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Bedside Assessment of Intravascular Volume Status in Patients Undergoing Coronary Bypass Surgery

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Background: **Management of intravascular volume is crucial in patients after cardiopulmonary bypass as myocardial dysfunction is common. The purpose of this study was to validate a novel bedside technique for real-time assessment of intravascular volumes.**

Methods: **Eleven patients undergoing cardiopulmonary bypass were studied. In addition to standard monitors, a fiberoptic thermistor catheter was placed in the descending aorta and central venous injections of 10 ml ice-cold indocyanine green dye were performed. Total blood volume was measured by a standard *in vitro* technique. Circulating and central blood volume were calculated by using cardiac output, mean transit times, and a newly developed recursive convolution algorithm that models recirculation. Measurements were performed after induction of anesthesia and at 1, 6, and 24 h after surgery.**

Results: **A two-compartment model of the circulation was required for adequate fit of the data. We found a significant correlation between total and circulating blood volumes (r = 0.87). One hour after surgery, central blood volume was decreased by 10% ($P < 0.05$). At 6 and 24 h after surgery, circulating blood volumes were significantly increased by 29% and 20%, respectively ($P < 0.01$), although central blood volume was similar to control values. Before surgery stroke volume index correlated with circulating blood volume (r = 0.87) but not with pulmonary capillary wedge and central venous pressures.**

Conclusions: **This study shows that bedside determinations of intravascular blood volumes are feasible and that these measurements are more indicative of intravascular volume status than are either pulmonary capillary wedge or central venous pressures in the post–cardiopulmonary bypass period. Our data also demonstrate that despite a normal central blood volume both circulating and total blood volume are significantly increased in the immediate post–cardiopulmonary bypass period. (Key words: Heart, left ventricular preload: blood volume. Pharmacokinetics: blood volume. Measurement techniques: dye dilution.)**

MANAGEMENT of intravascular blood volume is an important part of anesthesia and intensive care medicine. Although appropriate fluid therapy is important in all patients, it is more critical in patients with impaired myocardial function. Intravascular volume needs to be sufficient to adequately fill the left ventricle but not so great as to cause congestive heart failure. Patients undergoing cardiopulmonary bypass frequently exhibit myocardial dysfunction that is most likely due to ischemic arrest and surgical manipulation.[1] Thus, optimal intravascular volume management in these patients is desirable.

Conventional evaluation of intravascular blood volume is based on pressure measurements such as central venous pressure and pulmonary capillary wedge pressure. However, these parameters frequently fail to provide accurate volume information.[2] Currently available methods for direct measurement of intravascular blood volume such as radionuclide and dye dilution techniques[3,4] require serial blood sampling performed over several minutes and do not provide the type of real-time information needed for patient management.

In this paper, we describe the theory and method of a new technique for bedside assessment of intravascular volume status by measurement of circulating and central blood volume. This method is based on an intravenous injection of a cold dye bolus and *in vivo* measurement of light reflectance and temperature by a fiberoptic thermistor catheter. The aim of the present study was to compare this new bedside technique with

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the conventional dye dilution method in patients undergoing cardiopulmonary bypass for coronary artery surgery.

Materials and Methods

Patients and Anesthetic Technique

With Institutional Review Board approval and written informed consent, 11 patients without evidence of left ventricular dysfunction undergoing aortocoronary bypass surgery were studied. Premedication consisted of flunitrazepam 0.02–0.03 $mg \cdot kg^{-1}$, promethazine 0.2–0.4 $mg \cdot kg^{-1}$, and piritramide 0.1–0.2 $mg \cdot kg^{-1}$. In addition to standard monitors, we placed a 5-French introducer sheath in the left femoral artery. We induced general anesthesia with fentanyl 7 $\mu g \cdot kg^{-1}$ and etomidate 3 $\mu g \cdot kg^{-1}$. Pancuronium 0.1 $mg \cdot kg^{-1}$ was given to facilitate tracheal intubation. We mechanically ventilated the patients lungs with 50%/50% oxygen/N_2O. Anesthesia was maintained with fentanyl 3–6 $\mu g \cdot kg^{-1} h^{-1}$ and either bolus injections of midazolam 20–40 $\mu g \cdot kg^{-1}$ or halothane 0.3–1.0 vol% as needed.

After induction of anesthesia a thermodilution pulmonary artery catheter was placed *via* the right internal jugular vein. A combined 4-French fiberoptic-thermistor catheter (Fa. Pulsion, München, Germany) was inserted *via* the introducer sheath into the left femoral artery and advanced 30 to 40 cm up the thoracic aorta. Correct position of the catheter was verified by optical control of pulsatility of reflected light signal.

In addition to measurements of standard hemodynamics, total, circulating, and central blood volume per kilogram body weight were assessed as described in the following sections.

Measurement of Total Blood Volume

Total blood volume ($V_{d\,tot}$) comprises all blood volumes that are assessed by the dye tracer within 30 min. A bolus of indocyanine green (ICG) (0.2–0.4 $mg \cdot kg^{-1}$) in 10 ml ice-cold saline was injected into the proximal lumen of the pulmonary artery catheter. Mixed venous blood samples were drawn before injection of ICG (blank sample) and 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 27, and 30 min after bolus injection of ICG. The blood samples were analyzed for hemoglobin content and hematocrit and plasma was separated by centrifugation at 4,000 U min^{-1} for 10 min.

