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Inhibition of Angiotensin-II Production Increases Susceptibility to Acute Ischemia/Reperfusion Arrhythmia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Eylem Taskin*
CDEG 2 Kadir Ali Tuncer*
CDEF 3 Celal Guven
CEF 4 Salih Tunc Kaya
ABFG 2 Nurcan Dursun

1 Department of Physiotherapy and Rehabilitation, School of Health Sciences, Istanbul Bilim University, Istanbul, Turkey
2 Department of Physiology, Faculty of Medicine, University of Erciyes, Kayseri, Turkey
3 Department of Biophysics, Faculty of Medicine, University of Adiyaman, Adiyaman, Turkey
4 Department of Biology, Faculty of Science and Arts, Düzce University, Düzce, Turkey

* These authors contributed equally to this work

Corresponding Authors: Eylem Taskin, e-mail: eylemtaskin@yahoo.com, eylem.taskin@istanbulbilim.edu.tr, Celal Guven, e-mail: cgven@yahoo.com
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Background: Myocardial ischemia and reperfusion lead to impairment of electrolyte balance and, eventually, lethal arrhythmias. The aim of this study was to investigate the effects of pharmacological inhibition of angiotensin-II (Ang-II) production on heart tissue with ischemia-reperfusion damage, arrhythmia, and oxidative stress.

Material/Methods: Rats were divided into 4 groups: only ischemia/reperfusion (MI/R), captopril (CAP), aliskiren (AL), and CAP+AL. The drugs were given by gavage 30 min before anesthesia. Blood pressure and electrocardiography (ECG) were recorded during MI/R procedures. The heart tissue and plasma was kept so as to evaluate the total oxidant (TOS), antioxidant status (TAS), and creatine kinase-MB (CK-MB).

Results: Creatine kinase-MB was not different among the groups. Although TAS was not affected by inhibition of Ang-II production, TOS was significantly lower in the CAP and/or AL groups than in the MI/R group. Furthermore, oxidative stress index was significantly attenuated in the CAP and/or AL groups. Captopril significantly increased the duration of VT during ischemia; however, it did not have any effect on the incidence of arrhythmias. During reperfusion periods, aliskiren and its combinations with captopril significantly reduced the incidence of other types of arrhythmias. Captopril alone had no effect on the incidence of arrhythmias, but significantly increased arrhythmias score and durations of arrhythmias during reperfusion. MAP and heart rate did not show changes in any groups during ischemic and reperfusion periods.

Conclusions: Angiotensin-II production appears to be associated with elevated levels of reactive oxygen species, but Ang-II inhibitions increases arrhythmia, mainly by initiating ventricular ectopic beats.

MeSH Keywords: Arrhythmias, Cardiac • Captopril • Oxidative Stress • Renin-Angiotensin System • Reperfusion Injury

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Background

Cardiovascular events are still the leading cause of death worldwide and remain one of the main causes of death in modern society [1]. Multiple factors such as thrombolysis or coronary bypass surgery can cause myocardial ischemia-reperfusion (MI/R) damage. The most dangerous effector phase of MI/R can be observed during reperfusion of previously ischemic tissue. Although the restoration of blood flow is an important method to protect the heart from MI/R injury, reperfusion often exacerbates cardiac dysfunction, including arrhythmias, stunning, and microvascular damage. Cell death, therefore, is mainly induced by reperfusion injury [2].

The renin-angiotensin system (RAS) is of the vital importance in the hormonal cascade for cardiovascular function [1] and the pathogenesis of cardiovascular diseases [2]. Two types of RAS are recognized: systemic circulating RAS and local RAS. The systemic RAS plays a significant role in acute vascular tone regulation and aldosterone secretion by adrenal glands. However, the local RAS may have a significant role in tissue control (e.g., vasculature) and cardiac myocytes. The most active element of RAS is Ang-II. Angiotensin-converting enzyme (ACE) cleavages from angiotensin-I (Ang-I) to Ang-II. Studies suggest that ACE is present in coronary vessels, endocardium, and myocardium [3].

