Effect of atenolol pre-treatment in heart damage in a model of intestinal ischemia-reperfusion[1]

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Abstract

Purpose: To investigate the effects of atenolol in inflammatory mediator and oxidative stress in a myocardial injury by intestinal ischemia/reperfusion in rat model.

Methods: Adult Wistar male rats were randomly (n=8), anesthetized and divided in: Sham: submitted to operation only; group SS+IR: intravenous saline infusion following superior mesenteric artery occlusion during 60 minutes (ischemia) and open for 120 minutes (reperfusion); group AT+IR: intravenous atenolol infusion (2 mg/kg) following superior mesenteric artery occlusion during 60 minutes (ischemia) and open for 120 minutes (reperfusion); and group AT+I+AT+R: intravenous atenolol infusion following superior mesenteric artery occlusion during 60 minutes (ischemia) and in the time 45 minutes other atenolol doses were administrated and the artery was open for 120 minutes (reperfusion), all animals were submitted to muscular relaxation for mechanical ventilation. In the end of experiment the animals were euthanized and the hearts tissue were morphology analyzed by histology and malondialdehyde by ELISA, and the plasma were analyzed for tumor necrosis factor-alpha by ELISA.

Results: The group SS+IR demonstrated the higher malondialdehyde levels when compared with the atenolol treated-groups (p=0.001) in the heart tissue. The tumor necrosis factor-alpha level in plasma decrease in the treated groups when compared with SS+IR group (p=0.001). Histology analyses demonstrate pyknosis, edema, cellular vacuolization, presence of inflammatory infiltrate and band contraction in the heart tissue of the rats.

Conclusion: Atenolol significantly reduce the degree of cardiac damage after intestinal ischemia-reperfusion.

Key words: Adrenergic Antagonists. Atenolol. Ischemia. Reperfusion. Cytokines. Oxidative Stress. Rats.

■ Introduction

Ischemia and reperfusion (IR) injury of the intestine has been a significant health problem in terms of morbidity and mortality in many instances, such as abdominal aortic aneurysm surgery, intestinal transplantation, strangulated hernias, neonatal necrotizing enterocolitis, and other situations[1]. The intestinal IR can result in collapse of the systemic circulation (e.g., hypovolemic and septic shock) as well demonstrate[2-5].

Intestinal IR damages the intestinal mucosal barrier and induces systemic inflammation through the endogenous generation of the oxygen-derived free radicals (OFRs), proinflammatory cytokines (e.g. TNF-alpha), and a large amount of nitric oxide (NO) from inducible NO synthase (iNOS), thus, leading to the inflammatory injury and cell apoptosis[5-7]. The local and systemic inflammatory responses were caused by generation of a variety of proinflammatory mediators, such as TNF-alpha and oxygen free radicals in the circulation results in the systemic inflammatory response syndrome, one of major causes for morbidity and mortality during illness in general[5,8].

Activated polymorphonuclear neutrophils (PMN) and proinflammatory cytokines are then released into the systemic circulation, interact with the vascular endothelium of distant organs, therefore, contributing to the systemic inflammatory response[8,9].

Atenolol (an earlier-generation beta-1-selective blocker) is an antihypertensive agent with cardiac selectivity offer theoretical advantages over non-selective drugs in patients with bronchial asthma, peripheral vascular disease[10], decreased cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension[11]. Here we tested the hypothesis that treatment with AT would inhibit proinflammatory cytokine and diminish the production of oxygen free radicals in intestinal IR-induced heart injury in rats.

■ Methods

This study was approved by the Animal Experimentation Ethics Committee (CEUA - 5980160514), Universidade Federal de São Paulo (UNIFESP), complying with the guidelines of the Brazilian College of Animal Experimentation (COBEA).

Adult, male Wistar albino rats (n=32) weighing between 260 and 310 g, from the Center for Experimental Models Development in Medicine and Biology (UNIFESP) were used. Five animals per cage were kept with free access to filtered water and rodent chow (SuppraLab®, São Paulo, Brazil) under standard conditions of light (12/12 h dark cycle), humidity (45-55%) and temperature (25°C).