To improve the accuracy of the photometric method spectral instead of single- or dual-wavelength analysis of the plasma samples was performed. Absorption spectra of the plasma samples were measured from 490 to 996 nm with a CCD array-spectrophotometer (Theta-Systems, München-Olching, Germany). A four-point calibration procedure was performed for each determination of total blood volume with titrated ICG concentrations of 0.3125, 0.625, 1.25, and 2.5 $mg \cdot l^{-1}$ in the blank sample. A linear regression analysis of absorption *versus* ICG concentration was performed at each wavelength between 605 and 870 nm with a resolution of 0.94 nm. The result of these regression analyses was a spectrum of 282 absorption coefficients for the range between 605 and 870 nm. The spectra of the ICG containing plasma samples were then fitted to this absorption coefficient spectrum by a multiple linear-regression procedure. The advantage of spectral analysis *versus* single- or dual-wavelength measurement is the improved compensation for background absorption in the samples. The lower limit of detection of this assay[5] was 0.2 $mg \cdot l^{-1}$ with a coefficient of variation of 4% or less at all concentrations.

The resulting concentration–time course for ICG (c(t)) was fitted to a biexponential decay according to

$$c(t) = a \times e^{-k1t} + be^{-k2t} \quad (1)$$

where a and b = weighting factors and k1 and k2 = time constants.

The virtual concentration at the time of injection (c_0) was assumed to be

$$c_0 = c(t = 0) = a + b \quad (2)$$

and the volume of distribution for ICG as determined by *in vitro* analysis of blood samples ($V_{d\,tot}$) was calculated by[6]

$$V_{d\,tot} = m_0/c_0/BW \quad (3)$$

where m_0 = the administered amount of ICG and BW = body weight in kilograms.

In Vivo *Measurement of Circulating Blood Volume*

Circulating blood volume ($V_{d\,circ}$) is the blood volume that contributes to tracer turnover within the first 3 min after bolus injection. Thus, circulating blood volume includes central blood volume and is part of total blood volume. The initial concentration–time course immediately after injection of the dye bolus into the right atrium was recorded for 3 min *via* the aortic fiberoptic catheter (fig. 1), which was connected to a special optoelectronic device (IVS 4000, Pulsion Med-

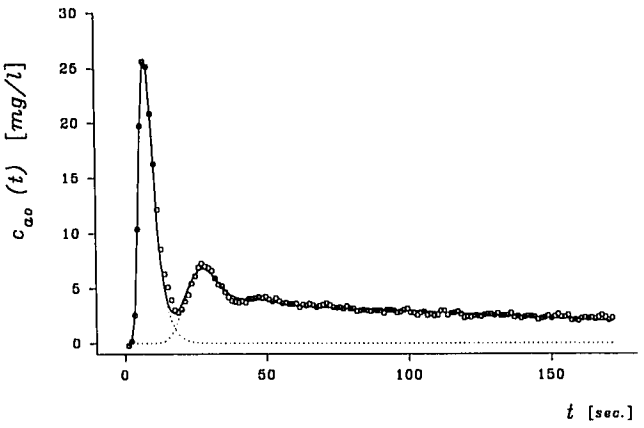

Fig. 1. Aortic concentration–time course of indocyanine green (ICG). A bolus of 25 mg ICG was injected into the right atrium. The concentration–time course immediately after the injection was measured by a fiberoptic catheter in the descending aorta (hollow circles). The first pass of the dye (c_{bolus} (t), dotted line) was modelled by a lagged normal density distribution function.[23] Recirculating dye (c_{recirc} (t), dotted line) was modelled by a recursive convolution algorithm, which is described in the appendix in more detail. The solid line represents the final result of the nonlinear least-squares fitting of the model to the data (c_{ao} (t)), which is the sum of c_{bolus} (t) and c_{recirc} (t).

izintechnik, München, Germany). The aortic dye curve and the thermodilution curves of pulmonary artery and aorta were digitized on-line and stored on hard disk on a personal computer. Cardiac output was determined from aortic and pulmonary thermodilution curves according to the Steward Hamilton procedure as described previously.[7] The average value of aortic and pulmonary cardiac output was used for further calculations.

The volume of distribution of a tracer can be calculated by the product of mean transit time and flow.[8] Thus, circulating blood volume ($V_{d\,circ}$) can be calculated by the product of cardiac output (CO) and mean transit time of the dye through the circulation (mtt_{circ}):

$$V_{d\,circ} = CO \times mtt_{circ}/BW \quad (4)$$

The mean transit time of the dye through the circulation was obtained by fitting of the dye curve to a recirculation model, which is described in the appendix in more detail. The model is based on a fast and a slow flow channel in parallel and also allows for quantification of cardiac output distribution between the two compartments (see appendix).

Measurement of Central Blood Volume

Central blood volume ($V_{d\,cent}$) is the blood volume between pulmonary artery valve and aortic valve. The mean transit time of the dye tracer between pulmonary artery and aorta (mtt_{cent}) was used to calculate central blood volume by the product with cardiac output:

$$V_{d\,cent} = CO \times mtt_{cent}/BW - 1.5\ ml \cdot kg^{-1} \quad (5)$$

Central mean transit time (mtt_{cent}) was calculated by the difference of mean transit times between the pulmonary thermodilution curve and the aortic dye dilution curve. Both curves were monoexponentially extrapolated on the downslope of the first peak between 70% and 30% of peak height to eliminate recirculation from the determination of respective mean transit times. A correction for prepulmonary extravascular heat exchange (cooling of the right ventricle by the cold dye bolus, which leads to a slight delay of the pulmonary temperature curve in comparison with a pulmonary dye curve) was used. A previous study with simultaneous measurements of dye and thermodilution curves in pulmonary artery[8] has shown that 1.5 $ml \cdot kg^{-1}$ body weight is an appropriate correction factor.

