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Original Article

Microcirculatory depth of focus measurement shows reduction of tissue edema by albumin resuscitation in burn patients

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A R T I C L E I N F O

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A B S T R A C T

Background: Severe burns induce volume shifts via capillary leaks, eventually requiring massive fluid resuscitation and promoting tissue edema. Albumin may help to mitigate the edema, thereby improving perfusion. This study shows that sublingual microcirculation measurements can quantify both tissue perfusion and edema.

Methods: This prospective observational study was conducted between November 2018 and December 2019 in the intensive care unit of Maasstad Hospital Burn Center, Rotterdam, The Netherlands. Patients with severe burns affecting >15% of the total body surface area were included. Fluid management was conducted in accordance with the Parkland formula. Albumin (20%) was administered at a rate of 0.5 mL/(kg·h), starting 12 h after the burn incident. Alterations in the sublingual microcirculation, including capillary perfusion and density, were measured at admission (T0) and 4 h (T4) and 12 h (T12) after admission. Sublingual depth of focus (DOF) of the microcirculation was used to quantify the tissue edema.

Results: Nine patients were recruited with a mean total body surface area of 36% ± 23%. By T12, a median of 4085 mL (interquartile range [IQR]: 3714–6756 mL) of crystalloids and 446 mL (IQR: 176–700 mL) of 20% albumin were administered. The DOF increased significantly after crystalloid administration (T4 *vs.* T0, mean difference [MD]=27.4 μm, 95% confidence interval [CI]: 3.4 to 50.9, P=0.040). Following albumin administration, DOF significantly decreased (T12 *vs.* T4, MD=−76.4 μm, 95% CI: −116.6 to −36.1, P=0.002). Total vessel density decreased significantly with crystalloid administration (T4 *vs.* T0, MD=−3.5 mm/mm^2, 95% CI: −5.7 to −1.4, P=0.004) but increased after albumin administration (T12 *vs.* T4, MD=6.2 mm/mm^2, 95% CI: 3.2 to 9.3, P=0.001).

Conclusion: Sublingual microcirculation measurement of DOF and other parameters provide a valuable tool for the assessment of tissue perfusion and edema in patients with severe burns. Further investigation is required to evaluate the role of albumin in increasing microcirculatory convection and reducing tissue edema.

Introduction

Severe burn injuries affecting >15% of the total body surface area (TBSA) elicit a pronounced inflammatory response accompanied by cardiovascular dysfunction, loss of endothelial-glycocalyx integrity, and rapid volume shift. Ultimately, these factors result in burn shock, which is fatal if left untreated or not adequately replaced with intravenous fluids.[1]

In patients with burn shock, plasma losses frequently exceed 4 mL/(kg·h), necessitating aggressive fluid resuscitation. Crystalloids and colloids have been employed to replace the lost volume and restore hypovolemia, maintain adequate

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tissue perfusion, and prevent hemodynamic collapse in these patients. In particular, albumin has been used concomitantly with crystalloids for their presumed volume-sparing effects in severe burns.[2,3] Furthermore, the addition of albumin has been linked to a reduced incidence of compartment syndrome and an improved mortality rate in patients with burn shock.[4] Additionally, the administration of albumin may prove beneficial for damaged endothelium, thereby reducing capillary leak, improving perfusion, and effectively increasing plasma volume.[5,6] However, fluid administered at the outset is largely retained as tissue edema and fluid creep, which could further impair tissue perfusion.[7,8]

It is paramount to assess tissue perfusion directly, particularly in burn patients with profound inflammation and fluid extravasation into third spaces. Sublingual microcirculation measurement, which can be performed using handheld vital microscopy (HVM), can be used for direct evaluation of tissue perfusion and thickness.[9,10] Although research exists regarding the indirect effects of albumin on body fluid compartments, data demonstrating its direct effects on tissues is scarce. In this context, HVMs can play a role in the quantification of the depth of focus (DOF) and tissue edema following fluid resuscitation.

