Differences in capillary recruitment between cardiac surgery and septic patients after fluid resuscitation

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A R T I C L E   I N F O

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Microcirculation
Fluid therapy
Hemodynamics
Edema

A B S T R A C T

Background: Clinical evaluation of the effects of fluid therapy remains cumbersome and strategies are based on the assumption that normalization of macrohemodynamic variables will result in parallel improvement in organ perfusion. Recently, we and others suggested the use of direct in-vivo observation of the microcirculation to evaluate the effects of fluid therapy.

Methods: A single-centre observational study, using in-vivo microscopy to assess total vessel density (TVD) in two subsets of ICU patients.

Results: After fluid resuscitation TVD showed no difference between sepsis patients (N = 47) and cardiac surgery patients (N = 52): 18.4[16.8–20.8] vs 18.7[16.8–20.9] mm/mm\(^2\), \(p = 0.59\). In cardiac surgery patients there was a significant correlation between the amount of fluids administered and TVD, with an optimum in the third quartile. However, such correlation was absent in septic patients.

Conclusions: TVD after fluid administration is not different between 2 subtypes of intensive care patients. However, only in septic patients we observed a lack of coherence between the amount of fluids administered and TVD. Further research is needed to determine if TVD may serve as potential endpoint for fluid administration.

1. Introduction

Over the last decade the awareness of potential harmful effects of fluid resuscitation is rising. On the one hand the administration of fluids is considered to be the corner stone in treatment of shock, irrespective of aetiology. On the other hand, an association between the administration of fluids and adverse outcome has been observed. Such unwanted side effects may not only be related to the chemical composition of the fluids, but also to the amount of fluids administered (Edul et al., 2016; Teixeira et al., 2013; Prowle et al., 2009; Kelm et al., 2015).

Incentives for fluid administration are diverse and include compensation for fluid- or blood loss, attenuation of increased resistance to venous return with consequent reduction of preload and maintenance of perfusion pressure under conditions of reduced vasomotor tone. Ultimately, the goal of fluid resuscitation is to optimize the requirements, needed to maintain cell homeostasis.

However, the clinical evaluation of the effects of fluid therapy remains cumbersome. Conventionally, the evaluation is based on normalization of systemic variables of circulation, i.e. heartrate, blood pressure and cardiac output. Such strategy is based on the assumption that normalization of these macrohemodynamic variables will automatically result in a parallel improvement in organ perfusion. However, direct in-vivo observation of the microcirculation by means of handheld microscopes has revealed that this coherence between macro- and microcirculation may not always be present. Well-known conditions in which loss of coherence has been observed include sepsis and obstructive heart failure, revealing sustained hypoperfusion despite correction of systemic variables by fluids and vasoactive compounds (Edul et al., 2016; Ince, 2015). Uncoupling between the macro- and microcirculation may be the intrinsic result of the disease state. Endothelial dysregulation may result in increased permeability, hypercoagulation and loss of vasomotor tone, causing altered microcirculatory blood flow, not sensed by macrohemodynamic variables. In addition, fluid therapy itself can also induce oxidative and nitrosative stress, contributing to reduced vascular regulatory capacity and reduced oxygen-carrying capacity to vulnerable organs such as the kidney (Aksu et al., 2012). Moreover, it must be acknowledged that adequate oxygenation of the cell is based on two key characteristics of perfusion. The first one...
is convective oxygen transport, that depends on red blood cell velocity and red blood cell oxygen-carrying capacity. Fluid therapy may increase red blood cell velocity and thereby increase oxygen delivery to the cells. However, fluids intrinsically do not have oxygen-carrying capacity, with the exception of red blood cell transfusion. The second determinant of oxygen transport to the cell is diffusion. Given the gas-specific characteristics, oxygen diffusion is related to the pressure gradient and inversely related to the distance between the capillary and the cell. Fluid therapy can potentially recruit initially unperfused capillaries, and thus reduce oxygen diffusion distance (van Genderen et al., 2014; Wu et al., 2015). Conversely, fluid therapy may also promote oedema formation with subsequent reduction of oxygen diffusion capacity (Hanson et al., 2013).

