

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

Corstiaan A. den Uil<sup>1\*</sup>, Wim K. Lagrand<sup>2</sup>, Martin van der Ent<sup>1</sup>,  
Lucia S.D. Jewbali<sup>1</sup>, Jin M. Cheng<sup>1</sup>, Peter E. Spronk<sup>3</sup>, and Maarten L. Simoons<sup>1</sup>

<sup>1</sup>Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Room V-017, s-Gravendijkwal 230, Rotterdam NL-3015 CE, The Netherlands; <sup>2</sup>Department of Intensive Care Medicine, Academic Medical Center, Amsterdam, The Netherlands; and <sup>3</sup>Department of Intensive Care Medicine, Gelre Hospitals, Apeldoorn, The Netherlands

Received 8 April 2010; revised 2 July 2010; accepted 23 July 2010; online publish-ahead-of-print 9 September 2010

## 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 ( $\Delta$ SOFA;  $\rho = -0.25$ ,  $P = 0.04$ ). Organ failure recovered more frequently in patients with PCD  $>$  median ( $>10.3 \text{ mm mm}^{-2}$ ;  $n = 33$ ) 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.<sup>1</sup> Although in-hospital survival of cardiogenic shock is improving with more intensive treatment, 30-day mortality rate remains high.<sup>2,3</sup> 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.<sup>4</sup> However, it has been shown that 45%

index (CI), indicating that optimization of macro-haemodynamic parameters alone may fail to save the patient.<sup>5,6</sup> 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.<sup>7</sup> These data indicate that cardiogenic shock is a primarily cardiac problem leading to subsequent derangements in the entire circulatory system.<sup>8</sup> It is currently accepted that cardiogenic shock

\* Corresponding author: Tel: +31 614673334, Fax: +31 10 70 32890, Email: c.denuil@erasmusmc.nl

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oxfordjournals.org.

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.<sup>9,10</sup> Indeed, several studies have reported that markers of SIRS are predictive of short-term mortality in cardiogenic shock.<sup>11–14</sup> 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.<sup>15,16</sup>

Sublingual microcirculation is a surrogate marker of splanchnic perfusion and can be measured at the bedside using the novel imaging technology.<sup>16–18</sup> 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

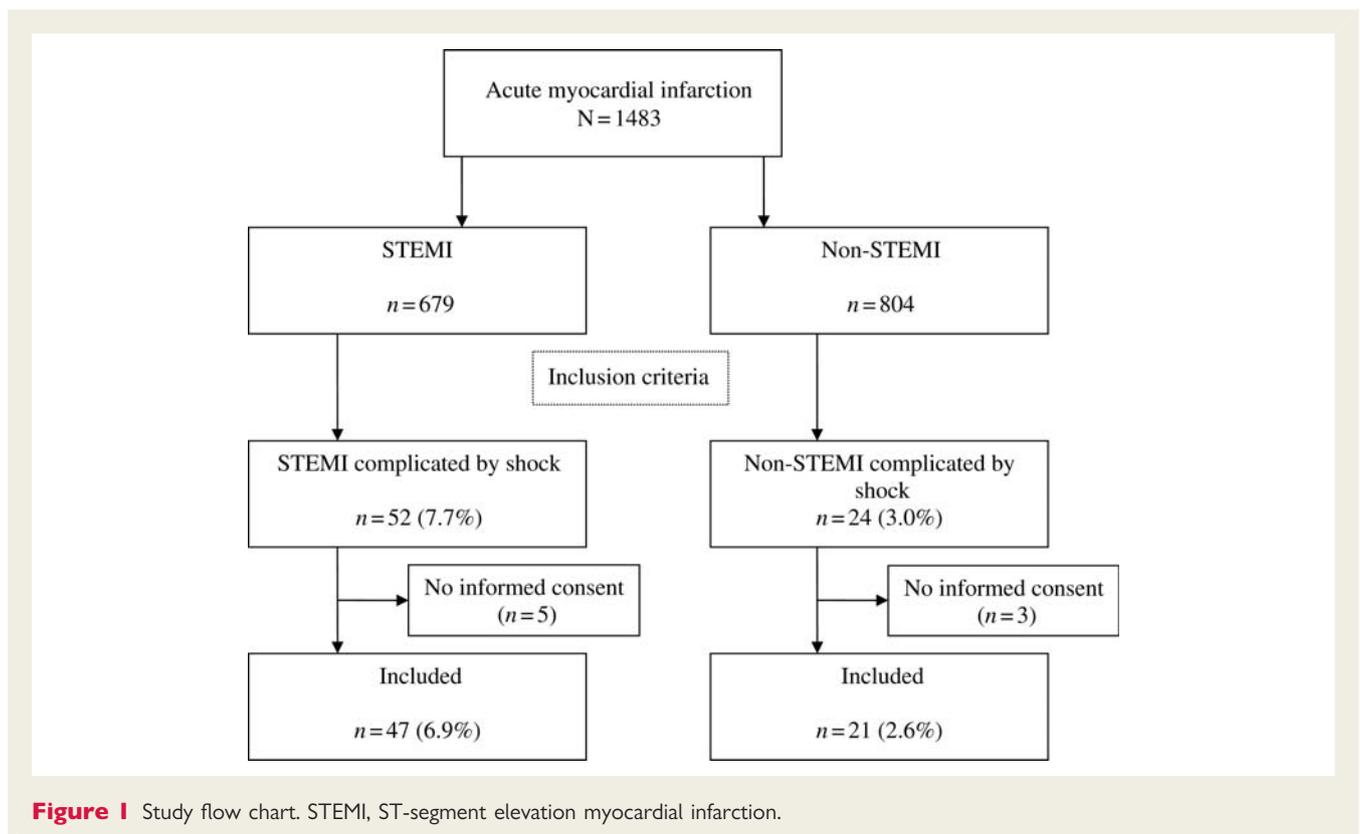
blood pressure < 90 mmHg) induced by heart failure together with the clinical signs of hypoperfusion (i.e. cold extremities, oliguria, or altered mental state), not responsive to fluid resuscitation.<sup>4</sup> The institutional ethical committee approved the protocol, and written informed consent was 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.<sup>19</sup>

