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Impaired microcirculation predicts poor outcome of patients with acute myocardial infarction complicated by cardiogenic shock

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Aims We investigated the relationship between sublingual perfused capillary density (PCD) as a measure of tissue perfusion and outcome (i.e. occurrence of organ failure and mortality) in patients with cardiogenic shock from acute myocardial infarction.

Methods and results We performed a prospective study in 68 patients. Using Sidestream Dark Field imaging, PCD was measured after hospital admission (T0, baseline) and 24 h later (T1). We compared patients with baseline PCD $\leq$ median to patients with baseline PCD $>$ median. Sequential organ failure assessment (SOFA) scores were calculated at both time points. The Kaplan–Meier 30-day survival analyses were performed and predictors of 30-day mortality were identified. The baseline PCD was a predictor of the change in the SOFA score between T0 and T1 (ΔSOFA; $\rho = -0.25$, $P = 0.04$). Organ failure recovered more frequently in patients with PCD $>$ median ($>$10.3 mm mm^{-2}; $n = 33$) than in patients with PCD $\leq$ median ($n = 35$; 52 vs. 29%, $P < 0.05$). Twenty-two patients (32%) died: 17 patients (49%) with PCD $\leq$ median vs. 5 patients (15%) with PCD $>$ median ($P = 0.004$). After adjustment, the cardiac power index [odds ratio (OR): 0.48, 95% CI: 0.24–0.94) and PCD (OR: 0.65, 95% CI: 0.45–0.92) remained significant predictors of 30-day outcome. Patients with baseline sublingual PCD $\leq$ median that improved at T1 had a considerable better prognosis relative to patients who had a persistently low PCD.

Conclusion Diminished sublingual PCD, at baseline or following treatment, is associated with development of multi-organ failure and is a predictor of poor outcome in patients with acute myocardial infarction complicated by cardiogenic shock.

Keywords Cardiogenic shock • Microcirculation • Organ failure • Outcome • Perfusion

Introduction

Cardiogenic shock is the most important cause of death in patients hospitalized with acute myocardial infarction.[1] Although in-hospital survival of cardiogenic shock is improving with more intensive treatment, 30-day mortality rate remains high.[2,3] Because cardiogenic shock is caused by extensive myocardial infarction and a decrease in cardiac output, timely reperfusion and normalization of haemodynamic parameters are the main objectives in the treatment of cardiogenic shock.[4] However, it has been shown that 45% of patients dying from cardiogenic shock have a preserved cardiac index (CI), indicating that optimization of macro-haemodynamic parameters alone may fail to save the patient.[5,6] In line with these data, *post hoc* analysis of data from the SHOCK trial demonstrated that the classic notion of systemic vasoconstriction as a response to low arterial pressure did not apply to all patients with cardiogenic shock. Indeed, a large variability in CI and systemic vascular resistance (SVR) has been reported among patients with cardiogenic shock, even despite application of vasopressor therapy.[7] These data indicate that cardiogenic shock is a primarily cardiac problem leading to subsequent derangements in the entire circulatory system.[8] It is currently accepted that cardiogenic shock

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causes a systemic inflammatory response (SIRS), which is characterized by the release of inflammatory mediators and neurohormones as well as by alterations in tissue microvasculature, which may result in multi-organ failure.[9,10] Indeed, several studies have reported that markers of SIRS are predictive of short-term mortality in cardiogenic shock.[11–14] Nevertheless, the mechanisms involved in the pathogenesis of multiple organ failure in cardiogenic shock patients remain largely unknown. Possibly impaired splanchnic perfusion at the microvascular level, modulated by the severity of heart failure, by the degree of SIRS, and by the administration of vasoactive agents, plays an important role in the pathogenesis of multi-organ failure and the persistence of shock.[15,16]

Sublingual microcirculation is a surrogate marker of splanchnic perfusion and can be measured at the bedside using the novel imaging technology.[16–18] Therefore, we investigated the relationship between sublingual microcirculation and outcome [i.e. (change in) sequential organ failure assessment (SOFA) score, occurrence of multi-organ failure, and mortality] in patients with acute myocardial infarction complicated by cardiogenic shock.