Recently, we and others have suggested the use of direct in-vivo observation of the microcirculation to evaluate the effects fluid therapy (van Genderen et al., 2014; Veenstra et al., 2014; Xu et al., 2013; Pranskunas et al., 2013; Ince, 2014).

The technique enables the quantification of both key characteristics of oxygen transport, needed to determine the line of demarcation between beneficial and detrimental effects of fluid resuscitation. In this study we aim to identify the reaction of microcirculation on fluid resuscitation, by means of diffusion distance, in two subsets of ICU patients.

2. Methods

2.1. Patients

The study was performed as a single centre observational study and conducted between October 2015 and April 2017. Local ethical committee waived the need for informed consent. The study was registered at ClinicalTrials.gov (NCT02661269). Our aim was to observe the microcirculation under clearly separate circumstances. Patients after elective cardiothoracic surgery (Group A) were assumed to represent a hypovolemic condition, whereas patients after septic shock (Group B) were assumed to represent a hypervolemic condition. ICU patients in both categories and above 18 years of age were considered eligible for the study. Exclusion criteria included inability to obtain Incident dark field (IDF) images, such as maxillofacial surgery or oropharyngeal bleeding.

2.2. Protocol

Patients in group A were enrolled in the study within 4 hours after admission to the intensive care. Patients in group B were enrolled at the peak of the cumulative fluid balance. Measurements were performed once and included: demographic data, IDF-imaging, bio-impedance measurements, weight, macrohemodynamic parameters, venous saturation, lactate and haemoglobin/haematocrit. According to our local protocol, patients in both groups were resuscitated with Ringers’ lactate. Routine resuscitation with colloids is not included. However, occasional use of balanced colloid (Volulyte®) in an individual patient patient is in compliance with the recommendations of a roundtable conference. Microvascular Flow Index (MFI) and heterogeneity were calculated per quadrant. The percentage of perfused vessels was expressed as the number of perfused vessels that crosses three equidistant grid lines divided by the total number of grid crossings (Boerma et al., 2005; De Backer et al., 2007).

2.4. Bio-impedance

Bio-impedance vector analysis (BIVA) is a non-invasive, quick and inexpensive technique to estimate body composition and showed good correlation between hydration state in ICU survivors and non-survivors with acute kidney injury (Hise & Gonzalez, 2018). This technique measures the resistance of body tissues to the flow of an alternating current of 800 μA at an operating frequency of 50 kHz. Bio-impedance measurements were measured using the BIA-101® (GLNP Medical Devices, Breda, The Netherlands). Reactance (Xc), resistance (R) and phase angle were recorded. Total body impedance can be considered a combination of resistance R (the opposition to the flow of an alternating current through intra- and extracellular electrolyte solutions) and reactance X (the capacity produced by the interfaces of tissues and cell membranes) (Kyle et al., 2004; Norman et al., 2012; Peacock, 2010).

2.5. Statistical analyses

Normal distributed data are presented as mean ± SD and were tested with a parametric t-test, non-normal distributed data are presented as median (IQR) and were tested with a non-parametric Mann–Whitney U test. Testing between multiple groups is done by a one-way ANOVA (Kruskal–Wallis test). Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS 21, Chicago Illinois, USA). Power calculation was performed to identify a 10% difference in total vessel density (TVD) between groups. Based upon an alpha of 0.05 and a power of 80%, we calculated a sample size of 50 patients per group.

A p value < 0.05 was considered statistically significant. Primary outcome was defined as the difference in TVD between both groups.

