Effect of sitaxentan on plasma biomarkers of proendothelin-1 synthesis in patients with chronic kidney disease
Jale Yuzugulen1, Robert Kimmitt2, Neeraj Dhanu3, Elizabeth G. Wood4, Jane G. Goddard5, David J. Webb6, Roger Corder6

1William Harvey Research Institute, London School of Medicine, Queen Mary University of London, UK
2BHF Centre of Research Excellence, University of Edinburgh, The Queen’s Medical Research Institute, Edinburgh, UK
E-mail address: j.yuzugulen@qmul.ac.uk (J. Yuzugulen)

Background: Endothelin-1 (ET-1) is implicated in the development and progression of chronic kidney disease (CKD). It has also been linked to increased cardiovascular risk in patients with CKD. Here we evaluated plasma levels of endothelin-like domain peptide (ELDP; preproET-1[193–166]) and CT-proET-1 (preproET-1[169–212]) in patients with proteinuric CKD after treatment with sitaxentan. Changes in proET-1 peptides were compared with various parameters of cardiovascular and renal function. Methods and results: Twenty-seven patients with proteinuric CKD receiving recommended renoprotective treatment were randomised to 6 weeks of placebo, sitaxentan (100 mg once daily), and nifedipine long-acting (30 mg once daily), in a double-blind, three-way crossover study design. Renal and cardiovascular function, and plasma biomarkers were measured at baseline, week 3, and week 6 of each treatment period. ELDP and CT-proET-1 were measured by specific sandwich ELISAs. Sitaxentan treatment resulted in significant increases in ELDP and CT-proET-1 at both 3 and 6 weeks compared to baseline (mean increases %± SEM at 3 and 6 weeks: ELDP + 17.5 ± 3.2, + 150.3 ± 3.5; CT-proET-1 + 129.2 ± 2.0, + 144.2 ± 2.6; p < 0.001 for all values). Placebo and nifedipine had no effect on plasma ELDP and CT-proET-1. After 6 weeks sitaxentan plasma ELDP and CT-proET-1 were negatively correlated with 24 h urinary Na+ excretion (p = 0.015, r² = 0.2149; p = 0.013, r² = 0.2227, respectively). Conclusions: Increases in proET-1 biomarkers after sitaxentan indicate that ETA antagonists block a negative feedback effect of ET-1 on EDN1 gene expression that is mediated via ETA receptors. The inverse relationship between plasma proET-1 biomarkers and urinary Na+ excretion after sitaxentan requires further investigation.

doi:10.1016/j.jfs.2014.01.022

Aging selectively impairs contractions to endothelin-1 but not to angiotensin II in murine carotid arteries
Matthias R. Meyer1,2, Matthias Barton3, Eric R. Prossnitz1

1Department of Cell Biology and Physiology, University of New Mexico Health Sciences Center, Albuquerque, NM, USA
2Division of Cardiology, Department of Internal Medicine, Triemli Hospital, Zurich, Switzerland
3Molecular Internal Medicine, University of Zurich, Zurich, Switzerland
E-mail address: matthias.meyer@bluewin.ch (M.R. Meyer)

Aging is a main risk factor for carotid artery disease and stroke. The constrictor peptides endothelin-1 and angiotensin II are important modifiers of age-induced vascular diseases, partly through altered activity of NADPH oxidase (Nox)-derived superoxide and constrictor prostanooids. Whether aging affects Nox- or prostanooid-mediated constrictor responses to endothelin-1 or angiotensin II in carotid arteries is unknown. We studied contractile responses to endothelin-1 (0.1–100 nmol/L) and angiotensin II (100 nmol/L) in isolated common carotid artery rings from young and old C57BL6 mice (4 and 24 months of age). The nitric oxide synthase inhibitor L-NAME (300 μmol/L) was used throughout the study to exclude endothelin ETB receptor- or angiotensin AT2 receptor-mediated nitric oxide release during contractions, which are given relative to KCl (60 mmol/L)-induced responses. Some arteries were additionally incubated with the Nox-specific inhibitor gp91 ds-tat (3 μmol/L) or the thromboxane-prostanoid receptor antagonist SQ 29548 (1 μmol/L) for 30 min. Aging markedly reduced maximal responses (Emax) and the sensitivity (pD2) to endothelin-1 (Emax 8.9 ± 1.8 % vs. 26.2 ± 3.8 %, 3-fold, P < 0.001; pD2 80.2 ± 0.7 vs. 85.4 ± 0.02, P < 0.01). Inhibition of Nox activity blunted endothelin-1-induced contractions by 42% and 63% in young and old animals, respectively (P < 0.05), while the thromboxane-prostanoid receptor antagonist had no effect in either group. Contractions to angiotensin II were weak in young and old animals (3.6 ± 0.4 % vs. 3.1 ± 0.2 %, P = n.s.) and unaffected by gp91 ds-tat or SQ 29548. In summary, aging selectively impairs contractions to endothelin-1 in carotid arteries, which depend on Nox activity, but not on constrictor prostanoids. Endothelin-1 but not angiotensin II seems to be involved in functional aging of carotid arteries.

