# Bedside Assessment of the Microvascular Venous Compartment in Cardiac Surgery Patients With Valvular Diseases Undergoing Cardiopulmonary Bypass

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**Objective:** Blood volume reserve for venous return and the effects of cardiopulmonary bypass (CPB) on microvascular bed partitioning and blood flow were examined in patients with valvular diseases.

**Design:** Prospective, consecutive, case-control study.

**Setting:** Single university hospital.

**Participants:** The study comprised 20 adult cardiac surgery patients and 20 healthy volunteers.

**Interventions:** Cardiovascular and microvascular variables were collected soon after the induction of anesthesia, after commencement of CPB, 20 minutes after separation from CPB, and in the intensive care unit.

**Measurements and Main Results:** The unstressed and stressed volumes (Vu, Vs) and pressures therein (Pit, Ps) were measured in the brachioradial muscle with near-infrared spectroscopy, applying incremental venous occlusions. At the first time point, Vs and Pit showed lower and higher values, respectively, than those of control patients, but Vs increased with Vu during the study, whereas Pit remained unchanged. Fluid balance correlated with Pit ($r = 0.83$, $p < 0.001$) and hemoglobin ($r = 0.78$, $p = 0.004$). A nonlinear regression was found between fluid balance and $\Delta Vu$ ($r = 0.90$, $p < 0.001$) [$y = 1.85 + 37.43^{(-0.01 \times x)}$]. The Vu/Pit and Vs/Ps ratios were lower than those of the control patients. Blood flow correlated to Vs/Ps ($r = 0.75$, $p < 0.001$). The time constant was lower than reference ($p = 0.005$) and increased 10 times after CPB.

**Conclusions:** Cardiac surgery patients have a limited blood volume reserve for venous return due to a reduced microvascular bed capacitance. This study demonstrated that during CPB a positive fluid balance induced an extravascular pressure increase and further reduced blood volume reserve.



***KEY WORDS:*** *skeletal muscle, venous compartment, near-infrared spectroscopy, microvascular bed, cardiopulmonary bypass, valvular disease*

CARDIOVASCULAR MONITORING normally is used to evaluate the relationship between cardiac load and output to maintain blood perfusion to organs and tissues. Cardiac surgery patients undergoing cardiopulmonary bypass (CPB) experience injury to organs and tissues in multiple systems.[1–3] The effects of CPB add to the cardiovascular adaptations induced by underlying cardiac diseases. In particular, valvular diseases induce compensatory mechanisms, resulting in pressure adjustments in the intravascular compartments that aim to maintain venous return.[4] Because approximately 80% of blood volume is present in veins and three-quarters of that is in small veins and venules,[5,6] the venous compartment of the microvascular bed plays a pre-eminent role in blood volumes and pressures, partitioning between the unstressed volume (Vu) and the stressed volume (Vs), in determining the amount of venous return. Whereas the Vu is a reserve of blood volume[7] that has only limited involvement in the blood volume expansion aimed at increasing cardiac output (CO), the Vs is involved actively in venous return and, consequently, cardiac preload.[8]

As a result of the microcirculation's leading role in maintaining organ function, many authors have focused their research on the effect of CPB on the microcirculation.[9–11] There is increasing evidence regarding CPB-induced changes in microvascular blood flow, capillary density, tissue oxygenation, and mitochondrial dysfunction.[12–16] However, there have been no clinical studies on the venous compartment of the microvascular bed and how it might be affected by CPB, probably due to the difficulty in assessing this vascular compartment. Recently, the authors used near-infrared spectroscopy (NIRS), a technology widely used for the in vivo evaluation of tissue oxygenation and blood flow, to measure microvascular bed volume (MBV) partitioning in Vu and Vs, and pressures therein, in humans.[17]

This noninvasive, observational study of cardiac surgery patients with valvular diseases and cardiac dysfunction was designed to extend the knowledge of microvascular changes affecting the blood volume reserve for venous return and cardiac load[18] during off-pump surgery and to evaluate the effects of CPB on microvascular bed volume partitioning and tissue blood flow (tBF).

The results of this study may help clinicians to assess the determinants of perioperative cardiovascular functional capacity and factors contributing to organ dysfunction. In addition to measurement of the MBV partitioning in Vs and Vu skeletal muscle and pressures therein, the authors examined pressure in the Vu (threshold pressure: Pit, pressure equals extravascular pressure) as an expression of interstitial fluid leakage. The authors also measured the elastic compliance (mvec) and microvascular blood flow. In addition, the possible relationships between microvascular and systemic variables, such as the systemic arterial and venous pressures, and CO or pump flow were assessed.

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## METHODS

### Patient Population

This observational, prospective study was conducted at the Cardiovascular Unit of Careggi Hospital, Florence, Italy, an academic center, from June to October 2013. The authors enrolled 20 adult patients with primary valvular disease scheduled for elective surgery with nonpulsatile CPB for a single or combined valve repair/replacement with or without concomitant coronary artery bypass grafting. The surgical risk in each patient was assessed using the EuroSCORE II model.[19] Patients requiring emergency cardiac procedures or needing axillary or femoral arterial cannulation were excluded. Patients also were excluded for the following criteria: age $<18$ years, pregnant patients and those with cirrhosis, left ventricular ejection fraction $<0.25$, advanced chronic obstructive pulmonary disease, severe arterial hypertension, and a body mass index $>29.9$.