2.6. Results

2.6.1. Primary endpoint

We included 52 patients in group A, and 47 patients in group B. Time between admission and measurements was in group A 38 [27–60] minutes, in group B 2 [1–3] days. Baseline characteristics are presented in Table 1, showing significant differences between groups in a variety in macrohemodynamic variables. There was a higher cumulative fluid balance in sepsis patients in comparison to cardiothoracic surgery patients (7 [5–10] vs 2.3 [1.7–2.8]L, p < 0.0001). Despite reticence to blood transfusion in septic shock, group B received significantly more red blood cell transfusions, but medium haemoglobin and haematocrit values were similar (Table 1). The primary outcome TVD showed no difference between group A and group B (18.4 [16.8–20.8] vs 18.7 [16.8–20.9] mm/mm², p = 0.59). Remaining microcirculatory values are displayed in Table 2. A statistical significant correlation was found between TVD and the cumulative fluid balance within group A (r² = 0.31, p 0.02, Fig. 1), but not in group B (r² = −0.012, p 0.94).

2.6.2. Secondary endpoints

Cumulative fluid balances were divided into interquartile ranges. In group A TVD showed a significant difference between interquartile fluid balance ranges, with a maximum of 19.9 [18.3–21.0] mm/mm² in Q3. Boxplots are included in Fig. 2. In group B there was no significant difference in TVD between interquartile fluid balance ranges, with a maximum of 19.8 [18.1–20.9] in Q1.

Bio-impedance-derived values indicative for (over)hydration were significantly higher in group B in comparison to group A. (Table 2).
The main finding of this study is the absence of a significant difference in total vessel density between sepsis and cardiothoracic ICU patients. In both groups the IQR of the maximum TVD was between 18 and 21 mm/mm². However, despite normalization of macrohemodynamics variables, TVD did not reach the level as observed in healthy volunteers (Aykut et al., 2015). The fact that these maximum values showed a significant decline in the highest cumulative fluid balance quartile in cardiac surgery patients (group A) is in line with the present theory. After recruitment of capillaries and restoration of flow, oedema formation further limits and even reduces (functional) capillary density. This finding suggests a ceiling value for the recruitment of capillaries by fluid resuscitation with crystalloids, and carries the

### Table 1
Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Cardio (N = 52)</th>
<th>Sepsis (N = 47)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man/Female %</td>
<td>71/29</td>
<td>64/36</td>
<td>0.44</td>
</tr>
<tr>
<td>Age, years</td>
<td>68 [58–78]</td>
<td>66 [55–71]</td>
<td>0.19</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 [25–30]</td>
<td>28 [26–34]</td>
<td>0.19</td>
</tr>
<tr>
<td>Apache IV score</td>
<td>44 [36–52]</td>
<td>86 [61–107]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Predicted mortality, %</td>
<td>1 [4–2]</td>
<td>35 [11–58]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SOFA score</td>
<td>3 [2–4]</td>
<td>8 [6–13]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fluid balance perioperative, l</td>
<td>2.0 [1.5–2.6]</td>
<td>0 [0–4]</td>
<td>0.06</td>
</tr>
<tr>
<td>Fluid balance intensive care, l</td>
<td>0.0 [0.0–0.4]</td>
<td>5.9 [4–7]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fluid balance cumulative, l</td>
<td>2.3 [1.7–2.8]</td>
<td>7 [5–10]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Admission reason, % (n)</td>
<td>CABG alone</td>
<td>57.7 [30]</td>
<td>1.9 (1)</td>
</tr>
<tr>
<td></td>
<td>AVR</td>
<td>11.5 (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CABG + AVR</td>
<td>15.4 (8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MV repair</td>
<td>7.7 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>5.8 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVR + MVR</td>
<td>1.9 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis, cutaneous/soft tissue</td>
<td>17 (8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis, unknown</td>
<td>10.6 (5)</td>
<td></td>
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<tr>
<td></td>
<td>Sepsis, gastro-intestinal</td>
<td>55.3 (26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis, meningitis</td>
<td>2.1 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis, pulmonary</td>
<td>14.9 (7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECC, minutes</td>
<td>91.5 [63–119]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiovascular risk factors, % (n)</td>
<td>36,5 (19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arterial hypertension</td>
<td>3.8 (2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left ventricle ejection fraction:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td>75 (39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>23 (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bad</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inotropes, %, μg/kg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0; 0</td>
<td>13; 1.8</td>
<td>[1.6–4.0]</td>
</tr>
<tr>
<td>Enoxime</td>
<td>4; 3.7 [2.4–3.7]</td>
<td>2; 2.5 [2.8–2.5]</td>
<td></td>
</tr>
<tr>
<td>Vasopressor, μg/kg/min</td>
<td>31; 0.1</td>
<td>0; 0</td>
<td>[0.1–0.2]</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>12; 0.05</td>
<td>77; 0.1</td>
<td>[0.03–0.1]</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>7.41</td>
<td>7.37</td>
<td>0.002</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>[7.37–7.45]</td>
<td>[7.32–7.41]</td>
<td></td>
</tr>
<tr>
<td>Base excess, mmol/l</td>
<td>1.4</td>
<td>1.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Chloride, mmol/l</td>
<td>110 [109–112]</td>
<td>108 [105–112]</td>
<td>0.032</td>
</tr>
<tr>
<td>Hemoglobin, mmol/l</td>
<td>6.1 [5.6–6.7]</td>
<td>6.2 [5.6–7.4]</td>
<td>0.39</td>
</tr>
<tr>
<td>Haematocrit, %</td>
<td>30 [28–33]</td>
<td>31 [28–37]</td>
<td>0.22</td>
</tr>
<tr>
<td>Received bloodtransfusion, %</td>
<td>9.6 (2)</td>
<td>43 (2)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as median [IQR] or as mean ± SD in case of normal distribution. APACHE: Acute Physiology And Chronic Health Evaluation. SOFA: Sequential Organ Failure Assessment. CABG: Coronary Artery Bypass Grafting; AVR: Aortic Valve replacement; MVR: Mitral Valve replacement; MV: Mitral Valve. ECC: ExtraCorporeal Circulation time.