Methods

Study design

This prospective study was conducted at the Intensive Cardiac Care Unit (ICCU) of the Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands. We included patients who were admitted with acute myocardial infarction complicated by cardiogenic shock in the time period November 2007–April 2009 (*Figure 1*). Cardiogenic shock was defined as sustained hypotension (systolic blood pressure < 90 mmHg) induced by heart failure together with the clinical signs of hypoperfusion (i.e. cold extremities, oliguria, or altered mental state), not responsive to fluid resuscitation.[4] The institutional ethical committee approved the protocol, and written informed consent was obtained from each patient or, in the case of patients who were sedated, from a relative authorized to consent on behalf of such a patient.

Haemodynamic monitoring

All patients were monitored with a radial artery catheter (arterial cannula with FloSwitch, Ohmeda, Swindon, UK). Forty-eight (71%) patients were monitored with a pulmonary artery catheter (PAC: Becton Dickinson Criticath SP5107H, Sandy, UT, USA, or CCOmbo, Edwards Lifesciences, Saint-Prex, Switzerland). In the remaining patients, central venous pressure (CVP) was measured via a three-lumen central venous catheter (Multicath; Laboratoires Pharmaceutiques Vygon, Ecouen, France), inserted into the right internal jugular vein. In these patients, CI was calculated according to the Cuschieri formula, which shows close correlation with the CI measured with a PAC.[19]

Data collection

Data collection included central body temperature, heart rate, mean arterial pressure (MAP), CVP, pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure, CI, SVR, lactate level, and mixed-venous oxygen saturation (SvO_2). When no PAC was available, we estimated SvO_2 by measuring venous oxygen saturation from blood sampled from the central venous line. Systemic vascular resistance was calculated as (MAP − CVP) × 80/cardiac output. Cardiac power index (CPI) was computed as MAP × CI/451. Glomerular filtration rate was estimated by the modification of diet in renal disease equation.

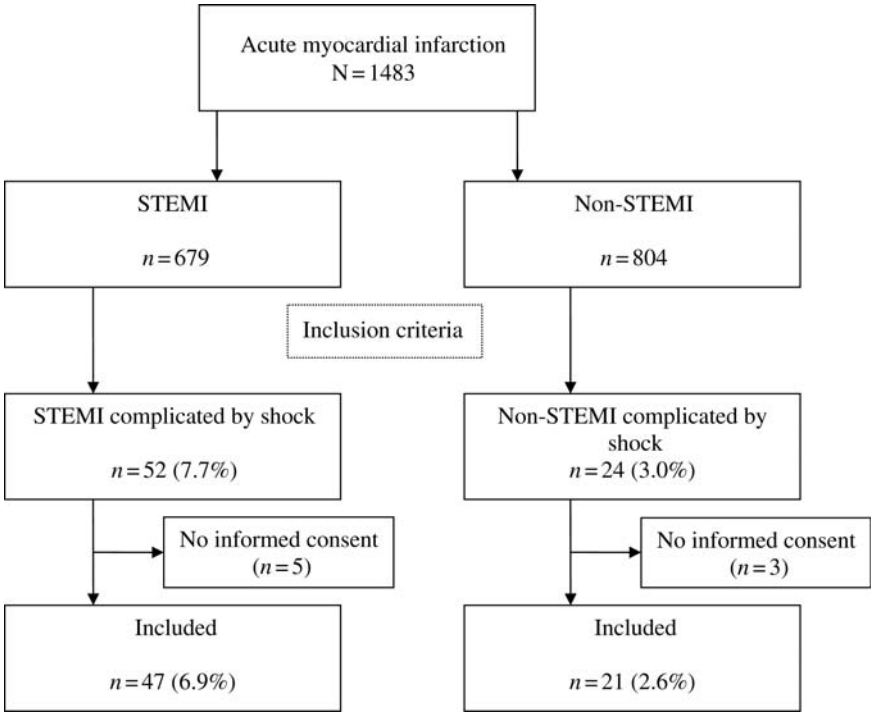

Figure 1 Study flow chart. STEMI, ST-segment elevation myocardial infarction.