The institutional review board approved the study procedures (M/CE/04 rev13), and each patient gave written, informed consent before inclusion. Data collected from a group of 20 healthy patients, 8 women and 12 men (average age $47.9 \pm 10.5$ years), who participated in a previous study,[20] were used as reference values (unpublished data). These patients, whose physical status was considered to be American Society of Anesthesiologists class I, underwent general anesthesia for elective maxillofacial surgery and did not experience disorders likely to influence the microcirculation (eg, diabetes, peripheral vascular disease, or chronic venous insufficiency). Anesthesia was induced with 2 mg/kg of propofol, a bolus injection of 1 μg/kg of remifentanil, and vecuronium bromide, 0.9 mg/kg, and was maintained with a continuous infusion of 4.5 mg/kg/hour of propofol, 0.3 μg/kg/min of remifentanil, and rocuronium, 0.3 mg/kg/min. The hemoglobin (Hb) value did not reach lower than 13.0 g/100 mL in control patients. Data were collected 30 minutes after tracheal intubation and mechanical ventilation.

### General Management

After patient placement on the operating table, a pneumatic cuff was placed around the arm, 5 cm proximal to the antecubital crease, and was connected to an automatic inflation system (Hokanson Rapid Cuff Inflator and AG101 Air Source; PMS Instruments Ltd, Maidenhead, UK) capable of reaching a predefined cuff pressure (Pcuff) in $<0.5$ seconds. A NIRS probe was positioned on the ventral surface of the brachioradial muscle. To avoid differences in hydrostatic pressure requiring a correction factor, the arm cuff and NIRS probe were kept at the same level by placing the patient's forearm in a plastic frame and keeping the arm and elbow at an angle of 135° at heart level.

### Time Points for Data Collection

Data on systemic cardiovascular and microcirculatory variables were collected 20 minutes after anesthesia induction (pre-CPB), 20 minutes after CPB started (CPB), 20 minutes after separation from CPB (post-CPB), and 1 hour after admission to the postoperative intensive care unit (ICU). In the control group, data were collected 20 minutes before the end of surgery.

### Anesthesia and Perioperative Management

After premedication with oral benzodiazepine (diazepam, 5 mg) and intramuscular atropine, 0.5 mg approximately 30 minutes before surgery, all patients underwent continuous electrocardiogram monitoring plus pulse oximetry and invasive arterial pressure monitoring. Anesthesia induction was achieved with sufentanil, 0.5 to 1 μg/kg, midazolam, 0.1 mg/kg, and rocuronium, 0.6 mg/kg, and was maintained with propofol, 2.5 to 4 mg/kg/hour, remifentanil, 0.2 to 0.4 μg/kg/min, and rocuronium, 0.3 μg/kg/min. Excluding CPB, mechanical ventilation was performed with a volume-controlled mode of 50% oxygen in air using a semi-open circle system. Tidal volume was set at 8 mL/kg (ideal body weight) with a positive end-expiratory pressure of 5 $cmH_2O$, and the ventilatory rate was adjusted to keep the partial pressure of arterial carbon dioxide between 35 and 40 mmHg.

After induction, an arterial catheter was inserted into the radial artery and a triple-lumen central venous catheter was inserted into the internal jugular vein (echo-guided procedure), connected via standard low-compliant tubing to disposable pressure transducers for arterial pressure and central venous pressure monitoring. Patients received an intravenous injection of 300 U/kg of porcine heparin before CPB and underwent aortic cannulation to obtain a target kaolin-activated coagulation time (ACT) of 400 seconds. Additional doses of 5,000 U of heparin were administered at ACT $<300$ seconds and 2,500 U at ACT $<400$ seconds. CPB pump flow was set at 2.4 $L/min/m^2$.

After the start of CPB and when ventilation was stopped, the body temperature was allowed to decrease to 34°C (mild hypothermia) using a heat exchanger. When surgery ended, patients were rewarmed actively and slowly to approximately 37°C with warm forced-air convection, and the spontaneous heartbeat was resumed with or without electrical defibrillation. Cardiac function was evaluated using transesophageal echocardiography before and during weaning from CPB. Stroke volume (SV) was calculated by measuring the cross-sectional area and the diameter (d) of the left ventricular outflow tract (LVOT) from the midesophageal long-axis view (LVOT cross-sectional area $= [d_{LVOT}/2]^2 \times \pi$), and the integral of velocity time (VTI) was measured at the same site ($VTI_{LVOT}$) with the pulsed-wave Doppler at the deep transgastric view: SV (mL) $= [(d_{LVOT}/2)^2 \times \pi] \times (VTI_{LVOT})$. CO was derived as the product of the average SV in 5 consecutive beats and the heart rate. Inotropic-vasoactive drugs were given according to a protocol-based approach that considered the echocardiographic evaluation of heart function and the mean blood pressure value. Allogeneic packed red blood cell (RBC) transfusions were considered on the basis of oxygen delivery and a hematocrit value $<20\%$.[21]

After weaning the patient from CPB, 0.6-to-1 mg of protamine hydrochloride was administered to neutralize the heparin previously administered; this dose is considered adequate if the postprotamine ACT value is within 10% of the preheparin value. After surgery, all patients were moved while under sedation with propofol (1 mg/kg/h) and remifentanil (0.1 μg/kg/min) to a cardiac surgery ICU, where they reached complete rewarming and hemodynamic and coagulation stability.

## NIRS and Calculation of Variables

The authors measured the absolute tissue oxyhemoglobin/myoglobin ([$HbO_2$/$MbO_2$]) and deoxyhemoglobin/myoglobin ([HHb/HMb]) concentrations in μM in the brachioradial muscle with a continuous-wave quantitative photometer using 4 different wavelengths and 5 laser diode sources (NIMO-4; Nirox Srl, Borgosatotollo, Italy).[22] Data were acquired at a sampling speed of 1 second, thus yielding adequate data to analyze rapid changes in the tissue Hb concentration.