The RAS is activated during acute myocardial ischemia. Ang-II exerts some effects that exacerbate the consequences of myocardial ischemia. The magnitude of the heart damage contributed by each of these factors and the extent of their interactions are unresolved issues [1,2]. Although ACE inhibitors and Ang-II type 1 (AT1) receptor blockers are beneficial during MI/R, their effects on the myocardium remain controversial [1,2]. The therapeutic success of ACE inhibitors is related to their unique pharmacological profile involving both a reduction of plasma and tissue Ang-II concentrations, and potentiation of endogenous kinins [1]. RAS inhibitors are reported to prevent heart failure and death in patients with myocardial infarction, resulting in decreased risk of acute and chronic coronary heart disease [3]. A previous study reported that local ACE inhibition can reverse cardiac dysfunction and reported involvement of local angiotensin-II in the ischemic myocardium. One of the most studied ACE inhibitors is ACE, which can effectively improve the extent of contractile function after myocardial infarction. Therefore, the renin-angiotensin system might intimately participate in aggravation of reperfusion injury [4]. Ang-II was reported to elevate myocardial arrhythmia [5]. The life-threatening effect of MI/R can occur within minutes after the onset of ischemia. Ischemia can also be prolonged, leading to irreversible cell damage and myocardial infarction. In light of that knowledge, the aim of this study was to investigate the effect of pharmacological inhibition of angiotensin-II production on heart tissue with acute ischemia-reperfusion damage, particularly on the incidence of arrhythmias and oxidative stress.

Material and Methods

Experimental design

All protocols were performed with approval of the Animal Ethics Committee of Erciyes University. Male rats were housed under standard conditions and had free access to food and water throughout the experiment. Rats were divided into 4 groups: control, captopril, aliskiren, and captopril+aliskiren. The control group (n=7) received the only saline as a standard ischemic control group. The captopril group (CAP, n=8) received captopril 10 mg/kg by gavage 1 h before I/R. The aliskiren group (n=5) received aliskiren 50 mg/kg by gavage 1 h before MI/R. The captopril+aliskiren group (CAP+AL, n=5) was received both captopril and aliskiren by gavage 1 h before I/R.

Rats were anesthetized with ketamine plus xylazine (40 and 5 mg/kg, i.m., respectively), then were orally intubated with polyethylene-240 (PE-240) tubing, connected to a rodent ventilator (Harvard Rodent Ventilator, Mod 683, USA) using a volume of 0.9 mL/100 g body weight at 60 breaths per min supplemented with room air. A median sternotomy was performed, and the proximal left coronary artery (LCA) was ligated to induce regional ischemia. At 30 min after ischemia, the ligature was removed and reperfusion was visually confirmed. During ischemia and reperfusion, 3-lead ECG and mean blood pressure (MP30 Biopac System, Inc., CA) were monitored.

The arrhythmias were analyzed according to the Lambeth conventions as ventricular tachycardia (VT), ventricular fibrillation (VF), and other types of arrhythmia, including single-ventricular extra-beat, bigeminy, and salvos. An arrhythmia score was determined in accordance with Lambeth conventions as follows [6]; 0=no arrhythmia; 1=≤10 s of VT and/or other types of arrhythmias, no VF; 2=11 to 30 s of VT and/or other types of arrhythmias, no VF; 3=31 to 90 s of VT and/or other types of arrhythmias, no VF; 4=91 to 180 s of VT and/or other types of arrhythmias, and/or <10 s of reversible VF; 5=≥180 s of VT and/or other types of arrhythmias, and/or >10 s of reversible VF; 6=irreversible VF or death of animals.

At the end of MI/R protocols, blood samples were taken and subsequently separated to plasma for measurement of oxidative stress index and creatine kinase-MB (CK-MB). The hearts were weighed and kept at –80°C until use.

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Table 1. Body weight, heart weight and creatine kinase-MB in groups.

	BW (g)	HW (mg)	CK-MB (U/l)	p Value
MI/R	147±2	410±24	288±38	
CAP	143±3	455±17	239±37	0.908
AL	146±4	448±22	265±34	0.989
CAP+AL	139±2	387±17	234±88	0.877

BW – body weight; CK-MB – creatin kinase-MB; HW – heart weight; MI/R – ischemia-reperfusion group; CAP – captopril group; AL – aliskren group; CAP+AL – captopril plus aliskren group. All data were expressed as mean ±SEM.