Experimental design and Surgery

After weighing, animals were anesthetized with a combination of xylazine (8-10 mg/kg; Ceva, São Paulo, Brazil) and ketamine (60-80 mg/kg; Cristália, São Paulo, Brazil) intramuscular injection the abdomen and groin were shaved and washed with 10% povidone iodine, intraperitonially injection at pancuronium (1 mg/kg) for muscle relaxation following mechanical ventilation (tidal volume, 5 mL/kg; positive end-expiratory pressure, 2 cmH$_2$O; fraction inspired of oxygen, 21% and respiratory rate, 60-70 ipm). The femoral vein was catheterized for fentanyl infusion (2 μg/kg/h). After confirmation of anesthetic plan, the midline laparotomy was performed and the superior mesenteric artery was identified, dissected and repaired, except in the Sham group. In all groups after mesenteric clamping the abdominal incision were then closed with

2-0 suture, opened for clamp removal and closed again until the end of reperfusion (the intestinal tract was placed between gauze pads that had been soaked with warmed 0.9% NaCl solution). The occlusion of the superior mesenteric artery was confirmed by observing loss of pulsation of the mesenteric artery and its branches as well as paleness of the jejunum and ileum and the blood recirculation was performed with a clip removal (confirmed by observing the pulsation of the artery and its branches on the intestine).

The animals were divided (n= 8/group) in: Sham: operated only; SS+IR: intravenous saline solution for 30 min following by superior mesenteric artery occluded for 60 min and 120 min of reperfusion; AT+IR: intravenous AT for 30 min following by superior mesenteric artery occluded for 60 min and 120 min of reperfusion; AT+I+AT+R: intravenous AT for 30 minutes following by superior mesenteric artery occluded for 60 min, and in the time 30 min of ischemia other dose of AT was administered and 120 min of reperfusion.

Atenolol protocol

Atenolol (Sigma, São Paulo, Brazil; 2 mg/kg) solution was administered (by femoral vein) 30 minutes before ischemia (group AT+IR) or 30 minutes before and after ischemia (group AT+I+AT+R).

Cytokine analyses

Blood sample of each animal was collected through cardiac puncture just before the sacrifice followed immediately by the centrifugation of the samples and stored at -80ºC until measurement of TNF-alpha. The detection of TNF-alpha in plasma of each animal was determined by the quantitative sandwich enzyme-linked immuno-sorbent assay techniques according to the manufacturer's instructions (Rat TNF-**α** ELISA Kit®, R&D System, Minnesota, USA).

Biochemical analyses

In the end of experiment, after cardiac puncture, anesthetized animals were euthanatized by T-61 Euthanasia Solution® (Schering-Plough, SP, Brazil) and the thoracotomy was performed and the heart was immediately removed and washing for removing the debris as well as the fat tissue around, the samples were divided for biochemical (stored at -80ºC) and histological analyses.

After reperfusion, myocardial tissue was homogenized in ice-cold phosphate buffer to make a 10% homogenate. Then the homogenate was centrifuged at 3.000 rpm for 15 min.

Malondialdehyde analyses

The lipid peroxidation is used for a index of oxygen free radical production. The tissue samples were homogenized in 1 mL of 1.15% KCl (Synth, São Paulo, Brazil) with sonicator (Q700®, QSonica, Connecticut, USA). The MDA content in cardiac tissue was measured using an OxiSelect™ MDA Adduct ELISA kit (Cell Biolabs, Inc., CA, USA) using a spectrophotometer (Genesys, Thermo Scientific, MA, USA) in absorbance at 450 nm.

Histologic evaluation

The other part of heart was fixed in 10% formalin, embedded in paraffin, and sections of 4-5 µm were done. The slides were stained with hematoxylin and eosin (HE) and evaluated under an optical microscope (x400 and x1.000) (Zeiss Axion Image A2®, Oberkochen, Germany) by an experienced pathologist blinded, descriptive analysis, to the

different groups. On histologic examination, the myocardium lesions were classified according to the presence of: hyperemic blood vessels, pyknosis, inflammatory infiltration, cardiomyocytes degeneration, loss of striation and interstitial edema.

The score for cardiac damage analysis was adapted from Aneja *et al.*[12]: 0= is no damage; 1 (mild)= hyperemic blood vessels, pyknosis; 2 (moderate)= hyperemic blood vessels, pyknosis and inflammatory infiltration; 3 (severe)= hyperemic blood vessels, pyknosis, inflammatory infiltration and cardiomyocytes degeneration; 4 (highly severe)= the same condition of score 3 with loss of striation.

Statistical analysis

Histological sections were interpreted by professionals blinded to the group and timing of the experiments. Quantitative data were summarized as means and standard deviations (m±SD) and compared using one-way analysis-of variance (ANOVA) using a SPSS software 13.0 (SPSS Inc., IL, USA). $P<0.05$ were considered statistically significant.