Protocol

Measurements were obtained after induction of anesthesia (control) as well as 1, 6, and 24 h after arrival at the intensive care unit. Two bolus injections of ICG were performed for each measurement. The sampling period for *in vitro* determination of blood volume followed the first bolus injection. After completion of blood sampling a second bolus injection of ICG was performed and a second set of *in vivo* dilution curves was obtained. The average central and circulating blood volume of both fiberoptic measurements were used for statistical analysis and further calculations.

Statistics

Data in text and tables are presented mean ± standard deviation. Data in figures are presented as mean ± standard error. Friedman's analysis of variance by ranks followed by Wilcoxon's matched-pairs test was performed to test for differences in comparison with control measurements. A P value less than 0.05 was considered to be statistically significant.

Results

Forty-four measurements were performed in 11 patients. Table 1 summarizes demographic data.

Table 1. Demographic Data

n	11
Male/female	7/4
Age (yr)	58.5 ± 6.8
Height (cm)	170.6 ± 11.9
Weight (kg)	76.9 ± 14.6
Body surface area (m^2)	1.89 ± 0.23
Perfusion time (min)	90.1 ± 39.5
Arrest time (min)	53.6 ± 22.4

Hemodynamic Results

Hemodynamics showed a typical pattern for patients undergoing coronary bypass surgery (table 2).

One hour after surgery heart rate was increased, as was cardiac index and mean pulmonary blood pressure. Pulmonary capillary wedge pressure was not significantly increased compared with control conditions as opposed to central venous pressure and mean pulmonary artery pressure, which showed a slight but significant increase. Stroke volume index was decreased in all patients at 1 h after surgery, although pulmonary capillary wedge pressure and central venous pressure indicated sufficient filling pressures.

At 6 and 24 h after surgery, heart rate and cardiac index were still increased; however, stroke volume index had returned to control, whereas systemic vascular resistance was significantly decreased in comparison with preoperative values.

Indicator Dilution Results

Changes of total, circulating, and central blood volume are shown in table 3. Control values of total blood volume were in the same range as reported by others.[3,9] One hour after surgery central blood volume was slightly but significantly decreased in all patients, whereas circulating and total blood volume showed no significant changes. Beginning 6 h after surgery a significant increase in circulating and total blood volume could be observed. Central blood volume had returned to control at this time. Circulating blood volume correlated with total blood volume throughout the study (fig. 2). No systematic difference with respect to the time of measurement was observed.

All fiberoptically measured dye curves could be fitted to the two-compartment model described in the appendix. Table 4 demonstrates the confidence intervals for the parameters of the nonlinear least-squares fitting. A typical example of the fitting result is shown in figure 1 and a typical two-compartment transport function modelled by the sum of two log-normal distribution functions is shown in figure 3. Under control conditions the mean transit time of the slow compartment was three times longer than that of the fast compartment (table 5). The volume of distribution of the slower circulating compartment was almost two times larger than the fast circulating compartment. However, only 37% of total blood flow was distributed to the slow compartment, whereas the fast compartment received 63%.

One hour after surgery the increase in cardiac index from 2.4 ± 0.35 to 3.1 ± 0.58 1 m^{-2} occurred almost exclusively in the fast compartment. Six hours after surgery a distribution of cardiac output similar to control values was observed, although at a higher total cardiac output. Twenty-four hours after surgery blood flow through the fast compartment was still increased, whereas blood flow to the slow compartment had returned to control levels.

Relation Between Blood Volume and Conventional Indicators of Preload

No correlation was found between central venous pressure and total or circulating blood volume (r = 0.12, r = 0.25, respectively) or between pulmonary capillary wedge pressure and total or circulating blood volume (r = 0.08, r = 0.24) throughout the study. For example, 1 h after surgery both central venous pressure and pulmonary capillary wedge pressure were increased. However, tachycardia and decreased stroke volume index (table 2) implied relative hypovolemia, which was reflected by the decreased central blood volume. Although central blood volume was only decreased by 10% 1 h after surgery, this decrease was routinely observed in all patients. Interestingly, circulating and total blood volume were not decreased 1 h after surgery but slightly increased.

A weak correlation (r = 0.65) between systemic vascular resistance and circulating blood volume was found (fig. 4). In contrast, central blood volume did not correlate with systemic vascular resistance (r = 0.22).

A positive correlation between either central, circulating and total blood volume *versus* stroke volume index could be demonstrated in the preoperative period (figs. 5–7). In particular the circulating blood volume showed a close correlation to stroke volume index preoperatively (fig. 6). Some of the patients required inotropic support by dopamine (4–8 $\mu g \cdot kg^{-1} min^{-1}$) after surgery. The data points of these patients

Table 2. Hemodynamics

	Control	1 h	6 h	24 h
HR (beats/min)	62 ± 10	101 ± 15↑*	99 ± 14↑*	93 ± 12↑*
$P_{art\ syst}$ (mmHg)	113 ± 18	127 ± 25	116 ± 12	125 ± 21
$P_{art\ diast}$ (mmHg)	69 ± 10	75 ± 15	66 ± 10	71 ± 13
PAP (mmHg)	15 ± 3.1	23 ± 3.7↑*	25 ± 6.8↑*	22 ± 4.0↑*
PCWP (mmHg)	9.3 ± 3.4	13.0 ± 5.1	14.2 ± 6.7	11.8 ± 3.1
CVP (mmHg)	6.8 ± 3.9	10.6 ± 2.45†	13.7 ± 6.9†	9.1 ± 3.9

Values are mean ± SD.

HR = heart rate; $P_{art\ syst}$ = systolic arterial pressure; $P_{art\ diast}$ = diastolic arterial pressure; PAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure.

