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RESEARCH ARTICLE

Distribution of fluids between body compartments following fluid therapy in cardiac surgery

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ABSTRACT

Distribution of fluids between body compartments following fluid therapy in cardiac surgery

Introduction: Intravenous fluids are commonly used to resuscitate cardiac surgery patients in the operating room and ICU, assuming they expand the intravascular compartment. However, the quantitative information for their distribution and shift between the tissue compartments is still lacking. This study aimed to assess how administered fluids distribute across compartments and their effects on micro- and macrocirculation during the long term of cardiac surgery.

Materials and Methods: Thirty-three consecutive patients undergoing major cardiac surgery were prospectively enrolled. Information regarding the body fluid distribution [total body water (TBW), extracellular water (ECW), intracellular water (ICW)], sublingual microcirculation (total vessel density (TVD), per-fused vessel density (PVD), and proportion of perfused vessel (PPV)], and hemodynamics were collected before surgery (T0), on the day of discharge from the intensive care unit (T1), and on the third day at the ward (T3). Correlations of the changes in microcirculatory and macrocirculatory parameters were determined by linear regression.

Results: Twenty-four patients were included in the analysis with available data. Body weight significantly increased from 86.0 ± 13.6 kg to 91.6 ± 13.3 kg at T1 and decreased to 87.8 ± 12.9 kg at T3 ($p < 0.001$). While TBW and ECW varied in parallel with body weight, ICW showed a continuous decrease throughout the study process. TVD, PVD, and PPV significantly decreased at T1, then increased at T3, but all remained lower than baseline ($p < 0.001$ for TVD and PVD, $p = 0.034$ for PPV). A cut-off point of a 5% increase in body weight predicted a 10% decrease in TVD with a sensitivity of 0.833 and specificity of 0.666. Besides, a cut-off point of a 4% increase in body weight predicted a 10% decrease in PVD with a sensitivity of 0.94 and specificity of 0.75.

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Conclusion: Administering fluid during operation and intensive care stay significantly reduces ICW and causes microcirculatory disturbances in cardiac surgery patients. Long-term microcirculation disturbances correlate with ECW and TBW in these patients.

Key words: Intracellular volume; sublingual microcirculation; incident dark-field imaging; nexfin device; body fluid compartments

ÖZ

Kardiyak cerrahi sonrası sıvı tedavisini takiben vücut sıvı kompartmanları arasındaki dağılımın incelenmesi

Giriş: Kardiyak cerrahi hastalarında, ameliyathane ve yoğun bakım ünitesinde intravasküler kompartmanda volüm genişletmek amacıyla intravenöz sıvılar yaygın olarak kullanılmaktadır. Ancak bu sıvıların doku kompartmanları arasında nasıl dağıldığı ve yer değiştirdiğine dair nicel bilgiler hala yetersizdir. Bu çalışmanın amacı, uygulanan sıvıların vücut kompartmanları arasında nasıl dağıldığını ve kardiyak cerrahi süresince mikro- ve makrodolaşım üzerindeki uzun dönem etkilerini değerlendirmektir.

Materyal ve Metod: Majör kardiyak cerrahi geçiren 33 ardışık hasta prospektif olarak çalışmaya dahil edildi. Vücut sıvı dağılımı [toplam vücut suyu (TBW), ekstraselüler su (ECW), intraselüler su (ICW)], sublingual mikrodolaşım [toplam damar yoğunluğu (TVD), perfüze damar yoğunluğu (PVD), perfüze damar oranı (PPV)] ve hemodinamik verilere ilişkin bilgiler; ameliyat öncesi (T0), yoğun bakım taburculuk günü (T1) ve serviste üçüncü gün (T3) olmak üzere üç zaman noktasında toplandı. Mikro- ve makrodolaşım parametrelerindeki değişimlerin korelasyonları, doğrusal regresyon analiziyle belirlendi.

Bulgular: Uygun verileri bulunan yirmi dört hasta analize dahil edildi. Vücut ağırlığı T0'da 86.0 ± 13.6 kg iken T1'de anlamlı şekilde 91.6 ± 13.3 kg'ye yükseldi ve T3'te 87.8 ± 12.9 kg'ye düştü ($p < 0.001$). Toplam vücut suyu ve ECW vücut ağırlığıyla paralel değişim gösterirken ICW çalışmanın tüm süreci boyunca sürekli azaldı. TVD PVD ve PPV T1'de anlamlı ölçüde azaldı T3'te tekrar artış gösterdi ancak tüm değerler bazal seviyelerin altında kaldı (TVD ve PVD için $p < 0.001$, PPV için $p = 0.034$). Vücut ağırlığında %5'lik bir artış TVD'de %10'luk bir azalmayı %83.3 duyarlılık ve %66.6 özgüllükle öngördü. Ayrıca vücut ağırlığında %4'lük bir artış PVD'de %10'luk bir azalmayı %94 duyarlılık ve %75 özgüllükle öngördü.

