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Prognostic implications of microcirculatory perfusion versus macrocirculatory perfusion in cardiogenic shock: a CULPRIT-SHOCK substudy

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Abstract

Background: After early revascularisation, restoration of macrocirculatory perfusion parameters is the primary objective in the management of cardiogenic shock complicated acute myocardial infarction. Nevertheless, vital organ perfusion may be compromised at the systemic microcirculatory level, even in patients with preserved macrohaemodynamics. Microvascular perfusion was shown to have independent prognostic value for early mortality. The present study aims to compare the prognostic value of microcirculatory versus macrocirculatory perfusion parameters.

Methods: This substudy of the culprit lesion-only percutaneous coronary intervention versus multivessel percutaneous coronary intervention in cardiogenic shock (CULPRIT-SHOCK) trial examined the sublingual capillary network using videomicroscopy post-percutaneous coronary intervention to determine the proportion of perfused capillaries (<20 µm) and perfused capillary density. Thirty-day follow-up was performed to obtain the occurrence of a combined clinical endpoint of all-cause death and renal replacement therapy.

Results: Videomicroscopy measurements were performed in 66 patients. There was a significant adjusted association between microcirculatory perfusion parameters and the combined clinical endpoint (proportion of perfused capillaries: *P*=0.020; perfused capillary density: *P*=0.035), whereas there was no significant adjusted association between macrocirculatory perfusion parameters and the combined clinical endpoint (systolic blood pressure: *P*=0.205). Normotensive patients with compromised microcirculatory perfusion parameters had a higher risk of the combined clinical endpoint than normotensive patients with preserved microcirculatory perfusion parameters (proportion of perfused capillaries: Breslow *P*=0.014; perfused capillary density: Breslow *P*=0.076).

Conclusions: There is a significant and independent association between microcirculatory perfusion parameters perfused capillary density and proportion of perfused capillaries and the combined clinical endpoint of all-cause death and renal replacement therapy at 30 days follow-up. In patients with loss of haemodynamic coherence between microcirculatory and macrocirculatory perfusion parameters, microcirculatory perfusion parameters confer dominant prognostic value.

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Introduction

Cardiogenic shock (CS) is characterised by a diminished cardiac output leading to hypoperfusion and hypoxia of vital organs. It is a major cause of mortality in patients hospitalised with acute myocardial infarction (AMI), and complicates 5–10% of patients after AMI. Critical loss of left ventricular function due to myocardial ischaemia is recognised as the predominant aetiology for vital organ hypoperfusion. Early revascularisation and maintenance of sufficient blood pressure are, therefore, the primary objectives in the management of CS.[1,2] However, despite substantial advances in revascularisation strategies and modern haemodynamic support by either vasopressor agents or mechanical unloading devices, inhospital mortality rates for patients with CS do not improve. Accumulating evidence suggests that microcirculatory haemodynamic alterations in addition to macrocirculatory alterations contribute substantially to vital organ hypoperfusion,[3–5] or may even comprise the sole cause in patients with preserved macrohaemodynamics.[6,7] Perfusion of the sublingual microvascular network is considered a validated surrogate marker of vital organ perfusion and can be quantified by means of videomicroscopy-derived parameters of microcirculatory perfusion.[8,9] It was shown previously that perfusion parameters of the microvascular capillaries have independent prognostic value for early mortality.[10,11] The present subanalysis of the culprit lesion-only percutaneous coronary intervention (PCI) versus multivessel PCI in CS (CULPRIT-SHOCK) study involving videomicroscopy aims to investigate the prognostic value of videomicroscopy-derived parameters of systemic microcirculatory perfusion versus macrocirculatory perfusion parameters for a combined clinical endpoint of all-cause death and renal replacement therapy.

Methods

Study oversight

The present study is a predefined multicentre subanalysis of the CULPRIT-SHOCK study. The design and outcome of the CULPRIT-SHOCK trial (ClinicalTrials.gov number: NCT01927549) have been published previously.[12,13] In brief, the CULPRIT-SHOCK study encompasses an investigator-initiated, open-label, European multicentre trial, that randomly assigned 706 patients with acute ST-segment elevation or non-ST-segment elevation myocardial infarction complicated by cardiogenic shock and multivessel disease to either culprit lesion-only revascularisation with potential planned staged revascularisation of non-culprit lesions or immediate multivessel revascularisation in a 1:1 fashion. CS was defined as systemic blood pressure (SBP) less than 90 mmHg for at least 30 minutes or dependence on inotropes to maintain a SBP of 90 mmHg or greater, signs of pulmonary congestion, and signs of impaired organ perfusion with at least one of the following: altered mental status, cold, clammy skin, urine output less than 30 ml/hour, or arterial lactate levels greater than 2.0 mmol/litre. Exclusion criteria were CS for more than 12 hours, cardiopulmonary resuscitation for over 30 minutes, severe cerebral deficit, mechanical causes of CS or shock by other cause, creatinine clearance less than 30 ml/hour, and severe concomitant disease with life expectancy less than 6 months. Patients for the microcirculation substudy were screened for participation in six centres with ample experience in sublingual microcirculatory imaging (Amsterdam UMC Academisch Medisch Centrum, The Netherlands (AMC); University of Leipzig Heart Centre, Germany (ULEIHC); University of Lübeck Heart Centre, Germany (ULHC), University of Düsseldorf Institute for Cardiology, Pulmonology and Angiology, Germany (UD); Erasmus MC, Rotterdam, The Netherlands (EMC); University of Vilnius, Vilnius University Hospital, Lithuania (VUHSK). The study protocol agreed with the Declaration of Helsinki and was approved by the relevant local institutional ethics committees. For all eligible patients informed consent was obtained according to a prespecified process that varied among participating centres according to local law or ethics committee requirements.

