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Preconditioning with high mobility group box 1 protein protects against myocardial ischemia–reperfusion injury

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Twenty six male Sprague-Dawley (SD) rats (250–300 g) were randomly assigned into 3 groups receiving the following treatments: Group 1: Sham-operated control (SO) (n = 6): rats were subjected to surgical manipulation without the induction of myocardial ischemia. Group 2: Ischemia–reperfusion (I/R) (n = 10): rats treated with PBS 24 h before ischemia, and then subjected to the left anterior descending coronary artery occlusion for 30 min followed by reperfusion for 4 h. Group 3: high mobility group box 1 protein (HMGB1) + I/R (n = 10): rats treated with HMGB1 (200 µg/kg, ip, Sigma, USA) 24 h before ischemia, HMGB1 was dissolved in PBS.

Infarct size was assessed by 2,3,5-triphenyltetrazolium chloride (TTC) method. Serum was taken to determine lactate dehydrogenase (LDH) and creatine kinase (CK) by using an Olympus AU 2700 Analyzer. Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels were measured using commercialized ELISA assay kits in myocardial tissue.

All values were expressed as mean±SD. t-test was used for between-group comparisons. One-way ANOVA was used for comparisons among groups and the least-significant difference was used for post-hoc multiple comparisons. Statistical significance was defined as p<0.05.

The infarct size was significantly reduced by HMGB1 preconditioning (30.5 ± 3.6%) compared to that in the I/R group (57.8 ± 4.1%) (p<0.05). Both LDH (2134.7 ± 172.6 U/L) and CK (29081.1 ± 192.8 U/L) were markedly increased in the I/R group compared to those in the SO group (789.4 ± 71.5 U/L and 1010.7 ± 79.2 U/L) (both p<0.05), respectively. Pretreatment with HMGB1 could prevent elevation of LDH (935.6 ± 91.9 U/L) and CK (1295.3 ± 99.2 U/L) in serum during myocardial I/R (both p<0.05). After 4 h reperfusion, the TNF-α (33.27 ± 2.84 pg/mg) and IL-6 (48.63 ± 3.75 pg/mg) levels of myocardial tissue in the I/R group were significantly increased compared to those in the SO group (16.85 ± 2.37 pg/mg and 25.74 ± 3.01 pg/mg) (both p<0.05), whereas pretreatment with HMGB1 could prevent elevation of the TNF-α (19.32 ± 2.07 pg/mg) and IL-6 (27.52 ± 2.32 pg/mg) levels of myocardial tissue (both p<0.05).

Endotoxin tolerance was first described in 1946 as the reduced capacity of animals or humans or of cultured macrophage and monocytes to respond to lipopolysaccharide (LPS) activation following a previous exposure to a relatively low concentration of LPS [1]. Previous study showed that Gram-negative bacterial LPS induces myocardial protection [2]. Specifically, pretreatment with LPS for 24 h reduces myocardial I/R injury in mice [2]. This effect is not unique to LPS, since lipoteichoic acid, a cell wall component of Gram-positive bacteria, also reduces infarct size when administered to rats 8–24 h before myocardial ischemia [3]. Recently, Izuishi et al [4] reported that preconditioning with HMGB1 also could protect against hepatic I/R injury. However, whether preconditioning with HMGB1 could provide a cardioprotection during myocardial I/R remains unknown.

HMGB1, a non-chromosomal nuclear protein that maintains the nucleosome structure and regulates gene transcription, could be released by necrotic cell or activated innate immune cells (such as macrophages and monocytes) [5]. HMGB1 has been identified as a new proinflammatory cytokine and as late mediator of inflammation, sepsis, acute lung injury, severe acute respiratory syndrome, autoimmune disease and etc., and which has been found to play a pivotal role in the pathogenesis of the above inflammatory disorders [5,6]. Recently, HMGB1 has been found that it acts as an early mediator of inflammation and cell injury during myocardial I/R [7]. These results suggest that HMGB1 play an important role in myocardial I/R injury. However, HMGB1 has been recognized as a member of endogenous compounds, called “alarmins,” which serve as danger signals to promote activation of the innate immune system in response to tissue injury as a result of trauma, I/R, or infection [8]. Izuishi et al [4] indicated that pretreatment of mice with HMGB1 protected against hepatic I/R injury and blunted the inflammatory response to this insult. And then, recently they found that preconditioning with HMGB1 could also induce LPS tolerance during hepatic I/R [8], indicating that preconditioning with HMGB1 may also protect against myocardial I/R injury as well as LPS.