The objective of this study was to investigate whether albumin administration in patients with severe burns might improve tissue perfusion and mitigate tissue edema. This was assessed by quantifying the DOF, microvascular perfusion, and functional capillary density (FCD) obtained from serial sublingual microcirculation measurements.

Methods

Study settings and population

This prospective observational study was conducted as a part of a study evaluating alterations in the microcirculation in burn patients between November 2018 and December 2019 in the intensive care burns unit of the Burn Center Maasstad Hospital, Rotterdam, The Netherlands (ethics committee approval number: NL60162.101.16).

Patients with second- or third-grade burns >15% of the TBSA and planned fluid resuscitation were included. The eligibility of patients and the extent of burn injury were calculated by expert nurses and medical specialists during intensive care admission. Consecutive patients fulfilling the eligibility criteria were enrolled.

The exclusion criteria were TBSA burn <15%, violation of the fluid resuscitation protocol (i.e., fluid resuscitation rate not in accordance with the Parkland formula), inability to acquire sufficient quality images (e.g., oral cavity inaccessible/damaged/covered with debris due to injury), age <18 years, pregnant status, and inability to consent.

Fluid resuscitation

The Parkland formula was used to estimate the amount of required fluid therapy. Briefly, 4 mL/kg per TBSA% of crystalloids – preferably Ringer's Lactate – was calculated for each patient, and half the volume was given in the first 8 h after the burn incident.[11,12] The adequacy of the fluid resuscitation was assessed hourly by urine output, which was aimed at 0.5 mL/(kg·h) per the recommendation of the Emergency Management of Severe Burn guidelines.[13] If the target was not achieved, the fluid infusion rate was increased. If urine output exceeded 0.5 mL/(kg·h), the infusion rate was decreased. Noradrenaline was administered whenever the mean arterial pressure fell <65 mmHg despite acceptable volume replacement and adequate urine output and was titrated as necessary. Albumin (20%) administration was initiated only 12 h after the burn incident at a rate of 0.5 mL/(kg·h). There were no additional contraindications for albumin or crystalloid infusions while resuscitation-related morbidities such as compartment syndromes were avoided. Applicable surrogates of the volume status such as central venous pressure, stroke volume variation, or fluid challenges were used for additional fluid bolus administration or reducing the rate of the fluid resuscitation. Net fluid balance was calculated as follows: fluid intake + water from the nasogastric tube (if any) - nasogastric tube drainage volume + urine output + volume from the surgical drainage (if any).

Sublingual image acquisition and microcirculation measurements

Sublingual microcirculation was measured immediately after admission (T0), 4 h after admission (T4), and 12 h after admission (T12) to the burns intensive care unit (ICU). Of note, the time interval between the burn injury and hospital admission was not deducted from the measurement hours. Therefore, T12 measurements do not necessarily coincide with the start of albumin administration.

At least three measurements were performed at each time point to ensure high-quality image acquisition. All measurements were performed in the sublingual triangle defined by Uz et al.[14] Each measurement was recorded for at least 4 s, according to the Massey criteria.[15] All images were captured by a built-in camera and stored for later offline analysis.

DOF measurements were performed by incident dark field illumination imaging (CytoCam, Braedius Medical, Huizen, The Netherlands). The CytoCam measures the distance from the tip of the device to the red blood cell within the region of interest, i.e., the tissue. The CytoCam has a focus range between 0 μm, i.e., the tip of the device, and 400 μm. Initially, the distance between the tip of the device and the protection cap – apparatus dead space – was measured as 20 μm. The measured distance was deducted from the observed DOF distance to reflect the actual distance. For example, if the measured DOF was 140 μm, 20 μm was deducted and 120 μm was considered as the final distance. Next, the CytoCam was put into direct contact with the sublingual mucosa for sublingual measurements in accordance with guidelines.[15] DOF was increased by 40 μm at each step by the built-in software of the CytoCam device. After observing the most superficial capillary network without capillary loops, the DOF was increased by 4 μm at each step for fine tuning of the focus until each red blood cell could be distinguished. Values observed from the CytoCam device were recorded.