When examining the microvascular bed, the authors focused mainly on the total Hb tissue concentration contained in venules, small veins, and, to a lesser extent, capillaries, because the Hb contained in the arterial vessels accounts for only 3% of the whole Hb measured with NIRS.[23] The MBV (in milliliters per 100 mL of tissue) was derived from the Hb concentration (g/dL)[17] in blood samples drawn from each patient, taking into account that Hb molecular weight equals 64,500 Da. Because tissue Mb at rest is almost fully oxygenated,[24] it is widely accepted that light absorption measured using NIRS is derived from [HHb] and from oxygenated Hb and Mb.[23–25]

To obtain the microvascular volume and pressure variables (Vu, Vs, Pit, Ps), the authors applied the same method of cuff venous occlusions used for strain-gauge plethysmography.[26–28] Using NIRS, changes in the MBV were measured during cumulative 45-second-to-1-minute steps of Pcuff, increasing from 5 mmHg to 10, 15, 20, 30, 40, and 50 mmHg.[17] Previous studies have demonstrated a close correlation between Pcuff and pressure in veins.[29] The authors of the study presented here limited Pcuff to a value 10 mmHg lower than the individual patient's diastolic pressure, thus affecting veins rather than arteries.[6] Because the Mb concentration in tissue remained constant, the authors attributed changes in light absorption during venous occlusions to only [$HbO_2$] and [HHb].

Vs (mL/100 mL of tissue) was measured by subtracting to the MBV, measured before venous occlusions by the absolute tissue $HbO_2$/$MbO_2$ and the HHb concentrations, the blood volume resulting from the extrapolation on the pressure axis of the first 2 changes in the MBV after repetitive Pcuff increases. Vu (mL/100 mL of tissue) was calculated by subtracting to the MBV, measured before venous occlusions, the Vs and the [$MbO_2$], considered as 40% of the NIRS signal due to [$HbO_2$/$MbO_2$], as previously described.[17] To calculate pressure in the MBV (PV), before cuff occlusions, the authors considered Pcuff at the first MBV increase, the sum of this blood volume increase, and baseline MBV, thus deriving pressure by proportion. Pit, pressure in the Vu at which intravascular pressure equals extravascular pressure (transmural pressure = 0), was measured by extrapolating linear regression of the first 2 MBV increases after the steps of Pcuff increase.[26] The authors considered Pit as the intercept on the pressure axis (x-axis), an independent variable, of the ΔMBV (y-axis), a dependent variable, when its value was 0 (Fig 1). The authors calculated pressure in the Vs (Ps) as the difference between PV and Pit.

Because the microvascular bed enlarges differently depending on the intravascular pressure values (see Fig 1), the term "capacitance" was used to refer to the ratio between blood volume changes at distending pressures lower than 30 mmHg

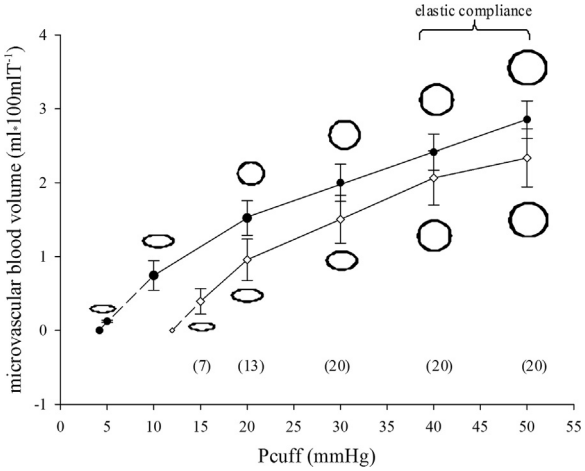


**Fig 1. Microvascular blood volume changes measured with NIRS at various cuff pressures in healthy patients *(black dots)* and cardiac surgery patients with valvular diseases before cardiopulmonary bypass *(white dots)*. Numbers in *brackets* represent the data measured at each cuff pressure. Cardiac surgery patients showed a higher threshold pressure (Pit: corresponding to the first unstressed volume data measured using NIRS) than that of healthy patients. Microvascular blood volume increase changes its linearity at a cuff pressure lower than 18 mmHg in healthy patients and 40 mmHg cardiac surgery patients. Based on the linearity of blood volume increase, the vascular shape is sketched.**

(reflecting mainly the vascular bed recruitment)[17,30]; the term microvascular "elastic compliance" (mvec) was used to refer to blood volume changes at distending pressures greater than 30 mmHg (reflecting the elastic properties of the vascular wall).[31] The following new NIRS variables were introduced: the capacitance of Vu or Vs, calculated by the ratios between these volumes and their respective pressures (Vu/Pit, Vs/Ps), and the time constant (τ), calculated by dividing the Vs by the tBF, as reported by Magder.[32] The mvec was measured by calculating the linear regression of ΔMBV in the range of 30-to- 50 mmHg Pcuff. Values were expressed as mL per mmHg in 100 mL of tissue, as previously reported.[17,33,34] The tBF, in milliliters per 100 mL of tissue per minute, was calculated from the increase in [$HbO_2$] during the first 20 seconds of venous occlusion at 30 mmHg Pcuff, as described elsewhere.[35,36] Methods and formulas for calculating microvascular volume variables (MBV, Vu, and Vs) and pressures in the MBV (PV), in the Vu (threshold pressure: Pit, equal to pressure outside vessels), and in the Vs (Ps, corresponding to mean circulatory pressure) are reported with the methods for calculating mvec and tBF in the supplemental material for this article.