Sonuç: Kardiyak cerrahi ve yoğun bakım süresince uygulanan sıvı tedavisi, kardiyak cerrahi hastalarında ICW'yi anlamlı şekilde azaltmakta ve mikrodolaşım bozukluklarına yol açmaktadır. Uzun dönem mikrodolaşım bozuklukları, bu hastalarda ECW ve TBW ile ilişkili görünmektedir.

Anahtar kelimeler: İntraselüler volüm; mikrodolaşım; incident dark-field görüntüleme; nexfin; vücut sıvı kompartmanları

INTRODUCTION

Fluid therapy is the main intervention for hemodynamically unstable patients during cardiac surgery and postoperative care (1). This frequently leads to fluid overload, which has been demonstrated to be independently associated with impaired tissue oxygenation and increased mortality (2,3). Conversely, inadequate fluid therapy is associated with reduced tissue perfusion and is also one of the main reasons for impaired tissue oxygenation (4).

In perioperative cardiac surgery, assessing a patient's volume status depends on macrohemodynamic parameters, such as heart rate (HR), cardiac output (CO), and blood pressure (5). These parameters offer insights into the fluid status of the intravascular compartment. However, it is well known that the intravenously administered fluid is accompanied by extravasation and distribution through various compartments during extracorporeal circulation (6). Therefore, a comprehensive approach to fluid therapy is essential, considering not only the intravascular space but also the potential disruption of extracellular fluid balance and its effect on tissue oxygenation. Another frequently overlooked aspect that merits critical consideration is the intracellular compartment, which plays a crucial role in main-

taining fluid balance and can be compromised during dehydration or overhydration.

During the early period of intravenous fluid therapy, a percentage of fluid moves through the interstitial, intracellular, and third spaces, where the amount depends on the type of fluid, the presence of endothelial injury, and capillary leakage (7). Few studies have discussed the early intracellular (ICW) and extracellular water (ECW) changes after fluid administration. Interestingly, they reported that the early phase of crystalloid administration is associated with increased ECW and decreased ICW in both healthy volunteers and septic patients (8,9). However, quantitative information on the prolonged effects of fluid therapy and the amount of the shift between tissue compartments in the long term remains scarce. Although the decision of adequate fluid therapy is one of the hottest topics in intensive care, the basics and physiological consequences of applied fluid are largely unknown among clinicians. Therefore, this study examined the association between body fluid status and tissue microcirculation, focusing on its clinical and physiological consequences through fluid compartments in perioperative cardiac surgery. Second, we aimed to evaluate the effects of fluid therapy on the coherence of mi-

microcirculatory and macrocirculatory parameters in the long term or during admission.

MATERIALS and METHODS

Study setting

This prospective observational study was conducted between September 1, 2018 and October 30, 2019, at the Cardiac Surgery Department of Academic Medical Center (AMC) (Amsterdam, The Netherlands). The study was approved by the institutional ethics committee (W19_380). Exclusion criteria were age under 18 years, length of stay in the ward less than 48 hours, ongoing oral disease or history of oral surgery, inability to give consent or mental disorder, morbid obesity, chronic renal failure, implantable cardioverter defibrillator, limb amputation, skin defect or inflammation affecting the use of BCM, moribund, or pregnancy. Patients undergoing open heart surgery who did not meet any of the exclusion criteria were included. Patients were screened weekly during a meeting between the investigators and the ward physicians, where patients scheduled for surgery in the following week were presented. Patient follow-up was performed according to routine clinical practice. All patients provided informed consent before enrollment after receiving information about the study. The attending anesthesiologist, intensivist, and cardiothoracic surgeon were blinded to microcirculatory and macrocirculatory findings and estimates of body fluid distribution.

Patient information

Demographic data and comorbidities were recorded at hospital admission. When possible, each patient was assessed at three different time points: Within 24 hours before surgery (baseline - T0), within three hours after discharge from the ICU to the ward (T1), and on the third day after discharge from the ICU (T3). The urinary catheter was removed before discharge from the ICU, and urine output was not recorded during the patient's stay in the ward. Therefore, the patients were followed only by body weight measurements on the ward. Microcirculatory and macrocirculatory parameters, body fluid distribution, body weight, and vital signs were recorded at each time point. The Nexfin device (BMEYE, Amsterdam, the Netherlands) and conventional sphygmomanometer techniques were used for non-invasive measurement of macrocirculatory parameters, the Cytocam-IDF (Braedius Medical, Huizen, the Netherlands) for assessment of sublingual microcirculation, and the

Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany) for estimation of fluid distribution within tissue compartments. The results of routine laboratory tests were obtained from the electronic health record.

Microcirculation parameters

Sublingual microcirculation was measured using the latest hand-held video microscopy (Cyto-cam-IDF, Braedius Medical, Huizen, the Netherlands). Total and perfused vessel density (TVD and PVD) and proportion of perfused vessel (PPV) were recorded. Two trained investigators (GG, JM) analyzed three image sequences per patient for each time point. Each image sequence was acquired at 25 frames/s and was excluded if it did not meet the Massey quality criteria (10). The average of three measurements was recorded. Two investigators blindly analyzed the image sequences offline using AVA software v3.2. Image sequences were first stabilized using CCTools 1.7.x and then analyzed for TVD, PVD, and PPV using microvessels smaller than 25 microns. TVD was expressed as the ratio of the total length of microvessels to the total surface area of the field of view. PVD was defined as the length of the perfused microvessels relative to the entire surface area of the field of view. Finally, PPV was calculated as the ratio of perfused microvessels to all microvessels.

