Original Paper

Prognostic Implications of Acute Renal Impairment among ST Elevation Myocardial Infarction Patients with Preserved Left Ventricular Function

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Key Words

Acute kidney injury · ST elevation myocardial infarction · Percutaneous coronary intervention · Ejection fraction

Abstract

Background: Only limited data is present regarding the incidence and prognostic implications of acute kidney injury (AKI) in ST elevation myocardial infarction (STEMI) patients with preserved left ventricular (LV) function in the primary percutaneous coronary intervention (PCI) era. **Methods:** We conducted a retrospective study of 842 consecutive STEMI patients with preserved LV function (ejection fraction $\geq 50\%$, assessed by echocardiography) who underwent primary PCI between January 2008 and January 2015. AKI was defined as an increase of ≥ 0.3 mg/dl in serum creatinine within 48 h following admission. Patients were assessed for all-cause mortality up to 5 years. **Results:** Fifty-two patients (6.2%) developed AKI. Patients with AKI were older, had impaired baseline renal function, and presented more often with heart failure throughout their hospitalization. Patients with AKI had a higher 5-year all-cause mortality (13.4 vs. 2.4%, $p < 0.001$). Compared to patients with no AKI, the adjusted hazard ratio for all-cause mortality was 2.64 (95% CI 1.25–5.56, $p = 0.01$). **Conclusions:** Among STEMI patients with preserved LV function undergoing primary PCI, AKI is associated with a higher long-term mortality.

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Introduction

Worsening of renal function is a frequent complication among ST elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) known to be associated with adverse outcomes [1–4]. Recent evidence suggested that among this patient population acute kidney injury (AKI) is related to an acute left ventricular (LV) systolic dysfunction [5] and hemodynamic compromise [6] resulting in reduced renal perfusion, in addition to contrast-induced nephropathy [7–9]. Limited and conflicting data is present regarding the incidence and prognostic implications of AKI in STEMI patients with preserved (ejection fraction $\geq 50\%$) LV function [10, 11]. Our aim was to determine the possible prognostic effect of AKI in patients with preserved LV function in a large cohort of STEMI patients undergoing primary PCI.

Methods

Study Population

We performed a retrospective, single-center observational study at the Tel Aviv Sourasky Medical Center, a tertiary referral hospital with a 24/7 primary PCI service as was described previously [1, 5, 6]. Included were all consecutive patients admitted to the Cardiac Intensive Care Unit between January 2008 and January 2015 with a diagnosis of acute STEMI. Patients who were treated either conservatively or by thrombolysis and those whose final diagnosis on discharge was other than STEMI (e.g. myocarditis or Takotsubo cardiomyopathy) were excluded. We also excluded all patients who died within 30 days of hospital admission, as well as patients requiring chronic peritoneal dialysis or hemodialysis treatment. The initial cohort included 1,704 patients whose baseline demographics, cardiovascular history, clinical risk factors, treatment characteristics, and laboratory results were all retrieved from the hospital electronic medical records.

Protocol

A diagnosis of STEMI was established in accordance with published guidelines including a typical chest pain history, diagnostic electrocardiographic changes, and serial elevation of cardiac biomarkers [12]. The study protocol was approved by the local institutional ethics committee. Primary PCI was performed on patients with symptoms of ≤ 12 h duration as well as in patients with symptoms lasting 12–24 h if the symptoms persisted at the time of admission. Following coronary interventional procedures, physiologic (0.9%) saline was given intravenously at a rate of 1 ml/kg/h for 12 h after contrast exposure. In patients with overt heart failure, the hydration rate was reduced at the discretion of the attending physician. The contrast medium used in procedures was iodixanol (Visipaque, GE Healthcare, Ireland) or iohexol (Omnipaque, GE Healthcare). Heart failure was defined as clinical or radiographic evidence of pulmonary congestion. All patients underwent a screening echocardiographic examination within 3 days of admission. Echocardiography was performed by Philips IE-33 equipped with S5-1 transducers (Philips Healthcare, Andover, Mass., USA) and GE Vivid 7 model equipped with M4S transducer. LV diameters and interventricular septal and posterior wall widths were measured from the parasternal short axis by means of a two-dimensional, or a two-dimensional-guided, M-mode echocardiogram of the left ventricle at the papillary muscle level using the parasternal short-axis view [13]. LV ejection fraction was calculated by the biplane method. The 16-segment model was used for scoring the severity of segmental wall motion abnormalities according to the American Society of Echocardiography [14]. Patients whose echocardiographic assessment demonstrated LV ejection fraction $< 50\%$ ($n = 862$) were also excluded, and thus the final study population included 842 patients.