■   Results

All animals survived during the total time of experiment. The MDA content (Figure 1) of heart samples from Sham (2.43 ± 0.28 pmol/mg) animals was statically significant when compared with all others groups ($P = 0.001$). The level of MDA in group SS+IR (8.0 ± 0.37 pmol/mg) was higher when compared with the treated groups. On the other hand, average MDA contents of tissues from AT+IR (5.6 ± 0.35 pmol/mg) and AT+I+AT+R (5.15 ± 0.49 pmol/mg) groups were statistically different ($P < 0.05$).
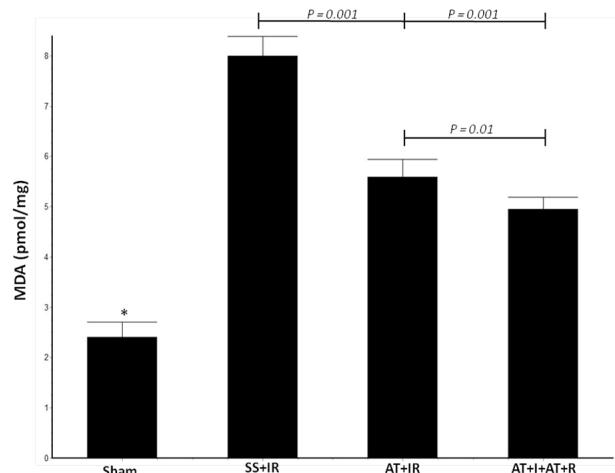

Figure 1 - Effect of AT on tissue MDA level after intestinal IR. Average MDA level of tissue samples collected from sham operated control, IR control, AT+IR, and AT+I+AT+R groups. Data are expressed as the mean ± standard deviation of the mean (p < 0.05, ANOVA, Tukey post hoc.).

TNF-alpha level (Figure 2) in the plasma samples from Sham (87.75 ± 5.339 pg/mL) group was statistical significant when compared with all others group ($P = 0.001$). In the group SS+IR (288.37 ± 10.04 pg/mL) the TNF-alpha was increased when compared with AT+IR (226.50 ± 26.19 pg/mL) group ($P = 0.001$) and AT+I+AT+R (194.25 ± 32.60 pg/mL) group ($P = 0.001$). The statistical difference was observed between AT+IR and AT+I+AT+R ($P < 0.05$).
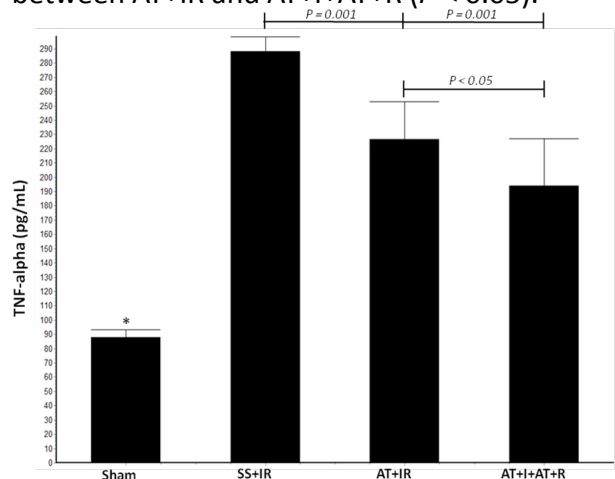

Figure 2 - Effect of AT on plasma TNF-alpha level after intestinal IR. Average TNF-alpha level of plasma samples collected from sham operated control, IR control, AT+IR, and AT+I+AT+R groups. Data are expressed as the mean ± standard deviation of the mean (p < 0.05, ANOVA, Tukey post hoc.).