In addition to the DOF measurement, total vessel density (TVD; mm/mm^2), percentage of perfused vessels (PPV; %), and FCD (mm/mm^2) were assessed automatically by the MicroTools Software.[16] Briefly, TVD is used as a surrogate of the diffusive capacity, whereas PPV describes the presence of flow within the capillaries. FCD is TVD times PPV and can be used to assess both aspects of the microcirculation network.

Statistical analysis

Values are presented as mean ± standard deviation and median (interquartile range [IQR]) depending on whether the data is normally distributed. Mixed-effects linear regression analysis was performed with random intercepts per patient. To account for the non-linear relationship, linear spline regression with a single knot at Timepoint 4 was employed. This allowed a separate fit for each time interval and distinguished the effect of albumin from crystalloids (i.e., Timepoint 0–4 represented the "pre-albumin phase" and Timepoint 4–12 represented the "post-albumin phase"). A two-sided *P*-value <0.05 was considered to indicate statistically significant differences. All analyses were performed using the R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Eleven patients met the inclusion criteria during the study period. One patient was excluded owing to violation of the fluid resuscitation protocol (volume administered was lower than calculated by the Parkland formula). Another patient was excluded because of the inability to acquire a high-quality sublingual microcirculation image due to debris in the oral cavity. Therefore, nine patients were included in the final analysis. The patients' burned TBSA was 36% ± 23%, and the mean age was (46.3 ± 15.0) years. All patients were male and the average Body Mass Index (BMI) was (27.7 ± 5.3) kg/m^2. On average, patients were admitted to the ICU (5.7 ± 2.3) h after sustaining a burn injury. The majority of the injuries was caused by flame (8/9), and a single case was caused by steam. Two patients had accompanying inhalational injuries and four out of nine patients required mechanical ventilation.

Fluid resuscitation

Individual cumulative fluid balances are presented in Figure 1. Three patients did not receive any fluid before ICU admission. The remaining six patients received a median of 3500 mL (IQR: 1000–6000 mL) of crystalloids. After ICU admission, patients received a median of 4085 mL (IQR: 3714–6756 mL) of crystalloids in 12 h. Ringer's lactate was the sole choice of the crystalloid in most patients (7/9). Two patients received saline in addition to the Ringer's lactate. Five out of nine patients received a median of 58 mL (IQR: 38–100 mL) of 20% albumin before T4 measurement (Figure 2). At the end of the study period, a median of 446 mL (IQR: 176–700 mL) 20% albumin was administered.

Sublingual microcirculation and DOF measurements

After appropriate exclusion as per the Massey criteria,[15] complete sublingual microcirculation analysis was obtained in 25 out of 27 possible (92.6%) events (excluded measurement: patient 2 at T12, inaccurate DOF analysis). In addition, one measurement could not be done because of a lack of research personnel available at that specific time point (patient 9 at T0) (Table 1 and 2).

DOF

The DOF had two different courses. Initially, DOF increased significantly until T4 compared with T0 (mean difference [MD]=27.4 μm, 95% confidence interval [CI]: 3.4 to 50.9, *P*=0.040). Afterward, DOF was decreased at T12 compared with T4 (MD=−76.4 μm, 95% CI: −116.6 to −36.1, *P*=0.002) (Figure 3A). There was no significant correlation between overall fluid balance at T12 and DOF (Winsorized Pearson Correlation [*r*]= −0.54, 95% CI: −0.9 to 0.27, *P*=0.170).

FCD

FCD had a similar trajectory. FCD decreased at T4 compared with T0 (MD=−2.8 mm/mm^2, 95% CI: −5.2 to −0.5, *P*=0.030). Albumin administration was associated with increased FCD at the end of the study period (T12 *vs.* T4, MD=6 mm/mm^2, 95% CI: 2.5 to 9.4, *P*=0.004) (Figure 3B).

TVD

TVD also had a similar trajectory. TVD decreased at T4 compared with T0 (MD=−3.5 mm/mm^2, 95% CI: −5.7 to −1.4, *P*=0.004). Albumin administration was associated with increased TVD at T12 (T12 *vs.* T4, MD=6.2 mm/mm^2, 95% CI: 3.2 to 9.3, *P*=0.001) (Figure 3C).