Separation of mitochondria and cytosol

Myocardial mitochondria were separated as described before [7,9]. The mitochondria and cytosol were kept at –80°C until use for measurement of oxidative stress index.

Biochemical studies

Creatine kinase-MB assay

The creatine kinase-MB (CK-MB) level in plasma was measured by using Beckman by Beckman Coulter LX-2000 commercial kits.

Total antioxidant status measurement

Total antioxidant status (TAS) was measured from myocytes cytosol, mitochondria, and plasma by using a kit (Rel Assay Diagnostics, Gaziantep, TURKEY) according to the manufacturer's protocol. TAS is expressed in mmol Trolox equiv./L.

Total oxidant status measurement

Total oxidant status (TOS) was measured from myocytes cytosol, mitochondria, and plasma by using a commercial kit (Rel Assay Diagnostics, TURKEY) according to the manufacturer's protocol. TOS is expressed in μmol H_2O_2/L.

Oxidative stress index calculation

Oxidative stress index (OSI) was calculated by dividing TOS to TAS [(TOS)/(TAS)/100].

Statistical data analysis

Data are presented as means ±SEM. One-way ANOVA with Tukey post hoc test was used for statistical analysis using SPSS. The incidence of arrhythmias and survival rate were compared by chi-squared test. A two-sided $p<0.05$ was considered significant.

Results

The influence of body weight, heart weight, and creatinine kinase levels on angiotensin inhibition in rats with cardiac ischemia/reperfusion damage

All groups had approximately the same body and heart weights, meaning that the 4 groups were homogenous. The CK-MB degree in plasma was first investigated as an excellent indicator of MI/R damage in the heart. Renin and/or ACE inhibition slightly decreased CK-MB level compared to only MI/R, but the difference was not significant (Table 1).

The influence of angiotensin inhibition on ECG and arrhythmia in rats with cardiac ischemia/reperfusion damage

ST segment elevation and an increase in QRS amplitude were observed in all experimental animals after coronary artery ligation. ST segment elevations were accepted as a sign of ischemia in ECG.

Following coronary artery ligations, arrhythmias were observed within 2–3 min. The incidence of arrhythmias, arrhythmia score, and the survival rate was not significantly different among any groups during the ischemic period (Table 2). Also, during the ischemic period, no VF was observed in any groups. However, VT was only found in CAP and AL groups. Captopril did significantly increase the duration of VT compared to aliskiren and aliskiren-captopril combinations (Figure 1). The length of other types of arrhythmias was not different among all groups, and there was no difference in the effect of drugs on durations of arrhythmias other than that on VT.

Reperfusion arrhythmias in all experimental groups appeared within 30–60 s after 30 min of ischemic period. During reperfusion, VF and VT were not observed in any groups; however, the incidence of other types of arrhythmias in AL and CAP+AL groups was significantly less than in other groups. Arrhythmia score, determined by type and duration of arrhythmias, was significantly higher in the CAP group than in the CAP+AL group

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Table 2. The incidence of arrhythmias during 30 min. of ischemia.

Groups	N	Survival (%)	Incidence of arrhythmia (n)				Arrhythmia score
			VF	VT	Others	BR	
MI/R	7	100	0	2	6	0	2.28±0.52
CAP	8	100	0	4 (p=0.398)	8 (p=0.268)	0	3.00±0.26 (p=0.205)
AL	5	100	0	0 (p=0.190)	5 (p=0.377)	0	2.40±0.24 (p=0.855)
CAP+AL	5	100	0	0 (p=0.190)	5 (p=0.377)	0	2.20±0.58 (p=0.891)

N – the number of animals at the beginning of the reperfusion; n – number of animals, arrhythmias observed; BR – bradycardia; VF – ventricular fibrillation; VT – ventricular tachycardia; Others – ventricular extra beat, bigeminy, and salvos. Data are mean ±SEM.