Microcirculatory assessment and analysis

The Sidestream Dark Field (SDF) imaging device (MicroScan; Microvision Medical, Amsterdam, the Netherlands) was used to obtain two-dimensional video images of sublingual microcirculatory blood flow as described previously.[20] In short, the camera emits green light that is absorbed by red blood cells within microvessels. In this way, red blood cells are used as the contrast agent to visualize sublingual blood flow in patent microvessels. Per time point, 3–5 steady video sequences of at least 20 s duration were obtained, stored, and analysed in a randomized and blinded fashion. Quantification of the images was done using dedicated software (Automated Vascular Analysis 3.0, Microvision Medical) by a blinded investigator. Perfused capillary density (PCD) was calculated by measuring total length of perfused capillaries divided by the image area. Capillaries were regarded as perfused if they had either of the following flow classifications obtained by visual inspection: sluggish, continuous, or hyperdynamic.[21,22] Unperfused capillaries (i.e. capillaries with absent or intermittent perfusion) were judged not to take part of the circulation and were not taken into account. Since SDF imaging enables visualization of flowing intravascular erythrocytes rather than microvessel walls, an increase in PCD was regarded as capillary recruitment. This approach has been validated previously and within-patient variability and inter- and intra-observer variability of the technique are low.[23–25] Capillaries were defined as microvessels with a diameter <20 μm. Reference values for sublingual PCD in control patients (i.e. patients awaiting cardiac surgery who were not in shock) have been reported previously, i.e. ≥ 11.7 mm mm^{-2} (2.5 percentile).[26,27]

Image acquisition is particularly comfortable in patients who are sedated and intubated, whereas in patients who are awake, movement of the tongue may more easily result in movement artefacts. However, we and other investigators extensively reported the feasibility of using this device in critically ill patients in several reports albeit in research settings.[25,28–30] In addition, Arnold *et al.*[30] recently compared a real-time point-of-care (POC) determination of the microcirculation to conventional off-line analysis. The POC assessment of microcirculation was 94% sensitive and 92% specific for detecting impaired microvascular flow.

Study protocol

The sublingual microcirculation was investigated as soon as possible after the patient's admission to the ICCU and after informed consent had been obtained (T0, baseline). Measurements were repeated 24 h after the first measurement or earlier, pending the individual clinical course of the patient (i.e. significant deterioration which might lead to death within 24 h). In addition, at both time points, all components of the SOFA score were calculated, with the exception of the central nervous system parameters, because the majority of the patients received central nervous system depressant drugs at the time of evaluation.[14,31] The total SOFA score was calculated by summing the scores for each of the components (i.e. cardiac, renal, respiratory, coagulation, and liver).[32]

Follow-up

Vital status at 30 days was registered for all patients. In patients who were transported to other hospitals or were discharged during the 30 days following baseline measurements, vital status was acquired from municipal civil registries. The response rate was 100% and no patients were lost during 30 days of follow-up.

Statistical analysis

Statistical analyses were performed using SPSS 15.0 for Windows. Categorical variables are presented as absolute numbers with percentages. Continuous variables are presented as mean ± standard deviation. Non-normally distributed continuous variables are presented as median (interquartile range). Because this study is the first study that presents PCD measurements in patients with cardiogenic shock, we decided *a priori* to compare the patients with baseline sublingual PCD ≤ median with the patients in whom baseline sublingual PCD was >median. Categorical variables were compared by the chi-square test or Fisher's exact test, when appropriate. Differences between groups were tested with Student's *t*-test or the Mann–Whitney test, when appropriate. Changes between time points were tested with the paired *t*-test or Cochran's *Q*-test, when appropriate. Correlations between variables were investigated with the Pearson or the Spearman correlation test, when appropriate. The Kaplan–Meier cumulative 30-day survival was calculated, and the Kaplan–Meier survival curves were compared by the log-rank test. Univariate and multivariate logistic regression analyses were performed to identify predictors of 30-day all-cause mortality. Final results are presented as unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95% CI). The multivariate logistic regression model selection was done with a backward stepwise method starting with the following variables: age >75 years, CPI, baseline SOFA score, nitroglycerine, left main coronary artery occlusion, left ventricular ejection fraction <30%, significant mitral valve regurgitation, and sublingual PCD. Variables that remained significantly associated with 30-day mortality were part of the regression equation and are presented. The multivariate model was confirmed by using the forward stepwise selection. We selected the variables based on differences in baseline characteristics among both subgroups and on previous reports on prognosticating factors in cardiogenic shock.[25,26,33–35] Given our hypothesis, we further added sublingual PCD and baseline SOFA score, which consists of multiple variables itself, including inotropic and vasopressor support. Sublingual PCD was entered into the model as a continuous variable. The cardiac power index was categorized into units of 0.10 W m^{-2}.[33] All tests were two-sided. A *P*-value of <0.05 was regarded statistically significant.

