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Risk indicators for acute kidney injury in cardiogenic shock

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ABSTRACT

Purpose: In critical illness, the relation between the macrocirculation, microcirculation and organ dysfunction, such as acute kidney injury (AKI), is complex. This study aimed at identifying predictors for AKI in patients with cardiogenic shock.
Materials and methods: Thirty-nine adult cardiogenic shock patients, with an admission creatinine <200 μmol l^{-1}, and whose microcirculation was measured within 48 h were enrolled. Patient data were analyzed if AKI stage ≥1 developed according to the Kidney Disease/Improving Outcomes classification within 48 h after admission. Variables with a $p < .05$ in the univariate analysis were considered for analysis with logistic regression.
Results: Twenty-four patients (61.5%) developed AKI within 48 h. The group that developed AKI had higher central venous pressures (CVP), lower diastolic arterial blood pressures and mean perfusion pressures, higher maximum ventilator pressures as well as positive end expiratory pressures and were treated with higher dosages of dobutamine. There was no difference of the microcirculation. In the multivariate logistic regression analysis, CVP was the only independent predictor for AKI (OR 1.241; 95% CI 1.030–1.495; $p = .023$).
Conclusions: In this population of patients with cardiogenic shock, CVP was associated with the development of AKI.

1. Introduction

Acute kidney injury (AKI) is a serious complication in critically ill patients, associated with an increased risk of morbidity and mortality [1-3]. Many potential risk factors of AKI have been described [4,5], including hemodynamic changes and mechanical ventilation [6]. In critically ill patients, the relation between the macrocirculation, microcirculation and organ dysfunction is not always predictable [7,8]. In the last few years it has become clear that the central venous pressure (CVP) might have in important role in the development of AKI. Several studies of patients with sepsis have shown an association between a higher CVP, impairment of the microcirculation and new onset of AKI [9,10]. Other studies of patients in heart failure also have demonstrated that an increased CVP was associated with the development of AKI [11-13]. The last decade, measurements of the sublingual microcirculation have received much attention in critical care. So far, no clinical studies were published that examined the relation between the development of AKI and changes in the microcirculation.

The purpose of this study was to test the hypothesis that global hemodynamic parameters, impaired sublingual capillary density (PCD) and airway pressures may be associated with new onset AKI in cardiogenic shock patients.

2. Patients and methods

We used a cohort of 104 cardiogenic shock patients consecutively admitted to the Intensive Cardiac Care Unit (ICCU). Cardiogenic shock was defined as: hypotension (a systolic blood pressure < 90 mmHg) associated with heart failure and clinical signs of hypoperfusion, i.e. cold extremities, oliguria or altered mental state. From this cohort we selected patients who stayed in the ICCU for >48 h. Also, the sublingual microcirculation had to be measured within the first 48 h after admission. We defined the time of admission as the moment that monitoring of vital parameters in the ICCU started. We excluded patients with

Abbreviations: AKI, acute kidney injury; AMI, acute myocardial infarction.; BP, blood pressure.; CI, confidence interval.; CMP, cardiomyopathy.; CVP, central venous pressure.; CVVH, continuous venovenous hemofiltration.; IABP, intraaortic balloon pump.; ICCU, intensive cardiac care unit.; IQR, interquartile range.; IV, intravenous.; KDIGO, kidney disease/improving global outcomes.; MMC, measurement of the microcirculation.; OHCA, out of hospital cardiac arrest.; OR, odds ratio.; PAC, pulmonary artery catheter.; PCD, perfused capillary density.; PCI, percutaneous coronary intervention.; PEEP, positive end expiratory pressure.; Pmax, maximum pressure.; RRT, renal replacement therapy.; SOFA, sequential organ failure assessment.; SVR, systemic vascular resistance.; VA-ECMO, veno arterial extracorporeal membrane oxygenation..

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significant kidney failure at presentation, that we defined as an admission serum creatinine of >200 μmol L^{-1} (2.26 mg dl^{-1}).

The data were prospectively collected between November 2007 and April 2009 in the ICCU by one of the authors (CU). The institutional ethical committee approved the protocol (MEC-2006-352) and written informed consent was obtained from each patient, or, if patients were sedated or otherwise unable to communicate, from a legal representative. Out of the original 104 patients in the cohort, a selection of 68 patients that presented with an acute myocardial infarction were used for a different publication [14].

