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 \( \beta \)-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-\( \alpha \) 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-\( \alpha \) 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 Ca\(^{2+}\) 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 RACAN1 promoter activity. BTP2, a selective TRPC channel blocker, significantly and dose-dependently inhibited activation of the RACAN1 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 Ca\(^{2+}\) 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 RACAN1 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 TRPC3/6 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 \( \beta \)-blocker, on cardiac endothelin system in a rat model of endotoxemia: 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 can play an important role in ameliorating the LPS-induced altered cardiac ET system in a rat model of endotoxemia. 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 increased blood lactate level, cardiac functional compensatory events without an effect on plasma TNF-alpha and ET-1 levels. Most strikingly, landiolol treatment has greatly normalized the various components of 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-\( \alpha \)

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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
cardiomyocyte hypertrophy is unknown. Previous study demonstrated that peroxisomal proliferator-activated receptor (PPAR)-α ligand (fenofibrate) prevents ET-1-induced cardiomyocyte hypertrophy. Though EPA is a ligand of PPAR-α, there was no study linking relationship between EPA and PPAR-α in the field of cardiomyocyte hypertrophy. The present study investigated whether ET-1-induced cardiomyocyte hypertrophy could be prevented by EPA pre-treatment with possible mechanistic insights. At day 4 of culture, neonatal rat cardiomyocytes were divided into three groups: control, ET-1 (0.1 mM) treated and EPA-pre-treated (10 μM) ET-1 groups. 2-fold increase in cardiomyocyte surface area, 1.8-fold increase in total protein synthesis rate and an enhanced α-actinin expression in cardiomyocyte were observed after ET-1 administration and these changes were greatly prevented by EPA pre-treatment. ET-1-induced hypertrophied cardiomyocytes showed increases in ANP and BNP mRNA expression, which were also suppressed by EPA pre-treatment. Pre-treatment of EPA could also attenuate phosphorylated JNK (an important component of MAPK cascade) and c-Jun (downstream molecules of JNK) in ET-1-induced hypertrophy. The present study investigated whether ET-1-induced hypertrophy and hypertrophic markers upregulation, and that this remodeling was effectively prevented by EPA pre-administration through the upregulation of PPAR-α and the suppression of phosphorylated JNK, and c-Jun.

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Higher circulatory level of endothelin-1 in hypertensive subjects screened through a cross-sectional study in rural Bangladeshi women
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Objective: Endothelins are powerful vasoconstrictor peptides that also play numerous other functions in many different organs. Endothelin-1 (ET-1) mainly produced by pulmonary vascular endothelium and increased concentration of ET-1 suggests endothelial dysfunction already in mild forms of hypertension without further risk factors or cardiovascular complications in this apparently healthy population.

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Inverse correlation between systemic endothelin-1 level and pulmonary artery pressure in adult patients with uncorrected atrial septal defect
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Patients with ASD have increased pulmonary blood flow and may cause increase in pulmonary arterial pressure. Endothelin-1 (ET-1) mainly produced by pulmonary vascular endothelium and increased plasma ET-1 level has been reported in patients with left-to-right shunt. ASD is the most common congenital shunting in adult. However, no study addressed specifically for ASD and has evaluated the role of ET-1 in this congenital shunting. Therefore, we aim to correlate the peripheral ET-1 level with pulmonary arterial pressure in adult patients with uncorrected ASD. From July 2012–April 2013 we enrolled 55 ASD patients; mean age 34.5 years-old. Confirmation of ASD and the measurement for pulmonary arterial pressure (mPAP), right ventricular systolic pressure (RVSP), and pulmonary flow ratio (Qp/Qs) were performed using TTE and TEE. These measurements were previously confirmed with right heart catheterization and showed positive correlation (r = 0.5; p = 0.0001 and r = 0.8; p = 0.0001 respectively). Peripheral blood was withdrawn from brachial vein. Forty (72%) patients have left-to-right and 28% with right-to-left shunting. Mean mPAP was 40.1 ± 14.9 mm Hg; mean circulating ET-1 was 5.6 ± 2.1 pg/dl. Unexpectedly, the correlation between circulating level of ET-1 and mPAP was significantly inversely (r = -0.452;p < 0.01), and with RVSP was also significantly negative (r = -0.405;p < 0.01). Accordingly, the reduced circulating ET-1 level might be explained by the decrease in Qp/Qs (r = 0.310;p < 0.05). However, no differences of ET-1 were found between LtoR vs RtoL shunts (5.7 ± 0.36vs.5.3 ± 0.52 pg/dl; NS). As a conclusion, we observed decreased ET-1 and mPAP that might partially be explained by the decreased in pulmonary flow. Further study to elucidate whether pulmonary derived ET-1 may play more roles in this disease is needed.

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Synchrotron radiation pulmonary micro-angiography to visualize pulmonary artery micro-vasculature for measurement of pulmonary arterial flow velocity in a high pulmonary flow rat model
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Objective: Synchrotron radiation pulmonary micro-angiography (SR-PA) has been developed for the visualization of pulmonary micro-vasculature. However, there is no report that SR-PA could visualize pulmonary blood flow velocity. The aim of this study is to visualize pulmonary artery micro-vasculature and determine the flow ratio in a high pulmonary flow rat model.

Materials and Methods: Four-week-old male Sprague-Dawley rats were used. A total of 20 rats were divided into 2 groups; control and high pulmonary flow group. In the high pulmonary group, right atrial shunt was made between the right atrium and common femoral artery. Pulmonary artery flow ratio (Qp/Qs) were determined using PA-Doppler. Synchrotron radiation pulmonary micro-angiography was performed using Synchrotron YBM, Tsukuba, Ibaraki, Japan. After performing Synchrotron radiation pulmonary micro-angiography, we visualized pulmonary artery micro-vasculature for measuring pulmonary blood flow velocity using SR-PA system.

Results: A total of 1802 rural Bangladeshi women with mean age of 44.16 years were studied using a cross-sectional survey. The prevalence of hypertension was 31.78%. Endothelin-1 levels were significantly higher in hypertensive than in non-hypertensive subjects (hypertensive vs non-hypertensive: 4.16 ± 0.32 vs. 3.00 ± 0.08 pg/ml, p < 0.001). After adjusting for age, ET-1 had significant positive associations with diastolic blood pressure (DBP) (β = 0.039, p = 0.013) and systolic blood pressure (SBP) (β = 0.020, p = 0.066). Unlike blood pressures, other variables including insulin, fasting blood glucose, triglycerides, high-density lipoprotein cholesterol, body mass index, waist circumference and vascular endothelial growth factor were not associated with ET-1. Stepwise multiple regression analysis, after adjusting for age and all other potential variables revealed that SBP and DBP were independent determinants of ET-1. Conclusions: The correlation of ET-1 needs further investigations to define the clinical utility and predictive value of serum ET-1 levels in hypertension for South Asian population. Higher concentration of ET-1 suggests endothelial dysfunction already in mild forms of hypertension without further risk factors or cardiovascular complications in this apparently healthy population.

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