Results

We investigated 68 patients with acute myocardial infarction complicated by cardiogenic shock; 47 patients had a STEMI and 21 patients had a non-STEMI (*Figure 1*, *Table 1*). Mean age was 60 ± 14 years and 69% of the patients were male. Ninety-seven per cent of the patients still met the inclusion criteria during baseline measurements. The remaining patients ($n = 2$) received high dosages of vasopressors, which resulted in systolic blood pressures >90 mmHg. Median PCD was 10.3 mm mm^{-2} (range: 4.3–15.9 mm mm^{-2}; please note the Supplementary material online for video samples of high- and low-sublingual PCD). Patients with PCD ≤ median ($n = 35$) were less frequently >75 years when compared with patients with sublingual PCD > median ($n = 33$; 9 vs. 30%, $P = 0.03$, *Table 1*). Patients with PCD ≤ median more frequently had an ejection fraction <30% (74 vs. 42%, $P = 0.01$). The median baseline SOFA score was not significantly different between both groups. Patients with a PCD ≤ median had a higher PCWP [23 (18–25) vs. 18 (14–22) mmHg, $P = 0.04$] than those with a PCD > median (*Table 2*).

Table 1 Baseline characteristics

	All patients ($n = 68$)	PCD ≤ median[a] ($n = 35$)	PCD > median[a] ($n = 33$)	*P*-value
Age (years; mean ± SD)	60 ± 14	59 ± 12	62 ± 15	0.24
Age > 75 years [*n* (%)]	13 (19)	3 (9)	10 (30)	0.03
Gender [male; *n* (%)]	47 (69)	24 (69)	23 (70)	0.99
Proportion of patients still meeting inclusion criteria during baseline measurements[b] [*n* (%)]	66 (97)	34 (97)	32 (97)	0.99
CV risk factors [*n* (%)]				
Hypertension	27 (40)	11 (31)	16 (49)	0.22
Diabetes mellitus	21 (31)	12 (34)	9 (27)	0.61
Current smoking	16 (24)	10 (29)	6 (18)	0.4
Dyslipidaemia	18 (27)	9 (26)	9 (27)	0.99
Electrocardiography [*n* (%)]				
Non-STEMI	21 (31)	11 (31)	10 (30)	0.99
STEMI	47 (68)	24 (69)	23 (70)	
Laboratory [median (IQR)]				
Haemoglobin (mmol L^{-1})	6.6 (5.9–7.7)	6.6 (5.8–7.7)	6.6 (6.0–7.7)	0.78
WBC count ($\times 10^9$ L^{-1})	11.9 (9.8–17.3)	12.9 (9.8–18.0)	11.4 (8.8–17.1)	0.35
CRP (mg L^{-1})	55 (15–138)	55 (18–136)	49 (9–149)	0.81
GFR (mL min^{-1})	58 (37–83)	55 (39–77)	66 (33–90)	0.55
NT-proBNP (pg mL^{-1})	3775 (1316–9140)	4127 (1958–10,873)	2839 (1186–8653)	0.54
Peak creatine kinase (U L^{-1})	3455 (403–6786)	3891 (355–7221)	3093 (413–5948)	0.47
Peak Troponin T (μg L^{-1})	5.7 (1.2–12.9)	7.8 (1.8–13.4)	4.0 (0.6–13.8)	0.54
Echocardiography [*n* (%)]				
Ejection fraction < 30%	40 (59)	26 (74)	14 (42)	0.01
Moderate-severe MR	17 (25)	10 (29)	7 (21)	0.58
Angiography [*n* (%)]				
No angiography	6 (9)	4 (11)	2 (6)	0.67
One-vessel disease	17 (25)	7 (20)	10 (30)	
Two-vessel disease	15 (22)	7 (20)	8 (24)	
Three-vessel or LM disease	30 (44)	17 (49)	13 (39)	
Occlusion of LM	15 (24)	8 (26)	7 (23)	0.99
Treatment [*n* (%)]				
ASA	67 (99)	35 (100)	32 (97)	0.49
Clopidogrel	52 (77)	28 (80)	24 (73)	0.57
UFH/LMWH	68 (100)	35 (100)	33 (100)	0.99
GP IIb/IIIa inhibitors	10 (15)	5 (14)	5 (15)	0.99
Enoximone and/or dobutamine and/or dopamine ≤ 5[c]	27 (40)	16 (46)	11 (33)	0.31
Dopa > 5 or Norepi ≤ 0.1[c]	16 (24)	6 (17)	10 (30)	
Dopa > 15 or Norepi > 0.1[c]	15 (22)	8 (23)	7 (21)	
Nitroglycerine	9 (13)	7 (20)	2 (6)	0.15
Mechanical ventilation	49 (72)	22 (63)	27 (82)	0.11
IABP	30 (44)	18 (51)	12 (36)	0.23
ECMO	3 (4)	1 (3)	2 (6)	0.61
Revascularization [*n* (%)]				
No revascularization	14 (21)	6 (17)	8 (24)	0.74
Thrombolysis	0 (0)	0 (0)	0 (0)	
PCI	49 (72)	26 (74)	23 (70)	
CABG	5 (7)	3 (9)	2 (6)	
TIMI flow after PCI	3 (3–3)	3 (3–3)	3 (3–3)	0.22