The clinical endpoint was the development of AKI stage ≥1 (an increase in serum creatinine of 26.5 μmol l^{-1} or ≥ 0.3 mg dl^{-1}) according to the Kidney Disease/Improving Global Outcomes (KDIGO) classification [15] within the first 48 h after admission into the ICCU. We did not use the urine output criteria, because prehospital administration of diuretics may be an important confounder in this population [16], and these data were not available. We defined the baseline creatinine as the lowest serum creatinine during the whole stay in the hospital, because we did not have a pre-hospital serum creatinine in a majority of the patients [17]. When renal replacement therapy (RRT) was started, we used the lowest serum creatinine before starting RRT as baseline.

All measurements were performed at the same time point that the sublingual microcirculation was measured. Data were retrieved from electronic medical records. These data were automatically collected and stored each hour during the stay of the patient in the ICCU. Creatinine plasma levels were collected within 2 h prior or after the time the microcirculation was measured. Blood samples collected at hospital admission were obtained within 1 h after arrival. All creatinine values used in the analyses were obtained within 48 h after hospital admission, except the majority of the lowest creatinine values during hospital stay that, per definition, were used as the baseline.

The perfused capillary density (PCD) was measured using a Sidestream Dark Field imaging device (MicroScan; Microvision Medical, Amsterdam, the Netherlands). The PCD was calculated dividing the total length of the perfused capillaries in mm, divided by the image area in mm2. Perfused capillaries were defined as capillaries that had the following flow classifications obtained by visual inspection: sluggish, continuous, or hyperdynamic as described previously [14]. PCD measurements were carried out at 3–6 different sublingual locations. The reported PCD is the mean of those measurements. The heterogeneity was calculated as the difference between the highest and lowest PCD divided by the mean PCD. As a reference, the PCD in patients waiting for cardiac surgery that were not in shock was ≥11.7 mm mm^{-2}.

The arterial blood pressure was measured with a radial artery catheter and the cardiac index with a pulmonary artery catheter (PAC). If no PAC was available, in 11 out of 39 patients (28.2%), the cardiac index was calculated according to the Cuschieri formula with blood drawn from a central venous catheter placed in the right jugular vein [18].

In patients that were not mechanically ventilated, we assumed a pressure of 0 cm of H_2O for the maximum pressure (Pmax) and positive end expiratory pressure (PEEP).

Continuous data are summarized as medians with interquartile ranges (25–75% range, IQR) and categorical data as numbers with percentages. Because most variables did not have a normal distribution, we used the Mann-Whitney *U* test for continuous data and the chi-squared test (Fisher exact, 2-sided) for categorical data. The Wilcoxon signed rank test was used to compare paired variables. We used a stepwise multivariable logistic regression model with backward elimination and a probability for entry of 0.05 and removal of 0.10. Results of the regression analysis are presented in odds ratios with 95% confidence intervals (CI). We included in the regression analysis variables that were relevant for answering the objective of this study and were significant with a p of <0.05 in the univariate analysis. To differentiate between the main analysis in which we defined the baseline creatinine as the lowest serum creatinine during the whole stay in the hospital, a sensitivity analysis was performed with serum creatinine at hospital admission as baseline. An additional sensitivity analysis was performed, excluding 7 patients who reached the AKI threshold at the moment of the measurement of the microcirculation. For computing correlations, the Pearson's correlation was used. A $p < .05$ was considered statistically significant. All statistical analyses were performed with IBM SPSS statistics version 24.

3. Results

In 75 patients of the 104 patients in the cohort, the sublingual microcirculation was measured within 48 h after admission into the ICCU and hospital admission lasted for at least 48 h. Ten of the 75 patients had an admission serum creatinine of >200 μmol l^{-1} (2.26 mg dl^{-1}) and were excluded. One patient had received a kidney transplant 6 months before admission in the ICU and was also excluded. Of the remaining 64 patients, 25 were excluded because they had AKI at admission when the lowest creatinine was used during the whole hospital stay as baseline. Ultimately, 39 patients were analyzed in this study (Fig. 1).

The baseline characteristics are presented in Table 1. Of the total of 39 patients, 24 (61.5%) developed AKI in the first 48 h after ICCU admission. We found no difference for gender, age and 30-day mortality between the groups that did and did not develop AKI. The sequential organ failure assessment (SOFA) score was higher in the group that developed AKI, but not the SOFA score without the renal component.