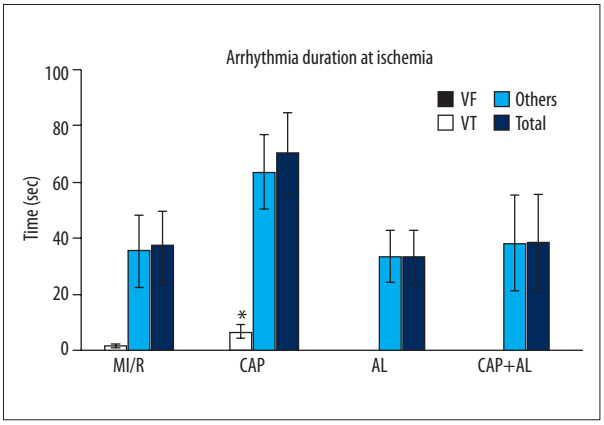

Figure 1. The duration of arrhythmias during ischemia in all groups. MI/R – ischemia-reperfusion group; CAP – captopril group; AL – aliskren group; CAP+AL – captopril plus aliskren group. Data are expressed as mean ±SE. * *p<0.05;* different from AL and CAP+AL.

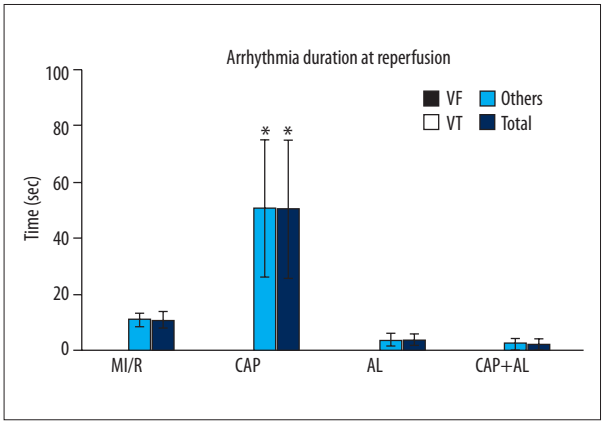

Figure 2. The arrhythmia duration during the reperfusion period in all groups. MI/R – ischemia-reperfusion group; CAP – captopril group; AL – aliskren group; CAP+AL – captopril plus aliskren group. Data are expressed as mean ±SEM. * *P<0.05;* different from CAP+AL.

Table 3. The incidence of arrhythmias during 30 min. of reperfusion.

Groups	N	Survival (%)	Incidence of arrhythmia (n)				Arrhythmia score
			VF	VT	Others	BR	
MI/R	7	100	0	0	7	0	1.42±0.20
CAP	8	100	0	0	5 (p=0.07)	0	1.75±0.67# (p=0.031)
AL	5	100	0	0	2* (p=0.017)	0	0.40±0.24 (p=0.151)
CAP+AL	5	100	0	0	1* (p=0.003)	0	0.20±0.20 (p=0.090)

N – the number of animals at the beginning of the reperfusion; n – number of animals, arrhythmias observed; BR – bradycardia; VF – ventricular fibrillation; VT – ventricular tachycardia; Other – ventricular extra beat, bigeminy and salvos. Data are mean ±SEM.
* *P*<0.05 different from MI/R; # *P<0.05* different from CAP+AL.

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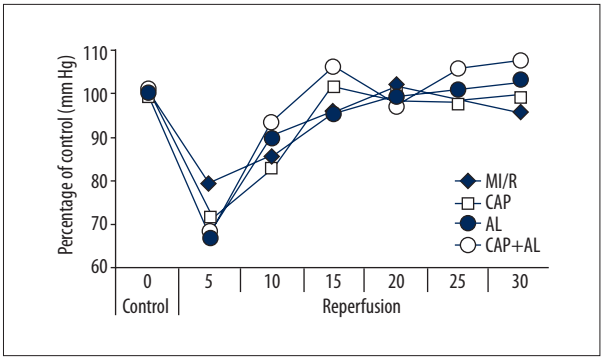

Figure 3. Mean blood pressure during the reperfusion period in all groups. MI/R – ischemia-reperfusion group; CAP – captopril group; AL – aliskren group; CAP+AL – captopril plus Aliskren group.

(Table 3). Similarly, captopril significantly increased durations of arrhythmias during the reperfusion period in comparison with captopril+aliskerin combinations (Figure 2).