Table 1
Hemodynamic parameters and laboratory values.

Parameters	T0	T4	T12
Heart rate (beats/min)	102 (67–111)	93 (84–103)	91 (84–96)
Mean arterial pressure (mmHg)	76 (74–95)	72 (64–93)	79 (74–95)
Lactate (mmol/L)	2.4 (1.4–3.3)	2.1 (1.7–3.9)	2 (1.3–3.4)
Albumin levels (g/L)	29.1 ± 8.6	NA	32.9 ± 6.1
pH	7.34 ± 0.06	7.32 ± 0.08	7.36 ± 0.04
$PaCO_2$ (mmHg)	39.5 (34.5–45.0)	45.0 (41.0–47.5)	41.0 (36.0–46.0)
Cumulative urine output (mL)	55 (10–150)	215 (130–350)	775 (550–900)
Hematocrit (%)	43.0 (42.0–49.0)	45.0 (41.0–53.0)	38.5 (26.0–42.0)
Sodium (mmol/L)	138 (137–140)	NA	NA
Potassium (mmol/L)	4.2 (4.0–4.5)	NA	NA

Data are presented as median and median (interquartile range) or mean ± standard deviation.
NA: Not available; $PaCO_2$: Partial pressure of carbon dioxide.

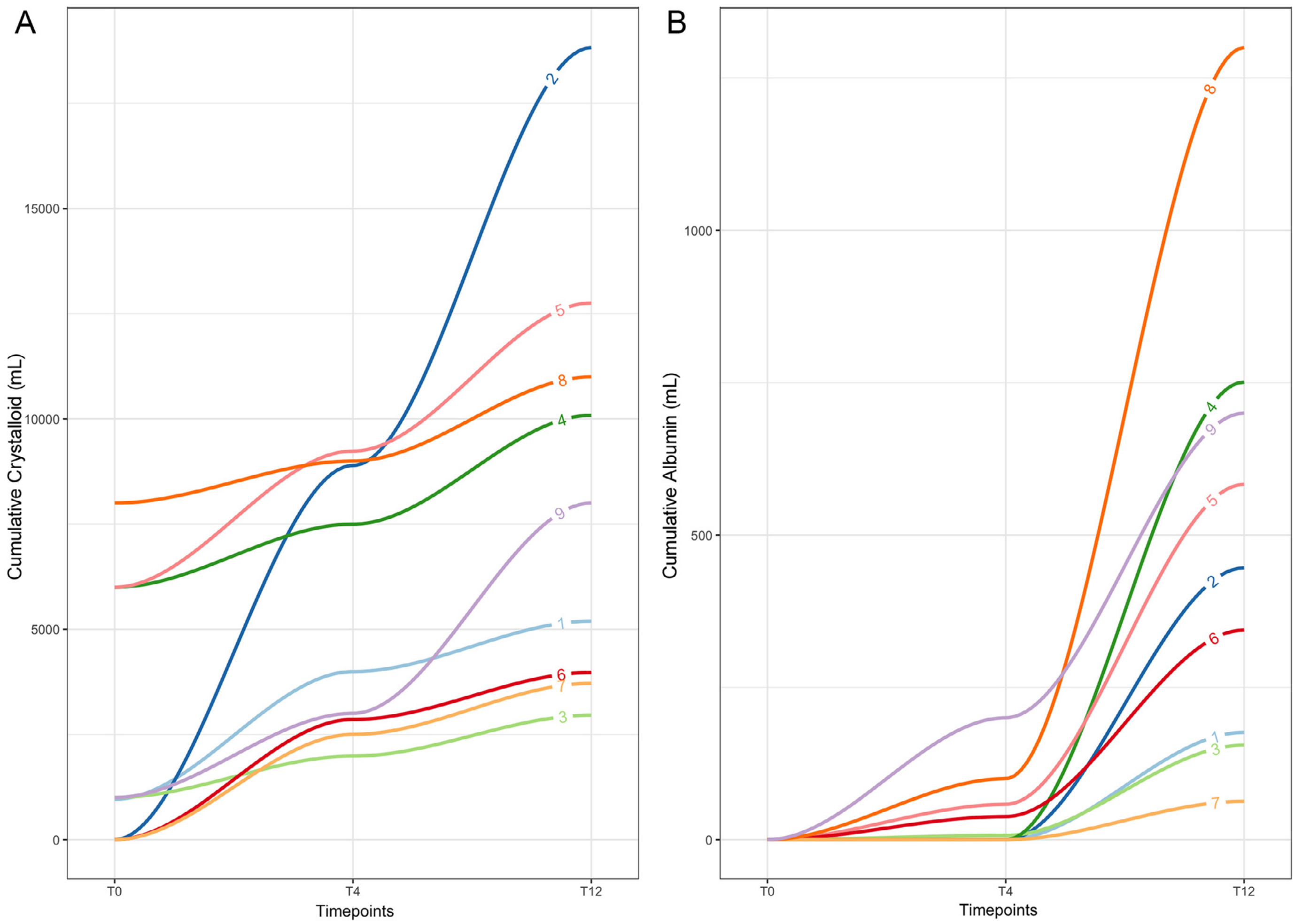

Figure 1. Individual cumulative fluid amounts. A: The quantity of crystalloids. B: The quantity of albumin administered.

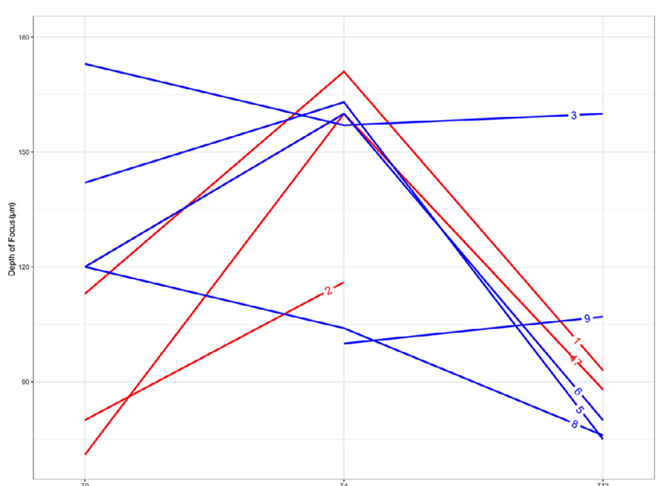

Figure 2. Grouped individual depth of focus values. The lines represent the patients who received albumin before T4 are depicted in blue, who did not receive albumin before T4 are depicted in red. The trajectories of patients 4 and 7 are presented in a stacked format.