The serum creatinine (sCr) level was determined upon hospital admission and at least once a day during the Cardiac Intensive Care Unit stay and was available for all analyzed patients. The estimated glomerular filtration rate (eGFR) was estimated using the abbreviated Modification of Diet in Renal Disease equation [15]. Baseline renal insufficiency was categorized as an admission eGFR of ≤ 60 ml/min/1.73 m² [16]. AKI was determined using the AKI network (AKIN) criteria [17] and defined as a sCr rise of > 0.3 mg/dl compared with admission sCr. Mortality was assessed over a median period of $1,225 \pm 511$ days (range 31–2,250) up to April 1, 2015. Assessment of survival following hospital discharge was determined from computerized records of the population registry bureau.

Table 1. Baseline characteristics

	AKI		p value
	no (n = 790)	yes (n = 52)	
Age, years	60 ± 12	67 ± 12	<0.001
Men	649 (82)	38 (73)	0.137
Hypertension	333 (42)	34 (65)	0.001
Hyperlipidemia	387 (49)	27 (52)	0.775
Smoking	429 (54)	19 (37)	0.01
Diabetes mellitus	160 (20)	15 (29)	0.157
Family history	146 (18)	8 (15)	0.576
Admission eGFR, ml/min/1.73 m ²	74 ± 18	63 ± 21	<0.001
Admission eGFR ≤60 ml/min/1.73 m ²	131 (17)	25 (48)	<0.001
Admission systolic blood pressure, mm Hg	136 ± 19	133 ± 28	0.204
Admission diastolic blood pressure, mm Hg	81 ± 13	79 ± 11	0.596
Number of narrowed coronary arteries			
1	346 (44)	23 (44)	0.416
2	268 (34)	13 (25)	
3	176 (22)	16 (31)	
Heart failure during hospitalization	14 (2)	8 (15)	<0.001
Peak CPK, IU/l	887 ± 911	1,039 ± 1,256	0.257
Contrast volume, ml	144 ± 44	111 ± 34	0.005
Contrast volume/eGFR ratio	1.94 ± 0.44	1.76 ± 0.61	0.656
Admission CRP, mg/dl	8.92 ± 19.7	8.52 ± 9.52	0.932
IABC insertion	2 (0)	5 (10)	<0.001
LV ejection fraction	54 ± 4	53 ± 4	0.03

Values are means ± SD or n (%). CPK = Creatine phosphokinase.

Statistical Analysis

All data were summarized and displayed as means (± SD) for continuous variables and as numbers (percentages) of patients in each group for categorical variables. The p values for the χ^2 test were calculated with Fisher's exact test. Continuous variables were compared using the independent samples t test or Mann-Whitney test. The identification of independent predictors of AKI was assessed using logistic regression. A binary logistic regression model was performed using the enter mode. The model was adjusted for age, hypertension, diabetes mellitus, past or present smoking history, baseline eGFR ≤60 ml/min/1.73 m², clinical heart failure, admission C-reactive protein (CRP) level, and use of intra-aortic balloon counterpulsation (IABC) to support PCI. The influence of AKI on the occurrence of all-cause mortality was evaluated using multivariate Cox regression. We adjusted for age, gender, hypertension, diabetes mellitus, smoking status, baseline eGFR ≤60 ml/min/1.73 m², clinical heart failure, admission CRP level, use of IABC, and AKI status. A two-tailed p value <0.05 was considered significant for all analyses. All analyses were performed with the SPSS 20.0 software (SPSS Inc., Chicago, Ill., USA).

Results

A total of 842 STEMI patients treated by primary PCI were enrolled in the study, 52 (6.1%) of whom developed AKI in accordance with the AKIN criteria. The median time to echocardiography was 1.4 days (interquartile range 1–2). The baseline clinical characteristics of patients with and without AKI are listed in table 1. Patients with AKI were more likely to be older, hypertensive, with lower baseline eGFR, and more likely to have heart failure throughout their hospitalization. Patients with AKI received less contrast volume during

Table 2. Predictors of AKI in STEMI

Correlates	OR	95% CI	p
Age	1.028	1.003–1.053	0.03
Hypertension	1.47	0.88–2.42	0.135
eGFR ≤60 ml/min/1.73 m ²	2.56	1.44–4.53	0.001
Smoking	0.58	0.52–1.43	0.865
Heart failure	4.88	2.78–8.59	0.001
Diabetes mellitus	1.04	0.61–1.78	0.865
CRP	1.01	1.001–1.013	0.02
IABP insertion	2.49	1.03–6.01	0.04

Table 3. Predictors of all-cause mortality in STEMI

Correlates	HR	95% CI	p
Age	1.045	1.02–1.08	0.02
Gender	1.95	0.94–4.04	0.07
Hypertension	0.56	0.26–1.25	0.16
Smoking	0.79	0.37–1.68	0.544
eGFR ≤60 ml/min/1.73 m ²	2.79	1.29–6.00	0.009
Heart failure	3.86	1.83–8.15	0.001
AKI	2.64	1.25–5.56	0.01
CRP	1.01	1.004–1.015	0.001
IABC insertion	4.51	2.05–9.97	0.001
Diabetes mellitus	1.51	0.74–3.08	0.257

HR = Hazard ratio.

primary PCI; however, no significant difference in the contrast volume/eGFR ratio was found between patients with and without AKI. Following the performance of a logistic multivariate analysis model, independent predictors of AKI included baseline eGFR <60 ml/min/1.73 m² [odds ratio (OR) 2.56, 95% CI 1.44–4.53, p = 0.001], heart failure (OR 4.88, 95% CI 2.78–8.59, p = 0.001), CRP (OR 1.01, 95% 1.001–1.013, p = 0.02), and IABC insertion (OR 2.49, 95% CI 1.03–6.01, p = 0.04; table 2).