* $P < 0.01$ *versus* control.

† $P < 0.05$ *versus* control.

were marked by open circles in figures 5, 6 and 7. In particular with respect to the relation of central blood volume to stroke volume index (fig. 5) it is noteworthy that data points above the regression line of the control measurements were always associated with dopamine therapy.

Discussion

Significance of Circulating Blood Volume

This study clearly demonstrated that our bedside assessment of blood volume status is a reliable index of total blood volume and left ventricular preload in patients undergoing cardiopulmonary bypass. However, our technique does not measure total blood volume. We can measure only compartments of total blood volume that significantly contribute to tracer circulation within 3 min of fiberoptic dye curve recording. Thus, as distribution of cardiac output to some of the total blood volume requires more than 3 min, circulating blood volume was lower than total blood volume (table 3 and fig. 2). According to the slope of the regression line in figure 3 we estimated the circulating blood volume to be 59% of total blood volume.

Currently no other technique for measurement of circulating blood volume is available that can be used for direct comparison and validation of the technique presented. Thus, *in vitro* measurement of ICG in blood samples and estimation of total blood volume by conventional exponential analysis of the elimination kinetics is the best alternative for reference measurements. We were able to demonstrate a good correlation between both techniques of blood volume measurements (fig. 2). The relation between circulating and total blood volume remained remarkably constant throughout the study and both were increased about 12 $ml \cdot kg^{-1}$ postoperatively (table 3).

Significance of Central Blood Volume

Central blood volume has been advocated as the most reliable guide to left ventricular preload. In healthy supine subjects volume changes preferentially alter volume in the intrathoracic compartment and central blood volume holds a key position: it serves as a reservoir for the left ventricle.[10] We found in this study that relative hypovolemia occurred 1 h after surgery as reflected by a significant decrease in central blood volume and stroke volume index. Neither circulating nor total blood volume showed significant changes at this time. However, at 6 h after coronary bypass surgery all patients had an increased circulating blood volume, whereas central blood volume and stroke volume index were normal. This indicated that relative hypovolemia after cardiopulmonary bypass at least in part is caused by an expansion of the extrathoracic blood volume and that an increased volume in the extrathoracic part of the circulation is necessary to maintain normal central blood volume.

Clinical Indices of Intravascular Volume Status

Typically central venous pressure or pulmonary capillary wedge pressure are used to guide fluid therapy. However, the results of this study confirm the findings of other investigators[2,11] that these pressure measurements correlate poorly with intravascular volume status. Central filling pressures are not only determined by intravascular blood volume but are also affected by the compliance of the intra- and extrathoracic low-pressure system.[12] As outlined above, an expansion of

Table 3. Total, Circulating, and Central Blood Volume

	Control	1 h	6 h	24 h
$V_{d\,tot}$ (ml/kg)	74 ± 8.7	76 ± 15.1	85 ± 12.4↑*	85 ± 13.5
$V_{d\,circ}$ (ml/kg)	42 ± 5.0	43 ± 7.5	54 ± 8.7↑*	50 ± 5.4↑†
$V_{d\,cont}$ (ml/kg)	11.6 ± 2.1	10.5 ± 2.1↓*	12.4 ± 3.1	11.6 ± 1.6
CI (l/m²)	2.4 ± 0.35	3.1 ± 0.58↑*	3.9 ± 0.84↑*	3.4 ± 0.64↑*
SVI (ml/m²)	39 ± 5.8	32 ± 5.7↓†	40 ± 8.5	37 ± 8.4
SVR (dyne·s·cm⁻⁵)	1,788 ± 516	1,538 ± 608	1,055 ± 296↓*	1,343 ± 274↓*

Values are mean ± SD.

$V_{d\,tot}$ = total blood volume; $V_{d\,circ}$ = circulating blood volume; $V_{d\,cont}$ = central blood volume; CI = cardiac index; CVI = stroke volume index; SVR = systemic vascular resistance.

* $P < 0.01$ *versus* control.

† $P < 0.05$ *versus* control.

the extrathoracic blood volume consistent with a decreased venous vasomotor tone occurs within the first hours after coronary bypass surgery. From these observations we deduce that, compared with preoperative conditions, optimal intravascular blood volume is higher in the post–cardiopulmonary bypass period. Thus, both central and circulating blood volume measurements are useful for evaluation of intravascular volume status. Central blood volume indicates volume deficits, whereas the circulating blood volume indicates the absolute blood volume increase required to maintain adequate preload.

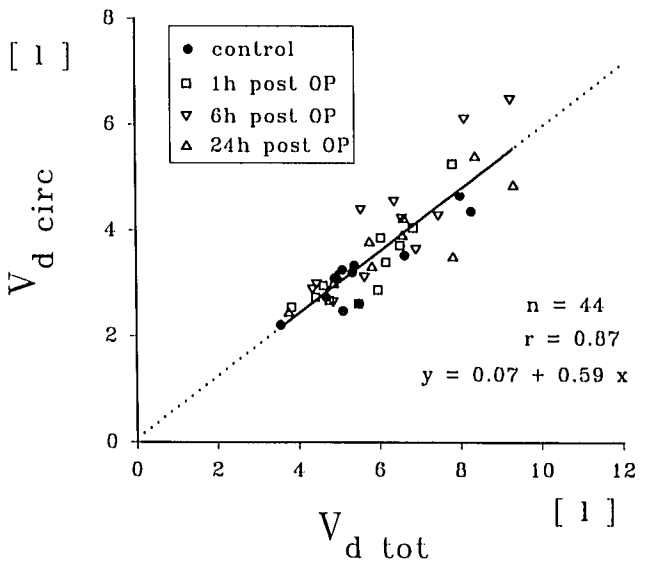

Fig. 2. Relation between total ($V_{d\,tot}$) and circulating blood volume ($V_{d\,circ}$). Circulating blood volume correlated very well with total blood volume (r = 0.87) for all measurements throughout the study (n = 44). No systematic difference with respect to preoperative or postoperative measurements was observed. According to the slope of the regression line average circulating blood volume was 59% of total blood volume.