Study procedures

Coronary revascularisation was performed with the use of standard interventional techniques according to contemporary clinical guidelines, regardless of the randomisation allocation. The use of mechanical circulatory support devices was left to the discretion of the operator and further therapy at the intensive care unit (ICU) was performed according to accepted intensive care guidelines. Systemic microvascular function was assessed by evaluating the sublingual microvascular network using videomicroscopy directly post-primary PCI. A total of three high-quality videomicroscopy loops of at least 50 frames were collected for analysis of microcirculatory perfusion. In AMC, ULEIHC, UL, UD and VUHSK the sublingual microcirculatory network was evaluated by videomicroscopy applying

the sidestream dark field (SDF) imaging technique (Microscan, Microvision Medical, Amsterdam, The Netherlands), whereas in EMC the incident dark field (IDF) imaging technique (CytoCam, Braedius, Huizen, The Netherlands) was used. The validated SDF and IDF techniques use handheld videomicroscopes equipped with green light-emitting diodes that illuminate the red blood cells of the sublingual microcirculatory network, thereby providing two-dimensional video images of the sublingual microcirculatory blood flow as described previously.[14,15]

Follow-up

Thirty-day follow up was performed to document the occurrence of all-cause death or severe renal failure leading to renal replacement therapy. Renal replacement therapy (dialysis, haemofiltration, or haemodiafiltration) was considered for otherwise untreatable volume overload, hyperkalemia (potassium level >6.0 mmol/litre), severe uremia (blood urea level >50 mg/decilitre), or persistent severe metabolic acidosis (pH <7.2).

Data analysis

Sublingual sequences were analysed offline in a core-lab at AMC by a trained investigator blinded to the treatment allocation and clinical outcome. Dedicated software (Automated Vascular Analysis (AVA) version 3.2, Microvision Medical, Amsterdam, The Netherlands) was used to quantify the sequences obtained by SDF and IDF. Imaging acquisition and offline analysis was performed according to the consensus on imaging acquisition and analysis.[14] Capillaries were defined as vessels with diameter less than 20 µm. Vessel flow was categorised as absent, intermittent, sluggish or normal, of which vessels with sluggish or normal flow were defined as perfused and vessels with absent or intermittent flow were defined as non-perfused. Perfusion parameter values were averaged over representative sequences and defined as:

De Backer's score = grid crossings/total vessel length

Total capillary density (TCD) = total length of capillaries/image area

Perfused capillary density (PCD) = length of perfused capillaries/image area

Proportion perfused capillaries (PPC) = (perfused capillaries/number of capillaries) × 100

Microvascular flow index (MFI) = average of predominant type of flow in the four quadrants of the image

In addition, macrocirculatory perfusion parameters were collected at the time of sublingual measurements. A mean arterial blood pressure (MAP) less than 65 mmHg or SBP less than 90 mmHg were considered abnormal.

Statistical analysis

The normality of the distribution of values was assessed using the Shapiro–Wilk statistic and Levene's test to assess homogeneity of variances. Continuous variables are presented as mean ± standard deviation or median (1st, 3rd quartile (Q1, Q3)), according to the distribution. Between-group differences were compared with Student's *t*-test or Mann–Whitney U-test according to the distribution. Categorical variables are presented as frequency (percentage), and between-group differences and were compared with the chi-square test. Prognostic receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was used to compare the discriminative value of videomicroscopy-derived microcirculatory perfusion parameters for the combined endpoint of all-cause death and renal replacement therapy at 30 days' follow-up. The optimal clinical cut points were defined as the cut point with the highest sum of specificity and sensitivity. The prognostic value of perfusion parameters for the composite endpoint of death and renal replacement therapy was assessed by Cox regression analysis. The best fit model for adjustment was identified by univariate Cox regression, in which candidate covariates were: clinical and procedural variables (Table 1). Variables with a significant association with the combined clinical endpoint ($P<0.05$) were used for adjustment. Cox proportional hazards models were preceded by verification of the proportional hazard assumption using Schoenfeld's residuals. Next, primary endpoint rates specified by normal or abnormal microcirculatory perfusion parameters were estimated using the Kaplan–Meier method, and compared using the Gehan–Breslow–Wilcoxon (Breslow) method. A *P* value below the two-sided α-level of 0.05 was considered statistically significant. The STATA 13.1 statistical software package (StataCorp, College Station, TX, USA) was used for all calculations.

Results

Patients and procedural characteristics

Between March 2013 and April 2017, 66 patients with CS complicated AMI and multivessel disease were enrolled. Of these, 27 had double-vessel disease and 39 had triple-vessel disease. Fifty-eight percent of patients (38 out of 66) presented with ST-segment elevation AMI, and 43% of patients (28 out of 66) with non-ST-segment elevation AMI. The median age of the study population was 69 (Q1, Q3: 60, 75) years, and 67% of patients were men (44 out of 66). The remainder baseline characteristics are summarised

Table 1. Baseline, procedural and haemodynamic characteristics of the study population.

