Acute kidney injury is associated with microvascular myocardial damage following myocardial infarction

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Acute kidney injury (AKI) is a frequent complication in patients with ST-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention. However, the pathophysiology of AKI in this setting is complex and goes beyond the administration of contrast media. Studies assessing the impact of infarct characteristics on AKI are currently lacking. Therefore, we investigated the association of AKI with myocardial as well as microvascular injury in an initial total of 361 consecutive STEMI patients treated by primary percutaneous coronary intervention. Of these, 318 patients were included in final analysis. Serum creatinine was measured on admission as well as 24, 48, and 72 hours thereafter with AKI defined as an increase in serum creatinine of 0.3 mg/dl or more. Cardiac magnetic resonance (CMR) scans were performed in the first week after infarction, with microvascular injury visualized by late gadolinium enhancement CMR defined as any region of hypoenhancement within the hyperenhanced area of infarction. Sixteen patients developed AKI. They showed significantly lower left ventricular ejection fraction (45[interquartile range 40-52]% vs. 54[47-59]%), larger infarct size (21[15-35]% vs. 12[7-22]%) of left ventricular myocardial mass, and more frequent microvascular injury (81 vs. 46%) than those free of AKI. Meaningfully, in multivariate analysis including all CMR data, microvascular injury was the sole independent predictor of AKI (odds ratio 6.74, 95% confidence interval of 1.49-30.43). Thus, among revascularized STEMI patients, the presence of microvascular injury assessed by CMR was independently associated with an increased risk of AKI. This suggests a potential pathophysiological link between cardiac microvascular disease and renal injury following STEMI.

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Acute kidney injury (AKI) occurs in multiple clinical settings and is associated with prolonged hospital stays, as well as increased morbidity and mortality rates.[1–3] AKI is also a common complication in patients with ST-elevation myocardial infarction (STEMI) treated by contemporary primary percutaneous coronary intervention and is associated with a poorer prognosis in this setting.[3–5] Previous studies revealed contrast-induced nephropathy as major cause of AKI after primary percutaneous coronary intervention.[6] Contrary to these data, in some investigations, contrast volume did not predict the risk of AKI in patients with STEMI who had undergone revascularization.[7] These controversial findings indicate a more complex pathophysiology comprising different mechanisms eventually leading to renal impairment beyond contrast media *per se*.[8] Adverse hemodynamic conditions, metabolic changes, and alterations of the renal microvasculature caused by fibrin deposits and congestion with leukocytes have been suggested to contribute to the development of AKI.[9–11] Indeed, an analysis by Shacham *et al.*[7] disclosed left ventricular (LV) ejection fraction assessed by echocardiography as an independent predictor of AKI. However, the association between the extent of myocardial damage and myocardial microvascular injury in particular, which is strongly associated with the post-STEMI inflammatory response and adverse outcomes,[12,13] and the development of AKI is currently unknown.

Cardiac magnetic resonance (CMR) is unique in its ability to provide a noninvasive, multiparametric tissue characterization of the jeopardized and infarcted myocardium with high spatial and temporal resolution. CMR is therefore not only used as the reference standard for the assessment of cardiac volumes and function, it can also be used to accurately visualize the infarcted myocardium and detect the presence of microvascular injury.[14] Thus we aimed to evaluate the association of CMR-determined cardiac function and myocardial damage with the development of AKI after primary percutaneous coronary intervention for acute STEMI.

RESULTS

Patient characteristics and CMR findings

The flow chart of the present study is shown in detail in Figure 1. The baseline characteristics of the overall STEMI cohort ($n = 318$) are provided in detail in Table 1. Admission serum creatinine concentration was 0.94 mg/dl (range, 0.83–1.07 mg/dl), resulting in an estimated glomerular filtration rate (eGFR) of 86 ml/min per 1.73 m^2 (range, 73–100 ml/min per 1.73 $m^{2)}$. Ninety-three percent ($n = 296$) of the overall cohort showed an admission eGFR $\geq$ 60 ml/min per 1.73 m^2.

CMR scans were performed a median of 2 days (range, 2–4 days) after STEMI. The CMR parameters are listed in Table 2. Approximately one-half of the patients displayed microvascular injury ($n = 151$, 48%). Patients with microvascular injury showed significantly higher admission values of creatine kinase (CK) (316 [137 to 1385] vs. 198 [107–507] U/l, $P < 0.001$) and peak creatine kinase (2817 [1736–4254] vs. 1162 [619–2069] U/l, $P < 0.001$), peak high-sensitivity C-reactive protein (hs-CRP) (31.6 [1.63–69.1] vs. 14.8 [6.6–28.5] mg/l, $P < 0.001$), and peak N-terminal pro B-type natriuretic peptide (1146 [526–2511] vs. 593 [242–1179] ng/l, $P < 0.001$). No other parameter listed in Table 1 showed a significant association with microvascular injury (all $P > 0.05$).