Hemodynamic parameters

Non-invasive blood pressure, HR, respiratory rate, and body temperature were measured using conventional techniques. Simultaneously, Nexfin (BMEYE B.V., Amsterdam, the Netherlands) was used to measure other macrohemodynamic parameters. Nexfin is a photoplethysmographic technology that monitors arterial blood pressure and CO continuously. It is used to assess macrohemodynamic parameters: systolic-diastolic-mean arterial pressures (SBP, DBP, MBP), stroke volume (SV), stroke volume index (SVI), HR, CO, cardiac index (CI), systemic vascular resistance (SVR). The parameters measured by Nexfin were recorded directly from the device at the bedside.

Body composition

Patients were weighed using a scale at each time point. Body fluid composition, including ICW, ECW, and TBW, was estimated using the Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany). The BCM device uses 5 to 1000 kHz frequencies to estimate cell membrane capacitance

and resistance. High-frequency current flows through the cell membrane and estimates the ECW and ICW. In contrast, low-frequency current measures the ECW. ECW and ICW can be calculated using the Hanai formula's equations. After cleaning with alcohol gauze, four adhesive skin electrodes were placed on the same side wrist and ankle. The ring, pendant, and watch were all removed to minimize electrical interference during the measurement. Recordings were included if the quality index was greater than 90% with an available Cole-Cole Gaussian curve. Data were analyzed using a proprietary software algorithm.

Statistics

Mean (standard deviation), median (interquartile range), or number and percentage were used to describe the variables when appropriate. Student t-test or Mann-Whitney U test was used to compare unpaired groups. Linear mixed-effect models were used to test for differences between time points, with time points as fixed effects and individual patients as random effects. Correlation of the variables was performed with Pearson correlation or Spearman correlation, and the relationship was also determined by linear regression. The agreement of the variables was tested with the Bland-Altman analysis. The variables were normalized as the change from the baseline if they were in different units. The presence of a ten percent decrease in TVD and PVD was dichotomized, and the predictor value of the change in body weight resulting in a maximum Youden index was presumed to represent its ideal cutoff value. Data management and all statistical analyses were performed using the R environment for statistical computing, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>).

RESULTS

A total of 33 patients were enrolled in the study. However, six patients were excluded due to technical issues causing poor quality of the microcirculation images. Additionally, three patients withdrew their consent during the study period. Therefore, 24 patients completed the study, with 14 patients providing data at three-time points and 10 at two-time points. The baseline characteristics of the 24 patients are shown in Table 1.

No complications were observed related to BCM, Cytocam-IDF, and Nexfin devices. All patients survived and were transferred to a spoke hospital. Postoperative complications included tamponade (n= 4), post-

Table 1. Patient demographics

	n= 24
Age (years)	65 ± 11
Sex (male/female)	19:5
Preoperative weight (kilogram)	86.0 ± 13.6
Fluid balance during OR (milliliter)	2617 ± 2251
Fluid balance during ICU stay (milliliter)	1419 ± 2585
Fluid balance total (milliliter)	4037 ± 3756
Duration of surgery (minutes)	121 ± 57
Cardiac surgery performed (n)	
CABG ± AVR	14
AVR ± MVR	8
Aortic surgery	2
Comorbidities (n)	
Hypertension	10
Diabetes	6
COPD	4
Heart failure	1
Chronic liver disease	2
Chronic kidney disease	3

OR: Operation room, ICU: Intensive care unit, CABG: Coronary artery bypass graft, AVR: Aortic valve replacement, MVR: Mitral valve replacement, COPD: Chronic obstructive pulmonary disease.

operative pneumonia (n= 1), new-onset atrial fibrillation (n= 5), third-degree atrioventricular block (n= 1), bilateral pneumothorax (n= 1), and re-thoracotomy due to bleeding (n= 1). In total, ten patients had complications. The percentage of weight gain and change in TVD and PVD did not differ significantly between patients who developed complications and those who did not (p= 0.968, p= 0.341, p= 0.445, respectively).

Fluid balance during operation and stay in the ICU

Fluid balance during operation and ICU are demonstrated in Table 1. During the operation, fluid intake and urine output were recorded as 4.1 ± 2.6 l and 1.5 ± 1.2 l, respectively. In the ICU, the patients received a mean cumulative 4.3 ± 3.7 l of fluid therapy and had 2.9 ± 1.9 l of urine out-put. The overall cumulative fluid balance was calculated as 4.0 ± 3.8 l before discharge from the ICU to the ward.