In the study, we showed that preconditioning with HMGB1 could decrease myocardial injury (infarct size, LDH and CK). In addition, preconditioning with HMGB1 could also decrease the levels of TNF-α and IL-6 which were important pathophysiological components of
myocardial I/R injury, indicating that it could blunt the inflammatory response. This is consistent with previous study, which demonstrated that there was a cross-talk between HMGB1 and inflammatory cytokines [5,6]. These results suggested that preconditioning with HMGB1 could induce HMGB1 tolerance and protect against myocardial I/R injury.

The authors of this manuscript have also certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [9].

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Left anterior descending artery length and coronary atherosclerosis in apical ballooning syndrome (Takotsubo/stress induced cardiomyopathy)

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Apical ballooning syndrome (ABS) is an increasingly diagnosed reversible cardiomyopathy [1,2]. It has been proposed that ABS is not a clinically distinct entity, but rather a manifestation of a spontaneously aborted myocardial infarction (MI) [3–5]. However, the regional wall motion abnormality in ABS extends beyond the distribution of a single coronary artery [2,6–8]. The proponents of the aborted MI hypothesis account for this fact by suggesting that ABS occurs in patients who have a left anterior descending artery (LAD) that “wraps around” the apex and supplies the inferior wall of the left ventricle. The hypothesis has been derived from data from a single case series of eleven patients [9] and warrants validation in other cohorts of ABS. Thus, the aim of our study was to test the hypothesis that patients with ABS have a higher frequency of a “wrap around” LAD.

We conducted a retrospective case-control study among ninety-seven consecutive, prospectively identified ABS patients, based on the Mayo Clinic diagnostic criteria [2]. Ninety-seven patients with an anterior STEMI undergoing successful primary percutaneous coronary intervention to the proximal or mid-LAD, matched for age, gender, and event date served as the control population. The study was approved by the Mayo Clinic Institutional Review Board and all patients consented to the use of their medical record for research purposes. Coronary angiograms in multiple views were analyzed, by an observer who was blinded to the echocardiographic and clinical data, for the length of the LAD, the presence and severity of coronary artery disease (CAD), and dominance of the coronary circulation. The visual grading system used to determine the length of the LAD is summarized in Fig. 1 [10,11]. CAD was defined as the presence of any atherosclerosis on the angiogram, and obstructive disease as the presence of >50% stenosis in any major epicardial artery (left anterior descending, circumflex, right coronary artery, posterior descending, and posterolateral arteries as well as diagonal or obtuse marginal branches >1.5 mm in diameter). Global and regional LV systolic function was measured as ejection fraction and regional wall motion score index, respectively, from transthoracic echocardiograms.

Table 1 summarizes the baseline characteristics of ABS patients and controls. The length of the LAD, measured as types I–IV were similar in the two groups (p = 0.45) (Table 2). The prevalence of any angiographic CAD was high in ABS (84%), but only thirteen (13%) patients had obstructive disease. The obstructive lesions were located in the LAD or diagonal branches (n = 7), circumflex artery (n = 4), and the right coronary artery (n = 2). Ejection fraction at presentation was lower and wall motion score index was higher at presentation in patients with ABS compared to STEMI controls (Table 2). There was no difference in the LV ejection fraction or the wall motion score index at presentation in the four different LAD length groups among the ABS patients (Fig. 2).

The major findings of this study are that patients with ABS: 1) do not have a higher prevalence of a “wrap around” LAD, 2) have greater left