Continued

Table 1 *Continued*

	All patients ($n = 68$)	PCD ≤ median[a] ($n = 35$)	PCD > median[a] ($n = 33$)	*P*-value
SOFA score [median (IQR)]				
Total	5 (4–7)	5 (3–8)	6 (4–7)	0.96
Cardiac subscore	2 (2–3)	2 (2–3)	3 (2–3)	0.65
Renal subscore	1 (0–1)	1 (0–1)	0 (0–2)	0.7
Respiratory subscore	1 (1–2)	2 (1–2)	1 (1–2)	0.59
Coagulation subscore	0 (0–1)	0 (0–1)	0 (0–1)	0.86
Liver subscore	0 (0–0)	0 (0–0)	0 (0–0)	0.62
Timing of baseline measurements [median (IQR)]				
Time from AMI (h)	16 (6–20)	16 (9–20)	12 (4–22)	0.36
Time from shock onset (h)	5 (3–10)	5 (4–8)	4 (2–11)	0.39

SD, standard deviation; NS, non-significant; AMI, acute myocardial infarction; CV, cardiovascular; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; NT-proBNP, N-terminal proB-type natriuretic peptide; IQR, interquartile range; WBC, white blood cell; CRP, C-reactive protein; GFR, glomerular filtration rate; MR, mitral valve regurgitation; LM, left main coronary artery; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; SOFA, sequential organ failure assessment.
[a]Median PCD = 10.3 mm mm^{-2}.
[b]Systolic blood pressure < 90 mmHg and clinical signs of hypoperfusion.
[c]Dosages in μg kg^{-1} min^{-1}.

Table 2 **Baseline haemodynamic parameters**

	All patients ($n = 68$)	PCD ≤ median[a] ($n = 35$)	PCD > median[a] ($n = 33$)	*P*-value
HR (b.p.m.)	93 (72–104)	92 (71–106)	93 (72–104)	0.80
MAP (mmHg)	69 (61–70)	66 (58–70)	70 (64–70)	0.07
CVP (mmHg)	15 (12–18)	16 (12–19)	14 (13–16)	0.23
PCWP (mmHg)[b]	21 (16–24)	23 (18–25)	18 (14–22)	0.04
MPAP (mmHg)[b]	28 (24–34)	30 (24–37)	27 (24–30)	0.18
CI (L min^{-1}m^{-2})	2.5 (2.1–2.9)	2.4 (1.8–2.9)	2.7 (2.1–2.9)	0.44
CPI (W m^{-2})	0.35 (0.26–0.42)	0.33 (0.24–0.39)	0.38 (0.30–0.42)	0.11
SVR (dynes s cm^{-5})	1075 (825–1242)	1075 (798–1237)	1052 (850–1256)	0.79
SvO_2 (%)	66 (61–73)	65 (60–70)	68 (62–75)	0.12
Lactate (mmol L^{-1})	2.8 (2.0–4.3)	2.9 (1.8–4.5)	2.8 (2.2–4.8)	0.58

HR, heart rate; NS, non-significant; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary artery pressure; CI, cardiac index; CPI, cardiac power index; SVR, systemic vascular resistance; SvO2, central-venous oxygen saturation.
[a]Median PCD = 10.3 mm mm^{-2}.
[b]Data available in 48 (71%) of the patients.

