Hatherill M, Marsh MJ, Morrison G, Anderson D, Murdoch IA (1997) Clinical validation of cardiac output measurements using femoral artery thermodilution with direct Fick in ventilated children and infants. Intensive Care Med 23:987–991
8. Berger RMF, van Poppelen R, Kruit M, van Vliet A, Witsenburg M, Hess J (1992) Impact of discrepancy between assumed and measured oxygen consumption for the calculation of cardiac output in children during cardiac catheterization. Neth J Cardiol 4:156–160
9. Tissot S, Delafosse B, Bertrand O, Bouffard Y, Viale JP, Annat G (1995) Clinical validation of the Deltatrac monitoring system in mechanically ventilated patients. Intensive Care Med 21:149–153
10. Weyland W, Weyland A, Fritz U, Redecker K, Ensink FB, Braun U (1994) A new paediatric metabolic monitor. Intensive Care Med 20:51–57
11. Glenski JA, Beynen FM, Brady J (1987) A prospective evaluation of femoral artery monitoring in pediatric patients. Anesthesiology 66:227–229