Expansion of Intravascular Space in the Postoperative Period

Increased intravascular blood volume requirements in our patients in the postoperative period probably result from dilation of arterial and venous vessels. The vasodilation in the postoperative period could have been due to activation of inflammatory mediators systems, which have been shown to be triggered by cardiopulmonary bypass and by surgery.[13,14]

We presume that the major site of blood pooling is the extrathoracic venous vessels. Total arterial capacity is about 10 ml·kg^{-1} and the compliance of the arterial system is 200 times less than the compliance of the venous system.[10] Thus, the increase of intravascular blood volume occurred mainly in the venous system. Arteriolar vasodilation cannot account for the observed intravascular blood volume increase because the magnitude of the increase is too large. Furthermore, the extrathoracic venous compartment is clearly more affected than the intrathoracic compartment because central blood volume remains essentially unchanged whereas total blood volume is increased.

Table 4. Confidence Intervals of Fitting Parameters

	Median	90% Percentile
R_1 (%)	2.91	<4.95
mtt_1 (%)	2.04	<3.16
R_2 (%)	6.01	<10.12
mtt_2 (%)	4.67	<7.78
$\sigma_{1,2}$ (%)	4.83	<7.55

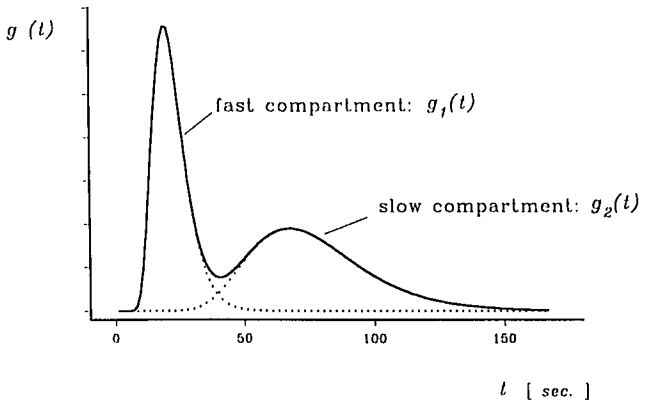

Fig. 3. Transport function of the circulation. A typical example of a circulatory transport function is shown. The transport function is characteristic for the dispersion process of the indicator during passage of the circulation. It represents the dye curve that would be seen on a single pass if an ideal bolus (Dirac impulse) was administered into the aorta and recirculating dye were monitored at the injection site. In all measurements, a two-compartment transport function was required to achieve a sufficient goodness of fit. A two-compartment transport function with a slow and a fast compartment in parallel was modelled by the sum of two log-normal distributions (see equation 8 and 9).

Distribution of Blood Flow in the Circulation

The difference between total blood volume and circulating blood volume represents a very slowly perfused compartment, which does not contribute to intravascular tracer transport within the first 3 min. It can be estimated that blood flow to this very slow compartment is probably only an insignificant portion of cardiac output. The recovery factor R in equation 7 (see appendix) accounts for all losses of indicator including hepatic clearance of ICG. If hepatic clearance is absent, than maximally 17% of cardiac output would be delivered to this slow compartment, because the recovery factor R for the dye was 0.83 ± 0.05%. However, 17% of cardiac output is in the same range as a normal hepatic ICG clearance. The loss of indicator quantified by R could therefore completely be explained by hepatic elimination of the dye. Hence, the blood flow to the slow compartment, which is not assessed by the fiberoptic method for measurement of circulating blood volume, is presumably negligibly small.

Transport Function of the Circulation

The initial attempt to fit the fiberoptically measured dye concentration–time courses to a simple transport function with a single compartment only was not successful in most of the curves. However, an excellent goodness of fit (fig. 1) was achieved when a two-compartment model with a rapid and a slow perfused volume of distribution in parallel was used to simulate the transport through the circulation. A similar pattern of blood flow distribution was observed in a recent experimental investigation in five dogs by Henthorn *et al.*[15] The existence of a fast and a slow channel in parallel in the circulation has also been indicated by previous studies that investigated in dog experiments the time constants of venous blood return adjustments after abrupt changes in hemodynamics.[16,17] Green[17] suggested that the slow compartment is presumably the splanchnic circulation. In fact, longer mean transit times for the splanchnic circulation could be expected because this is the only part of the circulation with a serial arrangement of two organ passages, *i.e.*, the intestine and the liver.

Table 5 shows the average mean transit times and volumes of the fast and slow compartments in the cir-

Table 5. Two-compartment Analysis of Circulating Blood Volume

	Control	1 h	6 h	24 h
mtt_{fast} (s)	14.9 ± 2.0	12.4 ± 1.5	12.4 ± 3.8	13.1 ± 1.8
$V_{d\,fast}$ (ml/kg)	8.0 ± 1.9	11.0 ± 1.7↑*	11.7 ± 2.8↑†	12.7 ± 2.2↑*
Cl_{fast} (L·min^{-1}·m^{-2})	1.51 ± 0.23	2.22 ± 0.45↑†	2.52 ± 0.47↑*	2.41 ± 0.52↑*
mtt_{slow} (s)	72.5 ± 12.3	59.2 ± 11.7↓†	54.9 ± 15.5↓*	65.0 ± 7.3
$V_{d\,slow}$ (ml/kg)	22.8 ± 3.5	21.8 ± 4.5	29.6 ± 6.8↑*	26.1 ± 3.5↑†
Cl_{slow} (L·min^{-1}·m^{-2})	0.91 ± 0.25	0.94 ± 0.25	1.42 ± 0.51↑*	0.98 ± 0.21

Values are mean ± SD.