### 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<sub>2</sub>). When no PAC was available, we estimated SvO<sub>2</sub> by measuring venous oxygen saturation from blood sampled from the central venous line. Systemic vascular resistance was calculated as  $(MAP - CVP) \times 80 / \text{cardiac output}$ . Cardiac power index (CPI) was computed as  $MAP \times CI / 451$ . Glomerular filtration rate was estimated by the modification of diet in renal disease equation.



## 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.<sup>20</sup> 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.<sup>21,22</sup> 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.<sup>23–25</sup> Capillaries were defined as microvessels with a diameter  $<20\ \mu\text{m}$ . 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.  $\geq 11.7\ \text{mm mm}^{-2}$  (2.5 percentile).<sup>26,27</sup>

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.<sup>25,28–30</sup> In addition, Arnold *et al.*<sup>30</sup> 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.<sup>14,31</sup> The total SOFA score was calculated by summing the scores for each of the components (i.e. cardiac, renal, respiratory, coagulation, and liver).<sup>32</sup>

## 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  $\pm$  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  $\leq$  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.<sup>25,26,33–35</sup> 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  $0.10\ \text{W m}^{-2}$ .<sup>33</sup> 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  $60 \pm 14$  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  $10.3\ \text{mm mm}^{-2}$  (range:  $4.3$ – $15.9\ \text{mm mm}^{-2}$ ; please note the Supplementary material online for video samples of high- and low-sublingual PCD). Patients with PCD  $\leq$  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  $\leq$  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  $\leq$  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 <sup>a</sup> (n = 35)	PCD > median <sup>a</sup> (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 <sup>b</sup> [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 <sup>-1</sup> )	6.6 (5.9–7.7)	6.6 (5.8–7.7)	6.6 (6.0–7.7)	0.78
WBC count (× 10 <sup>9</sup> L <sup>-1</sup> )	11.9 (9.8–17.3)	12.9 (9.8–18.0)	11.4 (8.8–17.1)	0.35
CRP (mg L <sup>-1</sup> )	55 (15–138)	55 (18–136)	49 (9–149)	0.81
GFR (mL min <sup>-1</sup> )	58 (37–83)	55 (39–77)	66 (33–90)	0.55
NT-proBNP (pg mL <sup>-1</sup> )	3775 (1316–9140)	4127 (1958–10,873)	2839 (1186–8653)	0.54
Peak creatine kinase (U L <sup>-1</sup> )	3455 (403–6786)	3891 (355–7221)	3093 (413–5948)	0.47
Peak Troponin T (μg L <sup>-1</sup> )	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 <sup>c</sup>	27 (40)	16 (46)	11 (33)	0.31
Dopa > 5 or Norepi ≤ 0.1 <sup>c</sup>	16 (24)	6 (17)	10 (30)	
Dopa > 15 or Norepi > 0.1 <sup>c</sup>	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 <sup>a</sup> (n = 35)	PCD > median <sup>a</sup> (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 pro-B-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.  
<sup>a</sup>Median PCD = 10.3 mm mm<sup>-2</sup>.