To assess the effect of fluid loading on microvascular variables during CBP, the authors calculated the balance of fluids infused or added to circuits and lost or subtracted during CPB between pre-CPB and post-CPB measurements.

## Statistical Analysis

Based on prior data, the authors calculated that a sample size of 20 patients would detect a difference in the variable means as low as ± 0.78, with a probability power higher than 80% and an alpha error $<0.05$ (PS Size Calculations software,

version 3.0; Informer Technologies). The Kolmogorov-Smirnov test was used to assess normal data distribution. A one-way analysis of variance for repeated measurements was used to test differences among values if normally distributed; otherwise, the data were analyzed using the Wilcoxon signed-rank test. For between-group comparisons, the *t*-test was used for paired data normally distributed; otherwise, the Mann-Whitney *U*-test was used. Correlations among variables were tested with Pearson's correlation test for normally distributed values or Spearman's test, and single or multiple regression analysis was used to determine possible correlations among variables. The relationship among variables was tested with linear or nonlinear regressions. All data were expressed as mean ± standard deviation or median 25% to 75% interquartile range, and p values $<0.05$ were considered statistically significant. Data were analyzed with Systat Software, Version 12.0 (Systat Software Inc, San Jose, CA).

## RESULTS

All 20 patients enrolled completed the study, and their airways were extubated within 8 hours of the end of surgery (median 6, range 3.30-7.40 hours). Patients' age ranged from 49 to 88 years, and 60% were male. Most of the patients had a medium or high cardiac surgical risk, and only 10% had a low risk (Table 1). Norepinephrine (NE) and epinephrine were administered to all patients only after CPB discontinuation and in the ICU. NE was administered in 14 patients (70%), with doses ranging from 0.04 to 0.20 μg/kg/min (mean 0.13 ± 0.11 μg/kg/min), and epinephrine was added to NE in 8 patients (mean 0.07 ± 0.09 μg/kg/min). None of the patients required nitroglycerine or other vasodilator drugs. The mean duration of CPB was 116.1 ± 34.9 minutes and ranged from 50 to 175 minutes. As expected, the hematocrit decreased during and soon after CPB and returned to pre-CPB values in the ICU. Eight patients received allogeneic packed RBC transfusions (40%) ranging from 200 to 600 mL (median 450 mL, interquartile range 350-600 mL). The fluid balance during CPB was positive in all patients and ranged from 100 to 1,690 mL (Table 2).

**Table 1. Demographic and Anthropometric Data, Surgical Procedures, Cardiac Surgical Risk, and Comorbidities for 20 Patients With Valvular Diseases Undergoing Elective Cardiac Surgery With Non-pulsatile Cardiopulmonary Bypass**

| | |
|---|---|
| Demographic and anthropometric data | |
| Sex, n, M/F | 12/8 |
| Age, mean (SD), years | 67.2 (4.6) |
| BMI, median (IQR), (kg/m$^2$) | 25.0 (23.5-27.5) |
| Surgical procedures, n (%) | |
| AVR | 17 (85) |
| MVR | 5 (25) |
| TVR | 4 (29) |
| MAZE | 3 (15) |
| CABG | 7 (35) |
| Valvular diseases, n (%) | |
| Aortic valve stenosis | 15 (75) |
| Regurgitation | 4 (20) |
| Mitral valve stenosis | 4 (20) |
| Regurgitation | 3 (15) |
| Tricuspid valve regurgitation | 4 (20) |
| EuroSCORE, median (IQR) | 4.6 (2.3-9.2) |
| Low risk, n | 2 (10) |
| Medium risk, n | 8 (40) |
| High risk, n | 10 (50) |
| Comorbidities, n (%) | |
| Myocardial infarction | 9 (45.0) |
| Hypertension | 15 (75.0) |
| Hyperlipidemia | 12 (60.0) |
| Chronic obstructive pulmonary disease | 11 (55.0) |
| Restrictive pulmonary disease | 3 (15.0) |
| Diabetes mellitus | 5 (25.0) |
| Chronic renal failure | 2 (10.0) |
| Peripheral arterial disease | 8 (40.0) |

Abbreviations: AVR, aortic valve replacement; BMI body mass index; CABG, coronary artery bypass graft; IQR (25%-75%) interquartile range; MAZE, maze procedure for atrial fibrillation; MVR, mitral valve replacement; SD, standard deviation; TVR, tricuspid valve replacement.

### Systemic Cardiocirculatory, Temperature, and Metabolic Variables

Among the systemic variables measured during cardiac surgery, the systolic pressure after CPB was lower than that measured before CPB, whereas diastolic pressure was unchanged. Mean and systolic arterial pressures measured in the ICU matched pre-CPB values and were higher than those measured after CPB. In contrast, diastolic pressure in the ICU was lower than that before CPB (see Table 2). The CO values before CPB matched those of pump flow and decreased by 12% soon after CPB and then reverted to initial values in the ICU. SV showed the same trend as CO, decreasing by 33% after CPB and then reverting to pre-CPB values in the ICU. Central venous pressure was unchanged during surgery but decreased in the ICU. As expected, temperature decreased by a mean of 22% during CPB (range from 14% to 28%) and increased when patients were rewarmed. Serum lactate concentration increased during and soon after CPB by no more than 2.5 mmol/L and decreased to pre-CPB values in the ICU. pH was unchanged during surgery and in the ICU, but baseline partial pressure of arterial carbon dioxide values increased after CPB and in the ICU (see Table 2). Blood Hb oxygen saturation was $\geq 97\%$ at all measurements in all patients.