	Overall	Survivor and no renal replacement therapy	Non-survivor or renal replacement therapy	*P* value
Baseline characteristics	*N*=66	*N*=34	*N*=32	
Age (years)	67 ± 10	64 ± 10	70 ± 9	0.022
Male	44 (66.7)	23 (67.6)	21 (65.6)	0.862
Cardiovascular risk factors				
BMI	27.5 ± 3.5	27.2 ± 3.5	28.8 ± 3.5	0.459
Current smoking	14 (21.2)	11 (32.4)	3 (9.4)	0.022
Hypertension	31 (47.0)	18 (52.9)	13 (40.6)	0.316
Hypercholesterolemia	18 (27.3)	13 (38.2)	5 (15.6)	0.039
Diabetes mellitus	20 (30.3)	11 (32.4)	9 (28.1)	0.709
Previous MI	10 (15.2)	6 (17.6)	4 (12.5)	0.560
Previous PCI	11 (16.7)	6 (17.6)	5 (15.6)	0.826
Previous CABG	5 (7.6)	3 (8.8)	2 (6.3)	0.693
Previous stroke	3 (4.5)	1 (2.9)	2 (6.3)	0.519
Positive family history	8 (12.1)	6 (17.6)	2 (6.3)	0.170
Peripheral artery disease	10 (15.2)	5 (14.7)	5 (15.6)	0.917
Signs of impaired organ perfusion on admission				
Altered mental status	40 (60.6)	21 (61.8)	19 (59.4)	0.834
Cold, clammy skin and limbs	37 (56.1)	21 (61.8)	16 (50.0)	0.129
Oliguria	16 (24.2)	5 (14.7)	11 (34.4)	0.052
pH <7.36	49 (74.2)	23 (67.6)	26 (81.3)	0.207
Arterial lactate >2.0 mm/litre	59 (74.2)	22 (64.7)	27 (84.4)	0.068
ST-segment elevated myocardial infarction	38 (57.6)	21 (61.8)	17 (53.1)	0.679
Infarct-related artery				
Left anterior descending artery	29 (43.9)	12 (35.3)	17 (53.1)	0.145
Left circumflex artery	20 (30.3)	10 (29.4)	10 (31.3)	0.874
Right coronary artery	15 (22.7)	10 (29.4)	5 (15.6)	0.182
Left main artery	2 (3.0)	2 (5.9)	0 (0.0)	0.164
Left ventricular ejection fraction, %	35.1 ± 13.0	39.4 ± 13.2	30.1 ± 11.3	0.057
Two-vessel disease	28 (42.4)	17 (50.0)	11 (34.4)	0.199
Three-vessel disease	38 (57.6)	17 (50.0)	21 (65.6)	0.295
Procedural characteristics				
Fibrinolysis <24 hours before randomisation	1 (2.0)	1 (2.9)	0 (0.0)	0.632
Resuscitation <24 hours before randomisation	35 (53.0)	19 (55.9)	16 (50.0)	0.632
Immediate PCI of non-culprit lesion	33 (50.0)	16 (47.1)	17 (53.1)	0.622
Successful immediate complete revacularisation	22 (33.3)	12 (35.3)	10 (31.3)	0.728
Mechanical circulatory support	10 (15.2)	2 (5.9)	8 (25.0)	0.030
Catecholamine therapy	59 (89.4)	29 (85.3)	30 (93.8)	0.265
Levosimendan therapy	0 (0.0)	0 (0.0)	0 (0.0)	–
Phosphodiesterase inhibitor therapy	0 (0.0)	0 (0.0)	0 (0.0)	–
Total dose of contrast material (ml)	200 (150–300)	200 (120–230)	220 (180–300)	0.086
Total duration of fluoroscopy (min)	13.8 (7.5–20.0)	12.0 (7.1–17.5)	15.4 (8.0–25.1)	0.128
ICU treatment (days)	4 (2–13)	10 (3–17)	3 (2–8)	0.013
Haemodynamic characteristics				
Macrocirculatory perfusion parameters (at admission)				
Systolic blood pressure (mmHg)	100 (87–120)	110 (90–132)	90 (82–107)	0.016
Diastolic blood pressure (mmHg)	64 (50–78)	70 (60–80)	60 (50–77)	0.278
Mean arterial blood pressure (mmHg)	77 (62–93)	81 (73–95)	69 (59–87)	0.066
Heart rate (*N*/min)	85 (70–102)	85 (70–98)	85 (70–110)	0.515
Macrocirculatory perfusion parameters (post-PCI)				
Time since revascularisation (hours)	6.5 (3.0–18.5)	7.0 (3.0–18.5)	6.0 (2.5–18.8)	0.946

(Continued)

Table 1. (Continued)

	Overall	Survivor and no renal replacement therapy	Non-survivor or renal replacement therapy	*P* value
Systolic blood pressure (mmHg)	102 (90–114)	106 (95–116)	95 (86–110)	0.048
Diastolic blood pressure (mmHg)	63 (54–70)	64 (54–70)	63 (54–69)	0.822
Mean arterial blood pressure (mmHg)	76 (68–84)	78 (70–86)	72 (66–81)	0.259
Heart rate (*N*/min)	86 (73–100)	86 (67–93)	86 (77–102)	0.199
Microcirculatory perfusion parameters (post-PCI)				
Time since revascularisation (hours)	6.5 (3.0–18.5)	7.0 (3.0–18.5)	6.0 (2.5–18.8)	0.946
de Backer score (*n*/mm)	11.9 (9.7–13.1)	12.4 (10.3–13.5)	10.3 (9.1–12.9)	0.078
TCD (mm mm^{-2})	18.0 (14.3–20.3)	19.0 (16.2–21.3)	16.7 (13.1–19.4)	0.057
PCD (mm mm^{-2})	14.1 (8.7–18.6)	16.6 (11.9–19.7)	12.3 (3.9–17.7)	0.065
PPC (%)	86.6 (51.5–94.5)	89.4 (75.4–97.2)	79.4 (27.6–93.8)	0.050
Capillary MFI	2.3 (1.5–3.0)	2.6 (2.0–3.0)	2.1 (0.8–2.8)	0.058