The admission creatinine was comparable between the groups that developed and did not develop AKI (Table 2). The highest creatinine concentration in the first 48 h after admission was 154 μmol l^{-1} (1,7 mg dl^{-1}) for the group that developed AKI and 90 μmol l^{-1} (1 mg dl^{-1}) for the group that did not developed AKI ($p < .001$). The use of intravenous contrast was not different between the two groups.

The median (IQR; range) time between ICCU admission and the measurement of the microcirculation was 17 (14; 8–22) hours (Table 1). We found a lower diastolic arterial blood pressure (52 vs. 66 mmHg, $p = .028$) and mean perfusion pressure (53 vs. 68 mmHg, $p = .027$) in the group that did develop AKI (Table 3). The central venous pressure (CVP) was 3.5 mmHg higher in the group that developed AKI (15.5 vs. 12 mmHg, $p = .018$). For most patients, we had a second measurement of CVP, 24 h after the initial measurement of the microcirculation. The result was that CVP did not change (so was static) in both AKI and non-AKI patients. In the group that developed AKI, patients received higher dosages of dobutamine (0 vs. 4.7 μg kg^{-1} min^{-1}, $p = .02$). No differences were found for cardiac index, systolic arterial blood pressure and PCD.

Twenty-eight (72%) of the 39 patients were mechanically ventilated at the time of the measurements (Table 4). Pmax (23 vs. 16 cm H_2O, $p = .039$) and PEEP (10 vs. 5 cm H_2O, $p = .021$) were both higher in the group that developed AKI.

In the regression analysis we included the CVP, diastolic blood pressure, PEEP and use of dobutamine. Because of multicollinearity between PEEP and Pmax (Pearson correlation 0.946) we included only PEEP. The Pearson's correlation coefficient between CVP and PEEP was 0.599. In the multivariate analysis (Table 5), CVP was associated with AKI (OR 1.241; 95% CI 1.030–1.495; $p = .023$).

We performed a sensitivity analysis using the creatinine concentrations at hospital admission as baseline. In this analysis ($n = 39$) we could include the same variables that were significantly different between AKI and non-AKI patients as in the original analysis (data not shown). 20 out of 39 (51.3%) had AKI. In this sensitivity analysis, CVP remained solely associated with AKI (OR 1.246; CI 1.029–1.507; $p = .024$).

Out of 24 patients who developed AKI, 7 had AKI around the moment the microcirculation was measured. We investigated whether there was a difference in CVP's between the 7 patients that did and the 17 patients that did not yet meet the threshold of AKI at the time the microcirculation was measured. There was no difference. In an additional sensitivity analysis, excluding the 7 patients who reached the AKI threshold at the moment of the measurement of the microcirculation,