Negative fluid balance was achieved in only three patients. The total volume of fluids administered during operation, and the ICU was as follows: crystalloid solutions (5.4 ± 2.4 l), blood products (1.2 ± 1.9 l),

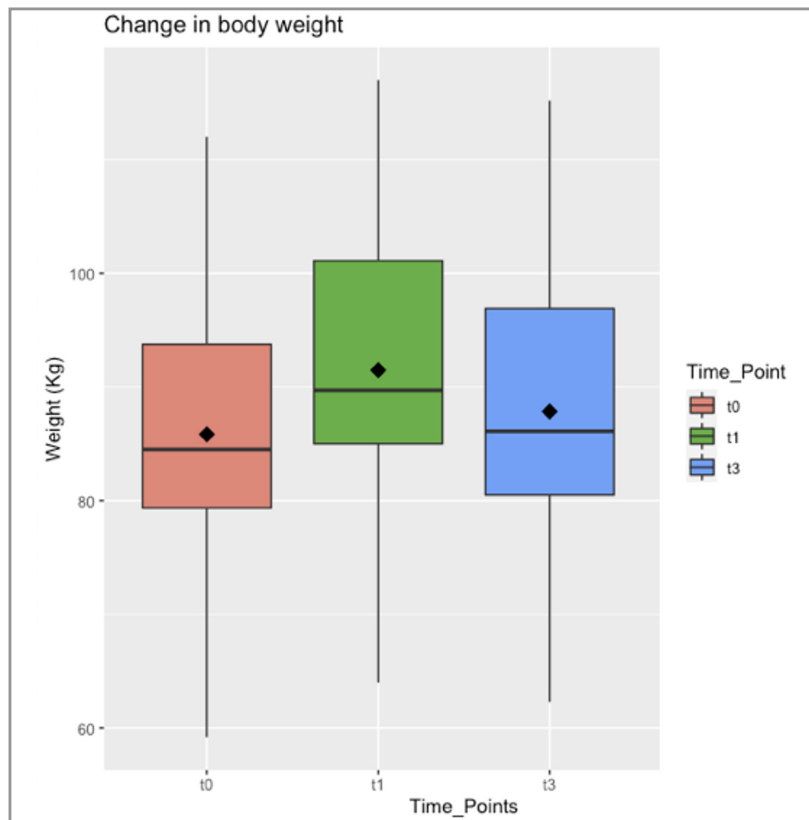


Figure 1. Body weight at different time points.

Figure 1 displays the changes of body weight at different time points. The bodyweight at T0, T1 and T3 were 86.0 ± 13.6 kg, 91.6 ± 13.3 kg, 87.8 ± 12.9 kg, respectively ($p < 0.001$ for T0-T1, $p = 0.001$ for T0-T3, $p = 0.002$ for T1-T3).

albumin (150 ± 72 mL), and mannitol (38 ± 49 mL). Crystalloid solutions accounted for 80% of the total fluid administered, making them the most preferred option.

The baseline body weight was recorded as 86.0 ± 13.6 kg (T0) and increased significantly to 91.6 ± 13.3 kg (T1) upon admission to the ward from the ICU (Figure 1). At T3, body weight decreased to 87.8 ± 12.9 kg; however, it remained higher than the baseline. A statistically significant difference in body weight was observed between time points ($p < 0.001$).

Change in body fluid compositions

BCM measurements were conducted on 17 patients; seven were excluded due to technical challenges and patient refusal. TBW and ECW showed a parallel trend between each time point (Figure 2). TBW was 38.9 ± 6.8 l at T0, 43 ± 8.3 l at T1, and 39.6 ± 7.3 l at T3 ($p < 0.001$). TBW at T1 was significantly higher than at T0 and T3 ($p = 0.034$ and $p = 0.035$,

respectively), but there was no statistical difference between T0 and T3 ($p = 0.081$). The ECW was 18.4 ± 3.2 l, 23 ± 4.8 l, and 21.3 ± 4.8 l at T0, T1, and T3, respectively ($p < 0.001$). ECW at T1 was significantly higher than both T0 ($p = 0.027$) and T3 ($p = 0.014$), while T0 and T3 levels did not differ significantly ($p = 0.092$). Conversely, ICW exhibited a divergent trend, with a modest decline throughout the study. The decrease in ICW was not found to be statistically significant between T0 (20.4 ± 4.0 l) and T1 (20.0 ± 4.7 l) ($p = 0.632$). However, a decrease to 18.3 ± 3.9 l was observed at T3 ($p = 0.030$ for T0-T3 and $p = 0.193$ for T1-T3).

Alterations in microvascular and macrovascular hemodynamic parameters

The macrovascular parameters were measured in 23 patients by the Nexfin device, and the results are shown in Table 2. A significant difference was observed in HR and blood pressure between the time points, with reductions noted at T1 and T3 compared