Numbers are given as *N* (%), mean ± standard deviation or median (Q1, Q3), or as specified otherwise.
BMI: body mass-index; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; LAD: left anterior descending; LCx: left circumflex; RCA: right coronary artery; ICU: intensive care unit; TCD: total capillary density; PCD: perfused capillary density; PPC: proportion perfused capillaries; MFI: microvascular flow index.

in Table 1. Complete multivessel revascularisation was performed as randomly assigned in 50% of patients (33 out of 66), of which successful complete revascularisation was achieved in 67% of patients (22 out of 33). Culprit lesion-only revascularisation was performed in 50% of patients (33 out of 66). All patients finalised complete follow-up.

Prognostic implications of sublingual videomicroscopy

Sublingual microvascular perfusion measurements were successful in 66 out of 66 patients. The relevant variables identified by univariate analysis for adjustment included age, oliguria at admission, smoking, mechanical circulatory support and duration of intensive care treatment. Cox proportion hazard models adjusted for these variables demonstrated that PCD, PPC and capillary MFI measured post-PCI were significantly and independently associated with the combined clinical endpoint at 30 days (PCD hazard ratio (HR) 0.947, 95% confidence interval (CI) 0.900–0.996, *P*=0.035; PPC HR 0.986, 95% CI 0.976–0.998, *P*=0.020); capillary MFI HR 0.614, 95% CI 0.424–0.890, *P*=0.010). Adjusted Cox regression analysis demonstrated a modest but insignificant association between TCD or de Backer score and the combined clinical endpoint (TCD HR 0.932, 95% CI 0.860–1.009, *P*=0.082; de Backer score HR 0.893, 95% CI 0.784–1.010, *P*=0.070; Table 2). In comparison, adjusted Cox regression analysis demonstrated no significant relation between macrocirculatory perfusion parameters, either at admission or post-PCI, and the combined clinical endpoint (Table 2).

The discriminative value for the combined endpoint of death and renal replacement therapy did not significantly differ between the systemic microcirculatory perfusion parameters (AUC PPC 0.640; AUC PCD 0.632), overall *P* value 0.801. Optimal discriminative cut points for the combined endpoint were identified at 86.4% or less for PPC and 10.1 mm mm^{-2} or less for PCD. Figure 1 shows the Kaplan–Meier curves for the combined endpoint according to normal versus abnormal PPC, PCD and SBP. The Kaplan–Meier estimate of the combined endpoint was significantly higher for patients with abnormal PPC (PPC ≤86.4 63.6% vs. PPC >86.4 33.3%; Breslow *P*=0.005; Figure 1(a)), and abnormal PCD (PCD ≤10.1 mm mm^{-2} 73.6% vs. PCD >10.1 mm mm^{-2} 38.3%; Breslow *P*=0.007; Figure 1(b)). Also, the Kaplan–Meier estimate of the combined clinical endpoint was significantly higher for patients with abnormal SBP than for patients with normal SBP (SBP <90 mmHg 62.5% vs. SBP ≥90 mmHg 44.0%; Breslow *P*=0.037; Figure 1(c)). The difference was mainly driven by a significantly lower mortality for patients with normal PPC or PCD (Table 3). However, the combined clinical endpoint was not significantly different for patients with abnormal versus normal MAP (MAP <65 mmHg 53.3% vs. MAP ≥65 mmHg 47.1%; Breslow *P*=0.274; Figure 1(d)).

Loss of haemodynamic coherence between macrohaemodynamic and microhaemodynamic parameters

Post-PCI SBP was 90 mmHg or greater in 75.8% of patients (50 out of 66). In patients with SBP of 90 mmHg or greater, PPC was abnormal in 42% of patients (21 out of 50) and normal in 58% of patients (29 out of 50), and PCD was abnormal in 20% of patients (10 out of 50) and normal in 80% of patients (40 out of 50). Figure 2 shows the Kaplan–Meier curves for the combined clinical endpoint for patients

Table 2. Univariate and adjusted Cox regression for the combined clinical endpoint (all-cause death or renal replacement therapy).