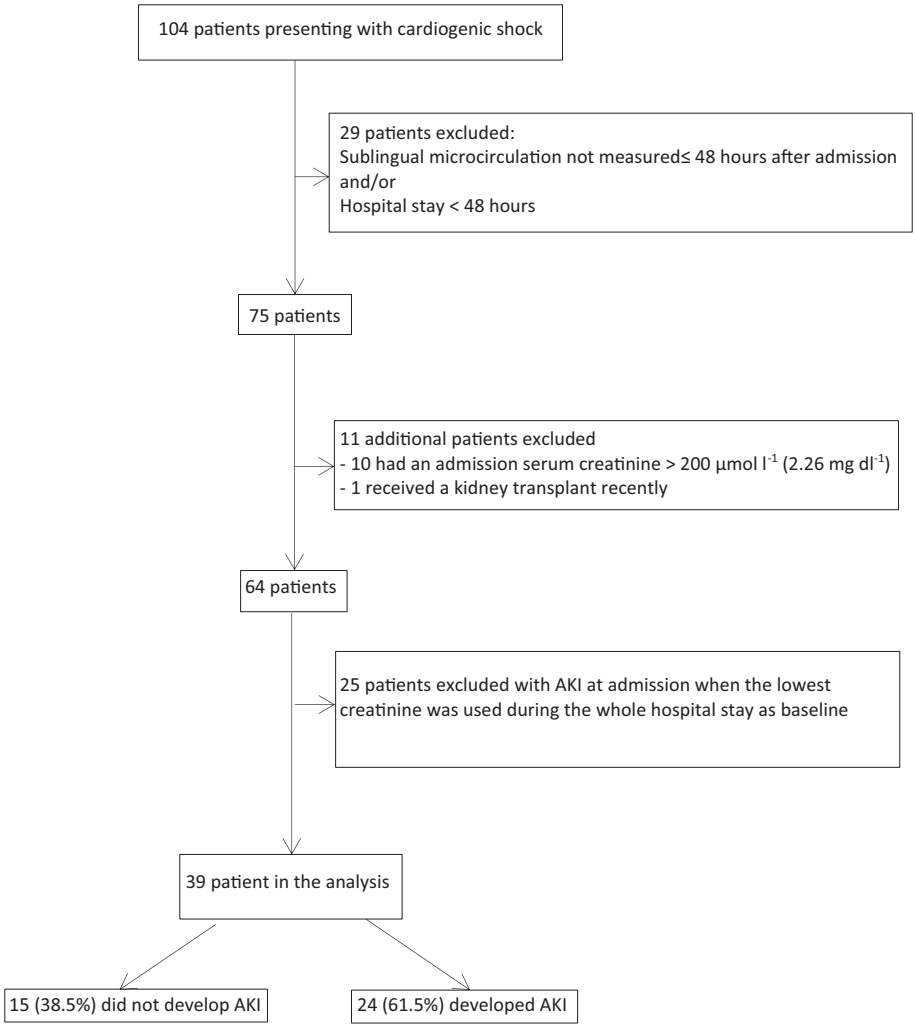

Fig. 1. Flow diagram of the selection of patients

CVP and dobutamine use were significantly different between AKI and non-AKI patients (data not shown). In this second analysis CVP was, accordingly, solely associated with AKI (OR 1.226; 95% CI 1.008–1.491; $p = .041$).

4. Discussion

In this study, we found that a higher CVP, Pmax, PEEP and dobutamine use on the one hand, and a lower diastolic arterial blood pressure

Table 1
Baseline characteristics.

	Total	No AKI	AKI	*P*
	39	15 (38.5%)	24 (61.5%)	
Male, n	21(54%)	11(73%)	10(42%)	0.098
Age, years	61(24)	54(18)	64(17)	0.057
Weight, kg	75(17)	80(25)	75(13)	0.921
Length stay ICCU, days	4(7)	4(9)	4(6)	0.931
Length stay Hospital, days	9(12)	10(28)	8(12)	0.184
Etiology cardiac failure, n				0.155
-AMI	27(69%)	13(87%)	14(58%)	
-CMP	8(21%)	1(7%)	7(29%)	
-Valve	2(5%)	1(7%)	1(4%)	
-Postoperative	2(5%)	0(0%)	2(8%)	
OHCA, n	13(33%)	4(27%)	9(38%)	0.728
Diabetes, n	7(18%)	3(20%)	4(17%)	1
Hypertension, n	16(41%)	4(27%)	12(50%)	0.192
SOFA calculated at time MMC, points	5(3)	3(4)	5(4)	0.029
SOFA, without renal component, calculated at time MMC, points	5(3)	3(5)	5(3)	0.051
30-day mortality, n	10(26%)	1(7%)	9(38%)	0.057
Time between admission and MMC, hours	17(14)	18(12)	17(14)	0.285

Categorical variables in n (%), continuous variables in median (IQR). AKI: acute kidney injury, ICCU: intensive cardiac care unit, AMI: acute myocardial infarction, CMP: cardiomyopathy, OHCA: out of hospital cardiac arrest, SOFA: sequential organ failure assessment, MMC: measurement of microcirculation.

Table 2
Kidney variables.

	Total	No AKI	AKI	*P*
	39	15 (38.5%)	24 (61.5%)	
Creatinine at admission, μmol l^{-1}	91(39)	85(44)	95(40)	0.279
Creatinine around moment of MMC, μmol l^{-1}	91(68)	85(59)	126(64)	0.012
Creatinine, lowest during hospital stay, μmol l^{-1}	85(40)	70(43)	88(37)	0.179
Creatinine, highest during first 48H, μmol l^{-1}	131(80)	90(55)	154(72)	<0.001
CVVH during hospital stay, n	2(5%)	0(0%)	2(8%)	0.514
Stages of AKI, n				<0.001
-Stage 0	15(39%)	15(100%)	0(0%)	
-Stage 1	17(44%)	0(0%)	17(71%)	
-Stage 2	4(10%)	0(0%)	4(17%)	
-Stage 3	3(8%)	0(0%)	3(13%)	
IV contrast, n	26(67%)	11(73%)	15(63%)	0.728
Contrast used for, n				0.810
-No contrast	13(33%)	4(27%)	9(38%)	
-PCI	24(62%)	11(73%)	13(54%)	
-CT-scan	1(3%)	0(0%)	1(4%)	
-Other	1(3%)	0(0%)	1(4%)	

Categorical variables in n (%), continuous variables in median (IQR). AKI: acute kidney injury, MMC: measurement of microcirculation, CVVH: continuous venovenous hemofiltration, IV: intravenous, PCI: percutaneous coronary intervention.