Baseline sublingual perfused capillary density

Baseline PCD correlated with MAP ($\rho = 0.34$, $P = 0.004$), PCWP ($\rho = -0.32$, $P = 0.03$), and CPI ($\rho = 0.25$, $P = 0.04$) but not significantly with the baseline SOFA score or with other parameters listed in *Table 2*. Baseline PCD predicted the change in the SOFA score between T0 and T1 (ΔSOFA; $\rho = -0.25$, $P = 0.04$). Patients with baseline sublingual PCD > median improved more frequently in the total SOFA score (52 vs. 29%, $P < 0.05$) and in the cardiac SOFA subscore (61 vs. 34%, $P = 0.03$) at 24 h, when compared with patients with sublingual impaired PCD ≤ median.

Twenty-two patients (32%) died during 30 days of follow-up. All these patients died in the hospital. Of the patients who had a PCD ≤ median, 17 (49%) died vs. 5 (15%) of the patients with PCD > median ($P = 0.004$, *Figure 2*). Inverse sublingual PCD as a continuous parameter had a greater predictive value on 30-day mortality than the baseline SOFA score (area under the receiver operator characteristic curve of 0.75 vs. 0.56). The threshold best predicting 30-day mortality was 10.0 mm mm^{-2} [area under the curve of 0.72 vs. 0.69 when the median (10.3 mm mm^{-2}) was used]. Left ventricular ejection fraction <30% (OR: 3.40, 95% CI: 1.07–10.8) was significantly associated with 30-day mortality, whereas CPI (OR: 0.42, 95% CI: 0.23–0.78) and sublingual PCD (OR: 0.61, 95% CI: 0.44–0.84) were significantly associated with improved 30-day survival. After adjustment, CPI (OR: 0.48, 95% CI: 0.24–0.94) and sublingual PCD (OR: 0.65, 95% CI: 0.45–0.92) remained significant predictors of 30-day outcome (*Figure 3*). Survival within 30 days according to the quartile of baseline sublingual PCD is shown in *Figure 4*.

Association between changes in PCD and outcome

In 54 patients (79%), PCD measurements were repeated (T1). In the remaining patients ($n = 14$), PCD measurements at T1 were not possible. One patient died immediately after the first measurements, five patients were sent back to the referring hospital before T1, and in eight patients, there was no investigator available to perform the measurements. Overall, sublingual PCD tended to increase at T1 relative to T0 (10.3 ± 2.2 mm mm^{-2} at T0 vs. 10.9 ± 2.2 mm mm^{-2} at T1, $P = 0.09$). At time point T0, 27% of patients had a PCD $\geq$ 11.7 mm mm^{-2} (reference value in control patients) and at T1, 43% of patients reached reference values (T0 vs. T1, $P < 0.05$). Changes in sublingual PCD were inversely correlated with changes in CVP ($\rho = -0.38$, $P = 0.009$). There was a modest correlation between PCD measured at 24 h and SOFA scores at T1 ($\rho = -0.40$, $P = 0.003$). In the total study group, no significant correlation between changes in PCD and changes in SOFA score was found. However, patients who had a PCD $\leq$ median at both time points had higher SOFA scores at T1 relative to patients who had a sublingual PCD $>$ median at T0 and T1 [7 (4–8) vs. 4 (3–5), $P = 0.03$]. Survival of patients stratified to the level of PCD at both time points is shown in *Figure 5*. Patients who had a PCD $\leq$ median at baseline, which improved at T1 ('low-high'), had a significant better prognosis when compared with patients who had a persistently low PCD ('low-low'). When patients in whom no second measurement was performed were regarded as the sicker patients (i.e. PCD T1 $\leq$ median), results were identical. Finally, an increase in PCD was significantly associated with a better outcome (OR: 0.73, 95% CI: 0.54–0.99).

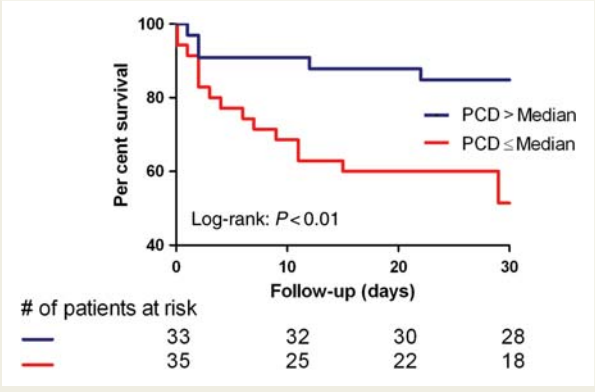

Figure 2 The Kaplan–Meier survival curve stratified according to perfused capillary density at baseline. Median perfused capillary density = 10.3 mm mm^{-2}.