Study population (*N*=66)					
Univariate analysis			Adjusted analysis*		
Variable	HR (95% CI)	*P* value	Variable	HR (95% CI)	*P* value
Macrocirculatory perfusion parameters (at admission)			Macrocirculatory perfusion parameters (at admission)		
Systolic blood pressure (mmHg)	0.984 (0.971–0.998)	0.025	Systolic blood pressure (mmHg)	0.998 (0.984–1.013)	0.820
Diastolic blood pressure (mmHg)	0.988 (0.967–1.009)	0.264	Diastolic blood pressure (mmHg)	–	–
Mean arterial pressure (mmHg)	0.983 (0.965–1.002)	0.078	Mean arterial pressure (mmHg)	–	–
Heart rate (beats/min)	1.007 (0.996–1.018)	0.237	Heart rate (beats/min)	–	–
Macrocirculatory perfusion parameters (post-PCI)			Macrocirculatory perfusion parameters (post-PCI)		
Systolic blood pressure (mmHg)	0.976 (0.957–0.995)	0.015	Systolic blood pressure (mmHg)	0.987 (0.966–1.007)	0.203
Diastolic blood pressure (mmHg)	0.996 (0.968–1.023)	0.752	Diastolic blood pressure (mmHg)	–	–
Mean arterial pressure (mmHg)	0.982 (0.957–1.009)	0.192	Mean arterial pressure (mmHg)	–	–
Heart rate (beats/min)	1.011 (0.992–1.030)	0.254	Heart rate (beats/min)	–	–
Microcirculatory perfusion parameters (post-PCI)			Microcirculatory perfusion parameters (post-PCI)		
de Backer's score (1/mm)	0.892 (0.798–0.997)	0.043	de Backer's score (1/mm)	0.889 (0.784–1.010)	0.070
Total capillary density (mm mm^{-2})	0.928 (0.862–0.999)	0.046	Total capillary density (mm mm^{-2})	0.932 (0.860–1.009)	0.082
Perfused capillary density (mm mm^{-2})	0.949 (0.906–0.994)	0.028	Perfused capillary density (mm mm^{-2})	0.946 (0.900–0.996)	0.035
Proportion perfused capillaries (%)	0.989 (0.980–0.999)	0.026	Proportion perfused capillaries (%)	0.986 (0.976–0.998)	0.020
Microvascular flow index	0.701 (0.510–0.963)	0.028	Microvascular flow index	0.614 (0.424–0.890)	0.010

[a]Adjusted for age, oliguria at admission, current smoking, mechanical circulatory support and duration of intensive care unit treatment.
PCI: percutaneous coronary intervention.

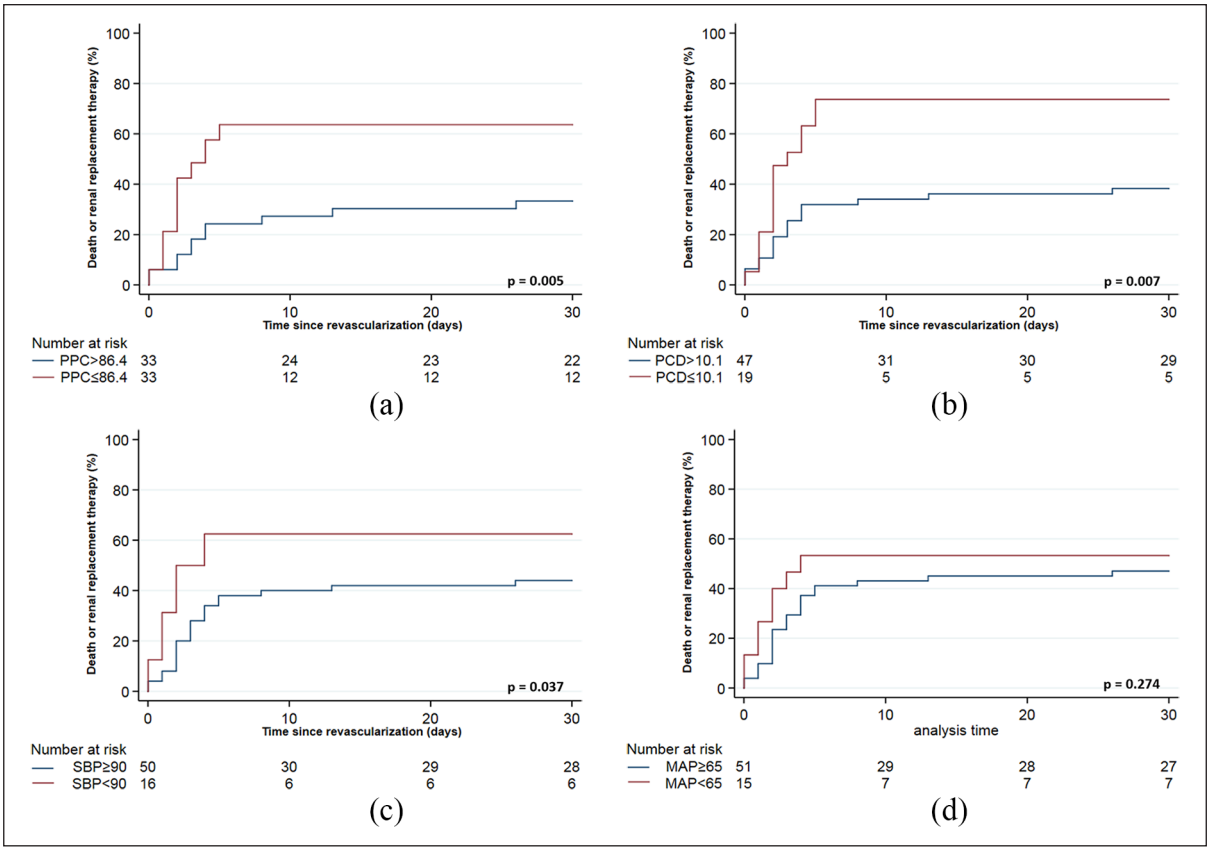

Figure 1. Kaplan–Meier estimates for patients with (a) normal or abnormal proportion perfused capillaries (PPC); (b) normal or abnormal perfused capillary density (PCD); (c) normal or abnormal systolic blood pressure (SBP); (d) normal or abnormal mean arterial blood pressure (MAP).

with SBP of 90 mmHg or greater and normal or abnormal PPC/PCD. A normal PPC or PCD was generally associated with a favourable outcome, whereas an abnormal PPC or PCD was generally associated with an adverse clinical outcome, despite normal SBP (SBP ≥90 mmHg and PPC >86.4 31.0% vs. SBP ≥90 mmHg and PPC ≤86.4 61.9%; Breslow *P*=0.014; Figure 2(a); SBP ≥90 mmHg and PCD >10.1 37.5% vs. SBP ≥90 mmHg and PCD ≤10.1 70.0%; Breslow *P*=0.076; Figure 2(b)). Clinical outcomes for patients with SBP less than 90 mmHg and normal or abnormal macrohaemodynamic parameters are show in Supplementary Figure 1.