Heart rate and blood pressure were determined from recorded ECG before and at basal, 5th, 10th, 15th, 20th, 25th and 30th min during ischemia and reperfusion periods. Although there was no significant difference in mean arterial blood pressure and heart rate among all groups (data not shown), at the end of the reperfusion period, mean arterial blood pressure was weakly increased by angiotensin-II inhibitions during the reperfusion period, but not significantly (Figure 3).

The influence of angiotensin inhibition on oxidative stress in rats with myocardial ischemia/reperfusion damage

MI/R rapidly promotes the generation of superoxide and other ROS products, especially in tissue, can reach blood supply again. Therefore, the aim of the present study was to determine how total oxidant and antioxidant status changed in the mitochondria, cytosol from heart tissue extract, and plasma. Cytosolic TOS was decreased by inhibition of renin and/or CAP ($p<0.001$ *vs.* MI/R; Figure 4). Cytosolic and mitochondrial TAS were slightly increased by inhibition of renin and/or CAP, but the difference was not statistically significant (Figure 5). TOS in plasma was greatly diminished by inhibition of renin and/or CAP ($p<0.01$ *vs.* MI/R; Figure 4). TAS in plasma was slightly increased by inhibition of renin and/or CAP (Figure 5). Inhibition of angiotensin-II production by renin and/or CAP drugs greatly restored the oxidative stress due to MI/R damage in mitochondria, cytosol, and plasma, as evident from decreased total oxidants and increased levels of antioxidants ($p<0.001$ *vs.* MI/R; Figures 4–7).

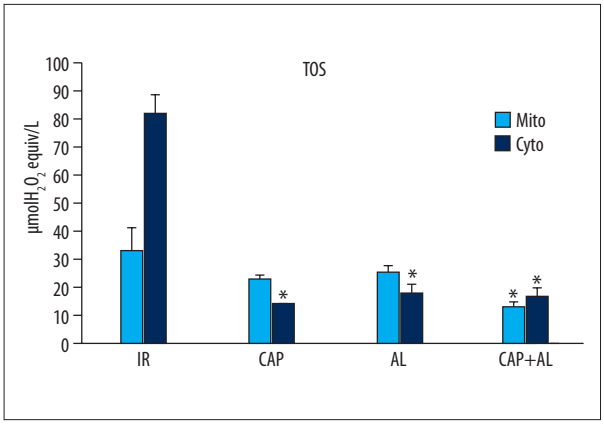

Figure 4. Total oxidant status in all groups. TOS – total oxidant status; Mito – mitochondria; Cyto – Cytosolic; MI/R – ischemia-reperfusion group; CAP – captopril group; AL – aliskren group; CAP+AL – Captopril plus Aliskren group. * $p<0.001$ *vs.* MI/R. All data are expressed as mean ±SEM.

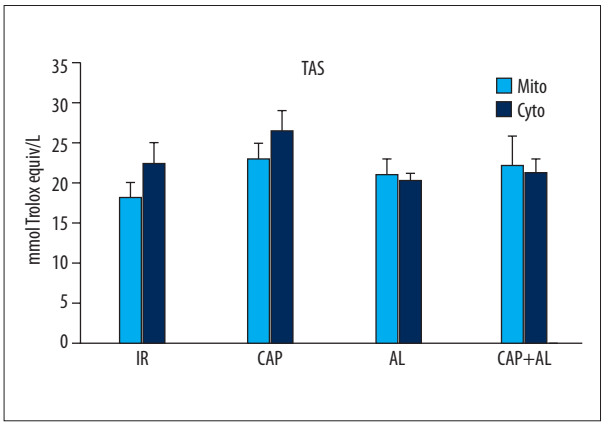

Figure 5. Total antioxidant status in all groups. TOS – total oxidant status; Mito – mitochondria; Cyto – cytosolic; MI/R – ischemia-reperfusion group; CAP – captopril group; AL – aliskren group; CAP+AL – captopril plus aliskren group. * $p<0.001$ *vs.* MI/R. All data are expressed as mean ±SEM.

Discussion

The results of the present study show that acute myocardial MI/R injury increases oxidative damage due to a primary elevation of oxidant status. CK-MB levels in heart tissue and plasma in the MI/R group were used as an index of cardiac damage. Heart function was, therefore, decreased and resulted in slightly reduced mean arterial blood pressure. The oxidative stress was attenuated after blocking Ang-II production via the enzymes level of renin and/or ACE by drugs (captopril and/or aliskiren) in the present study. However, arrhythmias, including ventricular ectopic beats and tachycardia, were elevated after pharmacologically blocking the Ang-II production during ischemia and reperfusion periods.