<sup>b</sup>Systolic blood pressure < 90 mmHg and clinical signs of hypoperfusion.

<sup>c</sup>Dosages in μg kg<sup>-1</sup> min<sup>-1</sup>.

**Table 2 Baseline haemodynamic parameters**

	All patients (n = 68)	PCD ≤ median <sup>a</sup> (n = 35)	PCD > median <sup>a</sup> (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) <sup>b</sup>	21 (16–24)	23 (18–25)	18 (14–22)	0.04
MPAP (mmHg) <sup>b</sup>	28 (24–34)	30 (24–37)	27 (24–30)	0.18
CI (L min <sup>-1</sup> m <sup>-2</sup> )	2.5 (2.1–2.9)	2.4 (1.8–2.9)	2.7 (2.1–2.9)	0.44
CPI (W m <sup>-2</sup> )	0.35 (0.26–0.42)	0.33 (0.24–0.39)	0.38 (0.30–0.42)	0.11
SVR (dynes s cm <sup>-5</sup> )	1075 (825–1242)	1075 (798–1237)	1052 (850–1256)	0.79
SvO <sub>2</sub> (%)	66 (61–73)	65 (60–70)	68 (62–75)	0.12
Lactate (mmol L <sup>-1</sup> )	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; SvO<sub>2</sub>, central-venous oxygen saturation.

<sup>a</sup>Median PCD = 10.3 mm mm<sup>-2</sup>.

<sup>b</sup>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 ( $\Delta$ SOFA;  $\rho = -0.25$ ,  $P = 0.04$ ). 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<sup>-2</sup> [area under the curve of 0.72 vs. 0.69 when the median (10.3 mm mm<sup>-2</sup>) 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 ( $10.3 \pm 2.2 \text{ mm mm}^{-2}$  at T0 vs.  $10.9 \pm 2.2 \text{ mm mm}^{-2}$  at T1,  $P = 0.09$ ). At time point T0, 27% of patients had a  $\text{PCD} \geq 11.7 \text{ mm mm}^{-2}$  (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  $\text{PCD} \leq \text{median}$  at both time points had higher SOFA scores at T1 relative to patients who had a sublingual  $\text{PCD} > \text{median}$  at T0 and T1 [7 (4–8) vs. 4 (3–5),  $P = 0.03$ ]. Survival of

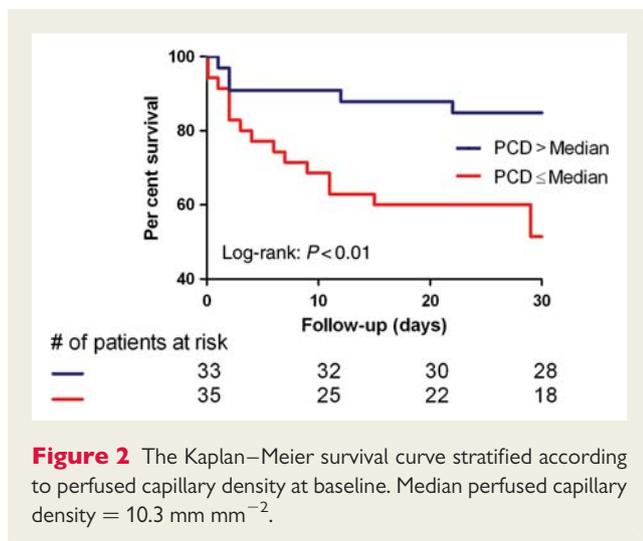
patients stratified to the level of PCD at both time points is shown in Figure 5. Patients who had a  $\text{PCD} \leq \text{median}$  at baseline, which improved at T1 ('low-high'), had a significant better prognosis when compared with patients who had a persistently low PCD ('low-low'). When patients in whom no second measurement was performed were regarded as the sicker patients (i.e.  $\text{PCD T1} \leq \text{median}$ ), results were identical. Finally, an increase in PCD was significantly associated with a better outcome (OR: 0.73, 95% CI: 0.54–0.99).