Post-PCI MAP was 65 mmHg or greater in 77.3% of patients (51 out of 66). In patients with MAP 65 mmHg or greater, PPC was abnormal in 41.2% of patients (21 out of 51) and normal in 58.8% of patients (30 out of 51), and PCD was abnormal in 17.6% of patients (nine out of 51) and normal in 82.4% of patients (42 out of 51). Figure 3 shows the Kaplan–Meier curves for the combined clinical endpoint for patients with MAP of 65 mmHg or greater and normal or abnormal PPC/PCD. A normal PPC or PCD was generally associated with a favourable outcome, whereas an abnormal PPC or PCD was generally associated with an adverse clinical outcome, despite normal MAP (MAP ≥65 mmHg and PPC >86.4 33.3% vs. MAP ≥65 mmHg and PPC ≤86.4 66.7%; Breslow *P*=0.005; Figure 3(a); MAP ≥65 mmHg and PCD >10.1 40.5% vs. MAP ≥65 mmHg and PCD ≤10.1 77.8%; Breslow *P*=0.054; Figure 3(b)). In normotensive patients the difference in clinical outcome was driven by a significantly lower mortality for patients with normal PPC and a lower rate of renal replacement therapy for PCD (Table 3). Clinical outcomes for patients with BP less than 65 mmHg and normal or abnormal macrohaemodynamic parameters are shown in Supplementary Figure 2.

Discussion

The present substudy of the CULPRIT-SHOCK trial demonstrates a potent association between systemic microvascular perfusion determined by sublingual videomicroscopy and the composite clinical endpoint of 30-day all-cause death and renal replacement therapy in patients with CS complicated AMI. Moreover, the present study shows that

Table 3. Clinical outcome according to macrocirculatory and microcirculatory perfusion parameters.

Overall cohort												
	PPC ≤86.4	PPC >86.4	Breslow *P*	PCD ≤10.1	PCD >10.1	Breslow *P*	SBP <90	SBP ≥90	Brewlow *P*	MAP <65	MAP ≥65	Breslow *P*
Combined clinical endpoint	63.6%	33.3%	0.005	73.7%	38.3%	0.007	62.5%	44.0%	0.037	53.3%	47.1%	0.274
All-cause death	60.6%	33.3%	0.012	68.4%	38.3%	0.011	62.5%	42.0%	0.064	53.3%	45.1%	0.134
Renal replacement therapy	18.8%	6.3%	0.120	22.2%	8.7%	0.166	20.0%	10.2%	0.266	0.0%	16.0%	0.120
	SBP ≥90 mmHg subgroup						MAP ≥65 mmHg subgroup					
	PPC ≤86.4	PPC >86.4	Breslow *P*	PCD ≤10.1	PCD >10.1	Breslow *P*	PPC ≤86.4	PPC >86.4	Breslow *P*	PCD ≤10.1	PCD >10.1	Breslow *P*
Combined clinical endpoint	61.9%	31.0%	0.014	70.0%	37.5%	0.076	66.7%	33.3%	0.005	77.8%	40.5%	0.054
All-cause death	57.1%	31.0%	0.049	60.0%	37.5%	0.325	61.9%	33.3%	0.012	66.7%	40.5%	0.178
Renal replacement therapy	20.0%	3.5%	0.061	33.3%	5.0%	0.014	28.6%	6.9%	0.033	44.4%	9.8%	0.033

Numbers are given in %, and represent the cumulative event percentage.
PCD: perfused capillary density; PPC: proportion perfused capillaries; SBP: systolic blood pressure; MAP: mean arterial pressure.