Combining group A and B, showed a significant linear correlation between the cumulative fluid balance and both reactance and resistance ($r^2 = 0.33$, $p < 0.05$ and $r^2 = 0.29$, $p < 0.05$ respectively). However, differences in bio-impedance-derived variables between subgroups of interquartile fluid balance ranges were non-significant.

### Table 2
Primary and secondary outcome.

<table>
<thead>
<tr>
<th></th>
<th>Cardio (N = 52)</th>
<th>Sepsis (N = 47)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macromhemodynamic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>90 ± 7</td>
<td>99 ± 17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>105 [97–118]</td>
<td>96 [87–108]</td>
<td>0.007</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>57 [53–65]</td>
<td>52 [44–59]</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>72 [66–83]</td>
<td>65 [58–77]</td>
<td>0.01</td>
</tr>
<tr>
<td>Central venous pressure, mmHg</td>
<td>9 ± 4</td>
<td>9 ± 5</td>
<td>0.16</td>
</tr>
<tr>
<td>Cardiac Index, l/m²</td>
<td>2.4 [2.1–3.0]</td>
<td>3.2 [2.7–4.1]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>St/VO2, %</td>
<td>69 [61–75]</td>
<td>74 [71–77]</td>
<td>0.01</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>1.7 [1.3–2.3]</td>
<td>1.3 [0.9–1.8]</td>
<td>0.004</td>
</tr>
<tr>
<td>Microvascular variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microvascular Flow Index</td>
<td>3.0 [2.9–3.0]</td>
<td>3 [2.9–3.1]</td>
<td>0.74</td>
</tr>
<tr>
<td>Microvascular Flow Index</td>
<td>3.0 [3.0–3.0]</td>
<td>3 [2.9–3.1]</td>
<td>0.04</td>
</tr>
<tr>
<td>Large vessels, AU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total vessel density, mm²/mm²</td>
<td>18.4</td>
<td>18.7</td>
<td>0.59</td>
</tr>
<tr>
<td>Total vessel length, mm</td>
<td>13.7</td>
<td>14.1</td>
<td>0.52</td>
</tr>
<tr>
<td>Percentage of perfused vessel, %</td>
<td>99 [98–100]</td>
<td>99 [97–99]</td>
<td>0.02</td>
</tr>
<tr>
<td>Perfused vessel density, mm²/mm²</td>
<td>18.2</td>
<td>18.6</td>
<td>0.78</td>
</tr>
<tr>
<td>De Backer score, AU</td>
<td>11.3</td>
<td>11.5</td>
<td>0.56</td>
</tr>
<tr>
<td>Heterogeneity index, AU</td>
<td>0 [0–0.12]</td>
<td>0 [0–0.12]</td>
<td>0.99</td>
</tr>
<tr>
<td>Bio-impedance variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactance, Ω</td>
<td>41.5</td>
<td>23.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Resistance, Ω</td>
<td>399 [360–456]</td>
<td>295 [260–350]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Phase angle, θ</td>
<td>5.7 [5.1–6.5]</td>
<td>4.1 [3.3–5.1]</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Outcome