Table 3
Hemodynamic variables.

	Total	No AKI	AKI	*P*
	39	15 (38.5%)	24 (61.5%)	
Ejection Fraction <30% ($n = 19$)	17(90)	6(86)	11(92)	1
Cardiac Index, l min^{-1} m^{-2} ($n = 38$)	2.1(1.1)	2.2(0.8)	2.0(1.2)	0.952
Heart rate, beats min^{-1}	94(32)	94(27)	97(37)	0.583
Systolic arterial blood pressure, mmHg	104(18)	104(20)	105(21)	0.795
Diastolic arterial blood pressure, mmHg	54(21)	66(28)	52(10)	0.028
Mean arterial blood pressure, mmHg	69(18)	80(27)	68(17)	0.034
Central Venous Pressure, mmHg (n = 38)	14.0(5)	12.0(4)	15.5(4)	0.018
Central Venous Pressure, 24 h after MMC, mmHg ($n = 37$)	13(6)	12(4)	15(7)	0.159
Mean perfusion pressure, (MAP-CVP), mmHg (n = 38)	58(25)	68(38)	53(23)	0.027
Systolic perfusion pressure, ($P_{systolic}$-CVP), mmHg, (n = 38)	95(21)	93(25)	95(20)	0.940
Diastolic perfusion pressure, ($P_{diastolic}$-CVP) (n = 38)	41(20)	56(33)	40(10)	0.056
Systolic pulmonary pressure, mmHg ($n = 28$)	38(15)	36(17)	38(13)	0.654
Diastolic pulmonary pressure, mmHg (n = 28)	21(8)	21(7)	23(8)	0.813
Mean pulmonary pressure, mmHg (n = 28)	29(11)	27(12)	30(8)	0.540
Wedge pressure, mmHg (n = 28)	20(8)	17(8)	21(6)	0.850
Systemic vascular resistance, dynes-s cm^{-5} (n = 37)	1156 (637)	1354 (660)	1071(514)	0.143
S(c)VO2 ($n = 36$)	0.68 (0.12)	0.65(0.09)	0.69(0.11)	0.153
Lactate, mmol l^{-1} (n = 37)	1.2(1,6)	1.2(0.8)	1.2(2.1)	0.285
Perfused Capillary Density, mm mm^{-2}	10.4 (3.1)	10.3(3.2)	10.0(3.2)	0.862
Heterogeneity of Perfused Capillary Density	0.24 (0.20)	0.25(0.23)	0.19(0.22)	0.897
Core temperature, °C (n = 36)	37.0 (3.3)	37.2(1.2)	36.3(4.2)	0.174
T difference central/periphery (n = 28)	6.4(4.5)	6.4(3.5)	6(5.6)	0.659
Hypothermia, n	10(28%)	4(27%)	6(29%)	1
IABP, n	12(31%)	4(27%)	8(33%)	0.734
VA-ECMO, n	2(5%)	2(13%)	0(0%)	0.142
Dobutamine, n	20(51%)	3(20%)	17(71%)	0.003
Dobutamine, μg kg^{-1} min^{-1}	2.8(5.2)	0(0)	4.7(5.5)	0.020
Norepinephrine, n	12(31%)	5(33%)	7(29%)	1
Norepinephrine, μg kg^{-1} min^{-1}	0.05 (0.09)	0.0(0.15)	0(0.09)	0.916
Dopamine, n	5(13%)	0(0%)	5(21%)	0.136
Dopamine, μg kg^{-1} min^{-1}	1.05(0)	0(0)	0(0)	0.062
Enoximone,n	5(13%)	2(13%)	3(13%)	1
Enoximone, μg kg^{-1} min^{-1}	0(0)	0(0)	0(0)	0.960
Nitroglycerine, n	6(15%)	3(20%)	3(13%)	0.658
Nitroglycerine, μg kg^{-1} min^{-1}	0(0)	0(0)	0(0)	0.646

Variables were obtained from the moment the microcirculation was measured.
Categorical variables in n (%), continuous variables in median (IQR). AKI: acute kidney injury, CVP: central venous pressure, IABP: intraaortic balloon pump, MAP: mean arterial pressure, $P_{diastolic}$: diatolic arterial pressure, $P_{systolic}$: systolic arterial pressure ECMO: venoarterial extracorporeal membrane oxygenation.

and mean perfusion pressure on the other, were associated with AKI in patients with cardiogenic shock. In the multivariate analysis, the CVP was the only variable that was significantly associated with the development of new onset AKI.