### Microvascular Volume and Pressure Variables

The MBV and Vu values before CPB matched reference values but increased after the onset of CPB, doubling their values at off-pump measurement. In contrast, Vs measured before CPB showed values half that of the reference, which increased at the on- and off-pump measurements. The MBV, Vu, and Vs values recovered in the ICU and matched the values measured before CPB (Table 3). The MBV changes during the study were related strictly to changes in Vu ($r = 0.99$, $p < 0.001$) and to a lesser extent to Vs ($r = 0.45$, $p = 0.004$).

The PV and Pit values measured before CPB were more than twice those of the reference values, whereas the Ps values matched those of the reference values. Tests performed to evaluate perioperative changes in pressure variables showed an increase in the Ps values after CPB discontinuation but no

**Table 2. Hemodynamic and Metabolic Variables, Vasoactive Medications, and Fluid Balance**

| Variables | Pre-CPB | CPB | Post-CPB | p Value | ICU | ICU vs Pre-CPB, CPB, Post-CPB (p Value) |
|---|---|---|---|---|---|---|
| Mean arterial pressure, mmHg | 77.6 (11.6) | 72.6 (12.5) | *67.2 (9.2) | 0.027 | 78.8 (14.5) | 0.834, 0.298, 0.032 |
| Systolic pressure, mmHg | 113.5 (14.2) | — | *98.2 (20.1) | 0.029 | 118.9 (19.2) | 0.489, 0.034 |
| Diastolic pressure, mmHg | 68.2 (10.1) | — | 60.75 (11.6) | 0.102 | 56.7 (12.2) | 0.038, 0.482 |
| Heart rate, beats/min | 66.1 (14.0) | — | 86.8 (11.6) | <0.001 | 76.3 (8.9) | 0.036, 0.016 |
| Cardiac output or pump flow (L/min) | 4.01 (0.34) | 4.27 (0.78) | *†3.54 (0.48) | 0.004 | 4.35 (0.45) | 0.039, 0.752, <0.001 |
| Stroke volume, mL | 63.5 (13.3) | — | 42.6 (7.8) | <0.001 | 54 (8.4) | 0.076, 0.048 |
| Central venous pressure, mmHg | 9.2 (4.7) | 10.4 (3.8) | 9.5 (5.6) | 0.076 | 7.3 (3.5) | 0.038, 0.024, 0.034 |
| Temperature, C | 36.3 (0.6) | ‡28.4 (3.3) | *30.2 (0.3) | 0.003 | 35.9 (2.2) | 0.738, 0.012, 0.045 |
| Hct, % | 37.9 (4.1) | ‡27.4 (3.5) | *†28.6 (4.6) | <0.001 | 35.3 (4.3) | 0.168, <0.001, 0.003 |
| pH | 7.43 (0.03) | 7.43 (0.08) | 7.41 (0.07) | 0.087 | 7.40 (0.04) | 0.387, 0.343, 0.876 |
| $pCO_2$, mmHg | 34.5 (3.5) | 37.4 (5.6) | *40.4 (3.9) | 0.003 | 43.2 (4.2) | 0.003, 0.023, 0.089 |
| Lactates, mmol/L | 1.03 (0.20) | [c]2.11 (0.37) | *1.60 (0.44) | 0.002 | 1.47 (0.34) | 0.038, 0.022, 0.342 |
| Vasoactive drugs, μg/kg/min | | | | | | |
| Norepinephrine, n (dose range) | — | — | 14 (0.03-0.20) | | 3 (0.03-0.15) | |
| Epinephrine n (dose range) | — | — | 8 (0.05-0.1) | | — | |
| Fluid balance, mL | — | — | 874.7 (445.0) | | | |

NOTE. Results are presented as values of variables before cardiopulmonary bypass (pre-CPB), 20 minutes after CPB started (CPB), 20 minutes after CPB recovery (post-CPB), and 1 hour after postoperative intensive care unit admission.

Abbreviations: Hct, hematocrit; $pCO_2$, partial pressure of carbon dioxide.

Bonferroni's test was used for post-hoc comparison among variables. Mean arterial pressure: *p = 0.036 versus pre-CPB; systolic pressure: *p = 0.010 versus pre-CPB; cardiac output: *p = 0.031 versus pre-CPB, †p = 0.004 versus CPB; temperature: ‡p = 0.002,*p = 0.012 versus pre-CPB, Hct:*‡p <0.001 versus pre-CPB; †p = 0.032 vs CPB; $pCO_2$: *p <0.001 versus pre-CPB; lactates: ‡p = 0.012, *p = 0.034 versus pre-CPB.

significant changes in Pit values. In the ICU, pressure variables matched those measured before CPB (see Table 3). No difference was found in volume-pressure variables when patients treated or untreated with vasoactive drugs were compared.

Correlation tests showed a positive correlation between net fluid balance and absolute Pit values ($r = 0.83$, $p < 0.001$) and blood Hb concentration measured after CPB ($r = 0.78$, $p = 0.004$). When testing the relationship between the balance of fluids given to patients during CPB, as an independent variable, and the CPB-induced changes in microvascular volume variables, a nonlinear regression was found between fluid balance and ΔVu ($r = 0.90$, $p < 0.001$) (Fig 2). Therefore, with a greater positive balance, the lower Vu change was measured with an exponential decay described by the following equation: $y = 1.85 + 37.43^{(-0.01 \times x)}$. In contrast, no correlation was found between the microvascular variables and the duration of CPB.