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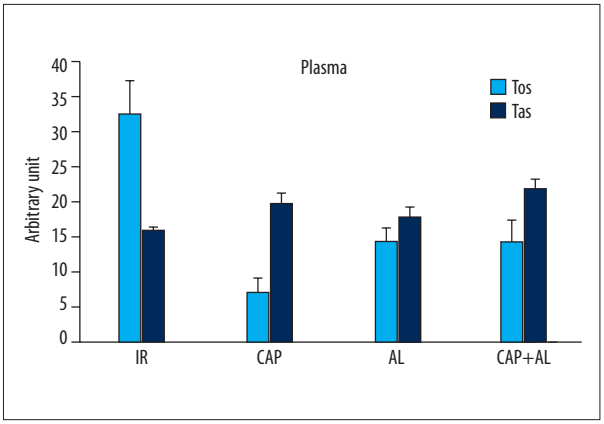

Figure 6. Plasma total oxidant and antioxidant status in all groups. TOS – total oxidant status; Mito – mitochondria; Cyto – cytosolic; MI/R – ischemia-reperfusion group; CAP – captopril group; AL – aliskren group; CAP+AL – captopril plus aliskren group. * p<0.01 *vs.* MI/R. All data are expressed as mean ±SEM.

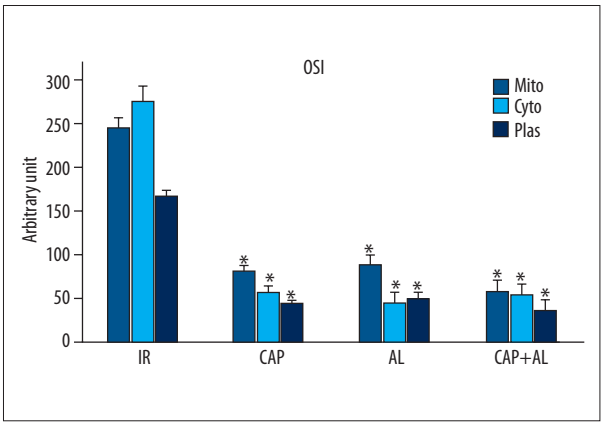

Figure 7. Oxidative stress index in all groups. OSI – oxidative stress index; Mito – mitochondria; Cyto – cytosolic; Plas – plasma; MI/R – ischemia-reperfusion group; CAP – captopril group; AL – aliskren group; CAP+AL – captopril plus aliskren group. * p<0.001 *vs.* MI/R. All data are expressed as mean ±SEM.

It is well established that myocardial injury leads to loss of structural integrity and increased permeability. Therefore, the degree of CK-MB leakage from myocardium corresponds well with myocardial injury [10]. In the present study, CAP (10 mg/kg) and AL (50 mg/kg) treatment slightly reduced leakage of myocardial enzyme CK-MB as compared to the control MI/R group. Since most deaths due to myocardial ischemia occur within the first half hour for arrhythmia resulting from an elevation of extracellular potassium concentration and falling pH [11], acute myocardial I/R damage was investigated in our study and the reperfusion period was limited to only 30 min. When the animals were pretreated with CAP and/or AL, coronary flow and CK-MB release were partially reduced, but not significantly. Moreover, it has been reported that 30-min MI/R does not cause structural changes [11], and this appears to be consistent with a limited reperfusion period. Therefore, CK-MB was still high in the present study.