<table>
<thead>
<tr>
<th></th>
<th>Cardio (N = 52)</th>
<th>Sepsis (N = 47)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Length of stay, days</td>
<td>1 [1–1]</td>
<td>10 [6–21]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospital mortality, % (n)</td>
<td>0 (0)</td>
<td>17 (8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Renal replacement therapy, %</td>
<td>0</td>
<td>13</td>
<td>0.008</td>
</tr>
<tr>
<td>Mechanical ventilation, hours</td>
<td>3.1 [2.3–4.1]</td>
<td>107 [36–295]</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as median [IQR] or as mean ± SD in case of normal distribution. S(c)VO2: central or mixed venous saturation. AU: arbitrary units.

3. Discussion

The main finding of this study is the absence of a significant difference in total vessel density between sepsis and cardiothoracic ICU patients. In both groups the IQR of the maximum TVD was between 18 and 21 mm/mm². However, despite normalization of macrohemodynamics variables, TVD did not reach the level as observed in healthy volunteers (Aykut et al., 2015). The fact that these maximum values showed a significant decline in the highest cumulative fluid balance quartile in cardiac surgery patients (group A) is in line with the present theory. After recruitment of capillaries and restoration of flow, oedema formation further limits and even reduces (functional) capillary density. This finding suggests a ceiling value for the recruitment of capillaries by fluid resuscitation with crystalloids, and carries the

Correlation between cumulative fluid balance and total vessel density in the cardiothoracic surgery group.

**Fig. 1.** Correlation between cumulative fluid balance and total vessel density in the cardiothoracic surgery group.
potential to serve as an endpoint for fluid resuscitation. However, in septic patients (group B) we observed an absence of correlation between the amount of fluids administered and capillary density. This observation may either be in line with an intrinsic uncoupling between the macro- and the microcirculation in distributive shock, previously referred to as an example of loss of hemodynamic coherence (Ince, 2015). Alternatively it may reflect the inability to recruit capillary density in sepsis with crystalloids beyond a certain level, due to enhanced capillary leakage of fluids under such conditions. A alternative explanation can be found in the high percentage of patient with arterial hypertension. A previous study showed that chronic hypertension was a major determinant of TVD and PVD in volunteers with cardiovascular risk factors. We should take into account that the difference between healthy volunteers and our study could be related to previous health problem and not to fluid therapy (Kanoore Edul et al., 2015). The most likely explanation for the lack of coherence between cumulative fluid balance and TVD in the septic shock group could be because the prehospital hydration state is unclear. I.e., some patients will enter the hospital with a fluid deficit that needs to be corrected and some will start with a normal hydration state and further administration of fluids may lead to fluid overload. This is supported by the BIVA data, in which the significant difference in reactance between Q2 and Q4 is absent. In other words, the absolute amount of fluid administered is not reflected by difference in overhydration.