### Microvascular Capacitance, Compliance, and Blood Flow

The mvec values measured before CPB matched those of the reference values and were unchanged during the study. In contrast, the microvascular bed capacitance (Vu/Pit and Vs/Ps ratios) before CPB was lower than that of the reference values, and CPB yielded a wide variability in volume/pressure ratios with no statistical significance (Fig 3). In the ICU, tests showed that Vs/Ps values were lower than those measured soon after CPB.

The tBF values measured before CPB matched reference values and remained statistically unchanged during the study but decreased in the ICU. Although the blood flow remained statistically unchanged during cardiac surgery, multiple linear regression analysis performed to assess the relationship between tBF, as a dependent variable, and microvascular volume or pressure showed that tBF was correlated weakly with Vs ($r = 0.59$, $p = 0.032$) and to a higher degree with Vs/Ps ($r = 0.75$, $p < 0.001$). The τ of the vascular bed contributing to perfusion (Vs) showed lower values (faster flow) than the reference values ($p = 0.005$) and increased (slower flow) approximately 10-fold after CPB discontinuation (Fig 4). No correlation between τ and Hct values was observed. No differences in the volume/pressure ratio, mvec, or tBF were observed between patients who did or did not receive vasoactive drugs after CPB and in the ICU.

Correlation tests showed no relationship between the microvascular volume or pressure variables and arterial pressure or cardiac or pump flow.

## DISCUSSION

This noninvasive, observational study showed that, as hypothesized, patients with valvular diseases and a medium or high cardiac surgical risk have altered skeletal muscle microvascular bed partitioning and pressures therein—the Vs was smaller and pressure in the Vu was greater than in healthy patients. The study presented here also showed that CPB enlarged microvascular Vs and Vu and increased pressure inside the Vs without changes in the microvascular elastic compliance or the overall blood flow. In addition, fluid overload increased pressure in the extravascular space and reduced the reserve of blood available to maintain filling pressure in the right heart. Finally, although the overall results showed no correlation between microvascular and macrovascular variables, the decreases in post-CPB CO and arterial pressure could have altered MBVs and pressures.

These results highlighted a reduced capacitance of the overall venous compartment of the microvascular bed, as evidenced by the lower volume/pressure ratios compared with healthy patients. However, Vs and Vu demonstrated opposite findings. Despite an inside driving pressure in the normal

**Table 3. Microvascular Variables**

| | Cardiac Surgery Patients (20) | | | | | | | Pre-CPB Versus Reference |
|---|---|---|---|---|---|---|---|---|
| | pre-CPB | CPB | post-CPB | p Value | ICU | ICU Versus pre-CPB to post-CPB p Value | Reference Control Patients (20) | p Value |
| Microvascular volume variables | | | | | | | | |
| MBV, mL/100 mL tissue | 3.34 (0.94) | *5.35 (1.83) | †6.80 (4.40) | 0.002 | 3.35 (2.30) | 0.990-‡0.009 | 3.44 (0.74) | 0.818 |
| Vu, mL/100 mL tissue | 3.16 (1.02) | *5.06 (1.68) | †6.37 (4.29) | 0.004 | 3.22 (2.27) | 0.932-‡0.017 | 3.06 (0.66) | 0.806 |
| Vs, mL/100 mL tissue | 0.19 (0.29) | *0.29 (0.25) | | 0.032 | 0.13 (0.07) | 0.525 to ‡<0.001 | 0.38 (0.18) | ‡0.027 |
| Microvascular pressure variables | | | | | | | | |
| PV, mmHg | 16.56 (6.95) | 15.60 (6.68) | †§22.81(10.56) | <0.001 | 15.72 (9.04) | 0.789-0.122 | 7.32 (3.67) | †0.002 |
| Pit, mmHg | 11.96 (8.00) | 9.97 (6.22) | 14.51 (8.33) | 0.082 | 10.84 (8.68) | 0.759-0.339 | 4.87 (4.41) | ‡0.034 |
| Ps, mmHg | 4.60 (5.26) | 5.64 (5.18) | ‡8.82 (5.44) | 0.045 | 4.88 (4.43) | 0.423-0.045 | 2.45 (2.32) | 0.405 |
| Microvascular compliance, capacitance, and blood flow | | | | | | | | |
| mvec, mL/mmHg × 100 mL of tissue | 0.041 (0.019) | 0.042 (0.024) | 0.055 (0.043) | 0.174 | 0.035 (0.022) | 0.423-0.166 | 0.056 (0.039) | 0.310 |
| Vu/Pit, mL/mmHg | 0.21 (0.25) | 0.34 (0.64) | 0.64 (2.43) | 0.783 | 0.32 (0.96) | 0.089-0.086 | 0.38 (0.75) | ‡0.019 |
| Vs/Ps, mL/mmHg | 0.07 (0.07) | 0.15 (0.29) | 0.08 (0.03) | 0.299 | 0.04 (0.02) | 0.271-0.049 | 0.26 (0.22) | ‡0.015 |
| mBF, mL/min/100 mL of tissue | 8.64 (8.86) | 7.85 (4.00) | 7.96 (7.26) | 0.908 | 2.65 (1.83) | ‡0.028-0.070 | 6.61 (5.69) | 0.635 |
| τ, mL/mL/min/100 mL of tissue | 0.027 (0.03) | 0.053 (0.05) | †0.229 (0.38) | 0.048 | 0.092 (0.11) | ‡0.012-0.671 | 0.06 (0.03) | 0.005 |