PPV

PPV had a weak positive linear trend throughout the study period, which was not affected by albumin administration (T4 *vs.* T0, MD=1.5%, 95% CI: −2.5 to 5.5, *P*=0.470 and T12 *vs.* T4, MD=1.6%, 95% CI: −4.0 to 7.0, *P*=0.590; effect of time trend analysis: T12 *vs.* T0, MD=4.7%, 95% CI: 0.3 to 9.1, *P*=0.053) (Figure 3D).

Discussion

This study reports the possibility of quantifying tissue edema due to fluid resuscitation by serial measurements of the sublingual microcirculation. In this context, albumin administration may have a role in improving the convective and diffusive capacity of microcirculation by reducing tissue edema in these critically ill patients with severe burns.

Table 2
Summary statistics of the microcirculation variables.

Microcirculation Variables	T0	T4	T12
DOF (µm)	117.4 ± 32.0	143.4 ± 28.0	95.9 ± 28.0
FCD (mm/mm^2)	21.3 ± 2.3	18.4 ± 2.1	22.1 ± 2.8
TVD (mm/mm^2)	23.6 ± 2.2	20.0 ± 1.3	23.3 ± 2.9
PPV (%)	89.8 ± 6.5	91.4 ± 6.4	95.0 ± 2.2

Data are presented as mean±standard deviation.
DOF: Depth of focus; FCD: Functional capillary density; PPV: Percentage of perfused vessels; TVD: Total vessel density.

