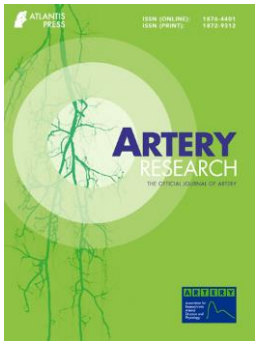

ATLANTIS PRESS

Artery Research

ISSN (Online): 1876-4401 **ISSN (Print): 1872-9312**
Journal Home Page: https://www.atlantis-press.com/journals/artres

P2.03: RECOMBINANT HUMAN ERYTHROPOIETIN ALTERS SUBCUTANEOUS RESISTANCE ARTERY ENDOTHELIAL FUNCTION THROUGH A MECHANISM INVOLVING OXIDATIVE STRESS AND ENDOTHELIN-1 IN PATIENTS WITH STAGE 4 CHRONIC KIDNEY DISEASE

M. Briet, T. Barhoumi, M. Davidman, D. Bercovitch, G. Frisch, S.J. Nessim, M.L. Lipman, E.L. Schiffrin

To cite this article: M. Briet, T. Barhoumi, M. Davidman, D. Bercovitch, G. Frisch, S.J. Nessim, M.L. Lipman, E.L. Schiffrin (2011) P2.03: RECOMBINANT HUMAN ERYTHROPOIETIN ALTERS SUBCUTANEOUS RESISTANCE ARTERY ENDOTHELIAL FUNCTION THROUGH A MECHANISM INVOLVING OXIDATIVE STRESS AND ENDOTHELIN-1 IN PATIENTS WITH STAGE 4 CHRONIC KIDNEY DISEASE, Artery Research 5:4, 153–153, DOI: https://doi.org/10.1016/j.artres.2011.10.024

To link to this article: https://doi.org/10.1016/j.artres.2011.10.024

Published online: 14 December 2019

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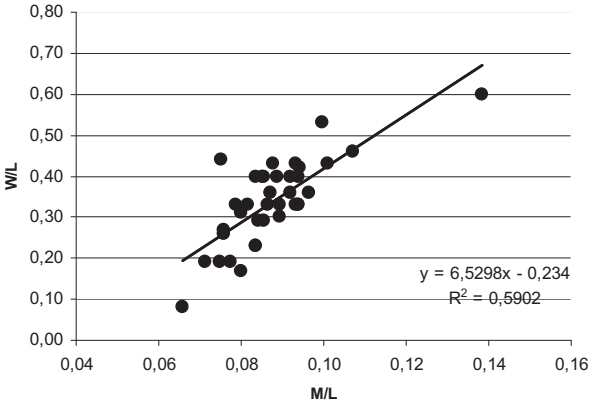
Structural alterations of subcutaneous small resistance arteries, as indicated by an increased media to lumen (M/L) ratio, are frequently present in hypertensive and/or diabetic patients, and may represent the earliest alteration observed. In addition, M/L of small arteries evaluated by micromyography has a strong prognostic significance; however its extensive evaluation is limited by the invasivity of the assessment, since a biopsy of subcutaneous fat is needed. Non-invasive measurement of wall to lumen (W/L) of retinal arterioles using scanning laser doppler flowmetry (SLDF) has been recently introduced (Harazny J et al, Hypertension 2007; 50:623-629). However, this new technique was never compared with micromyographic measurement, considered the gold standard approach.
Methods and Results: We have investigated 37 subjects and patients. Twenty-three of them were hypertensives and 14 normotensives. Blood pressure values were 139/88±17/10 mmHg and 125/71±17/12 mm Hg, respectively ($p<0.05$). All patients underwent a biopsy of subcutaneous fat during an elective surgical intervention. Subcutaneous small resistance arteries were dissected and mounted on a wire myograph, and M/L was measured. In addition, an evaluation of W/L of retinal arterioles by SLDF was performed (Heidelberg Retina Flowmeter, Heidelberg Engineering). A close correlation was observed between M/L of subcutaneous small arteries and WL of retinal arterioles: $r=0.77$, $p<0.001$ (see Figure).
Conclusion: A non invasive and easily repeatable procedure (intraobserver and interobserver variation coefficient around 10%) such as an evaluation of the arterioles in the fundus oculi by SDLF may provide similar information regarding microvascular morphology compared in respect with an invasive, accurate and prognostically relevant micromyographic measurement of M/L.



