A potential role of endothelins in rheumatic mitral stenotic valves


Background: The genesis of rheumatic mitral valve stenosis has been correlated with the action of endothelin subtype 1 (ET-1) and its receptors (ETAR and ETBR). We aim to analyze, through real time PCR (polymerase chain reaction), the gene expression of ET-1 in rheumatic mitral valves. Methods: This is a randomized and experimental study. We collected ten mitral valves in two hospitals of Aracaju, Brazil. Each valve has suffered fragmentation, originating three segments that were subjected to extraction of total RNA. Then, each sample of total RNA was quantified by spectrophotometry. Through reverse transcriptase reaction, the total cDNA was obtained from each sample and then, the technique of amplification of target fragment by real time PCR with the quantification of each sample was performed. Data were tabulated and analyzed by CFX96 Real Time System (BIORAD), and the calculations of relative expression were performed by use of the Delta Ct. Results: The analyzed by CFX96 Real Time System (BIORAD), and the calculations of technique of amplification of target fragment by real time PCR with the quantification of each sample was performed. Data were tabulated and analyzed by CFX96 Real Time System (BIORAD), and the calculations of relative expression were performed by use of the Delta Ct. Results: The calculated amount of ET-1 gene relative expression was 0.78 ± 0.10 fold in samples from valves with stenosis compared to normal valves. Conclusions: The expression of ET-1 was detected in all samples analyzed, and the average gene expression relative to ET-1 was 0.78 ± 0.10 fold in samples from valves with stenosis compared to normal valves.

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Blood pressure independent downregulation of plasma endothelin-1 levels in a lavage-induced surfactant depleted rabbit ARDS model: Effects of various respiratory maneuvers on endothelin-1 levels

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Background: The pathogenesis of acute lung injury (ALI) is poorly defined. Endothelin (ET)-1, a potent vasoconstrictor, is a mediator of vascular inflammation, cell proliferation, and is, in addition, a potent vasoconstrictor. Previously, treatment with ET-1 antagonists was shown to reduce pulmonary vascular leak and inflammation in several models of lung injuries as well as in experimental acute respiratory distress syndrome (ARDS). The current study used an experimental model of lavage-induced surfactant depleted ARDS, to investigate the circulatory and pulmonary levels of ET-1. In addition, we also tested the effects of open endotracheal suctioning (OES) [a known inducer of alveolar de-recruitment] and the post-OES hyperinflation (HI) (performed to recover the alveolar de-recruitment using bagging) on ET-1 levels. Briefly, 18 Japanese White Rabbits were anesthetized and intubated. Normal saline was instilled into the lung and washed mildly. After instillation, rabbits were ventilated at definite settings; total OES and HI duration was for 3 h and performed every 15 min from the beginning of the protocol. Circulatory levels of ET-1 were found to have decreased from baseline (3.26 ± 1.01) to after lavage (1.82 ± 1.59, p = 0.003), without any significant change in mean blood pressure (baseline 112 ± 13.8; after lavage 113 ± 12.5, p = 0.848). In contrast, pulmonary ET-1 levels were almost unchanged irrespective of the induction of lavage-induced lung injury from baseline. It must be noted that, in lung injury state, PaO2 was significantly decreased, having a parallel relation with ET-1. Either OES or HI failed to recover the down-regulated circulatory ET-1 level. For now, we cannot rule out the mechanism of differential pattern of circulatory ET-1 levels observed in the current model compared to other ARDS models.

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Upregulated pulmonary endothelin-1 in acute lung injury is not normalized through landiolol hydrochloride treatment, an ultra-short-acting β-blocker, in a rat model of endotoxemia

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Background: The genesis of acute lung injury (ALI) is poorly defined. Endothelin (ET)-1, a potent vasoconstrictor, is a mediator of vascular inflammation, cell proliferation, and is, in addition, a potent vasoconstrictor. Previously, treatment with ET-1 antagonists was shown to reduce pulmonary vascular leak and inflammation in several models of lung injuries as well as in experimental acute respiratory distress syndrome (ARDS). The current study used an experimental model of lavage-induced surfactant depleted ARDS, to investigate the circulatory and pulmonary levels of ET-1. In addition, we also tested the effects of open endotracheal suctioning (OES) [a known inducer of alveolar de-recruitment] and the post-OES hyperinflation (HI) (performed to recover the alveolar de-recruitment using bagging) on ET-1 levels. Briefly, 18 Japanese White Rabbits were anesthetized and intubated. Normal saline was instilled into the lung and washed mildly. After instillation, rabbits were ventilated at definite settings; total OES and HI duration was for 3 h and performed every 15 min from the beginning of the protocol. Circulatory levels of ET-1 were found to have decreased from baseline (3.26 ± 1.01) to after lavage (1.82 ± 1.59, p = 0.003), without any significant change in mean blood pressure (baseline 112 ± 13.8; after lavage 113 ± 12.5, p = 0.848). In contrast, pulmonary ET-1 levels were almost unchanged irrespective of the induction of lavage-induced lung injury from baseline. It must be noted that, in lung injury state, PaO2 was significantly decreased, having a parallel relation with ET-1. Either OES or HI failed to recover the down-regulated circulatory ET-1 level. For now, we cannot rule out the mechanism of differential pattern of circulatory ET-1 levels observed in the current model compared to other ARDS models.

