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Coronary flow reserve is associated with tissue ischemia and is an additive predictor of intensive care unit mortality to traditional risk scores in septic shock

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ABSTRACT

Background: Reduced coronary velocity flow reserve (CFR) is associated with poor outcome in patients with cardiovascular disease. We investigated whether CFR is associated with tissue ischemia and acidosis, impaired myocardial deformation and adverse outcome in patients with septic shock.
Methods: In 70 mechanically-ventilated patients with septic shock, we examined: a) S′ and E′ mitral annular velocities using tissue Doppler imaging (TDI), b) CFR of the left anterior descending artery after adenosine infusion using transesophageal Doppler echocardiography and c) lactate, pyruvate and glycerol in tissue by means of a microdialysis (MD) catheter inserted into the subcutaneous adipose tissue as markers of tissue ischemia and acidosis. SOFA and APACHE II prognostic scores and mortality in the intensive care unit (ICU) were recorded.
Results: Reduced CFR, S′ and E′ as well as increased E/E′ correlated with increased SOFA, APACHE II and MD lactate to pyruvate ratio ($p < 0.05$ for all correlations). Impaired TDI markers also correlated with increased MD glycerol ($p < 0.05$). Reduced CFR correlated with decreased E′ ($p < 0.05$). CFR was 1.8 ± 0.42 in non-survivors ($n = 34$) versus 2.08 ± 0.44 in survivors ($p = 0.007$). A CFR < 1.90 predicted mortality with sensitivity of 70% and specificity of 69% (area under the curve 77%; $p = 0.003$). CFR had an additive value to APACHE (chi-square change: 4.358, $p = 0.03$) and SOFA (chi-square change: 3.692, $p = 0.04$) for the prediction of mortality.
Conclusion: Tissue ischemia and acidosis is a common pathophysiological link between decreased CFR and impaired LV myocardial deformation in septic shock. CFR is an additive predictor of ICU mortality to traditional risk scores in septic shock.

1. Introduction

Sepsis, severe sepsis and septic shock are increasingly grave stages of the systemic inflammatory response to infection. The initial infection triggers complex inflammatory, neuroendocrine and metabolic interactions that lead to hemodynamic compromise, tissue hypoperfusion, hypoxia and acidosis. Impaired microcirculation, loss of endothelial integrity and tissue injury in combination with mitochondrial dysfunction on the subset of septic shock finally result in multiple organ failure with high rates of mortality (approximately 60%), which is the main cause of death in the intensive care unit (ICU) patients [1–3]. Traditional risk scores such as APACHE II and SOFA are widely used for assessment of outcome in ICU patients [4,5].

Sepsis and septic shock are responsible for abnormal metabolism including increased protein catabolism, lipolysis and hyperglycemia [6]. It has recently been indicated that in vivo microdialysis (MD) is a bedside advanced technique for immediate analysis of markers of ischemia and metabolic changes in the interstitial fluid of tissues [7]. Studies support that MD derived metabolic abnormalities differ in relation to sepsis severity [8].

Coronary flow reserve (CFR) is impaired on the grounds of epicardial coronary artery stenosis [9,10] or coronary microcirculatory damage due to endothelial dysfunction, perivascular fibrosis and elevated filling pressure causing extravascular compression of the small coronary arterioles (i.e., dilated cardiomyopathy, hypertension, diabetes) [11–16]. Integrity of coronary microcirculation is reliably assessed by calculating the coronary flow reserve after adenosine or dipyridamole-induced hyperemia using transthoracic or transesophageal Doppler echocardiography [9,17].

Studies have shown that CFR, as assessed by Doppler echocardiography, is associated with poor outcome in various groups of patients with

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cardiovascular related disease [11–15]. Additionally, the association of scaling values of CFR with prognosis is independent of the degree of pre-existent epicardial artery stenosis [16].

Tissue Doppler imaging (TDI) is an accurate method for assessment of subtle changes in systolic and diastolic myocardial function and longitudinal myocardial deformation [18]. Reduced CFR has been linked with impaired TDI markers of LV in hypertension [11] and diabetes [13]. Abnormal diastolic TDI markers are associated with higher in-hospital mortality in critically ill patients with preserved ejection fraction [19]. It has also been recently indicated that systolic TDI markers are also associated with outcome in septic shock patients [20].