Heart tissue has been documented to be much more vulnerable to oxidative damage because of limited of antioxidant defense [7,12]. Therefore, one of the leading causes of myocardial ischemia and reperfusion injury is the imbalance between oxidants and antioxidant defenses [13]. In the present study, total oxidant and oxidant status were evaluated without paying attention to the types of antioxidants and oxidants in cardiac mitochondria, cytosol, and plasma. We also assessed the systemic (plasma) and local (heart tissue) and subcellular compartments (cytosolic and mitochondrial in the heart tissue) oxidative stress. As a result, oxidative stress index (OSI) was calculated in the cardiac mitochondria, cytosol, and plasma. OSI was increased only in the MI/R group due to increasing TOS compared to inhibition of all angiotensin-II production groups. We also found that MI/R injury increased TOS, especially in the cytoplasmic part of heart tissue and plasmal. Because ROS can freely cross intracellular membranes [14–16], plasma can be significantly exposed to the harmful effect of ROS at subcellular levels, as shown by previous studies [14–16]. One of these previous studies reported that myocardial lipid peroxidation is an indicator of oxidative damage in tissue, myocardial GSH content, and SOD, and CAT activity was depleted significantly following ischemia and reperfusion-induced injury [10]. Importantly, RAS also contributes to the further generation of ROS via the effects of Ang-II on the angiotensin type 1 receptor (AT 1 R), activating a membranous NADPH oxidase enzyme [3,17,18]. This activations results in activation of PKA and CaMKII, subsequently triggering myocardial arrhythmia [19] by prolongation of action potential duration by inhibiting repolarization currents in the heart [18]. Ang-II aggravates MI/R-induced heart dysfunction and injury characterized by decreased heart function [10]. The other explanation for attenuation of oxidative damage is that Ang-II has strong vasoconstrictive [20], myocardial contractor [21], and cause sympathetic nervous activity effects, resulting in elevated norepinephrine levels in plasma [22]. Therefore, blocking Ang-II by drugs could decrease heart contractions and oxygen utilization, eventually causing less oxidative stress. Finally, inhibition of Ang-II probably reversed those pathologies. There are 2 different types of renin-angiotensin systems – the local RAS and the systemic RAS [18] – which is why ACE and renin enzyme inhibitors were used to decrease cardiac (local) angiotensin-II production in the present study [23,24]. Under pathophysiologic conditions, the local RAS may be more efficient in heart tissue than is the systemic RAS [25]. A previous study reported aliskiren attenuated the inducibility of arrhythmias [26]. This discrepancy might be explained by drug dose and duration (6 mg/kg/day and 6 weeks after MI/R) [26].

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ACE plays a critical role by cleaving the carboxy-terminal His-Leu dipeptide from angiotensin-I to produce angiotensin-II, a potent vasopressor octapeptide [27]. We did not measure infarct size because we were able to measure biochemical parameters from the heart tissue. However, ACE blockers were shown to decrease infarct size in animal studies [3,28]. Hemodynamics in patients with AMI and heart failure were demonstrated to improve after ACE inhibition, resulting in elevated cardiac output [3]. Attenuation of vasoconstriction and left ventricular dilatation might regulate coronary flow and cardiac load [3]. The other beneficial effect of CAP is that it has a similar antioxidant character [29]. ACE inhibitors can also elevate the kallikrein/kinin system [27], so it may cause volume overload in the heart [30]. Probably, ACE inhibitor restored oxidative stress, and eventually caused cardiac ischemia-reperfusion damage.

In contrast, local or tissue RAS (tRAS) plays a more important role under pathophysiological conditions due to its autocrine/paracrine interactions [24]. Its pathophysiologic effects are related to reactive oxygen species (ROS). Importantly, these ROS are generated by some enzymes (e.g., NAD(P)H oxidase, eNOS, and xanthine oxidase enzyme) [17]. It should also be noted that the role of cardiac renin production is still unclear. Although some researchers suggest the heart can produce renin, others disagree. Additionally, the first and rate-limiting step in Ang-II production is primarily renin enzyme, which catalyzes angiotensinogen to the physiologically inactive decapeptide, Ang-I. Therefore, one of the renin inhibitors, aliskiren, was used in the present study to prevent Ang-II production and local RAS effects on the heart [3].