The histological analysis was performed using the cardiac tissue from each group and the description made by two pathologists who were unaware groups to which the samples belong. The most several alterations were observed in the SS+IR, interstitial edema, hyperemic blood vessels, pyknosis, inflammatory infiltration and derangement of myocardium fibers. In the Sham group, normal configuration was evident. Pretreatment with one and two AT doses resulted in reduction of damage (Figures 3 and 4). The score of cardiac tissue damage (Figure 5) was significant when compared the group SS+IR (3.85 ± 0.35) with the treated groups ($P = 0.001$).
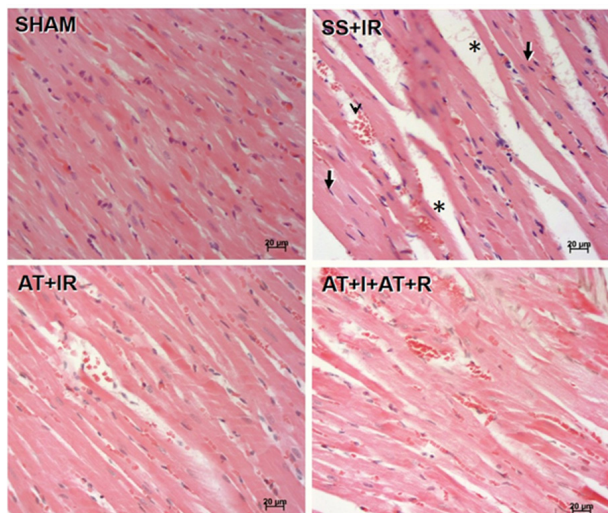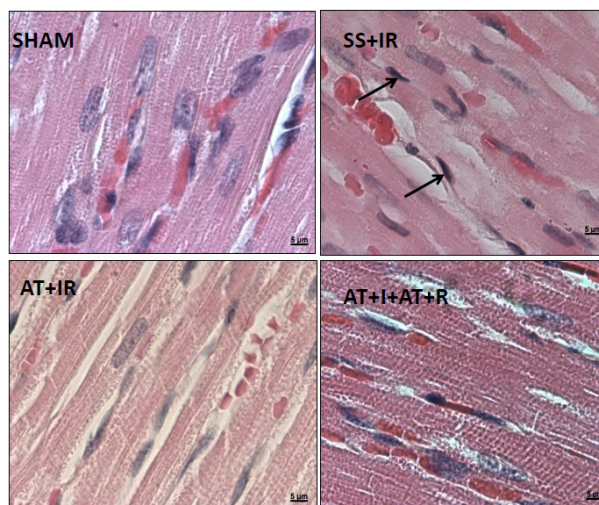

Figure 4 - Photomicrographs of the cardiac tissue from Sham, saline solution infusion and ischemia-reperfusion (SS+IR), and atenolol pretreated groups (AT+IR and AT+I+AT+R). Observe in SS+IR group the presence at pyknotic nucleus (*arrows*), degeneration of cardiomyocytes evidenced by loss of striations and no presence of this alterations in the treated groups. HE, x1.000.

Figure 3 - Photomicrographs of the cardiac tissue from Sham, saline solution and ischemia-reperfusion (SS+IR), and atenolol treated groups (AT+IR and AT+I+AT+R). Observe in SS+IR group the damage tissue with derangement of myocardium fibers and band contraction, dispersed pyknotic nucleus (*arrows*), hyperemic blood vessels (*arrowhead*), and interstitial edema (*). In pretreated groups (AT+IR and AT+I+AT+R) this effects were diminished. HE, x400.
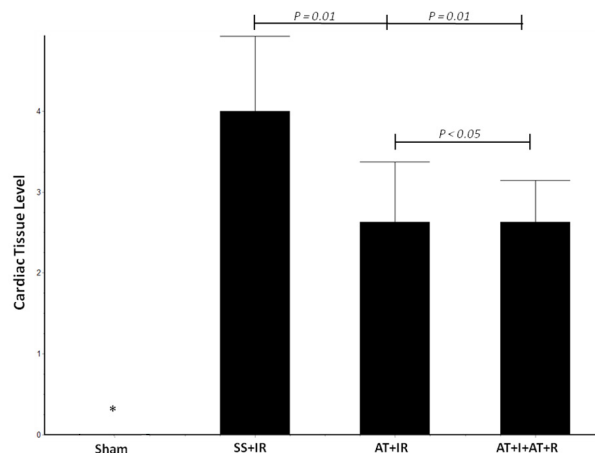

Figure 5 - The cardiac tissue injury scores in rats submitted to intestinal ischemia-reperfusion (IR) associated or not to the treatment with atenolol (AT), according to the morphological evaluation. Data are expressed as the mean ± standard deviation of the mean ($p < 0.05$, ANOVA, Tukey post hoc.).

■ Discussion

The present work showed in an acute rat model of intestinal ischemia-reperfusion that administration of AT before ischemia and during reperfusion protects the heart against systemic inflammation by the generation of the oxygen-derived free radicals and TNF-alpha and all animals survived at the end of experiment.

The phenomenon of intestinal ischemia and reperfusion is a frequent event in the clinic and is associated with deleterious effects on the distance organs, especially the heart. The IR, and consequent oxidative stress is associated with medical and surgical conditions such as: sepsis, arterial occlusive trauma, cardiac arrest, thrombosis, embolism, vasospasm, transplantation and resection of organs and myocardial infarction[13].