We hypothesized that a) acidosis, hypoxia and inflammation are related with impaired endothelial function leading to reduced CFR, and b) impaired CFR is associated with myocardial dysfunction as assessed by systolic and diastolic TDI markers and consequently carries an impact on prognosis in septic shock patients. Therefore, we examined: a) coronary flow reserve (CFR) of left anterior descending coronary artery (LAD) after adenosine infusion using transesophageal echocardiography (TEE), b) systolic (S′), early (E′) and late diastolic (A′) mitral annulus velocities and E to E′ ratio (E/E′) using TDI and c) glucose and lactate, in peripheral blood samples and glucose, lactate, pyruvate and glycerol in tissue after inserting a MD catheter into the subcutaneous adipose tissue of the upper thigh of septic shock patients to assess tissue cell damage, acidosis and ischemia.

2. Methods

2.1. Study population

This prospective single-center study included serial recruitment of septic shock patients, of age older than 18 years, requiring support with mechanical ventilation and admitted in our general ICU from March 2009 to July 2012. The study was approved by the hospital's ethics committee, and informed consent was obtained from patients' relatives. Exclusion criteria included age less than 18 years, chronic heart failure (defined by known history of hospitalization due to heart failure decompensation and/or an LV ejection fraction (LVEF) of less than 50% on admission echocardiography) and coronary artery disease (CAD) (defined by patient's history, history of exertional angina, previous hospitalization for an acute ischemic syndrome, treatment with antianginal medication, ECG abnormalities indicative of previous MI or current myocardial ischemia, positive treadmill, myocardial scintigraphy and/or dobutamine stress echocardiography, presence of segmental wall motion abnormalities and/or EF less than 50% on admission echocardiography).

Patients' clinical information included age, sex, reason for admission, disease severity according to the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and degree of organ dysfunction quantified by the Sequential Organ Failure Assessment (SOFA) score. APACHE II score [4] includes history of chronic organ insufficiency or immunocompromise, presence of acute renal failure on admission, age, rectal temperature, mean arterial pressure (MAP), pH of arterial blood, heart rate, respiratory rate (spontaneous or ventilated), serum sodium and potassium, serum creatinine, hematocrit, white cell blood count, Glascow Coma Score, and A-a gradient if $FiO_2 > 0.5$ and PO_2 if $FiO_2 < 0.5$. SOFA score [5] is based on six different scores one each for the respiratory (PO_2/FiO_2), cardiovascular (MAP), hepatic (bilirubin), coagulation (platelet count), renal (serum creatinine or urine output) and neurological systems (Glascow Coma Scale). All patients were under vasopressor administration (noradrenaline). Mean arterial pressure (MAP), and central venous pressure (CVP) were also recorded. Blood gas analysis, including partial pressures of oxygen (PO_2) and carbon dioxide (PCO_2), and lactate, was also available. Sepsis, severe sepsis and septic shock were diagnosed according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee [21].

Septic shock was defined as any episode of hypotension (systolic arterial pressure of <90 mm Hg) on the substrate of infection, persistent despite adequate fluid administration and requiring vasopressors.

We chose ICU and mortality during ICU hospitalization as outcomes of interest.

2.2. Microdialysis technique

Upon ICU admission (day 1) a MD catheter (CMA 60, CMA Microdialysis AB, Stockholm, Sweden) was inserted under sterile conditions into the subcutaneous adipose tissue of the upper thigh. The length of the dialysis membrane at the distal end of the catheter was 30 mm. The cut-off value of this membrane was 20,000 Da. The catheter was continuously perfused with a lactate-free Ringer's solution (Perfusion fluid T1, CMA Microdialysis AB, Stockholm, Sweden; Na^+, 147 mM; K^+, 4 mM; Ca^{2+}, 2.3 mM; Cl^-, 156 mM; pH, 6) and was pumped at a speed of 0.3 μl/min using a CMA 106 pump (CMA Microdialysis AB, Stockholm, Sweden). The length of the MD membrane and the slow perfusion flow rate guarantee a high recovery rate for molecules up to 20,000 Da, providing thus true tissue concentrations [22,23]. The first dialysate samples were collected in microvials at the last two hours after the insertion of the catheter to avoid the effect of placement trauma on metabolite measurements. Samples were analyzed immediately for lactate by a mobile, fully automated analyzer (CMA 600 Microdialysis Analyzer, CMA Microdialysis AB, Stockholm, Sweden).

Sampling was performed 6 times per day for a maximum of 6 days from study enrollment. The exact sampling time-intervals during the day were the following: (1) 05:00–09:00; (2) 09:00–13:00; (3) 13:00–17:00; (4) 17:00–21:00; (5) 21:00–01:00; and (6) 01: 00–05:00. The daily mean values of MD measurements were calculated for each patient. Glucose, lactate, pyruvate, glycerol and lactate to pyruvate (L/P) were measured. Glucose and lactate levels were also measured in peripheral blood. MD lactate is a marker of ischemia and anaerobic metabolism [23]. Lactate to pyruvate (L/P) ratio is a marker of tissue ischemia and acidosis [8,24]. Glycerol is a marker of ischemia and cell membrane damage [23,24]. Hyperglycemia in peripheral blood reflects increased gluconeogenesis and insulin resistance, but low tissue glucose levels reflect lack of energy substrate due to tissue ischemia [25–27].