Although our assumption to use cardiothoracic and sepsis patients as models for different stages of (over)resuscitation may be arbitrary, the observed bio-impedance values suggest indeed a clear separation between groups.

These data are difficult to compare with the existing literature. To our knowledge we are the first to report TVD in different categories of patients in relation to resuscitation status. In accordance with previous publications we observed a decrease in capillary density after cardiopulmonary bypass in comparison to healthy controls (Koning et al., 2012; Bienz et al., 2016; De Backer et al., 2009). Similar observations were done in human sepsis (Top et al., 2011; Ince & Sinasappel, 1999; Spanos et al., 2010). However, comparing exact values is virtually impossible, since the number of capillaries visualized during in-vivo microscopy is device dependent (Aykut et al., 2015; Aykut et al., 2014).

The majority of previous data has been obtained by means of side-stream dark-field-imaging. Nevertheless, the observed irresponsiveness of the microcirculation to fluid resuscitation in the late phase of sepsis may alternatively be explained by the same ceiling effect (Ospina-Tascon et al., 2010). In other words, in case the maximal number of recruitable capillaries is reached, further crystalloids fluid administration may ad best result in the maintenance of the number of perfused capillaries, or even result in a decrease of perfused capillary density due to oedema formation.

There are certainly limitations to our study. Firstly, we performed a single measurement in two different stages of (over)resuscitation. Multiple observations of the microcirculation over time during fluid resuscitation would clearly further clarify the underlying mechanisms. Secondly, it is of note that we did not observe an anticipated decline in TVD in the extremes of overhydration. This may simply due to inadequate statistical power as a result of small subgroups of patient in each quartile of cumulative fluid balance. Alternatively, Q4 in each patient group did not contain enough subgroups of patients that received red blood cell transfusion. It is reported that the microcirculation can be ‘resuscitated’ by blood transfusions in both cardiac surgery as septic shock patients. However, it is of note that haemoglobin and haematocrit concentrations were significantly different between groups. As a result it remains unclear in the present study whether microcirculatory abnormalities have been influenced by these differences in macrohemodynamic conditions. Also, there is no control group of volunteers matched for age and comorbidity. There is a major difference in the number of patients that received red blood cell transfusion. It is reported that the microcirculation can be ‘resuscitated’ by blood transfusions in both cardiac surgery as septic shock patients. However, it is of note that haemoglobin and haematocrit concentrations were equal between groups (Yuruk et al., 2011; Atasever et al., 2012; Stowell et al., 2017; Donati et al., 2014; Sakr et al., 2007; Nielsen et al., 2017).

We acknowledge that the observed maximum in capillary density needs further exploration. Prospective trials are needed to test the clinical relevance of the observed upper limit of capillary density in terms of clinically relevant outcome. Further research is needed to determine whether this cut-off value may serve as a line of demarcation between beneficial and detrimental effects of fluid resuscitation.

4. Conclusion

After fluid resuscitation there is no significant difference in (functional) capillary density between cardiac surgery and septic patients. In cardiac surgery patients there is a significant correlation between the amount of fluids administered and capillary density, with an optimum in the third quartile. However, such correlation is absent in septic patients, suggesting lack of hemodynamic coherence between the macro- and the microcirculation under these conditions.

Competing interests

Dr. Ince has developed SDF imaging and is listed as inventor on related patents commercialized by MicroVision Medical (MVM) under a license from the Academic Medical Center (AMC). He has been a consultant for MVM in the past but has not been involved with this company for more than 5 years now, holds no shares. Braedius Medical, a company owned by a relative of Dr. Ince, has developed and designed a handheld microscope called CytoCam-IDF imaging. Dr. Ince has no financial relation with Braedius Medical of any sort, i.e., never owned shares or received consultancy or speaker fees from Braedius Medical.

The other authors have no competing interests.
List of abbreviations

IDF incident darkfield
LED light emitting diode
BIVA bio-impedance vector analysis
TVD total vessel density

References