### Discussion

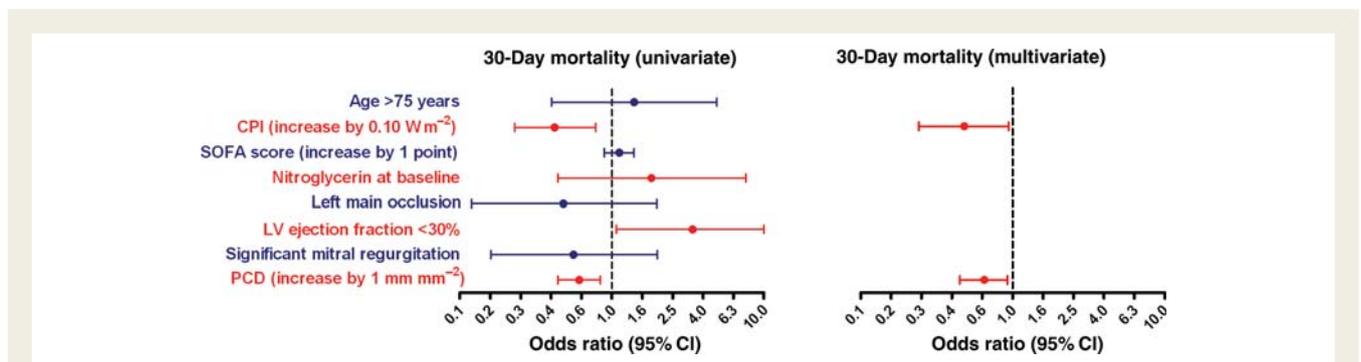
In this study, we demonstrated that patients with cardiogenic shock from acute myocardial infarction who had a sublingual  $\text{PCD} \leq \text{median}$  had a higher risk to die. Baseline PCD was a significant predictor for change in the SOFA score within the next 24 h. In addition, the sublingual 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  $\text{PCD} \leq \text{median}$  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  $\text{PCD} > \text{median}$  at both time points.

Using a semi-quantitative analysis technique, De Backer *et al.*<sup>36</sup> 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.<sup>37</sup> 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.<sup>38</sup>

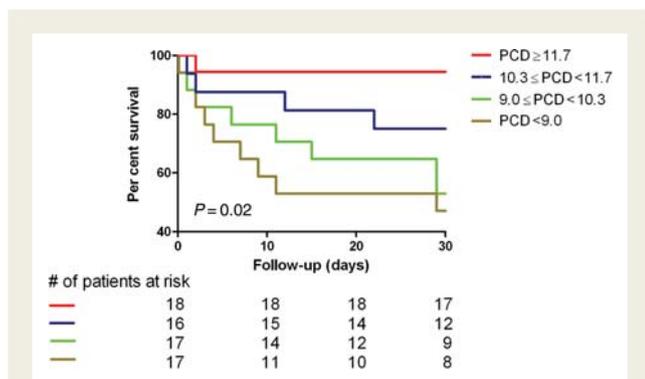
Downloaded from eurheartj.oxfordjournals.org by guest on February 13, 2011



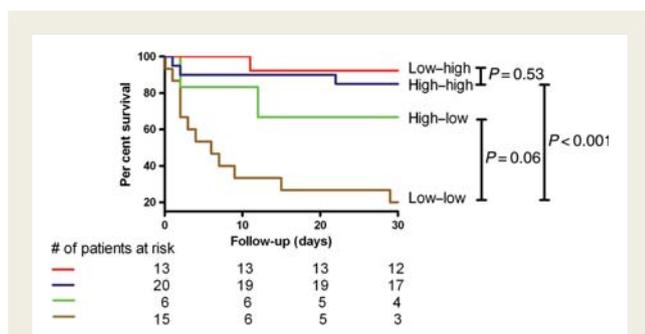
**Figure 2** The Kaplan–Meier survival curve stratified according to perfused capillary density at baseline. Median perfused capillary density =  $10.3 \text{ mm mm}^{-2}$ .



**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  $\leq$  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  $\leq$  median at T1; Low–low, perfused capillary density  $\leq$  median at T0 and perfused capillary density  $\leq$  median at T1.

Trzeciak et al.<sup>39</sup> 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  $\leq$  median at T0 as well as at T1 had the highest SOFA scores at T1.

Hasdai et al.<sup>40</sup> 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.<sup>36</sup> 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)<sup>25,26</sup> as well as by mechanical circulatory support.<sup>29</sup> 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.<sup>41</sup> 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.<sup>16,36,42,43</sup> 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.