The main reason behind our arbitrary, but a priori choice to exclude patients with an admission creatinine >200 μmol l-1 was the downward convex association of serum creatinine and GFR, meaning that a small rise in serum creatinine usually reflects a marked fall in GFR when kidney function is (near) normal, whereas a large rise of serum creatinine reflects a small absolute reduction in GFR in severe (chronic) kidney failure. If there would be a correlation between any factor and AKI, we expected this correlation to be more robust when (1) true new onset AKI would develop, so when pre-existent kidney function was in the (near) normal range and when (2) microcirculation and hemodynamic measurements could be performed in patients who did not already have AKI at hospital admission.

The clinical endpoint was the development of AKI stage ≥1 according to the KDIGO classification in the first 48 h after admission. We presumed that the major hit on the kidney was the start of cardiogenic shock. We used the first 48 h after admission to the ICCU because we expected a rise in creatinine concentration, and possibly the development of AKI, within this timeframe. As explained in the methods section, we did not use the urine criteria of the KDIGO classification. When the lowest creatinine concentration during hospital stay is used as baseline, as we did in this study, it is possible to overestimate the occurrence of AKI [17]. Indeed, the sensitivity analysis showed 10% less AKI when admission creatinine was used as baseline compared to lowest creatinine concentration during hospital stay.

Out of the 24 patients who developed AKI according to our definition, 7 patients appeared to have already AKI at the moment that the microcirculation was measured. The other 17 had not yet reached the threshold of the KDIGO definition of AKI. To study risk factors in the development of new onset AKI, it is important that the measurements of those potential risk factors are carried out before the outcome develops. We therefore excluded patients who already had AKI at hospital admission. In principle, one could question why we included the 7 patients who had AKI around the time of the baseline measurements. We decided to include these patients because creatinine plasma levels were not collected exactly at the moment of assessing the other baseline measurements. We performed a sensitivity analysis excluding the 7 patients and in this analysis. CVP was still solely associated with AKI.

A reduced cardiac output is, counterintuitively, not the main cause of AKI. Recently, several authors showed that CVP, and not cardiac output, is a major risk factor for AKI [11-13]. The mechanism of the development of AKI in heart failure is complex and involves, among others, hypotension, venous congestion and neurohormonal changes [19,20]. A relation between raised CVP and mortality was described in a broad cardiovascular population [13]. In other forms of shock, like septic shock, CVP also seems to be an important factor in the development of AKI [10,21] and mortality [22]. The most likely explanation of the effect of the macrocirculation on the development of AKI is the relation between a higher CVP and a lower diastolic arterial blood pressure that causes a lower mean perfusion pressure, as was recently confirmed by Ostermann et al. [23]. However, this was not confirmed by our analysis.

Table 4
Pulmonary variables and ventilator settings.

	Total	No AKI	AKI	*P*
	39	15 (38.5%)	24 (61.5%)	
Mechanical ventilation, n	28(72%)	8(53%)	20(83%)	0.068
Mode mechanical ventilation, n				0.090
-No mechanical ventilation	11(28%)	7(47%)	4(17%)	
-Pressure controlled	23(59%)	6(40%)	17(71%)	
-Pressure support	5(13%)	2(13%)	3(13%)	
PaO2, kPa	14.1(9.4)	13.5(7.1)	14.2(9.8)	0.920
PaO2, mmHg	106(71)	101(53)	107(74)	0.920
P/F, mmHg	309(188)	335(197)	266(172)	0.299
Pmax, cm H_2O[a]	17(2)	16(22)	23(8)	0.039
Pmax, cm H_2O ($n = 28$)	12(6)	22(3)	23(7)	0.398
PEEP, cm H_2O[a]	7(2)	5(10)	10(5)	0.021
PEEP, cm H_2O ($n = 28$)	10(3)	10(3)	10(3)	0.203
Expiratory tidal volume, ml kg^{-1} ($n = 28$)	6.1(1.9)	6.4(1.2)	6.0(3)	0.309

Variables were obtained from the moment the microcirculation was measured. Categorical variables in n (%), continuous variables in median (IQR). AKI: acute kidney injury, Pmax: maximum pressure, PEEP: positive end expiratory pressure.
[a] For non-ventilated patients we assumed a pressure of 0 cm H_2O.