Discussion

In this study, we demonstrated that patients with cardiogenic shock from acute myocardial infarction who had a sublingual PCD $\leq$ median had a higher risk to die. Baseline PCD was a significant predictor for change in the SOFA score within the next 24 h. In addition, the sublingual PCD at 24 h correlated with the SOFA score at T1. Patients with a higher baseline sublingual PCD were more likely to improve in the total SOFA score as well as in the cardiac SOFA subscore at 24 h. Furthermore, the baseline PCD was strongly and independently associated with 30-day outcome. Finally, in a large subgroup of patients in whom measurements were repeated, we demonstrated that patients who had a sublingual PCD $\leq$ median at baseline as well as after 24 h were at high risk of poor outcome, as opposed to those patients in whom microcirculation recovered within 24 h. In the latter patients, survival rates were similar to those of patients with PCD $>$ median at both time points.

Using a semi-quantitative analysis technique, De Backer *et al.*[36] previously described sublingual microcirculatory alterations in 31 patients with cardiogenic shock. The authors reported a weak correlation of the proportion of perfused capillaries with MAP, which is in line with our findings. We also found a weak correlation between sublingual PCD and CPI. Such relative dissociation between macrocirculation (haemodynamic measurements) and microcirculation (perfusion) has been demonstrated previously.[37] Since PCD was strongly associated with 30-day outcome, monitoring of microcirculation may therefore have an additional value for risk stratification as well as for the treatment of patients with cardiogenic shock.[38]

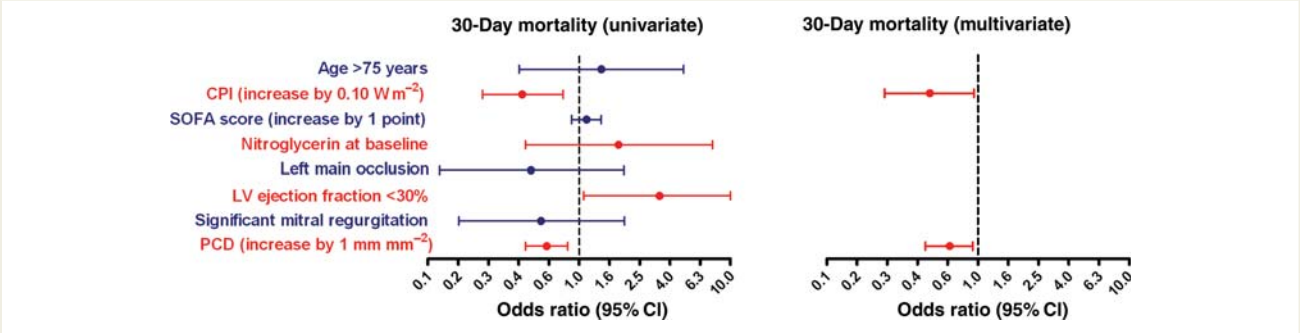

Figure 3 Predictors of 30-day mortality (univariate and multivariate analyses). The multivariate logistic regression model selection was done with the backward stepwise method starting with the following variables: age $>$ 75 years, CPI, baseline sequential organ failure assessment score, nitroglycerine, left main coronary artery occlusion, left ventricular ejection fraction $<$ 30%, significant mitral valve regurgitation, and sublingual perfused capillary density. Variables that remained significantly associated with 30-day mortality were part of the regression equation and are presented. The multivariate model was confirmed by using the forward stepwise selection.

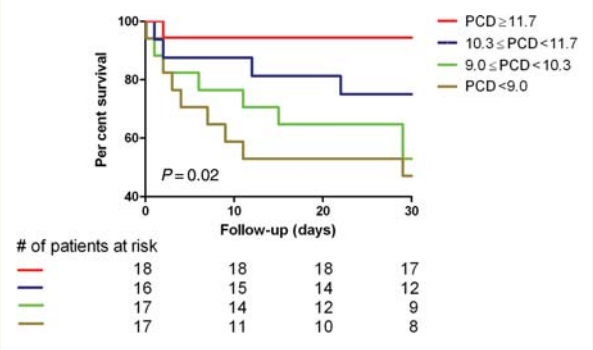

Figure 4 The Kaplan–Meier survival curve stratified according to the quartile of baseline sublingual perfused capillary density.