Intestinal ischemia followed by reperfusion is closely related to the generation and modulation of reactive oxygen species phenomenon. Local changes in the gut promote humoral and cellular responses that, spread into the bloodstream, affect the homeostasis by inducing cardiac tissue related responses with generation of the oxygen-derived free radicals[1,14-17]. Inflammatory cells and free radicals have been shown to contribute to cardiac dysfunction caused by intestinal ischemia-reperfusion injury[18,19].

Malondialdehyde (MDA), the product of lipid peroxidation, is a good marker of free radical-mediated damage and oxidative stress. Increased levels of lipidic peroxidation products, by measurement of MDA, have been associated with various conditions and pathological states of diseases, including states of ischemia and reperfusion. The increases of oxygen inside cells favor the production of free radicals, causing damage in biological membranes rich in lipids[19].

We observed in our study, the MDA content of heart samples from Sham animals was statically significant when compared with all others groups, and level of MDA in group SS+IR was higher when compared with the treated groups.

The NADPH oxidase is a group of enzymes with oxidase intracellular expression, perinuclear and present in many tissues, and their presence in significant cardiovascular tissue[20]. This system is involved in the production of reactive oxygen species, vasomotor control and apoptosis. Inflammatory cytokines, including TNF-alpha, act as modulators of gene expression of NADPH system[21].

In our study, TNF-alpha level in the plasma of pre-treated groups, were decreased when compared with SS+IR, and statistical difference was observed between AT+IR and AT+I+AT+R groups. The TNF-alpha derived from macrophages can be interacting with endothelial cells, inducing the expression of adhesion molecules ICAM-1, VCAM-1 and E-selectin, permitting the access of leukocytes in inflammatory focus, favoring adherence, chemotaxis, degranulation and oxidative burst[22]. Previous reports demonstrated the importance of TNF-alpha in lesions and lethality associated with ischemia and reperfusion, evaluated local and systemic lesions, and the use of strategies to diminish TNF-alpha production are associated with reduction of lethality[23].

In relation to intestine lesion, besides local tissue damage, occurs the risk of systemic compromise by the amplification of process to distant organs, e.g. heart[24,25]. This hypothesis can be reinforce by the histological analysis of heart, where most several alterations were observed in the SS+IR group. Intestinal ischemia active sympatric nervous system, can be resulting increase of arterial blood pressure[26], with more blood inside heart, making the myocardium muscle work with more power to eject this blood to the rest of body, with

increase of intracellular calcium, oxygen and metabolites. Theses intracellular products can be response with dysfunction in myocardial contraction and relaxation, a consequence of intestinal ischemia-reperfusion in experimental animals[19,27].

The actions of beta-blocker were different in the lipophilicity, cardioselectivity, and vasodilatation. Drugs, such as carvedilol, metoprolol and labetalol are lipid solubility and have peripheral vasodilators effects; other drugs, such atenolol and practolol are not lipid solubility and not have peripheral vasodilator effects, moreover possess cardiac selectivity[10,28,29].

Earlier studies have shown that carvedilol, a beta-blocker commonly used to treat cardiovascular diseases, such as hypertension, prevents lipid peroxidation and depletion of endogenous antioxidants[28].

Atenolol, a beta-1-selective blocker, is implicating with cross-talk between adrenoceptors and adenosine receptors to promote cardioprotection and other cytoprotective effects[29]. Campos *et al.*[30] where AT attenuated the motor and neural dysfunctions in rat small bowel caused by ischemia-reperfusion.

Ischemia-reperfusion injury of the gastrointestinal tract not only causes local damage, but may also be a factor in the development of multiple organ dysfunction syndrome associated with reperfusion injury, and atenolol, probably cause inference in adenosine receptors to promote local and systemic cytoprotection[30]. In our experiments, the heart injury was distally induced, by intestinal IR, as well the preventive action, by AT infusion.

The extrapolation the cardiac dysfunction in a rat model of intestinal IR to the human patients is necessary extreme caution, because was expected, in humans, to reduce diastolic filling and ejection fraction when exist intestinal hypoperfusion. In this context, the study of new pharmacological interventions is very important to reduce organic lesions caused by intestinal ischemia and reperfusion, with important repercussion in mortality of patients.

■ Conclusion

The treatment with atenolol attenuated the cardiac dysfunctions in rat small bowel caused by ischemia-reperfusion.

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