doi:10.1016/j.jfs.2014.01.024
Cardiovascular Division, Institute of Clinical Medicine, Graduate School of Comprehensive Human Science, Tsukuba University, Japan
E-mail address: happa_y0714@yahoo.co.jp (Y. Ito)

Introduction. Inflammation is thought to be one of the major factors in the progression of arrhythmogenic atrial remodeling that promote atrial fibrillation (AF). The aim of this study was to investigate the effects of inflammatory state before and immediately after catheter ablation on clinical outcomes after catheter ablation of persistent AF. Methods. We investigated 176 patients with long-standing persistent AF (sustained AF duration: 1 to 20 years, with a mean of 3.4 ± 3.8 years) undergoing catheter ablation. The high-sensitivity C-reactive protein (hs-CRP) level was measured as an inflammatory marker before and immediately after the catheter ablation. Patients were divided into two groups according to the hs-CRP level in the baseline: high hs-CRP group (n = 84, >0.075 mg/dl) and low hs-CRP group (n = 92, <0.075 mg/dl). Results. Catheter ablation was successfully performed in all patients. After 12-month follow-up, 53.4% of the patients had AF recurrence. The hs-CRP level before catheter ablation was significantly associated with AF recurrence (p = 0.024), however, neither the hs-CRP level immediately after catheter ablation nor the increment of hs-CRP after catheter ablation was not associated with AF recurrence. Multivariate Cox regression analysis revealed that longer duration of AF (p < 0.001), larger left atrial diameter (p = 0.049), and higher hs-CRP level (p = 0.033) were significantly associated with AF recurrence. In Kaplan–Meier AF free curves, there is a significant difference in AF free rates between low hs-CRP group (57% at 1 year) and high hs-CRP group (35% at 1 year) (p = 0.007). Conclusions. The increased hs-CRP level reflecting an inflammatory state before catheter ablation may be one of the important predictors of recurrence of AF after catheter ablation in patients with long-standing persistent AF.

doi:10.1016/j.lfs.2014.01.025

Pericardial resistance artery contractile responses to endothelins
Thomas M. Leurgans, Maria Bloksgaard, Akhmadjon Irmukhamedov, Lars M. Rasmussen, Jo G.R. De Meya

Abstracts
e67

Regional differences in the effect of hypoxia on endothelin-1-induced contraction in rat arteries
Masashi Tawa, Takashi Shimosato, Hirotaka Iwasaki, Takeshi Imamura, Tomio Okamura

Department of Pharmacology, Shiga University of Medical Science, Shiga, Japan
E-mail address: tawa@belle.shiga-med.ac.jp (M. Tawa)

Acute arterial occlusion due to an embolus or a thrombus causes hypoxia in the vascular bed, usually resulting in critical injury. Hypoxia affects more or less vascular function, but the response to low oxygen differs in individual vascular beds. The present study examined the influence of hypoxia on endothelin-1 (ET-1)-induced contraction in isolated rat carotid and mesenteric arteries. Although the addition of ET-1 (10−10 to 10−8 M) produced a dose-dependent contraction either in carotid or mesenteric arteries, the response to ET-1 was significantly attenuated by hypoxia in carotid, but not in mesenteric, arteries. The impaired contraction to ET-1 in carotid arteries was also observed in endothelium-denuded preparations or in the presence of an endothelin type B (ETB) receptor antagonist (BQ-788, 10−6 M). Meanwhile, ET-1-induced contraction of carotid arteries in the presence of an endothelin type A (ETA) receptor antagonist (BQ-123, 10−6 M) was not affected by hypoxia. Incidentally, ET-1-induced contraction was largely inhibited by antagonism of ETA receptors either in carotid or mesenteric arteries. In addition, IRL-1620 (10−7 M), a selective ETB receptor agonist, did not cause any contraction in both arteries. Although a crucial feature of the response to hypoxia is to produce reactive oxygen species like superoxide, the treatment with superoxide dismutase (200 U/mL) did not affect the influence of hypoxia on ET-1-induced contraction in both arteries. These findings suggest that although ET-1 induces contraction through ETA receptors either in carotid or mesenteric arteries, hypoxia impairs this pathway only in carotid arteries. Furthermore, extracellular superoxide seems not to be a causal factor responsible for this regional difference.

doi:10.1016/j.lfs.2014.01.026

Urinary ET-1 excretion after exposure to radio-contrast media in diabetic patient and patients with preexisting impaired renal function
Fabian Heinisch, Gina-Franziska von Einem, Markus Alter, Axel Kretschmer, Berthold Hocher

Abstracts
e66

Preclinical studies indicate that the renal endothelin system is involved in the pathogenesis of acute renal failure. Contrast media