Contrary to our hypothesis, the sublingual PCD was not different between the groups that did and did not develop AKI. Changes in the sublingual microcirculation have been described in cardiogenic shock [14,24]. The relation between macrocirculation, microcirculation and organ failure is complex [8,25]. Differences in mortality and organ failure were described when changes in the microcirculation persisted but the macrocirculation in the meantime had resolved [26]. Inconsistent with these results, Stenberg et al. recently reported an experimental porcine model of severe cardiogenic shock [7]. They showed that in a state of deep cardiogenic shock with hypoperfusion of organs, the microcirculation is preserved and the renal and hepatic mitochondrial respiration is upregulated. They did not use any treatment to reverse the shock. They hypothesize that microvascular changes seen in some clinical studies may be due to treatment modalities like vasoactive drugs and may not be a representation of the pathophysiology of cardiogenic shock itself. An example of a potential confounder is hypothermia which can influence the microcirculation and is not always correlated to changes in macrocirculation [26,27]. One-third of the patients in this study presented with a cardiac arrest and most of them were treated with hypothermia. No difference was found between body temperatures in the groups that did and did not develop AKI (Table 3). The temperatures during the measurements were in the normal range.

PEEP and Pmax were higher in the group that developed AKI, but not after multivariate analysis. We assumed a pressure of 0 cm of H_2O for Pmax and PEEP in patients that were not mechanically ventilated. We do realize that there are negative and positive pressures generated when a patient breathes spontaneously. We assumed that the pressure variations around 0 cm of H_2O were small during spontaneous breathing without respiratory distress compared to the pressures applied with the mechanical ventilator. Patients in respiratory distress received invasive mechanical ventilation.

Table 5
Univariate and multivariate regression analysis ($n = 62$).

	Univariate			Multivariate		
	Odds ratio	95%CI	*P*	Odds ratio	95%CI	*P*
Central Venous Pressure, mmHg ($n = 38$)	1.199	1.007–1.428	0.041	1.241	1.030–1.495	0.023
Diastolic arterial blood pressure, mmHg	0.950	0.902–1.000	0.049	0.952	0.897–1.010	0.105
PEEP, cm H_2O[a]	1.180	1.017–1.369	0.029	–		
Dobutamine, μg kg^{-1} min^{-1}	1.239	0.985–1.559	0.067	1.264	0.976–1.639	0.076

CI: confidence interval. PEEP: positive end expiratory pressure.
[a] For non-ventilated patients we assumed a pressure of 0 cm H_2O.

There are several limitations of this retrospective study that need to be addressed. The study was performed 10 years ago. It is possible that current medical practice has changed, although no major novel therapeutics became available in this time frame. We included patients having a cardiogenic shock defined as a systolic blood pressure of <90 mmHg, among other symptoms. At the time the microcirculation was measured, with a median (IQR; range) of 17 (14; 8–22) hours after admission, the median (IQR) cardiac index was 2.1(1.1) L min^{-1} M^{-2} and the systolic blood pressure was normalized to 107 (21) mmHg. Therefore, initial abnormalities in the microcirculation could have been corrected by the initiated treatment. In addition, the study consists of a sample of heterogeneous etiologies of cardiogenic shock. Also, some patients were transferred to our center from other hospitals and were thus treated there for different time periods before inclusion into this study.

5. Conclusions

We could clearly show, despite aforementioned limitations, that a higher CVP, Pmax, PEEP, dosage of dobutamine, a lower diastolic arterial blood pressure and mean perfusion pressure, were all related to the development of AKI. However, in multivariable logistic regression analysis only CVP was significantly related to the development of AKI in these patients. These findings warrant interventional studies with active manipulation of CVP as an endpoint of resuscitation to prevent kidney injury.

During the preparation of the manuscript, professor A.B. Johan Groeneveld passed away after a long illness. He was not able to work on the last versions of the manuscript. He was a source of great inspiration to us and we miss him.

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