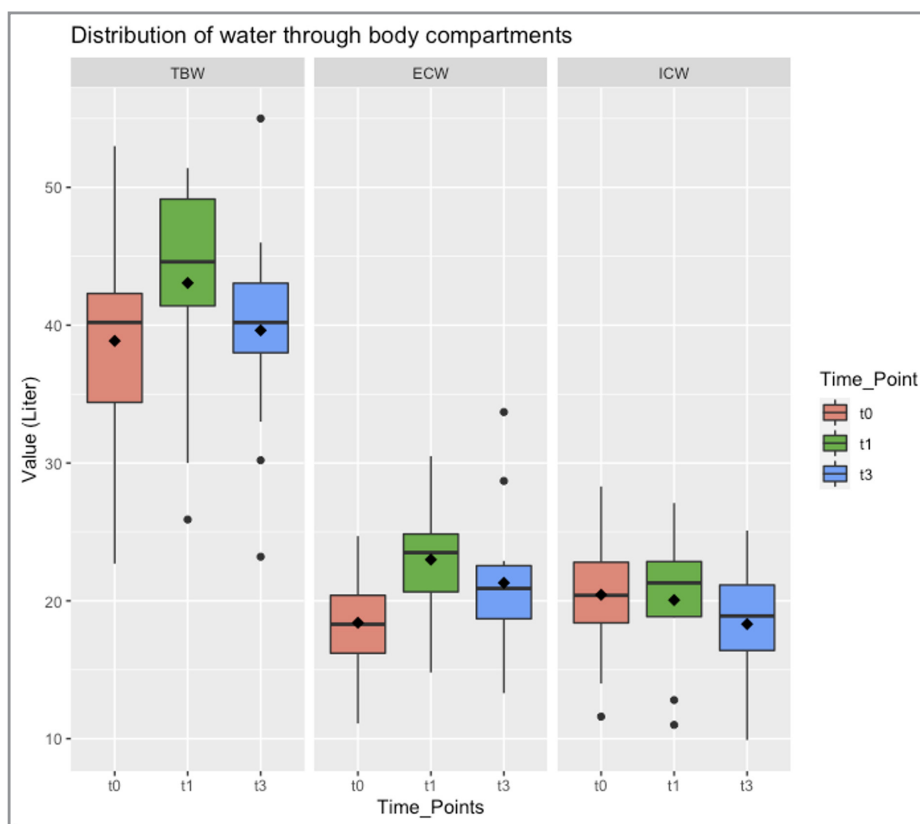


Figure 2. Body fluid composition at different time points.

Figure 2 displays the changes of TBW, ECW, and ICW at different time points. TBW at T0, T1 and T3 were 38.8 ± 6.8 , 43 ± 8.3 , and 39.6 ± 7.3 , respectively ($p = 0.034$ for T0-T1, $p = 0.081$ for T0-T3, $p = 0.035$ for T1-T3). ECW at T0, T1 and T3 were 18.4 ± 3.2 , 23 ± 4.8 , and 21.3 ± 4.8 , respectively ($p = 0.027$ for T0-T1, $p = 0.092$ for T0-T3, $p = 0.014$ for T1-T3). ICW at T0, T1 and T3 were 20.4 ± 4.0 , 20 ± 4.7 , and 18.3 ± 3.9 ($p = 0.632$ for T0-T1, $p = 0.030$ for T0-T3, $p = 0.193$ for T1-T3).

to the baseline. Con-versely, there were no statistical-ly significant differences in CO and CI between the different time points. However, SV and SVI showed a decreasing trend over time and significantly differed between the time points.

Microcirculatory parameters were measured at base-line for all patients. Baseline TVD, PVD, and PPV were 24.0 ± 2.5 mm/mm², 23.9 ± 2.5 mm/mm², and $96.4 \pm 2.7\%$, respectively (Table 3, Figure 3); all three parameters changed significantly at three time points ($p < 0.001$, $p < 0.001$, and $p = 0.034$, respectively). The TVD, PVD, and PPV were decreased from the base-line when the patient was admitted to the ward and slightly increased at T3 despite remaining lower than the baseline.

The change in the pattern of TVD and PVD was concomitant with the change in body weight and body fluid compartments, except for ICW. The TVD showed

a strong correlation with the change in body weight ($r = -0.76$, $p < 0.001$), TBW ($r = -0.72$, $p < 0.001$), and ECW ($r = -0.78$, $p < 0.001$). However, no correlation was observed between the change in ICW and TVD ($r = -0.03$, $p = 0.847$). PVD demonstrated a strong correlation with the change in body weight ($r = -0.72$, $p < 0.001$), TBW ($r = -0.63$, $p < 0.001$), and ECW ($r = -0.69$, $p < 0.001$). However, its correlation with ICW was non-significant ($r = -0.007$, $p = 0.84$). In contrast to TVD and PVD, PPV was not correlated with the change in body weight ($r = -0.22$, $p = 0.58$), TBW ($r = -0.05$, $p = 0.75$), ECW ($r = -0.01$, $p = 0.95$), and ICW ($r = -0.11$, $p = 0.51$). The fluid did not demonstrate a comparable distribution within body fluid compartments. The change in TBW exhibited a high correlation with the change in ECW ($r = 0.94$, $p < 0.001$) and a moderate correlation with the change in ICW ($r = -0.48$, $p = 0.02$). Conversely, no correlation was observed between the changes in ECW and ICW