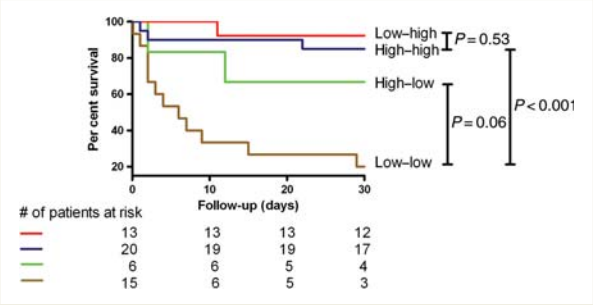

Figure 5 The Kaplan–Meier survival curve of short-term survival of cardiogenic shock patients stratified according to the sublingual perfused capillary density at baseline and after 24 h. Low–high, perfused capillary density ≤ median at T0 and perfused capillary density > median at T1; High–high, perfused capillary density > median at T0 and perfused capillary density > median at T1; High–low, perfused capillary density > median at T0 and perfused capillary density ≤ median at T1; Low–low, perfused capillary density ≤ median at T0 and perfused capillary density ≤ median at T1.

Trzeciak *et al.*[39] recently demonstrated that increased sublingual microcirculatory flow during resuscitation of septic shock was associated with lower SOFA scores at 24 h. In contrast, we did not find a relationship between changes in the sublingual PCD and changes in the SOFA score between T0 and T1. Nevertheless, we demonstrated that the sublingual PCD at baseline was predictive for recovery from organ failure. In addition, patients who had a PCD ≤ median at T0 as well as at T1 had the highest SOFA scores at T1.

Hasdai *et al.*[40] demonstrated the predictive value of a cold, clammy skin on 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction. In addition, De Backer *et al.*[36] reported that the proportion of sublingual perfused capillaries, measured after hospital admission, was higher in patients who survived than in patients who did not survive (64 vs. 43%, $P < 0.05$). In our (larger) study, we confirmed these observations and demonstrated that in patients all having clinical signs of hypoperfusion, sublingual PCD can be used to better define the severity of cardiogenic shock and to refine the prediction of outcome.

Clinical perspectives

These findings raise the question whether sublingual PCD can be used as a therapeutic target at the bedside and, if so, whether interventions directed at improving PCD will be associated with improved outcome. We demonstrated recently that PCD can be improved by pharmacologic therapy (nitroglycerine)[25,26] as well as by mechanical circulatory support.[29] The current study demonstrates that patients who had a low PCD at baseline which recovered at 24 h had a similar prognosis as those who had a higher PCD at both time points. Taken together, these results suggest that assessment of sublingual PCD by SDF imaging, followed by prompt interventions directed at improving microvascular perfusion, might optimize therapy in order to improve the outcome of patients with cardiogenic shock.

Limitations

Several limitations of our study need to be acknowledged. First, measurements of the pulmonary circulation by a PAC were missing in some patients when the attending clinicians were unwilling to use this monitoring device, even in a research setting. Second, PCD measurements could not be repeated in some patients. Third, we measured patients only after informed consent had been obtained. This implies that, in most cases, it consumed hours before baseline measurements could be performed. Nevertheless, our study clearly demonstrates that in these patients, already being resuscitated, sublingual PCD can be used to identify patients who are at a high risk of dying. Fourth, we used PCD as the marker of microcirculatory perfusion, a software-derived parameter in which microvascular flow and density are combined. This parameter does not take into account the heterogeneity of perfusion, which may be increased in disease states.[41] However, the problem of heterogeneous blood flow, visualized sublingually as fields of absent or intermittent capillary blood flow, seems to be more specific for septic shock than for cardiogenic shock.[16,36,42,43] Finally, since our study was an observational study, significant correlations, e.g. between baseline PCD and changes in SOFA score, do not prove causality.

Conclusions

In conclusion, impaired microcirculation, as assessed by sublingual PCD, is associated with the development of (multi-)organ failure. In addition, this parameter is an independent, strong predictor of outcome. Because of the independent and strong association with prognosis in cardiogenic shock, assessment of sublingual PCD using SDF imaging should be considered as a simple non-invasive tool to assess outcome in patients with cardiogenic shock. Whether a strategy of improving sublingual PCD will improve the survival of patients with cardiogenic shock, should preferably be tested in a future, multicentre randomized trial.

Supplementary material

Supplementary material is available at *European Heart Journal online*.

Conflict of interest: none declared.

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