entered as independent predictors of aortic pulse wave velocity (PWV, a traditional index of arterial stiffness) into the stepwise regression analysis of sex, antihypertensive medication use, body mass index, blood test results, resting blood pressure, daily physical activity and diastolic blood pressure and HR during the exercise ($r^2 = 0.634$, $P < 0.001$). In subgroup analyses according to average SBP during the exercises, aortic PWV was higher in the high SBP group than the low SBP group independent of resting SBP ($P < 0.001$). We concluded that SBP during resistance exercise is independently correlated with arterial stiffness. The following steps are to elucidate whether excessive blood pressure elevation during resistance exercise increases arterials stiffness by prospective study and to investigate its relationship to ET-1 system.

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A study of endothelins and endothelin receptors in rheumatic mitral valves

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Introduction: Rheumatic fever represents a serious public health problem in Brazil, with thousands of new cases each year. It is an inflammatory and autoimmune disease, which occurs in response to infection by *Streptococcus* A group. The aim of this study was to evaluate the immunolabeling for ET-1,ET-A and ET-B receptors in rheumatic mitral valves. Methods: This study focused in quantitative immunoreactivity of ten mitral valves which were collected at a hospital in Aracaju, SE, Brazil. The quantitative analysis of the immunocytochemistry area of each receptor in relation to the total area of each slide was performed by ImageJ software. Statistical analysis was performed using measures of central tendency and standard deviation. In inferential analysis, we used the Pearson partial correlation (R), with significance level of <0.05. Results: In 10 samples, immunohistochemical expression for ET-1 and for its receptors was observed in eight and seven samples, respectively. In quantitative analysis, it was observed that the average area with expression of ET-1 was 18.21 ± 14.96%. For ETrA and ETrB, the mean expressed areas were respectively 15.06 ± 13.13% and 9.20 ± 11.09%. The correlation between the expression of both endothelin receptors was strongly positive (R: 0.74, p: 0.02), but the correlation between ET-1 and its receptors were negative for both ETrA (R: −0.37, p: 0.25), and ETrB (R: −0.14, p: 0.39). Conclusion: The strong positive correlation between endothelin receptors (ETrA more demonstrated than ETrB) suggests that both have a role in the pathophysiology of rheumatic mitral stenosis.

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Complement C5a antagonism is associated with reduced big-endothelin level after experimental cardiac tamponade

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Objective: Cardiac tamponade is a severe clinical syndrome most often caused by high-energy thoracic injuries. Following tamponade, the release of vasoconstrictive mediators contributes to circulatory redistribution, leading to peripheral macro- and microcirculatory complications including gastrointestinal hypoperfusion. As a consequence of hypoxia the complement system is activated and anaphylatoxin C5a may be produced. Our aim was to investigate the modulator effects of complement C5a antagonist (C5aA) treatment on the endothelin system and the accompanying circulatory and inflammatory changes in a large animal model of experimental cardiac tamponade. Methods: In anaesthetized, ventilated and thoracotomized minipigs (n = 7) tamponade was induced for 60 min by intrapericardial fluid administration, meanwhile the mean arterial pressure (MAP) was reduced to 40–45 mm Hg. Group 2 was treated with C5aA (AcPepA, Nagoya, Japan) at the 45th min of tamponade (4 mg/kg iv; n = 6), while group 3 (n = 6) served as sham-operated control. Macrohemodynamics were monitored for 240 min, whole blood superoxide production, plasma HMGB-1 and big-endothelin (big-ET) levels, small intestinal myeloperoxidase (MPO) activity were measured. Average red blood cell velocity (a-RBCV) in the small intestinal mucosa was determined by intravital orthogonal polarization imaging (OPS) technique. Results: After tamponade plasma levels of big-ET were increased together with superoxide production, HMGB-1 levels and MPO activities. The C5aA treatment normalized the macrohemodynamics, and besides the a-RBCV was increased, SOX, HMGB-1, MPO and big-ET levels were reduced. Conclusion: These results demonstrate the possible connections between the activation of complement- and endothelin systems, and the potential for C5aA to decrease the potentially harmful inflammatory consequences of experimental cardiogenic shock. Grant supports: OTKA-K104656; TAMOP-4.2.2A-11/1/KONV-2012-0035; TAMOP-4.2.2.A-11/1/KONV-2012-0073; TET-JP-16/09.

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Endothelin A receptor blockade and long term outcome in patients with ST elevation acute coronary syndrome

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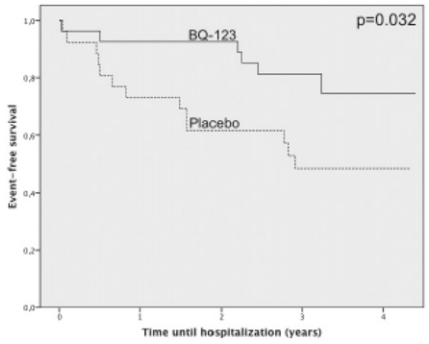
Background: ST-elevation acute coronary syndrome (STE-ACS) is characterized by thrombotic coronary occlusion compromising blood flow at the epicardial and microvascular levels. Coronary thrombi are a source of large amounts of endothelin-1 (ET-1), a pro-fibrotic vasoconstrictor and a mediator of microvascular dysfunction and cardiac remodeling. Methods: Patients with posterior-wall STE-ACS were randomly assigned to intravenous BQ-123 or placebo as described elsewhere (n = 54). During a three-year follow-up period, patients were followed and kept on optimal medical treatment by an investigator who was blinded to the acute treatment allocation. Results: During the median follow-up period of 3.3 years (IQR 2.9–3.7), no deaths occurred. The reasons for rehospitalisation (n = 19) were unplanned coronary revascularization (n = 10, 52%), worsening angina (n = 3, 17%), hypertensive urgency (n = 2, 11%), as well as stroke (n = 1), dyspnoea (n = 1), ventricular tachycardia (n = 1) and cerebrovascular disease (n = 1). We observed a longer event-free survival in patients randomized to receive BQ-123 compared

with patients randomized to placebo (3.8 years (95% CI: 3.3–4.2) for BQ-123 versus 2.8 years (2.1-3.4) for placebo, p = 0.032, Figure 1). Conclusion: Short-term administration of BQ-123 in patients undergoing primary PCI for STE-ACS leads to a longer cardiovascular event-free survival.