Table 2. Body fluid composition and macrohemodynamic variables

Body Fluid Components				
	T0	T1	T3	p
TBW	38.9 ± 6.8	43 ± 8.3	39.6 ± 7.3	0.001
ECW	18.4 ± 3.2	23 ± 4.8	21.3 ± 4.8	<0.001
ICW	20.4 ± 4.0	20 ± 4.7	18.3 ± 3.9	<0.001
Weight	86.0 ± 13.6	91.6 ± 13.3	87.8 ± 12.9	<0.001
Macrohemodynamic Variables				
Heart rate (nexfin)	65.8 ± 9.8	80 ± 14.2	80.1 ± 17.6	0.001
Systolic blood pressure	141.5 ± 20.7	110 ± 17.2	109 ± 24.1	<0.001
Diastolic blood pressure	68.5 ± 10.7	59.3 ± 7.7	60.8 ± 9.5	0.015
Mean blood pressure	94.6 ± 14	76.5 ± 10.6	77.3 ± 14.1	<0.001
SO ₂ (%)	96.2 ± 1.7	94.1 ± 2.5	95.0 ± 2.4	0.010
SV (milliliters)	95.8 ± 21.1	84 ± 20	77.4 ± 21.5	<0.001
SVI (milliliters/meter ²)	47.7 ± 10.3	41.2 ± 9.6	38 ± 10	<0.001
CO (liters per minute)	6.3 ± 1.7	6.8 ± 2.2	6.2 ± 1.9	0.30
CI (liters per minute/meter ²)	3.1 ± 0.8	3.3 ± 1.0	3.1 ± 0.9	0.46
SVR (dynes.sec.cm ⁻⁵)	1356 ± 464	1055 ± 459	1191 ± 464	0.015
SVRI (dynes.sec.cm ⁻⁵ .m ²)	35.6 ± 15.4	23 ± 17	29.1 ± 17.7	0.020
Temperature (°C)	36.8 ± 0.6	37.5 ± 0.4	37.3 ± 0.5	0.001
Post-hoc comparisons for HR (p= 0.002 for T0-T1, p= 0.001 for T0-T3, p= 0.345 for T1-T3); for SBP (p= 0.010 for T0-T1, p= 0.016 for T0-T3, p= 0.968 for T1-T3); for DBP (p= 0.012 for T0-T1, p= 0.036 for T0-T3, p= 0.495 for T1-T3); for MBP (p= 0.006 for T0-T1, p= 0.010 for T0-T3, p= 0.693 for T1-T3); for (p= 0.015 for T0-T1, p= 0.002 for T0-T3, p= 0.044 for T1-T3); for SVI (p= 0.002 for T0-T1, p= 0.002 for T0-T3, p= 0.139 for T1-T3); for SVR (p= 0.006 for T0-T1, p= 0.001 for T0-T3, p= 0.609 for T1-T3). Post-hoc comparisons for TBW (p= 0.034 for T0-T1, p= 0.081 for T0-T3, p= 0.035 for T1-T3); for ECW (p= 0.027 for T0-T1, p= 0.092 for T0-T3, p= 0.014 for T1-T3); for ICW (p= 0.632 for T0-T1, p= 0.031 for T0-T3, p= 0.014 for T1-T3).				
TBW: Total body water, ECW: Extracellular water, ICW: Intracellular water, SO ₂ : Oxygen saturation, SV: Stroke volume, SVI: Stroke volume index, CO: Cardiac output, CI: Cardiac index, SVR: Systemic vascular resistance, SVRI: Systemic vascular resistance index.				

Table 3. Microhemodynamic variables

	T0	T1	T3	p
TVD (mm/mm ²)	24.0 ± 2.5	20.5 ± 3.2	23.3 ± 3.7	<0.001
PVD (mm/mm ²)	23.9 ± 2.5	19 ± 2.9	22.1 ± 3.8	<0.001
PPV (mm/mm ²)	96.4 ± 2.7	92.8 ± 7	95.2 ± 4	0.034
TVD: Total vessel density, PVD: Perfused vessel density, PPV: Proportion of perfused vessel.				

($r = 0.14$, $p = 0.96$). Notably, all correlations were performed after data normalization, with the data expressed as percentage changes to the baseline value. The laboratory parameters at different time points are presented in Table 1.

Table 2 shows the correlation between HR, SBP, DBP, and MBP measured using conventional techniques and the Nexfin device. Figure 1 presents the bias, precision, and limits of agreement between the conventional techniques and the Nexfin.

A cut-off point of a 5% increase in body weight predicted a 10% decrease in TVD with a sensitivity of 0.833 and a specificity of 0.666. Besides, a 4% increase in body weight cut-off point predicted a 10% decrease in PVD with a sensitivity of 0.94 and specificity of 0.75. Only three patients exhibited a 10% decrease in PPV compared to baseline, thereby underscoring the inability of the cut-off point to predict PPV.