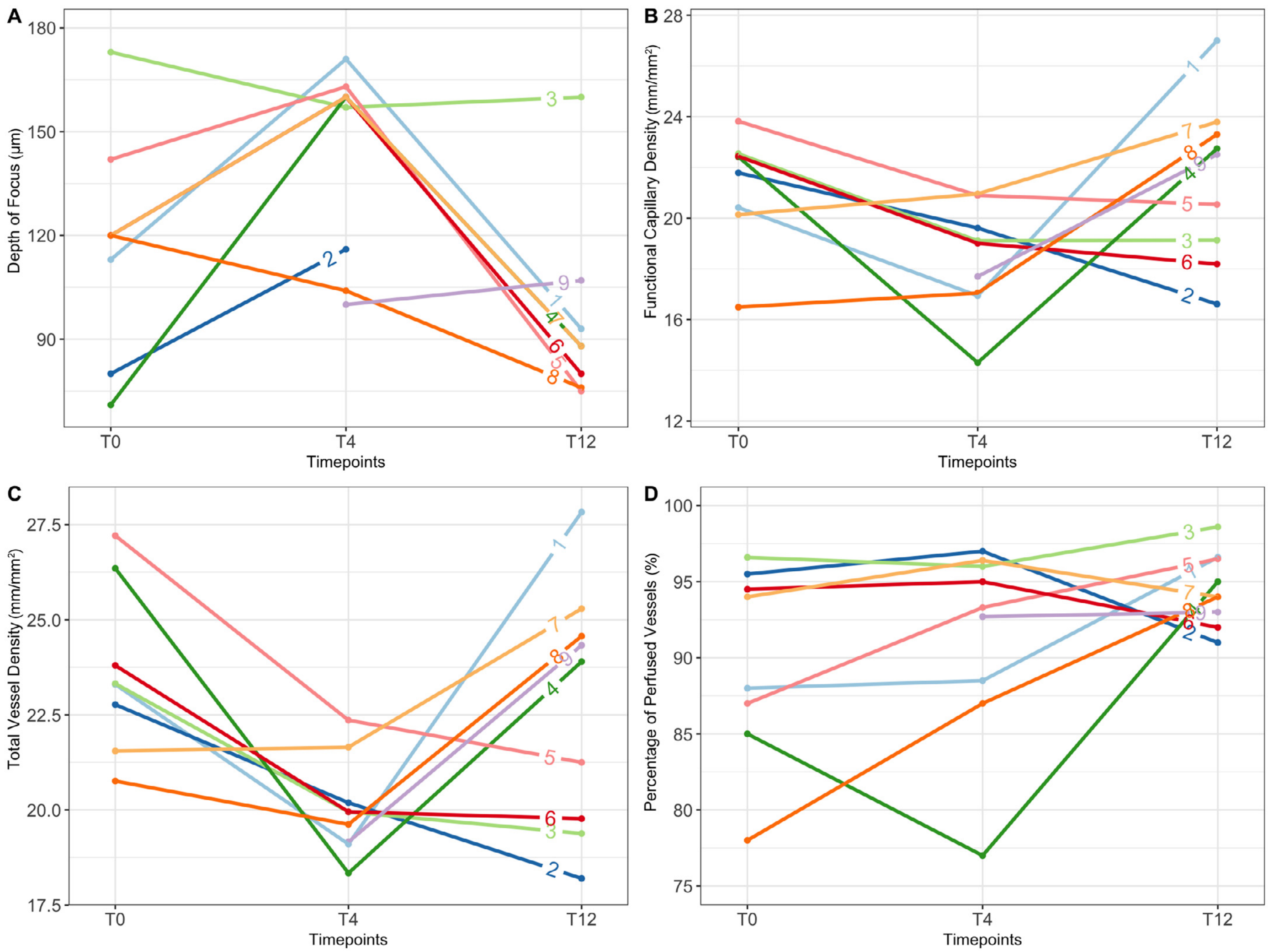

Figure 3. Individual trajectories of the microcirculation parameters. A: depth of focus, B: functional capillary density, C: total vessel density, D: percentage of perfused vessels.