$mtt_{fast,slow}$ = mean transit time of fast and slow compartment; $V_{d\,fast,slow}$ = volume of distribution for fast and slow compartment; $Cl_{fast,slow}$ = cardiac index flowing through fast and slow compartment.

* $P < 0.01$ *versus* control.

† $P < 0.05$ *vesus* control.

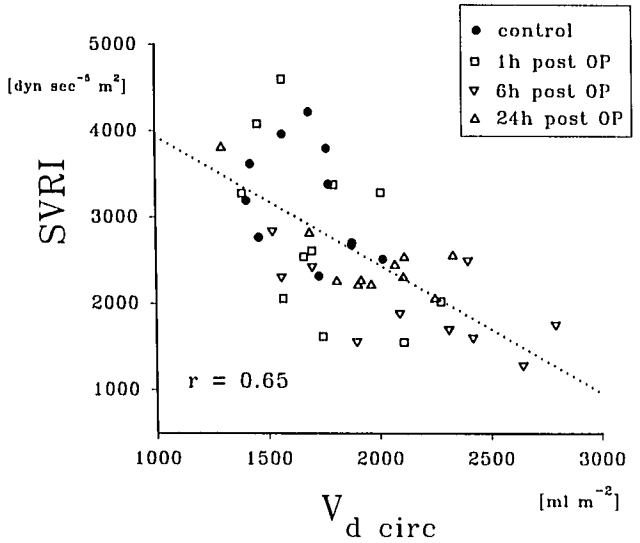

Fig. 4. Relation between circulating blood volume ($V_{d\,circ}$) and systemic vascular resistance index (SVRI). A moderate correlation between $V_{d\,circ}$ and SVRI was observed (r = 0.65). To eliminate interindividual cofactors of variation both systemic resistance and circulating blood volume were normalized by body surface area.

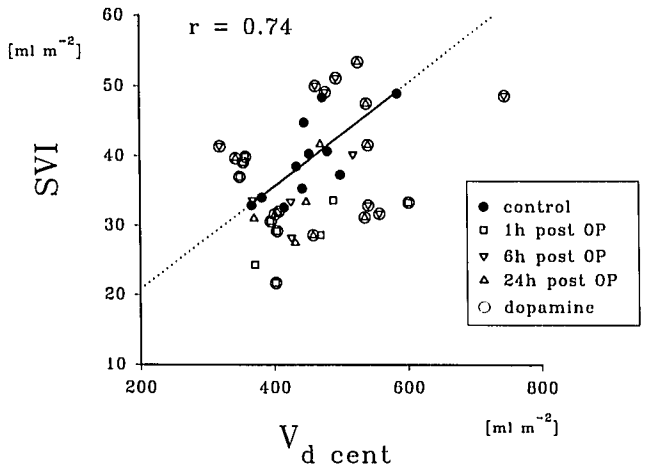

Fig. 5. Relation between central blood volume ($V_{d\,cent}$) and stroke volume index (SVI). At control SVI showed a positive linear correlation with $V_{d\,cent}$ (r = 0.74). After surgery many of the patients required inotropic support by dopamine (4–8 $\mu g\ min^{-1}\ kg^{-1}$, open circles). Patients without dopamine demonstrate a trend of low stroke volumes in comparison with central blood volume, whereas all patients who achieved high stroke volumes in comparison with central blood volume (data points above the regression line of control measurements) received dopamine therapy.

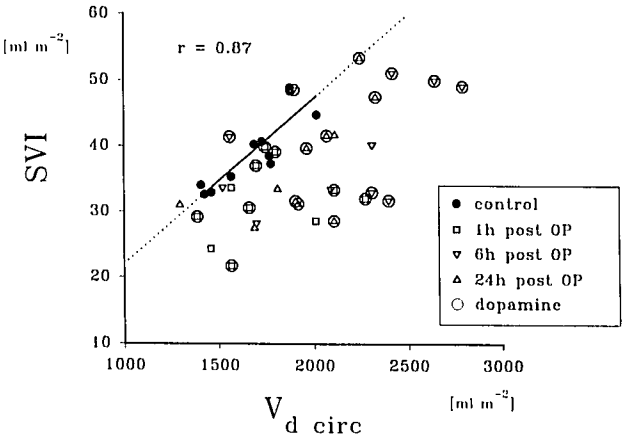

Fig. 6. Relation between circulating blood volume ($V_{d\,circ}$) and stroke volume index (SVI). A close correlation between $V_{d\,circ}$ and SVI was observed at control conditions (r = 0.87). After surgery a higher circulating blood volume was required to achieve the same stroke volume index.

culating blood volume. On the basis of the current data no morphologic substrate can be assigned to these compartments. We speculate that the fast compartment represents areas with very short intravascular mean transit times such as the heart and kidneys. Interestingly, significant postoperative changes of these compartments were be observed. One hour after surgery, the blood flow is mainly increased in the fast circulating compartment, whereas blood flow to the slow circulating compartment remained unchanged. These