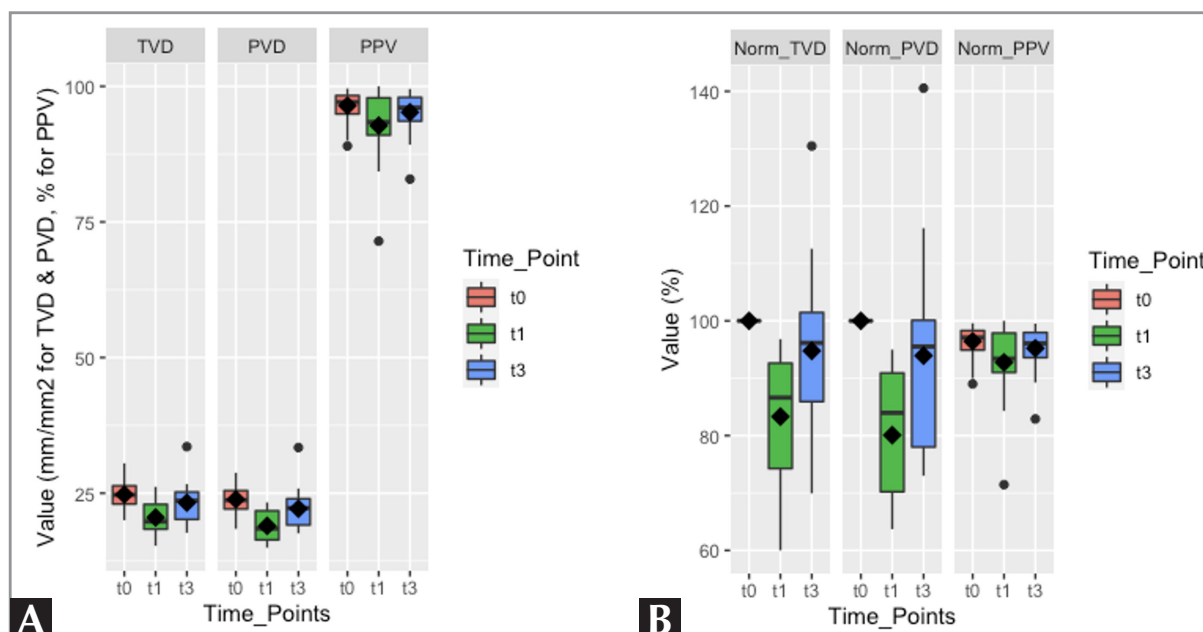


Figure 3. Microcirculatory parameters at different time points.

Figure 3a indicates the changes in raw data between different time points. TVD at T0, T1 and T3 were 24.0 ± 2.5 , 20.5 ± 3.2 , and 23.3 ± 3.7 , respectively ($p < 0.001$ for T0-T1, $p = 0.234$ for T0-T3, $p = 0.615$ for T1-T3). PVD at T0, T1 and T3 were 23.9 ± 2.5 , 19 ± 2.9 , and 22.1 ± 3.8 , respectively ($p = 0.038$ for T0-T1, $p = 0.148$ for T0-T3, $p = 0.461$ for T1-T3). PPV at T0, T1 and T3 were 96.4 ± 2.7 , 92.8 ± 7 , and 95.2 ± 4 ($p = 0.043$ for T0-T1, $p = 0.145$ for T0-T3, $p = 0.030$ for T1-T3). Figure 3b shows the changes of the TVD, PVD and PPV as the percentage different of baseline values.

DISCUSSION

To the best of our knowledge, this study is the first observational research to thoroughly examine the pathophysiological effects of net fluid gain on body fluid compartments as well as microcirculatory and macrocirculatory variables in the postoperative period of cardiac surgery patients. A perioperative increase in body weight was found to be associated with increased ECW, a decreased ICW, and a compromise in microcirculation. These changes persisted after being discharged from the ICU with restored macrohemodynamic parameters. Additionally, alterations in sublingual microcirculation showed a strong correlation with changes in ECW, not ICW.

ICW, ECW, and TBW are expected to increase with fluid therapy and then decrease in the deescalation phase. However, in this study, ICW showed a distinct pattern, gradually declining, while ECW, TBW, and body weight increased progressively after ICU discharge. Only a few studies have evaluated the fluid dynamics between fluid compartments and reported consistent findings with the current research. Finn and colleagues have assessed fluid distribution across compartments in trauma and septic patients, reveal-

ing a steady decrease in ICW and concomitant loss of intracellular protein (9). Concurrently, Haussinger et al. have proposed that this interaction demonstrates a cause-effect relationship in which cellular shrinkage triggers proteolysis. This process is especially important in critical illness contexts, as it may lead to impaired wound healing, sarcopenia, and immune dysfunction (9,11). In a recent study involving hemodialysis patients with overhydration, an increase in ECW and TBW, accompanied by a significant decrease in ICW, has been demonstrated. This decrease was also reported to be correlated with muscle wasting and inflammation. Although TBW and ECW levels were not linked to mortality in hemodialysis patients, notably, low ICW was found to be a significant risk factor for mortality (12).

In healthy volunteers, Ernstbrunner et al. evaluated the acute effects of intravenous fluid therapy (8). The volunteers received a crystalloid infusion over a 60-minute period and were then observed for an additional five hours. TBW and ECW were increased during the infusion and remained significantly elevated throughout the study period. However, ICW decreased during the infusion and gradually returned

to baseline. The findings of this study have paramount importance since the fluid distribution between fluid compartments has similar consequences, even if there is a lack of inflammation, capillary leak, and organ dysfunction in their study population. The clinical implications of altered ICW remain unclear; however, examining the clinical significance of decreased ICW may prompt further studies to develop fluid therapy algorithms incorporating ICW assessment.