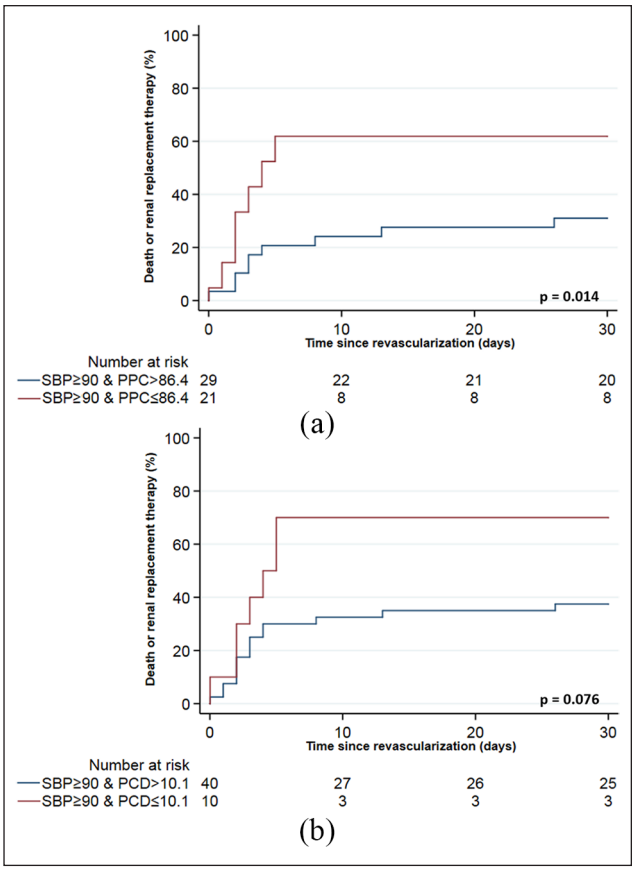

Figure 2. Kaplan–Meier estimates for patients with (a) normal systolic blood pressure (SBP) and normal or abnormal proportion perfused capillaries (PPC); (b) normal SBP and normal or abnormal perfused capillary density (PCD).

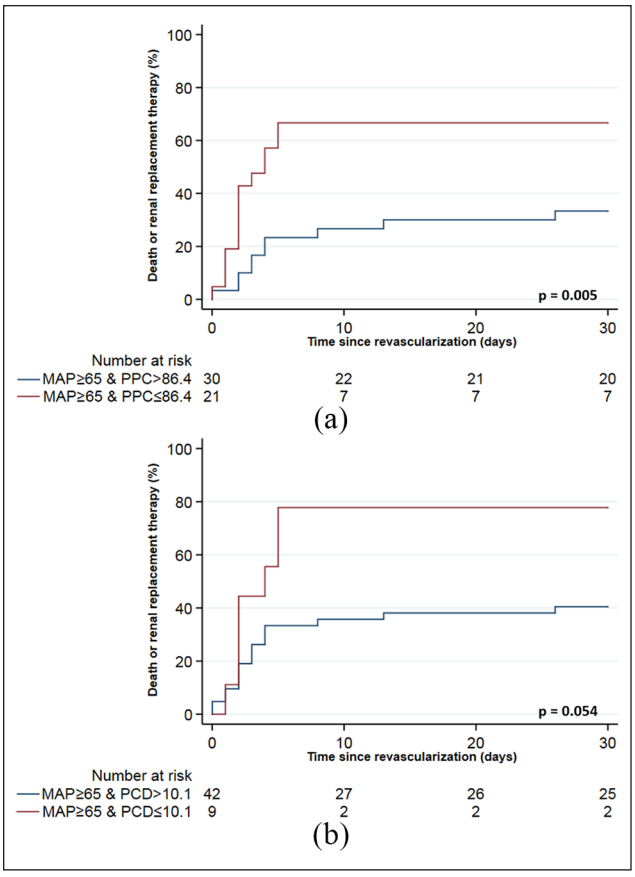

Figure 3. Kaplan–Meier estimates for patients with (a) normal mean arterial blood pressure (MAP) and normal or abnormal proportion perfused capillaries (PPC); (b) normal MAP and normal or abnormal perfused capillary density (PCD).

microcirculatory perfusion parameters have dominant prognostic value over macrocirculatory perfusion parameters for the combined clinical endpoint.

Prognostic implications of systemic microcirculatory perfusion parameters

Restoration of haemodynamic parameters is the primary endeavour in the management of CS complicated AMI. In addition to emergency revascularisation of the culprit vessel, pharmacological treatment with vasopressor agents and/or inotropes or mechanical haemodynamic support are routinely required to improve cardiac output and SBP to ensure vital organ perfusion. Although international guidelines recommend continuous blood pressure monitoring,[1] there is currently no international consensus for guidance of haemodynamic support in patients with CS complicated AMI. A target MAP in the range of 60–65 mmHg or normal SBP (≥90 mmHg) is generally recommended, but this target blood pressure has not been validated in randomised clinical trials.[1,2] Notwithstanding the technical and clinical improvements in macrocirculatory support modalities to maintain normal blood pressure, the mortality for CS complicated AMI has not improved. This may be explained by perfusion abnormalities that extend beyond the macrocirculation subsequently determining organ failure. Accumulating evidence suggests that CS complicated AMI not only involves perfusion abnormalities of the systemic macrocirculation, but also involves perfusion abnormalities of the systemic microcirculation.[3,4,10,11] In the present cohort, we documented a potent association between systemic microcirculatory perfusion parameters and the combined clinical endpoint, while there was no association between macrocirculatory perfusion parameters and the combined clinical endpoint. Our data show that patients with impaired systemic microcirculatory perfusion parameters are associated with an adverse clinical outcome, whereas patients with normal microcirculatory perfusion parameters are associated with a favourable clinical outcome. More interesting, we demonstrated that post-PCI normotensive CS patients with impaired microvascular perfusion have a significantly higher risk of mortality or renal replacement therapy than normotensive patients with normal microvascular perfusion. This benefit is mostly

driven by a significant difference in mortality. These observations confirm loss of haemodynamic coherence between macrocirculatory and microcirculatory perfusion parameters and show that microvascular perfusion is the profound determinant for clinical outcome after CS complicated AMI, regardless of macrohaemodynamic conditions.[10] In the present subcohort of the CULPRIT-SHOCK study the revascularisation strategy (immediate multivessel versus culprit only) was not identified as a predictor for the combined clinical endpoint nor was there a significant difference in microvascular perfusion between patients with culprit-only versus immediate multivessel PCI (PPC culprit only vs. PPC immediate multivessel 86.0% (Q1, Q3: 65.8%, 93.5%) vs. 88.1% (Q1, Q3: 44.3%, 94.5%) (P=0.763); PCD culprit only vs. PCD immediate multivessel 13.9 mm mm^{-2} (Q1, Q3: 10.2 mm mm^{-2}, 21.2 mm mm^{-2}) vs. 14.2 mm mm^{-2} (Q1, Q3: 7.9 mm mm^{-2}, 17.4 mm mm^{-2}) (P=0.390)). It is therefore unlikely that the revascularisation strategy interfered with the outcomes of the present study.