RAS inhibition can also be achieved by renin inhibitors, which are thought to be more efficient than other inhibitors such as ACE or ARBs, and (in theory) is the first rate-limiting step in RAS. Also, RAS blockade has been shown to compensate for elevated renin release. This theoretical efficiency of renin inhibitors is based on results showing that the renin inhibitor enalkiren has more effect on vasodilatation renal response compared to CAP. On the other hand, renin inhibitors have not been successful used in clinical practice because of lack of potency and poor bioavailability. Additionally, the use of aliskiren in renin inhibition in rats might have affected the drug bioavailability. Aliskiren has been shown to have a higher specificity for human and mouse renin compared to rats because renin is a species-specific enzyme [9,31], which is why there is a limited ability to evaluate aliskiren in animal models. Ideally, we would have measured plasma renin or angiotensin-II levels in the present study. Angiotensin-II is also produced via alternative pathways that are independent of renin activity, such as chymase [32]. Therefore, renin inhibition by use of aliskiren might be able to decrease only one path of renin production, but not the other/others. However, the significance of other pathways is still a mystery.

Exposure of the heart to oxidative stress has been shown to depress left ventricular function and decrease blood pressure [10]. Following reperfusion in our study, a slight fall in MAP and HR were observed, which continued until the end of the reperfusion period. Decreased MAP ideally elicits reflex sympathetic activation, which should have increased heart rate. This may be explained in several ways. First, it was probably due to anesthesia-induced blunting of the neural reflex activity, and the fall in MAP might not be biologically adequate for reflex neural activation and impairment of conduction (arrhythmia and fibrillation) of the heart following ischemia and reperfusion-induced injury [10]. Second, blood pressure is a vital factor for blood supply and function in many different tissues. Its regulation is, therefore, complexly associated with local and systemic factors. The mere blunting of neural reflex activation is not meant to affect the blood pressure. The other possible reason is that Ang-II potentiates sympathetic coronary vasoconstriction in humans. ACE inhibition was shown to diminish sympathetic outflow, resulting in attenuation of blood pressure [3]. If the coronary flow is cut for 15–30 min, plasma renin activity increases. ACE and renin antagonists were shown to increase coronary blood flow by modulation of systemic vascular resistance and atrial pressure. The inhibition of RAS was indicated to decrease the heart dysfunction by modulation of blood and myocardial pressures in MI/R. Therefore, Ang-II aggravated the MI/R-induced heart dysfunction and injury characterized by decreased heart function [3].

ST-T alternation was observed in severe MI/R [33]. Moreover, antiarrhythmic drugs were reported to cause lethal arrhythmia [34]. When ACE-I blocks Ang-I production, renin can increase. Ang-II can, therefore, be produced by alternative pathways that are called nonACE. Combination therapy with ACE and renin inhibitions can give rise to elevated extracellular potassium concentration (hyperkalemia) [21]. The other reason for hyperkalemia is that most deaths due to myocardial ischemia occur within the first half hour [11], which may be why ACE inhibition-initiated arrhythmia results from an elevation of extracellular potassium concentration and falling pH.

There is some clinical evidence that RAS activity may be related to acute coronary syndrome. A recent study indicated that high ACE and angiotensinogen affect the structure and function arteries and the heart. The D allele of ACE was reported to influence plasma level and activity of the ACE enzyme, resulting in elevation of Ang-II sensitivity; this is believed to involve the interaction of MI/R, ventricular hypertrophy, and hypertension [35]. ECG elevation in patients is not the only parameter used to diagnose acute MI/R; it also has to be measured by a series of ECG for diagnosis. ECG alternation including ST elevation is also reported to occur in some other pathologies, such as left ventricular hypertrophy, left bundle branch block, and acute pericarditis. RAS inhibition by a using ACE or angiotensin

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receptor blockers (ARB) should begin within the first 24 h in patients with acute coronary syndrome. ACE-I has also been reported to decrease mortality in MI/R patients [36], but RAS inhibition may also cause hypotension, hyperkalemia due to aldosterone inhibition, and an increase of plasma creatinine level [36]. However, another study reported the opposite effect on aldosterone levels. CAP treatment of post-MI/R patients has been reported to decrease aldosterone levels. RAS inhibition by using ACE, ARB, or aldosterone inhibitors in acute coronary syndrome patients with large infarcts and decreased left ventricular function was indicated to increase survival rate and improve myocardial remodeling [37].

Conclusions

Angiotensin-II production appears to be associated with elevation of reactive oxygen species. On the other hand, Ang-II inhibition increases arrhythmias, mainly by initiating ventricular ectopic beats.

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Disclosures

The authors have no conflicts of interest to disclose.

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