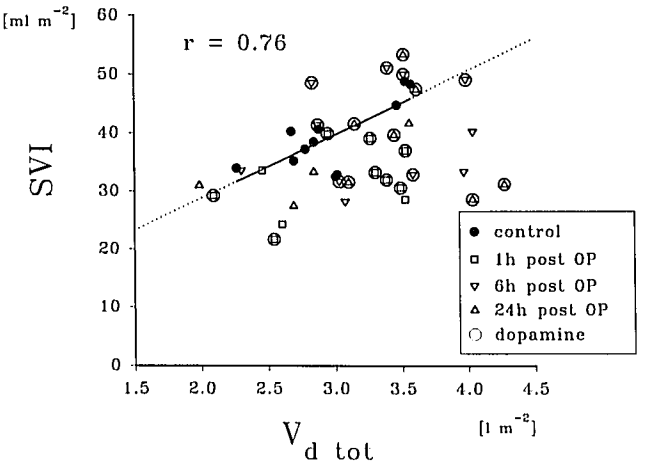

Fig. 7. Relation between total blood volume ($V_{d\,tot}$) and stroke volume index (SVI). Similar to $V_{d\,cent}$ and $V_{d\,circ}$ (figs. 5 and 6) a positive correlation between SVI and $V_{d\,tot}$ was observed for control measurements (r = 0.76).

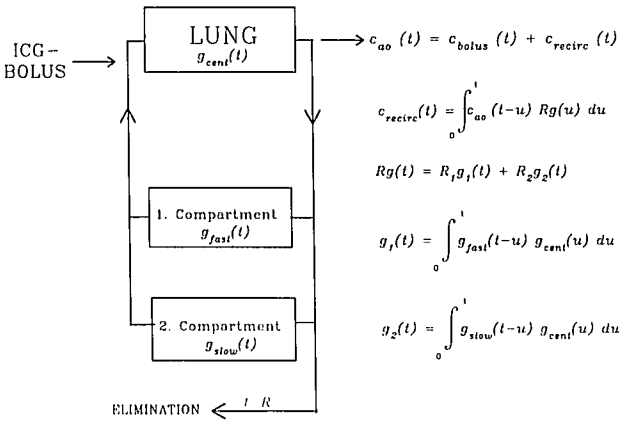

Fig. 8. Pharmacokinetic model for intravascular indocyanine green distribution and elimination. A mathematical model was developed to simulate the concentration–time course of a dye tracer in the aorta (c_{ao} (t)) after bolus injection into the right atrium. A typical example of c_{ao} (t) is shown in figure 1. c_{ao} (t) is the sum of the first pass of the dye bolus after lung passage (c_{bolus} (t), first dotted line) and the recirculating dye (c_{recirc} (t), second dotted line). The transport process of the dye through the system is mathematically described by a convolution integral.[9] The input to the system is the concentration–time course entering the circulation at the site of measurement, which is c_{ao} (t). The output of the system is recirculating dye c_{recirc} (t), which arrives in the aorta after passage of the circulation. However, the recirculating dye (c_{recirc} (t)) reenters the system and contributes to c_{ao} (t), because c_{ao} (t) is the sum c_{bolus} (t) and c_{recirc} (t). Thus, a recursive convolution algorithm describes the dye distribution and elimination process in the circulation. The transport function (g(t)) is characteristic for the distribution of the tracer in the circulation and is determined from measured dye curves by nonlinear least square fitting. The simplest model for g(t), which resulted in acceptable fitting of the measured data was a two-compartment transport function comprising the sum of two log-normal distribution functions (g_1 (t) and g_2 (t)). Because central circulation is always an obligatory part of the recirculation, g_1 (t) and g_2 (t) represent a functionally fast and slow compartment: the transport function of the central compartment (g_{cent} (t)) is lumped into the transport functions of a fast and a slow peripheral compartment ((g_{fast} (t) and (g_{slow} (t)), which can mathematically be described by convolution of the respective transport functions. The recovery factor (R) is always less than 1; in the case of a two-compartment transport function the sum of the weighing factors (R_1, R_2) is less than 1.

changes could indicate a centralization pattern of blood flow distribution with preferential perfusion of heart, brain, and kidneys. Six hours after surgery the blood flow to both compartments is increased. The blood flow distribution pattern resembles the blood flow distribution pattern at control conditions, although at a higher level. This study was not designed to investigate compartmental blood flow in circulation. However, the data provide evidence that the distribution pattern of the cardiac output could be assessed by compartmental analysis of fiberoptically measured dye curves. Further systematic investigation is warranted to evaluate the physiologic and pathophysiologic significance of these observations.

We conclude that a bedside assessment of intravascular volume status by fiberoptic dye measurements is useful and reliable. We demonstrated its utility in patients undergoing coronary bypass surgery. The data of the present study demonstrate that the intravascular space increases to a significant degree within 1–6 h postoperatively. This additional intravascular volume expansion has to be taken into account for postoperative fluid management of these patients. Our bedside fiberoptic measurement of central and circulating blood volume reliably assessed intravascular volume status and left ventricular preload. This may be valuable in patients with critical preload requirements.