Several factors including myocardial depression, disruption of the endothelial barrier, and hypovolemia can lead to burn shock. One common approach to addressing this is the administration of several liters of fluids within a few hours to improve convective flow within the capillaries which may result in the formation of tissue edema and fluid creep.[7,17,18] This study observed an increase in the DOF of the microcirculation during the early stages of fluid resuscitation, which can be partially attributed to positive fluid balance. As sublingual microcirculation images are acquired from the most superficial layer, serial measurements can be used to quantify the developing tissue edema and help in defining safety endpoints of fluid resuscitation. Additionally, this study observed that the effect of crystalloids on the microcirculation network and the tissue perfusion is heterogeneous. This can even be deleterious as functional capillaries, which are responsible for delivering oxygen to the tissue were reduced.

Adjuncts to crystalloids such as albumin can be used to mitigate the fluid overload and tissue edema. However, early studies have indicated that albumin may increase the morbidity and mortality for various reasons and is best avoided during the initial stages of the burn shock.[7] Nevertheless, there is a continued use of albumin in patients with severe burns, with several studies indicating that albumin may be beneficial to these patients through a number of mechanisms, including improvements in intravascular volume and systemic hemodynamics, as well as reductions in both the total volume of resuscitation and the extent of tissue edema.[19,20] The findings of this study indicate an association between albumin infusion and a reduction in the DOF of microcirculation, which may be attributed to a decrease in tissue edema. It is crucial to acknowledge that other factors such as endothelium regeneration or the improvement of shock because of ongoing resuscitation may also have influenced the results.[21] Nevertheless, an increase in the functional capillary network in this study indicates that albumin administration itself was not associated with a further increase in the tissue edema. It may thus be concluded that albumin administration may play a role in improving the convective and diffusive capacity of microcirculation in patients with severe burns.

To the best of our knowledge, this study is among the first to demonstrate that albumin administration may benefit tissue perfusion in severely burned patients. Limitations of the study include a small sample size and the absence of a control group making it challenging to validate the results. Additionally, the study did not measure endothelial injury markers or cytokine levels, which prevents us from confirming whether the improvement in the microcirculation was associated with a decrease in such biomarkers. Finally, we did not measure the distribution of excess fluid to the interstitium, the extravascular lung water index, or the transcapillary escape rate of albumin.[22,23] More studies are required to ascertain whether albumin administration reduces tissue edema.

Conclusion

Massive fluid resuscitation with crystalloids results in tissue edema and microcirculatory disturbance in patients with severe burns. The potential role of sublingual DOF measurements with a hand-held vital microscope to quantify the extent of tissue edema warrants further investigation. It may be hypothesized that the administration of albumin could prove beneficial in mitigating tissue edema in patients with severe burns.

CRediT Authorship Contribution Statement

Olcay Dilken: Writing – original draft, Visualization, Formal analysis, Conceptualization. **Annemieke Dijkstra:** Writing – original draft, Software, Project administration, Funding acquisition, Data curation, Conceptualization. **Göksel Güven:** Writing – review & editing, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Bülent Ergin:** Writing – review & editing, Project administration, Data curation. **Nicole Trommel:** Software, Resources, Project administration, Formal analysis, Data curation. **Margriet E. van Baar:** Writing – review & editing, Software, Resources, Project administration, Formal analysis, Data curation. **Helma WC Hofland:** Writing – review & editing, Supervision, Project administration. **Can Ince:** Resources, Data curation, Software, Project administration. **Cornelis H. van der Vlies:** Supervision, Writing – review & editing, Data curation, Funding acquisition, Project administration.

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Ethics Statement

This study was approved by the Maasstad Hospital Ethical Committee (approval number: NL60162.101.16).

Conflicts of Interest

Can Ince is CSO of Active Medical BV, Leiden, The Netherlands, a company which provides devices, software, education and services related to clinical microciruclation. Other authors declare no conflict of interest.

Data Availability

The dataset and the code are available upon reasonable request.

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