Long-Term Outcome

Over a mean period of 3.3 ± 1.4 years, 26 (3.0%) patients of the entire cohort died. Figure 1 shows the Kaplan-Meier survival curve for long-term survival according to the presence or absence of AKI. Mortality was significantly higher among those with AKI (7/52, 13.4%) following STEMI than those without AKI (19/790, 2.4%, p = 0.001). In the Cox regression model for all-cause mortality, AKI was an independent predictor of mortality reaching a hazard ratio of 2.64 (95% CI 1.25–5.56, p = 0.01) compared to patients without AKI. Other predictors of mortality included age, heart failure, CRP, and need for IABC insertion (table 3).

Discussion

In this cohort of STEMI patients undergoing PCI with preserved LV function, the occurrence of AKI following primary PCI, while being much less frequent than previously reported, still maintained its negative prognostic impact. This finding highlights the detrimental effect of AKI, even in patients considered previously to have a better outcome. The sudden myocardial

Fig. 1. Cumulative survival rates for 842 patients with STEMI with preserved LV function with and without AKI (unadjusted hazard ratio 6.44, 95% CI 2.96–14.01, $p < 0.001$).

insult in STEMI with a subsequent acute reduction of cardiac output leads to reduced effective renal blood flow, consequently causing renal hypoxia and the synthesis of reactive oxygen species. Following the resumption of coronary flow and the improvement of LV function as well as the resolution of acute arrhythmias, hemodynamic impairment often resolves while renal function may still remain impaired or lag in recovery. Contrast material is still considered a major reason for AKI development in STEMI patients following PCI. Contrast-induced AKI is a prevalent and deleterious complication of coronary angiography and reported to be the third most common cause of hospital-acquired renal failure [7–9]. The contrast volume/eGFR ratio, recently shown to be a better predictor of AKI among patients undergoing PCI [18, 19], was not found to differ significantly between patients with and without AKI development in our cohort. This finding points to the possible impact of other factors besides contrast volume and reduced renal perfusion on the development of AKI in the setting of STEMI. These include anemia [20], elevated CRP [21], and admission hyperglycemia [22], all shown to possibly harm renal function in STEMI patients. Even small differences in renal function within the normal range have been shown to be related to adverse outcomes [23]. Only limited data is present on the possible prognostic effect of AKI following primary PCI on patients with preserved LV function. Pyxaras et al. [10] reported that among 387 STEMI patients with preserved (ejection fraction >40%) LV function following primary PCI, the occurrence of AKI was associated with worse 1-year outcomes. In this cohort, however, the standard definition for AKI was not used. Moreover, the quantitative assessment of LV function was performed using angiography in the vast majority of patients, rather than echocardiography, thus being less accurate and missing potential improvement in acute LV stunning following PCI. A report by Lazzeri et al. [11] demonstrated that among STEMI patients with preserved (ejection fraction >45%) LV function submitted to primary PCI, worsening renal function was associated with increased early death but not with a poorer survival rate at long-term follow-up. Our findings highlight that the development of AKI in STEMI patients with preserved LV function identifies a subset of higher-risk patients who are older, hypertensive, with more baseline renal insufficiency, inflammatory activation, and heart failure complicating the

hospitalization. The data strongly supports the implementation of dedicated renal protection protocols even among STEMI patients with preserved LV function [24, 25] and suggests the clinical need of a close monitoring of renal function and of a more intensive treatment in those who develop AKI [26].

We acknowledge several important limitations of our study. First, this was a single-center retrospective and nonrandomized observational study and may have been subject to bias, even though we included consecutive patients and attempted to adjust for confounding factors using the multivariate regression model. Second, the definition of the AKIN criteria refers to sCr change within a time frame of 48 h [17]. As the change in sCr can lag beyond this period due to delayed effects of contrast material and drugs, worsening of renal function might have occurred following hospital discharge in some patients, thus the true incidence of AKI described in our study may have been underestimated. Echocardiographic systolic function early after primary PCI may still represent stunned myocardium which may theoretically recover, thus overestimating the true severity of LV function. Finally, as data regarding concomitant use of statins, renin/angiotensin blockers, β -blockers, and antiaggregants prior to hospital admission and upon discharge was not available for many patients, their effect on long-term outcomes could not been assessed. No information was present on other end points including recurrent myocardial infarction, need for repeat revascularization, heart failure, stroke, and need for chronic dialysis.

In conclusion, among STEMI patients undergoing primary PCI and with preserved LV function, AKI is associated with a higher long-term mortality.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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