NOTE. Microvascular variables were measured in 20 cardiac surgery patients 20 minutes after anesthesia induction (pre-CPB), 20 minutes after CPB started (CPB), 20 minutes after CPB recovery (post-CPB), and 1 hour after ICU admission. Data measured in healthy patients were used as reference controls. Bonferroni's test was used for post-hoc comparison to identify the following: MBV, microvascular bed volume: *†$p = 0.002$ versus pre-CPB; Vu, unstressed volume: †$p < 0.001$, *$p = 0.0032$ versus pre-CPB; Vs, stressed volume: *$p = 0.002$, †$p = 0.026$ versus pre-CPB; PV, pressure in the microvascular bed volume: *$p = 0.001$ versus pre-CPB, §$p < 0.001$ versus CPB; Ps, pressure in the stressed volume †$p = 0.045$ versus pre-CPB; τ, time constant: †$p = 0.003$ versus pre-CPB. ‡$p < 0.05$.

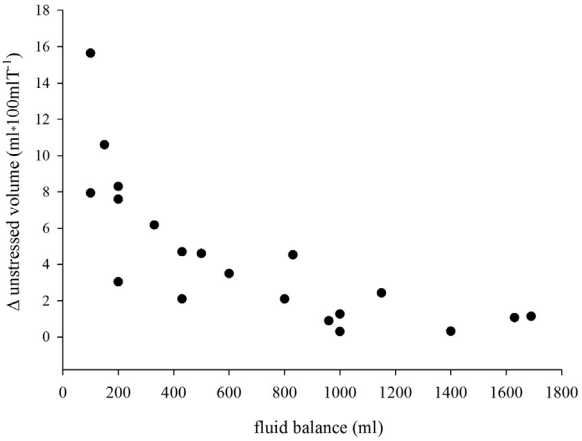


**Fig 2. Scatter plots of the unstressed volume changes (ΔVu) and balance of fluids (net fluid balance in milliliters from time point before and after cardiopulmonary bypass) in the 20 cardiac surgery patients during the study. Values are related with an exponential decay described in the equation: $y = 1.85 + 37.43(-0.01 \times x)$ and a regression coefficient 0.90 ($p < 0.001$), so that the greater the positive balance, the lower ΔVu is measured.**

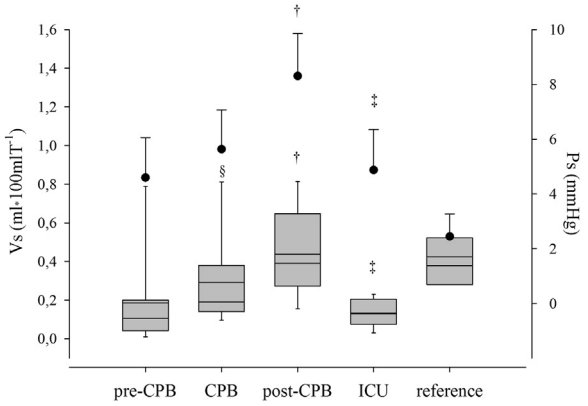


**Fig 3. Box plots and scatter plots with standard errors of the stressed volume (Vs) (box plots: mean, median, standard error, and percentiles) and pressure therein *(black dots)* in the forearm microvascular bed of the 20 cardiac surgery patients and the 20 reference healthy control patients. Variables were collected before cardiopulmonary bypass (pre-CPB), 20 minutes after CPB began (CPB), 20 minutes after recovery from CPB (post-CPB), and in the postoperative intensive care unit. §†$p < 0.05$ versus pre-CPB; ‡$p < 0.05$ versus post-CPB.**

range, the stressed (hemodynamically active) microvascular bed in patients with valvular disease supplied less volume to venous return compared with that of healthy patients; hence, cardiac surgery patients could have a limited blood volume reserve for venous return and CO. Conversely, the unstressed (hemodynamically inactive) vascular bed required pressure values of up to 2.5 times greater than reference values to remain open. Therefore, in those patients, most of the venous pressure was spent preserving the overall microvascular bed volume but not tissue perfusion. Because pressure in the Vu and Pit equals pressure outside the vessels in the interstitium, the cardiac surgery patients experienced an extravascular pressure higher than that in the healthy patients, probably due to their underlying cardiovascular diseases. In addition, high interstitial pressure, likely caused by an increase in fluids in the extravascular space, is an obstacle to oxygen diffusion from capillaries to cells, thus limiting the chance of tissue oxygenation. Also, as shown by the time constant, a low Vs with a normal blood flow entails a fast transit time for erythrocytes in the microcirculation, which could be detrimental to the ability of cells to extract oxygen for their needs.[37] The authors found that the reduced capacitance (low volume/pressure ratio) of the microvascular bed, with the elastic properties of the vascular wall unchanged, may reflect a poorly recruited vascular bed.

## CPB

From these results, it appeared that CPB had an effect on the microvascular bed in which volumes and pressures already were altered. The increases in Vs and Vu, with unchanged volume/pressure ratios and compliance, suggested that recruitment of the vascular bed was the result of factors triggered by the use of CPB itself.

## Fluid Balance

The strong positive correlation between Pit and fluid balance in these patients on CPB suggested that fluid overload increased the interstitial pressure due to capillary leak. The findings of this study confirmed the CPB-induced extravascular fluid leakage demonstrated in adults and children caused by the diffuse inflammatory response that was believed to contribute to postoperative morbidity.[38–43] A rise in the extravascular pressure, due to fluid overload, could explain the smaller the changes in the Vu the more positive the balance of fluids during CPB.