Comparison with previous studies

The observations in the present study confirm previous studies that microcirculatory perfusion parameters have distinct prognostic value in the setting of CS complicated AMI. Den Uil and colleagues, as well as Jung and colleagues documented that abnormal PCD measured post-PCI is associated with adverse clinical outcomes.[10,11] The distribution of PCD in the present study is comparable with the distribution reported by den Uil and colleagues, which suggest interobserver repeatability of sublingual assessment in patients with CS complicated AMI.[10] In addition, we demonstrated profound dissociation between macrocirculatory and microcirculatory perfusion parameters in the present cohort: a substantial proportion of normotensive patients show abnormal PCD or PPC. Previous studies documented loss of haemodynamic coherence between macrocirculatory and microcirculatory perfusion parameters.[6,16–18] This indicates that normal macrocirculatory perfusion parameters do not necessarily ensure perfusion, and thus oxygen exchange, at the microvascular level. The present study is the first to demonstrate that loss of haemodynamic coherence between macrocirculatory parameters and microcirculatory perfusion parameters translates into meaningful prognostic value.

Clinical considerations

Although emergency revascularisation is indisputably associated with improved clinical outcome, the clinical benefit of potent vasopressors or mechanical haemodynamic support remains debated.[11,19] A recent meta-analysis demonstrated that haemodynamic management of CS patients with epinephrine is even associated with a threefold increase in mortality.[20] This may be explained by observational studies involving patients with septic shock showing no improvement or even worsening in impaired microvascular perfusion after vasopressor therapy,[21–23] and are supported by studies showing that increasing MAP to over 65 mmHg in septic shock patients does not improve oxygen consumption, lactate levels nor renal function.[24] These observations are supported by our data, in which the use of catecholamine therapy was not identified as an independent predictor for the combined clinical endpoint. We showed that microvascular perfusion may be compromised during normotensive macrohaemodynamic conditions, and that microvascular perfusion confers dominant prognostic value. Yet, contemporary clinical practice thrives solely on macrocirculatory perfusion parameters for guidance of haemodynamic support therapy. Microvascular perfusion monitoring, in addition to macrohaemodynamic monitoring, may enhance risk stratification of patients with CS complicating AMI and, more importantly, may direct appropriate treatment to those likely to benefit. In short, hypotensive patients with normal microvascular perfusion may benefit from mechanical or pharmacological haemodynamic support, while studies suggest that this treatment strategy may negatively affect or does not affect patients with abnormal microvascular perfusion.[21–23] In contrast, small reports suggest that normotensive patients with impaired microvascular perfusion may benefit from low-dose intravenous nitroglycerin infusion or levosimendan.[25] The time has come for large randomised trials involving microcirculation measurements to investigate the clinical benefit of a tailored approach in the management of CS complicated AMI.

Limitations

The outcomes of the present study need to be interpreted considering some limitations. First of all, no formal sample size calculation was performed for this analysis, and patient numbers were based on a recent publication in the same setting.[10] The small patient cohort in the present analysis limits the statistical power of our conclusions, and may increase the probability of a type 1 statistical error, as well as the possibility that the difference recorded in the study may be sensitive to the play of chance. Secondly, videomicroscopy assessment of the sublingual capillary network is sensitive to pressure artefacts. Although sublingual recordings were analysed for quality by an independent analyst, we cannot exclude with certainty any effect of pressure artefact on the association between microcirculatory perfusion parameters and the combined clinical endpoint. Third, we only included patients with successful PCI, either culprit lesion-only or immediate multivessel PCI. Hence, the incidence of mortality is lower in this selected group of patients as we were unable to include patients who ceased before admission, during PCI, or shortly following PCI. We

did not examine systemic microvascular perfusion before PCI. Hence, we were not able to identify patients with pre-existing microvascular dysfunction nor the prognostic value of the reversibility of microvascular perfusion. Yet, baseline characteristics between patients with preserved versus impaired microvascular dysfunction did not differ (Supplementary Table 1). Fourth, bedside videomicroscopy requires trained operators. As a corollary, direct post-PCI assessment of the sublingual capillary network was not possible in all patients due to logistic ambiguities. Nevertheless, the time between revascularisation and sublingual assessment did not differ between the groups. Fifth, we did not routinely measure cardiac output, pulmonary artery pressure, or central venous pressure. Nevertheless, guidance by blood pressure reflects contemporary clinical practice. Finally, microvascular density and flow parameters do not take perfusion heterogeneity into consideration, which may be increased in the setting of CS.[26]

Conclusion

There is a significant and independent association between the microcirculatory perfusion parameters PCD and PPC and the combined clinical endpoint of all-cause death and renal replacement therapy at 30 days follow-up. When loss of haemodynamic coherence between macrocirculatory and microcirculatory perfusion parameters occurs, microcirculatory perfusion parameters confer dominant prognostic value.

Conflict of interest

The authors declare that there is no conflict of interest.

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Supplemental material

Supplementary material for this article is available online.

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