The second key finding of the current study is that the microcirculatory compromise continued even after ICU discharge. All patients were discharged from the ICU with optimal macrohemodynamics and did not require vasopressor or inotrope support, indicating an improvement in microcirculation. However, the TVD, PVD, and PPV were still lower than baseline at ward admission and had a trend to improve within two days, although these measurements were still below baseline. The unexpected inconsistency between microcirculation and macrocirculation occurred despite these patients fulfilling the ICU discharge criteria. This condition may be called latent/prolonged loss of hemodynamic coherence, and its clinical significance needs further exploration in future research. The current study found no correlation between prolonged loss of hemodynamic coherence and early-term complications. Furthermore, we demonstrated that a 5% increase in body weight resulted in a 10% decrease in TVD. Since ECW, but not ICW, exhibited a similar pattern to overall postoperative weight gain, the increase in ECW may account for the reduction in TVD and PVD. This is because fluid extravasation disrupts capillary structure, leading to capillary collapse.

The critical question that must be addressed is whether the compromise in tissue microcirculation is attributable to the administered fluid therapy or the inflammation caused by cardiac surgery. Research indicates that TVD and PVD decrease with anesthesia induction but later recover during cardiac surgery (13). However, not all studies have confirmed these findings, and it is still unclear whether microcirculatory alterations are transient or how long they persist during the postoperative period. An observational study by De Backer et al. reported that although macrohemodynamic parameters improved, microcirculatory compromise continued until the end of the surgery. Twenty-four hours after the surgery, there was an improvement in PVD and TVD; however, PPV remained below baseline levels (14). Similarly, Bauer et al. observed a decrease in PVD, which returned to baseline within

one hour after the termination of cardio-pulmonary bypass (CPB) (15). In contrast to previous studies, the current study revealed a decline in TVD, PVD, and PPV that persisted for at least two days after cardiac surgery and ICU stay. This indicates that several confounding factors may have impacted tissue microcirculation during the patient's stay in the ICU. The inflammation associated with surgery and positive fluid balance due to excessive fluid administration during the operation and ICU stay may contribute cumulatively to prolonged microcirculatory alterations. Two studies including patients undergoing coronary artery bypass grafting showed that a conservative approach to fluid administration for priming positively impacted postoperative organ function and significantly reduced oxidative stress. In other words, excessive fluid administration may contribute to increased postoperative inflammation (16,17). In a study conducted by our research group, the microcirculatory assessment of post-cardiac surgery patients was performed when they were discharged from the ICU and admitted to the ward. All patients experienced fluid overload and received diuretic therapy, resulting in a significant increase in TVD and PVD after fluid removal (18). Taken together, it may be postulated that microcirculatory alterations associated with surgical intervention demonstrate early recovery; however, they subsequently deteriorate following fluid administration. Notably, a reduction in fluid load appears to facilitate the restoration of tissue perfusion.

The current study used the sphygmomanometric method and the Nexfin device to measure blood pressure and showed a moderate and marked degree of correlation. The Nexfin device has significantly correlated with the conventional sphygmomanometric method in healthy populations and cardiac surgery patients. However, its reliability notably decreases, especially in hypotensive or critically ill patients receiving vasopressors (19,20). Due to the lack of alternative methods for measuring cardiac index and stroke volume in this study, the values obtained from the Nexfin device must be interpreted cautiously, as controversial results have been noted in critically ill patients (19,21-24). However, this device is not intended to replace invasive techniques used during surgeries and intensive care. It may be an alternative for hemodynamically stable patients or those not eligible for invasive monitoring.

The present study is subject to several limitations. First, the number of patients is relatively small, with

only fourteen patients analyzed at three-time points. Nevertheless, the results are consistent among patients and align with existing knowledge, making it unlikely that the small sample size led to incorrect conclusions. Second, the sublingual microcirculation may not represent other vascular beds. Multiple studies have confirmed that sublingual microcirculation is a reliable surrogate for microcirculation in other essential organs, such as the kidneys and intestines (25,26). Third, macrohemodynamic variables were not compared with invasive techniques, which are considered the gold standard.

CONCLUSION

In conclusion, fluid administration during the operation and intensive care stay significantly reduced intracellular volume and caused microcirculatory disturbances in postcardiac surgery patients despite their discharge to the ward with normal macrocirculation. The significant effects of intracellular dehydration and prolonged loss of hemodynamic coherence between microcirculation and macrocirculation merit further investigation.

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Ethical Committee Approval: This study was approved by The Academic Medical Center Medical Ethical Committee Ethics Committee (Decision no: W19_380, Date: 10.10.2019).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: GG, JM, CI, BM, WJB

Analys/Interpretation: GG, JM

Data acquisition: GG, JM, SR, EF

Writing: GG, JM, CI

Clinical Revision: GG, JM, AT, CI, BM, WJB

Final Approval: All of authors

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