P2.02
INVESTIGATION OF THE EFFECTS INDUCED ON ENDOTHELIAL FUNCTION BY THE HUMAN T2238C ANP GENE MOLECULAR VARIANT

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Objective: The T2238C ANP gene molecular variant has been related to increased risk of cardiovascular events. *In-vitro* investigations of its pathogenetic mechanisms demonstrated that the 2238C allele variant induced detrimental effects on endothelial cells through increased ROS production. Based on these observations we hypothesized that T2238C ANP gene variant could exert a pathogenic impact on endothelial function *in-vivo*.
Design and methods: We enrolled 10 double mutant CC2238/ANP healthy subjects and 10 healthy subjects carrying the 2238TT wild type genotype. NT-proANP levels were measured in a fasting venous sample. Endothelial-dependent vasodilation was assessed through FMD procedure at brachial level and endothelial endothelial-independent vasodilation was evaluated by means of FMD after sublingual nitrate administration. All subjects underwent carotid ultrasonography.
Results: No significant differences were observed between the two groups in terms of prevalence of cardiovascular risk factors. NT-proANP plasma levels were comparable in double mutant and in wild type subjects (2200±190 vs 2353±340, respectively). Endothelial-dependent vasorelaxation was significantly lower in 2238C as compared to 2238T allele carriers (6.97±2.4 vs 9.31±1.6, $p=.02$). No significant differences were observed regarding endothelial-independent vasodilation (13.4±3.4 vs 14.5±5.6, NS). Carotid ultrasonography did not show any significant alteration of arterial wall in either group.
Conclusions: The 2238C ANP molecular variant, responsible for detrimental effects on endothelial cells *in-vitro*, leads to significant early impairment of endothelial function *in-vivo*. The functional derangement induced by T2238C ANP gene variant may contribute to the increased predisposition to cardiovascular events observed in 2238C allele carriers. Further studies are needed to fully explore this issue.

P2.03
RECOMBINANT HUMAN ERYTHROPOIETIN ALTERS SUBCUTANEOUS RESISTANCE ARTERY ENDOTHELIAL FUNCTION THROUGH A MECHANISM INVOLVING OXIDATIVE STRESS AND ENDOTHELIN-1 IN PATIENTS WITH STAGE 4 CHRONIC KIDNEY DISEASE

M. Briet [1,2], T. Barhoumi [1], M. Davidman [2], D. Bercovitch [2], G. Frisch [2], S. J. Nessim [2], M. L. Lipman [2], E. L. Schiffrin [1,3]
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Objective: Recent studies have raised concern about the safety of recombinant human erythropoietin (RhuEPO) because of evidence of an increase in the risk of cardiovascular disease in chronic kidney disease (CKD) patients. In the present study we investigated the effect of RhuEPO on the function of resistance arteries isolated from CKD patients.
Design and method: 19 patients (mean age 63 ± 14 years) with stage 4 CKD (mean eGFR 20 ± 5 mL/min/1.73m^2), none treated with RhuEPO, were included. Resistance arteries from gluteal subcutaneous tissue were assessed on a pressurized myograph. Endothelium-dependent and independent relaxations were tested with acetylcholine and sodium nitroprusside respectively, with RhuEPO (0, 1, 10 and 20 UI/mL). Tempol (10^{-3} M), a superoxide dismutase mimetic, was used to inhibit oxidative stress. ABT-627 (10^{-7} M) was used as a selective endothelin subtype A receptor antagonist.
Results: At 20 UI/mL, RhuEPO had no effect on norepinephrine-induced vasoconstriction ($n=10$) nor on sodium nitroprusside-induced relaxation ($n=10$). RhuEPO altered endothelium-dependent relaxation in a dose-dependent manner (maximal relaxation with RhuEPO at 0, 1, 10, 20 UI/mL, 77.7 ± 3.5 %, 68.5 ± 4.7%, 53.2 ± 3.8 %, 45.7 ± 4.6 %, $P<0.001$, $n=7$-14). Tempol and ABT-627 partially reversed the altered endothelial function in presence of RhuEPO 20 UI/mL ($P<0.01$, $P<0.01$, respectively).
Conclusion: RhuEPO alters endothelial function of subcutaneous resistance arteries in predialysis CKD patients via a mechanism in part involving oxidative stress and signaling through endothelin subtype A receptors, which could contribute to the deleterious effect of RhuEPO described in large interventional trials.

P2.04
PARADOXICAL INVOLVEMENT OF THE ENDOTHELIAL MINERALOCORTICOID RECEPTOR IN PLATELET ACTIVATION AND VASCULAR THROMBOSIS IN MOUSE

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Our aim was to investigate whether mineralocorticoid receptor (MR) overexpression in the vascular endothelium modifies the *in vitro* thrombin generation using thrombography and enhances the thrombotic risk *in vivo*. We used our mouse model with conditional overexpression of the MR in endothelial cells (MR-EC) (Nguyen Dinh Cat et al, FASEB J. 2010;24:2454-63).
The plasma level of von Willebrand factor was significantly increased in 3 month-old MR-EC mice compared with that in control mice (CT). In the presence of the activated protein C (APC) anticoagulant system, thrombin generation was lower in the plasma of MR-EC mice than in CT. Maximal platelet aggregation in