Clinical parameters and AKI

Sixteen patients (5%) developed AKI. The clinical parameters of patients with and without AKI are displayed in Table 1. Patients with AKI were older ($P = 0.03$) and more frequently had diabetes ($P = 0.001$). Furthermore, the primary percutaneous coronary intervention delay for patients with AKI was significantly longer as compared with that for patients without AKI ($P = 0.03$). Age and diabetes mellitus were independently associated with AKI (Table 3). Regarding biomarkers, patients with AKI showed significantly higher admission CK ($P = 0.01$) and peak ($P = 0.02$) CK levels, peak hs-CRP ($P = 0.001$) and admission hs-CRP ($P = 0.03$) levels, and peak ($P = 0.01$) N-terminal pro B-type natriuretic peptide levels. In multivariate analysis, only the peak hs-CRP level was independently correlated with AKI ($P = 0.01$, Table 3).

Absolute or relative doses of contrast medium did not correlate with AKI (all $P > 0.33$) (Table 1).

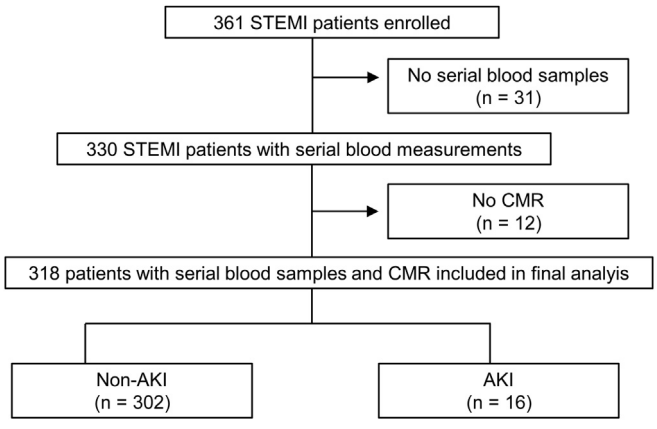

Figure 1 | Study flow chart. AKI, acute kidney injury; CMR, cardiac magnetic resonance; STEMI, ST-segment elevation myocardial infarction.

CMR parameters and AKI

Patients who developed AKI displayed lower LV ejection fraction (45% [40%–52%] vs. 54% [47%–59%], $P = 0.004$) and a larger infarct size (21% [15%–35%] vs. 12% [7%–22%] of LV myocardial mass, $P = 0.002$) than patients without AKI (Table 2). Moreover, patients with AKI were significantly more likely to have microvascular injury (81% vs. 46%, $P = 0.02$). The multivariate CMR model for the prediction of AKI is shown in Table 3. Only microvascular injury was independently related to AKI ($P = 0.01$); infarct size and LV ejection fraction did not show independent associations. The significant association of microvascular injury with AKI is further illustrated in Figure 2. Patients without microvascular injury ($n = 167$, 52%) showed AKI rates of 1.8%, whereas the patients with microvascular injury ($n = 151$, 48%) had AKI rates of 8.6% ($P = 0.006$).

Risk score and AKI

A stepwise increase in risk of AKI was observed for patients with higher risk scores ($P < 0.001$): very low (0% AKI), low (2.6% AKI), intermediate (21% AKI), and high (60% AKI) (Figure 3).

Health outcomes and AKI

Health outcome data at 12 months after STEMI were available for all patients. Ten patients (3.1%) experienced major adverse cardiac events (MACEs). Of these, 4 patients died (1.3%). Patients with AKI had a significantly higher MACE rate when compared with those without AKI (18.8% vs. 2.3%, $P < 0.001$; hazard ratio: 8.44, 95% confidence interval: 2.18–32.67, $P = 0.002$). The corresponding MACE-free survival graphs are shown in Figure 4.

DISCUSSION

This is the first CMR study investigating the association between parameters of cardiac injury and the occurrence of AKI in patients with STEMI undergoing primary percutaneous coronary intervention. AKI is significantly associated with worse LV ejection fraction, larger infarct size, and more extensive microvascular injury. However, only microvascular injury emerged as an independent CMR predictor of AKI. These findings indicate a possible novel pathophysiologic link between cardiac microvascular injury and AKI after revascularization in patients with STEMI, which requires further evaluation in well-designed studies.

The incidence of AKI after STEMI varies from 2% to 30%, depending on baseline renal function, as well as the definition of AKI.[8] In agreement with these data, in our study cohort, which included mainly patients with well-preserved renal function at baseline, 5% developed AKI. Moreover, the higher