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Clinical features between heart failure and sleep disordered breathing

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Introduction: Little has been known about clinical background of the patients with heart failure (HF) and sleep disordered breathing (SDB). The aim of this study was to elucidate the relationship between HF and SDB. Methods: 1121 patients admitted to our institute with the diagnosis of HF between 2006 and 2012 was enrolled. SDB was defined >5/h of apnea–hypopnea index (AHI). Obstructive sleep apnea (OSA) group and central sleep apnea (CSA) group were defined based on the data of type III sleep monitor (Morpheus). Results: Among 1121 patients 328 (29%) underwent screening of type III sleep monitor. In the 328 patients, 275 (84%) patients showed SDB. Among these 275 SDB patients, 135 (41%) were OSA, and 140 (43%) were CSA. AHI was significantly higher (OSA: 22.5 ± 16.2, CSA: 29.8 ± 14.9, $P < 0.05$) and ejection fraction (EF) was significantly lower (OSA: 40.1 ± 17.1%, CSA: 33.5 ± 14.1%, $P < 0.05$) in CSA group between two groups. Among 140 CSA patients, 80 (57%) patients have heart failure with reduced ejection fraction (HFREF) and among 135 OSA patients, 60 (44%) patients have HFREF. Conclusions: SDB was highly associated with HF and the clinical features between OSA and CSA with HF were different. CSA patients were associated with lower EF and higher AHI than OSA patients. This study suggested that SDB was one of an important target of treatment HF and to treat HF according to these clinical subsets of SDB was clinically required in the future.

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Selective deletion of endothelin B receptors from vascular smooth muscle does not inhibit neointimal lesion formation

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Pharmacological inhibition and genetic deletion (Murakoshi et al., 2002; Kirkby et al., 2012) suggest that endothelin (ET) A-selective antagonists are preferable to mixed ETA/B antagonists for prevention of neointimal lesion formation. ETB receptors expressed in smooth muscle cells may, however, contribute to lesion development. It was proposed that ETB deletion from smooth muscle (SM) would reduce lesion formation following arterial injury. Methods: Mice bearing a floxed ETB gene or expressing cre-recombinase under the SM22 promoter were crossed to produce SM-selective ETB deletion. SMETB knockout mice were identified by genotyping and backcrossed to C57Bl/6J (4–6 generations). Functional confirmation of ET deletion was determined by exposing trachea, and mesenteric artery and vein, to sarafotoxin 6c in a myograph. Femoral injury was performed in adult, male SMETB knockout mice and littermate controls and arteries were harvested 33 days later for structural analysis. Results: SMETB knockout reduced (~55%), but did not abolish, ETB-mediated contraction in trachea. In contrast, S6c-mediated contraction in mesenteric veins (130 + 46% KPSS, n = 4), and in mesenteric arteries cultured for 24 h (72 + 24% KPSS, n = 4), was abolished by SMETB deletion (5.1 + 3.4% KPSS and 0% KPSS, respectively). Femoral artery injury produced large, neointimal lesions (47.4 + 10.6%; n = 7) but SMETB knockout did not alter lesion size (42.2 + 4.5%; n = 9; P = 0.64). Conclusions: Stimulation of ETB receptors in SM does not influence neointimal lesion formation. This supports the suggestion that ETA-selective antagonists are preferable to non-selective antagonists for prevention of neointimal proliferation. The study was funded by the BHF (project grant and CoRE). Murakoshi et al. (2002) Circulation 106:15; Kirkby et al. (2012) Cardiovasc Res, 95, 19.

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Neointimal lesion formation does not induce endothelin (ET) B-mediated contraction in murine femoral arteries

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Incubation of arteries ex vivo induces ETB-mediated contraction (Adner et al., 1998), possibly via transcriptional mechanisms (Skovsted et al., 2012). ETB receptors are also expressed in neointimal lesions (Azuma et al., 1994). It was proposed that ETB-mediated contraction would be induced by neointimal lesion formation. Methods: Femoral arteries from adult, male C57Bl/6J mice (n = 6) were harvested 36 +/− 2 days after ligation. Isolated mesenteric and femoral veins and arteries from uninjured mice were cultured (DMEM; 37 °C; 5% CO_2; 5 days) before analysis in a myograph. Contractile function was assessed using phenylephrine (10^{-9}–3×10^{-5} M), endothelin-1 (10^{-11}–10^{-7}M) and sarafotoxin 6c (10^{-11}–10^{-7}M). Relaxant function was assessed using endothelium-dependent (acetylcholine; 10^{-9}–3×10^{-5} M) and independent (sodium nitroprusside; 10^{-9}–3×10^{-5}M) agents after contraction with phenylephrine. Results: Freshly isolated mesenteric veins contracted in response to S6c whereas mesenteric arteries and femoral veins did not. Some (4/10) femoral arteries produced small S6c-induced contractions (21.86 +/− 3.72% KPSS,