Appendix

Cardiac output (CO) was calculated from the thermodilution curve with standard formulas as described previously.[7] The mean transit time through the circulation (mtt_{circ}) was derived from the fiberoptically measured dye curve, which was fitted with a nonlinear least-squares program[18] to a newly developed pharmacokinetic model. The model simulates dye distribution, recirculation and elimination by a recursive convolution procedure in a similar manner as previously described by Cutler,[19] Dienes,[20] and van Rossum *et al.*[21] and as schematically depicted in figure 8. Van Rossum gave the theoretical solution for the recirculation model in LaPlace domain, whereas Cutler and Dienes described recirculation by a recursive convolution integral in time domain as applied in the present study. The present model is based on the assumption that the time course of the measured dye concentration in the aorta ($c_{ao}(t)$, fig. 1) results from the sum of the initial bolus injection ($c_{bolus}(t)$) after its first appearance in the aorta and recirculating dye ($c_{recirc}(t)$).

$$c_{ao}(t) = c_{bolus}(t) + c_{recirc}(t) \quad (6)$$

Transport of the dye through the circulation can be mathematically described by a convolution integral of the aortic input to the circulation ($c_{ao}(t)$) and a transport function (g(t)).[22] The transport function g(t), which is technically an impulse response function, characterizes the dispersion process of the indicator during the transport through the circulation.[23] Thus, $c_{recirc}(t)$, which is the result of the transport process of the dye through the circulation, can be calculated by the convolution integral of $c_{ao}(t)$ and g(t):

$$c_{recirc}(t) = R \int_0^t c_{ao}(t - u)\, g(u)\, du. \quad (7)$$

where u = a dummy variable for integration.

By definition the area under the transport function (g(t)) equals 1. Hence, the recovery factor R equals 1 when no tracer is lost. R is less than 1 when part of the indicator is removed during passage of the circulation (*i.e.*, hepatic elimination).

Combining equation 6 and 7 results in equation 8, which is a recursive convolution algorithm as $c_{ao}(t)$ is represented on both sides of the equation:

$$c_{ao}(t) = c_{bolus}(t) + R \int_0^t c_{ao}(t - u)\, g(u)\, du \qquad (8)$$

The shape of $c_{bolus}(t)$ can be appropriately modelled with a lagged normal density function.[24] This function was therefore also used in the present study to separate the initial bolus from recirculating tracer.

The transport functions for the passage of an intravascular tracer through most organs can be adequately described by a left skewed distribution function.[25] However, all attempts to fit a single left skewed transport function to our data showed systematic differences between data and fitting results, indicating that a one-compartment model might not be appropriate. Moreover, the recovery factor R, which was expected to be less than 1, often showed values higher than 1, which is not possible. The next simplest model for a body transport function is the sum of two transport functions instead of a single one. In fact, a good fit could be obtained with a two-compartment model by using the sum of two weighted log-normal distributions that represent a fast and a slow compartment in parallel:

$$Rg(t) = R_1 g_1(t) + R_2 g_2(t)$$

$$g_1(t) = \frac{1}{\sqrt{2\pi}\sigma_1 t}\, e^{-(1/2)|\ln(t/mtt_1)+(\sigma_1^2/2)|^2/\sigma_1^2}$$

$$g_2(t) = \frac{1}{\sqrt{2\pi}\sigma_2 t}\, e^{-(1/2)|\ln(t/mtt_2)+(\sigma_2^2/2)|^2/\sigma_2^2} \qquad (9)$$

These are log-normal distribution functions for g_1 and g_2, where R_1 and R_2 = weighting factors, $R_1 + R_2 < 1$, $\sigma_{1,2}^2$ = variance, and $mtt_{1,2}$ = mean transit time.

This approach is similar to the semi-Markov stochastic compartmental model suggested by Matis and Wehrly.[26] We chose to use log-normal distribution functions for description of the compartments because in earlier studies these had proven to describe organ transport functions very well and only two parameters (mean transit time mtt and variance σ^2) are required to be determined by the fitting process. However, a body transport function comprising the sum of two left skewed transport functions is not exactly isomorphic to the model depicted in figure 8. The transport function of the central compartment, *i.e.*, the pulmonary circulation ($g_{ccmt}(t)$), is lumped into the transport functions of the fast and the slow peripheral compartments ($g_{fast}(t)$ and $g_{slow}(t)$) with $g_1(t) = g_{ccmt}(t) * g_{fast}(t)$ and $g_2(t) = g_{ccmt}(t) * g_{slow}(t)$ (where the operator * denotes the convolution procedure). This is justified, because convolution of two left-skewed distribution functions ($g_{ccmt}(t)$ with $g_{fast}(t)$ and $g_{ccmt}(t)$ with $g_{slow}(t)$, respectively) will result in another left skewed distribution ($g_1(t)$ and $g_2(t)$), which also can be parameterized by a log-normal distribution function. For the sake of numerical stability it is advantageous to restrict the model to a minimum of parameters. We therefore chose to determine the parameters of the "lumped" transport functions ($g_1(t)$ and $g_2(t)$), only. By using this two compartment model, the mean transit time of the circulatory system (mtt_{circ}) including the pulmonary circulation and the mean transit times of the peripheral fast and the slow compartments (mtt_{fast} and mtt_{slow}) can be calculated from the individual mean transit times of the lumped fast and the lumped slow compartments (mtt_1 and mtt_2) by

$$mtt_{circ} = (R_1 \times mtt_1 + R_2 \times mtt_2)/(R_1 + R_2)$$

$$mtt_{fast,\,slow} = mtt_{1,2} - mtt_{ccmt} \qquad (10)$$

The respective volumes of distribution ($V_{d\,circ\,1,2}$ and $V_{d\,fast,\,slow}$) and the flow to respective compartments ($CI_{1,2} = CI_{fast,\,slow}$) are:

$$V_{d\,circ\,1,2} = [R_{1,2}/(R_1 + R_2)] \times mtt_{1,2} \times CO/BW$$

$$V_{d\,fast,\,slow} = [R_{1,2}/(R_1 + R_2)] \times mtt_{fast,\,slow} \times CO/BW \qquad (11)$$

$$CI_{1,2} = R_{1,2}/(R_1 + R_2) \times CI \qquad (12)$$

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