## References

- Wu AH, Parsons L, Every NR, Bates ER. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMII-2). *J Am Coll Cardiol* 2002;**40**:1389–1394.
- Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. *Circulation* 2009;**119**:1211–1219.
- Cheng JM, Valk SDA, den Uil CA, van der Ent M, Lagrand WK, van de Sande M, van Domburg RT, Simoons ML. Usefulness of intra-aortic balloon pump counterpulsation in patients with cardiogenic shock from acute myocardial infarction. *Am J Cardiol* 2009;**104**:327–332.
- Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;**29**:2388–2442.
- Lim N, Dubois MJ, De Backer D, Vincent JL. Do all nonsurvivors of cardiogenic shock die with a low cardiac index? *Chest* 2003;**124**:1885–1891.
- Cheng JM, Den Uil CA, Hoeks SE, Van der Ent M, Jewbali LS, Van Domburg RT, Serruys PW. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. *Eur Heart J* 2009;**30**:2102–2108.
- Kohsaka S, Menon V, Lowe AM, Lange M, Dzavik V, Sleeper LA, Hochman JS. Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Arch Intern Med* 2005;**165**:1643–1650.
- Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation* 2008;**117**:686–697.
- Hasper D, Hummel M, Kleber FX, Reindl I, Volk HD. Systemic inflammation in patients with heart failure. *Eur Heart J* 1998;**19**:761–765.
- Reilly PM, Wilkins KB, Fuh KC, Haglund U, Bulkley GB. The mesenteric hemodynamic response to circulatory shock: an overview. *Shock* 2001;**15**:329–343.
- Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, Bennett ED. Base excess and lactate as prognostic indicators for patients admitted to intensive care. *Intensive Care Med* 2001;**27**:74–83.
- Geppert A, Dorninger A, Delle-Karth G, Zorn G, Heinz G, Huber K. Plasma concentrations of interleukin-6, organ failure, vasopressor support, and successful coronary revascularization in predicting 30-day mortality of patients with cardiogenic shock complicating acute myocardial infarction. *Crit Care Med* 2006;**34**:2035–2042.
- Nicholls SJ, Wang Z, Koeth R, Levison B, DelFraino B, Dzavik V, Griffith OW, Hathaway D, Panza JA, Nissen SE, Hochman JS, Hazen SL. Metabolic profiling of arginine and nitric oxide pathways predicts hemodynamic abnormalities and mortality in patients with cardiogenic shock after acute myocardial infarction. *Circulation* 2007;**116**:2315–2324.
- Jarai R, Fellner B, Haoula D, Jordanova N, Heinz G, Delle-Karth G, Huber K, Geppert A. Early assessment of outcome in cardiogenic shock: Relevance of plasma N-terminal pro-B-type natriuretic peptide and interleukin-6 levels. *Crit Care Med* 2009;**37**:1837–1844.
- Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation* 2003;**107**:2998–3002.
- den Uil CA, Klijn E, Lagrand WK, Brugts JJ, Ince C, Spronk PE, Simoons ML. The microcirculation in health and critical disease. *Prog Cardiovasc Dis* 2008;**51**:161–170.
- Ware LB, Matthay MA. Measuring microvascular blood flow in sepsis—a continuing challenge. *Lancet* 2002;**360**:1187–1188.
- Struijker-Boudier HA, Rosei AE, Bruneval P, Camici PG, Christ F, Henrion D, Lévy BI, Pries A, Vanoverschelde JL. Evaluation of the microcirculation in hypertension and cardiovascular disease. *Eur Heart J* 2007;**28**:2834–2840.
- Cuschieri J, Rivers EP, Donnino MW, Katilios M, Jacobsen G, Nguyen HB, Pamukov N, Horst HM. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. *Intensive Care Med* 2005;**31**:818–822.
- Goedhart PT, Khalilzade M, Bezemer R, Merza J, Ince C. Sidestream Dark Field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. *Opt Express* 2007;**15**:15101–15114.
- Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF. Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet* 2002;**360**:1395–1396.
- De Backer D, Hollenberg S, Boerma C, Goedhart P, Büchele G, Ospina-Tascon G, Dobbe I, Ince C. How to evaluate the microcirculation: report of a round table conference. *Crit Care* 2007;**11**:R101.
- Hubble SM, Kyte HL, Gooding K, Shore AC. Variability in sublingual microvessel density and flow measurements in healthy volunteers. *Microcirculation* 2009;**16**:183–191.