Despite ample evidence to prove that a variety of inflammatory mediators were involved in the pathogenesis of the systemic inflammatory response during CPB,[44] the mechanism involved in the capillary leak syndrome still is controversial.[45–49] Evidence that the protein content in the interstitial space did not increase in children undergoing CPB suggested that lymphatic

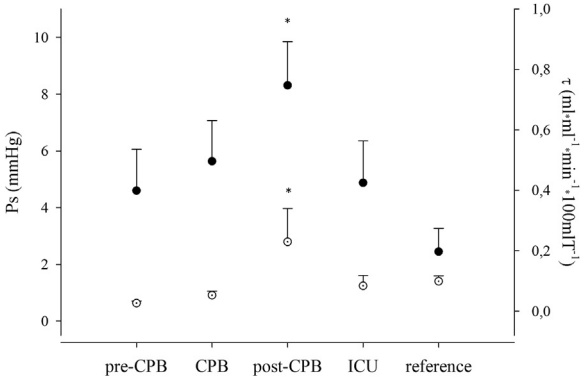


**Fig 4. Scatter plots with standard error bars of pressure in stressed volume (Ps) *(black dots)* and microcirculation time constant (τ) *(white dots)* were used to calculate the stressed volume/tissue blood flow rates in the forearm microvascular bed of the 20 cardiac surgery patients and the 20 reference healthy control patients. Variables were collected before cardiopulmonary bypass (pre-CPB), 20 minutes after CPB began (CPB), 20 minutes after recovery from CPB (post-CPB), and in the postoperative intensive care unit. *$p < 0.05$ versus pre-CPB.**

drainage impairment, increased microvascular filtration caused by hypothermia, a decreased glycocalyx thickness, and hemodilution may be causative factors of fluid leakage.[40,41,43,50] The results of this study, showing a correlation between fluid balance and blood Hb concentration, proved that hemodilution was involved in CPB-induced fluid leakage.

### Tissue Blood Flow

The "in vivo" results of this study showed that during cardiac surgery, microvascular blood flow in skeletal muscle varied according to the capacitance of the Vs compartment. The increase in Vs with constant blood flow entailed a slower transit time for erythrocytes during and soon after CPB, resulting in an increase in oxygen extraction from cells together with a decrease in blood Hb concentration.

### Vasoactive Drugs

Because vasoactive drugs were used almost exclusively to wean patients from CPB, the authors hypothesized that in hemodynamically unstable patients the use of these drugs may have contributed to maintaining constant capacitance and compliance of the microvascular bed. Nevertheless, these results showing higher Ps values after CPB discontinuation compared with those measured before and after the onset of CPB suggested a role for endogenous or exogenous vasoactive drugs in reduced Vs capacitance. Reduced Vs capacitance in turn limited the blood flow, as demonstrated by the correlation between Vs/Ps and tBF, and this could be another effect of the vasoactive drugs.

### After CPB

Although mean arterial pressure and CO decreased after CPB discontinuation, they showed no correlation with microvascular variables. This added to the abundant evidence demonstrating the independence of the microcirculation from the macrocirculation[51-53] within the observed pressure range. Despite the absence of a correlation between CO and volume or pressure microvascular variables, the decrease in macrovascular variables after CPB weaning probably would exert an effect on the increase in pressure in Vs, which remained enlarged. If the transit time measured before on-pump surgery was faster than that measured in healthy patients, it reduced markedly after CPB.

### Intensive Care Unit

Recovery of microvascular variables in the ICU to the values measured before CPB may indicate the effects of CPB on the microcirculation. As previously reported, among the factors affecting the microvascular bed during and immediately after CPB, excess fluids play a preeminent role in impairment of the microvascular bed and tissue perfusion. The removal of fluids using diuretics resulting in a negative fluid balance is probably a determinant in the recovery of variables in the postoperative period.

### Limitations

This study had some limitations. The microvascular bed of skeletal muscles contributed approximately 20% to the overall blood volume.[54] This relatively small contribution could have made these results less meaningful. Despite this drawback, according to other authors,[55] the measurements of Vs and pressure in the forearm could be extended to the microcirculation in other body areas. Another limitation was the possible inaccuracy in estimating Mb concentration. Although the absolute Mb value may have been inaccurate, the authors considered the measurement of microvascular bed partitioning before venous occlusion to be reliable and regarded any changes in the NIRS signal during the study to be due to Hb only. A final limitation was the small number of patients studied, although differences measured in small groups often yield useful data for clinical purposes.

### Future Studies

The findings of this study indicated the need to extend the knowledge on other aspects of cardiac surgery, such as the volume of RBC transfusions or the effects of CPB in patients without valvular diseases involving the venous compartment of the microvascular bed. Because these were preliminary results, the effects of changes in the therapeutic strategy (ie, blood volume limitation) require further investigation. Future research also should provide greater insight into cardiac disease progression according to age in a large number of patients.

## CONCLUSION

These results showed that cardiac surgery patients with valvular diseases and a medium or high cardiac surgical risk had a limited blood volume reserve to maintain filling pressure for venous return to the right heart due to highly reduced capacitance in the venous compartment of the microvascular bed. This in vivo study also demonstrated that during CPB, fluid overload, which increased the extravascular pressure, reduced oxygen diffusion to cells and the reserve of blood available for venous return. These findings added to the knowledge on factors that could have injurious effects on organs and tissues during cardiac surgery.

## APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1053/j.jvca.2016.06.001.

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