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has been implicated in the pathogenesis of sepsis. We recently demonstrated that ET-1 plays an important role in the development of ALI in a rat model of sepsis. As an extension of recent study, in this investigation we investigated whether landiolol hydrochloride, an ultra-short-acting β-blocker, can play an important role in ameliorating LPS-induced ALI through the normalization of ET-1. Male Wistar rats at 8 weeks of age were administered with either saline or lipopolysaccharide (LPS) for 3 h and some LPS-administered rats were continuously treated with landiolol for 3 h. The features of acute lung injury were observed at sepsis model. At 3 h after LPS administration, both circulatory and pulmonary TNF-α levels increased and PaO2 significantly decreased LPS administration. LPS induced a time-dependent expression of ET-1 in the lungs compared to control, peaking and increasing by 3 fold at 6 h after induction of endotoxemia, whereas levels of ET (B) receptor, which has vasodilating effects, were remarkably down regulated time-dependently. We conclude that time-dependent increase of ET-1 and ET (A) receptor with the down regulation of ET (B) receptor may play a role in the pathogenesis of acute lung injury in endotoxemia. Finally, treatment of LPS-administered rats with landiolol for 3 h failed to normalize the upregulated pulmonary ET-1 and TNF-α levels. Another study found that landiolol can ameliorate ALI in LPS-induced sepsis model. These data taken together, led us to conclude that landiolol mediated ALI improvement in sepsis does not involve pulmonary ET system.

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Blockade of TRPC6 is a novel therapeutic approach against pathological cardiac remodeling
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Background: Expression of transient receptor potential subfamily C (TRPC) 6, receptor-operated Ca2+ channels, is increased in hypertrophic and failing hearts. TRPC6 has been shown to be a positive regulator of calcineurin-NFAT signaling that drives pathological cardiac remodeling. In this study we examined the effect of TRPC inhibition on the pathological cardiac hypertrophy. Methods and results: In cultured neonatal rat ventricular myocytes, overexpression of TRPC6 increased basal and ET-1 induced NFAT-dependent RCAN1 promoter activity. BTP2, a selective TRPC channel blocker, significantly and dose-dependently inhibited activation of the RCAN1 promoter, and attenuated hypertrophic response of cultured cardiac myocytes. Knocking-down of TRPC6 and 3 using siRNAs significantly inhibited ET-1- or Ang II-induced increases in Ca2+ oscillation, and knocking down either TRPC6 or 3 had a similar effect. In model mice lacking GC-A, which is a common receptor for atrial and brain natriuretic peptides, the expression of TRPC6 and RCAN1 was increased and BTP2 significantly attenuated the cardiac hypertrophy observed in GC-A KO mice without affecting blood pressure. BTP2 also inhibited AngII-induced cardiac hypertrophy in mice. Compatible with the notion that TRPC6 and 3 form heteromultimeric cation channels, Pyrazole-3, a selective TRPC3 blocker, which can inhibit the ion channel activity of TRPC6 hetero-complex, also significantly inhibited Ang-II induced cardiac hypertrophy in mice. Conclusions: Blockade of TRPC6 could be a novel therapeutic strategy for preventing pathological cardiac remodeling.

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Effects of landiolol hydrochloride, an ultra-short-acting β-blocker, on cardiac endothelin system in a rat model of endotoxia: A possible relevance with cardiac functional compensatory events at the early phase of sepsis
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Landiolol, an ultra-short-acting and highly cardioselective beta-1 blocker, has become useful for various medical problems. Recent studies have demonstrated that co-treatment with landiolol protects against acute lung injury and cardiac dysfunction in a rat model of lipopolysaccharide (LPS)-induced systemic inflammation which was associated with a significant reduction in serum levels of the inflammation mediator HMGB-1 and histological lung damage. Endothelin (ET)-1, a potent vasoconstrictor, has been implicated in the pathogenesis of sepsis and sepsis-induced multiple organ dysfunction syndrome. In the current study, we investigated whether landiolol hydrochloride could play an important role in ameliorating the LPS-induced altered cardiac ET system in a rat model of endotoxia. Male Wistar rats at 8 weeks of age were administered LPS for 3 h and some LPS-administered rats were continuously treated with landiolol for three hours. At 3 h after LPS administration, circulatory TNF-alpha level was highly increased. Blood lactate concentration and percentage of fractional shortening of heart have also significantly increased after LPS administration. In addition, LPS induced a significant upregulated expression of various components of ET-1 system in the cardiac tissues compared to control. Finally, treatment of LPS-administered rats with landiolol for 3 h potentially normalized the ET-1 system in endotoxemic heart. These data taken together, led us to conclude that landiolol may be cardio protective in endotoxemia normalizing the vasoactive peptide like endothelin without altering the circulatory level of potential inflammatory cytokine like TNF-alpha.

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Inhibitory effect of eicosapentaenoic acid on cardiomyocyte in endothelin induced hypertrophy via PPAR-α
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Growing body of evidences state the cardiovascular benefit of fish oil including eicosapentaenoic acid (EPA) in humans and experimental animals, but the effect of EPA on endothelin (ET)-1-induced