Finally, troponin T blood levels were measured in all patients on the day of admission in ICU (Roche Diagnostics Elecsys assay, Basel, Switzerland, normal values < 0.03 ng/ml).

2.3. Transesophageal echocardiography

Transesophageal echocardiography was performed within the first 48 h from ICU admission, using a transesophageal probe connected to a Vivid 4 (GE Medical Systems, Horten, Norway) ultrasound system. All studies were digitally stored in a computerized station (Echopac GE, Horten, Norway) and were analyzed by two observers (I.I. and G.M.) blinded to clinical and laboratory data. All patients had adequate images for analysis.

Transesophageal Doppler echocardiography was performed in all septic shock patients under mechanical ventilation. The left main coronary artery (LMCA) was visualized by placing the transducer at a level just above the aortic leaflets, approximately 30 cm from the teeth. The left anterior descending artery (LAD) was identified with the aid of color-wave Doppler echocardiography and was often found to be almost perpendicular to the LMCA. Coronary blood flow was recorded by pulsed-wave Doppler exploration of the LMCA. Because of cyclic cardiac movement the LMCA does not always lie in the same position throughout the cardiac cycle. However, during diastole, because of the absence of ventricular contraction, the position of the LMCA is much more stable, which makes its exploration by ultrasound methods much more feasible. Because of this, pulsed-wave Doppler sample-volume positioning was performed by considering the diastolic position of the vessel being explored. The position of the probe and the sample volume were adjusted in order to orient the Doppler signal parallel to coronary flow; angles of −30° to flow were always achieved. However, because the aim of our evaluation was the assessment of coronary flow reserve the ratio of two measured velocities, both the effect of the angle between the direction of blood flow and ultrasound beam and the absolute values of coronary flow velocities insignificantly affected the final result.

Coronary flow velocity profiles in the LAD were obtained using color-guided pulse-wave Doppler. We measured (i) resting peak diastolic coronary flow velocity, and ii) peak hyperemic diastolic velocity after adenosine infusion (140 μg/kg/min) for 3 min. CFR was calculated as the ratio of hyperemic to resting peak diastolic velocity. Measurements from three cardiac cycles were averaged. Inter- and intra-observer variability of these measurements in our laboratory were ~4 and 2%. The feasibility of recording the peak diastolic coronary flow velocity at rest and after adenosine was 100% for all patients in our study. Previous studies have defined a CFR less than 2 [28–30] as significantly abnormal, between 2 and 2.5 as borderline normal [30] and greater than 2.5 as normal [29].

2.4. Transthoracic echocardiography

Transthoracic echocardiography was performed within the first 48 h of ICU admission, before transesophageal echocardiography using a Vivid 4 (GE Medical Systems, Horten, Norway) phased-array system. Studies were digitally stored and analyzed by two observers (I.I., GM.) blinded to clinical and laboratory data using a computerized station (Echopac GE). Seventy out of 72 patients screened initially had adequate images for analysis. For the analysis of segmental wall motion abnormalities, a 16-segment protocol was used [31]. However, none of our patients showed evidence of segmental wall motion abnormalities. The following parameters were measured from cross-sectional echocardiographic images of the LV: 1) end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) (millimeters); 2) interventricular septal (IVS) thickness and posterior wall (PW) thickness (millimeters), 3) fractional shortening, 4) ejection fraction (EF) (%) and 5) left atrium dimension (millimeters). Transmitral pulsed-wave Doppler velocities were recorded in the four-chamber view with the sample volume at the tip of mitral valve leaflets.

E and A wave velocities and deceleration time of early transmitral flow velocity were measured. Myocardial velocities were recorded using color TDI to record low-velocity, high-intensity myocardial signals at a high frame rate (120 MHz). A 5-mm sample volume was placed in septal and lateral corners of the mitral annulus in the apical four-chamber views to record the systolic velocity (S′), early diastolic velocity (E′), and late diastolic velocity (A′). The mean value of the S′, E′, and A′ in the septal and lateral corners was used for analysis. The ratio of E wave of the mitral inflow measured by pulsed wave Doppler to the mean E′ was calculated as an index of LV diastolic filling pressures. All Doppler markers were measured at the end-expiration. Inter- and intra-observer variability of S′, E, and E′ were 0.7%, 1.2%, and 1.1% and 2.9%, 0.6% and 1.6%, respectively. Among 72 initially recruited patients only two had inadequate acoustic window.