- Dobbe JG, Streekstra GJ, Atasever B, van Zijderveld R, Ince C. Measurement of functional microcirculatory geometry and velocity distributions using automated image analysis. *Med Biol Eng Comput* 2008;**46**:659–670.
- den Uil CA, Caliskan K, Lagrand WK, van der Ent M, Jewbali LS, van Kuijk JP, Spronk PE, Simoons ML. Dose-dependent benefit of nitroglycerin on microcirculation of patients with severe heart failure. *Intensive Care Med* 2009;**35**:1893–1899.
- den Uil CA, Lagrand WK, Spronk PE, van der Ent M, Jewbali LS, Brugts JJ, Ince C, Simoons ML. Low-dose nitroglycerin improves microcirculation in hospitalized patients with acute heart failure. *Eur J Heart Fail* 2009;**11**:386–390.
- den Uil CA, Lagrand WK, Spronk PE, van Domburg RT, Hofland J, Lüthen C, Brugts JJ, van der Ent M, Simoons ML. Impaired sublingual microvascular perfusion during surgery with cardiopulmonary bypass: a pilot study. *J Thorac Cardiovasc Surg* 2008;**136**:129–134.
- Boerma EC, Koopmans M, Konijn A, Kaferova K, Bakker AJ, van Roon EN, Buter H, Bruins N, Egbers PH, Gerritsen RT, Koetsier PM, Kingma WP, Kuiper MA, Ince C. Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: a double-blind randomized placebo controlled trial. *Crit Care Med* 2009;**38**:93–100.
- den Uil CA, Maat AP, Lagrand WK, van der Ent M, Jewbali LS, van Thiel RJ, Spronk PE, Simoons ML. Mechanical circulatory support devices improve tissue perfusion in patients with end-stage heart failure or cardiogenic shock. *J Heart Lung Transpl* 2009;**28**:906–911.
- Arnold RC, Parrillo JE, Phillip Dellinger R, Chansky ME, Shapiro NI, Lundy DJ, Trzeciak S, Hollenberg SM. Point-of-care assessment of microvascular blood flow in critically ill patients. *Intensive Care Med* 2009;**35**:1761–1766.
- Vincent JL, Angus DC, Artigas A, Kalil A, Basson BR, Jamal HH, Johnson G, Bernard GR. Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. *Crit Care Med* 2003;**31**:834–840.
- Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;**22**:707–710.
- Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG, Lejemtel TH, Cotter G. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. *J Am Coll Cardiol* 2004;**44**:340–348.
- Garcia-Alvarez A, Arzamendi D, Loma-Osorio P, Kiamco R, Masotti M, Sionis A, Betriu A, Brugada J, Bosch X. Early risk stratification of patients with cardiogenic shock complicating acute myocardial infarction who undergo percutaneous coronary intervention. *Am J Cardiol* 2009;**103**:1073–1077.
- Picard MH, Davidoff R, Sleeper LA, Mendes LA, Thompson CR, Dzavik V, Steingart R, Gin K, White HD, Hochman JS. Echocardiographic predictors of survival and response to early revascularization in cardiogenic shock. *Circulation* 2003;**107**:279–284.
- De Backer D, Creteur J, Dubois MJ, Sakr Y, Vincent JL. Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. *Am Heart J* 2004;**147**:91–99.
- De Backer D, Ortiz JA, Salgado D. Coupling microcirculation to systemic hemodynamics. *Curr Opin Crit Care* 2010;**16**:250–254.
- Kaluski E, Milo-Cotter O, Cotter G. Death and life are in the power of the tongue. *Cardiology* 2009;**114**:39–41.
- Trzeciak S, McCoy JV, Dellinger RP, Arnold RC, Rizzuto M, Abate NL, Shapiro NL, Parrillo JE, Hollenberg SM. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. *Intensive Care Med* 2008;**34**:2210–2217.
- Hasdai D, Holmes DR, Califf RM, Thompson TD, Hochman JS, Pfisterer M, Topol EJ. Cardiogenic shock complicating acute myocardial infarction: predictors of death. GUSTO Investigators. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. *Am Heart J* 1999;**138**:21–31.
- Spanos A, Jhanji S, Vivian-Smith A, Harris T, Pearse RM. Early microvascular changes in sepsis and severe sepsis. *Shock* 2010;**33**:387–391.
- Klijn E, Den Uil CA, Bakker J, Ince C. The heterogeneity of the microcirculation in critical illness. *Clin Chest Med* 2008;**29**:643–654.
- Wan Z, Ristagno G, Sun S, Li Y, Weil MH, Tang W. Preserved cerebral microcirculation during cardiogenic shock. *Crit Care Med* 2009;**37**:2333–2337.