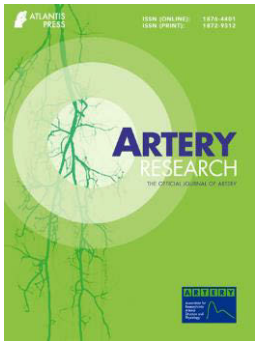

Artery Research

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

3.3: EFFECT OF CELIPROLOL ON PREVENTION OF CARDIOVASCULAR EVENTS IN VASCULAR EHLERS-DANLOS SYNDROME

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To cite this article: K.T. Ong, J. Perdu, H. Plauchu, J. De Backer, A. De Paepe, J. Emmerich, X. Jeunemaitre, D. Germain, P. Collignon, G. Georgesco, E. Bozec, J.S. Hulot, S. Laurent, P. Boutouyrie (2009) 3.3: EFFECT OF CELIPROLOL ON PREVENTION OF CARDIOVASCULAR EVENTS IN VASCULAR EHLERS-DANLOS SYNDROME, Artery Research 3:4, 153–154, DOI: https://doi.org/10.1016/j.artres.2009.10.154

To link to this article: https://doi.org/10.1016/j.artres.2009.10.154

Published online: 14 December 2019

Artery Research (2009) 3, 153–154

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

Oral Presentation Abstracts

3.1
AORTIC STIFFNESS IN MIDDLE AGED WOMEN IS HERITABLE AND RELATES TO BLOOD PRESSURE AND AORTIC CALCIFICATION: A TWIN STUDY

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Background: Pulse wave velocity (PWV), measure of aortic stiffness, is predictive of cardiovascular events. PWV is strongly related to age and blood pressure but its relation to other risk factors and presence of calcification is unclear. We sought to determine the association between PWV and cardiovascular risk factors, aortic calcification and heritability of PWV.
Methods: Subjects were 900 female twins (504 dizygotic, 396 monozygotic), 53-63 years (interquartile range), from TwinsUK cohort. PWV was determined over the carotid-femoral region using the SphygmoCor system. Age matched women ($n = 40$) with PWV in the 1st and 3rd tertiles of the PWV distribution (entire cohort) underwent computed tomography from the carotid to iliac bifurcation to determine calcification. Calcium content was scored using the Agatston method. Heritability of PWV was determined using structural equation modelling.
Results: In multivariate regression PWV was significantly correlated with age, mean arterial blood pressure (MAP) and heart rate (standardized regression coefficients, $\beta = 0.41$, 0.39 and 0.20 respectively, each $P<0.001$). PWV was not significantly associated with LDL-cholesterol, HDL-cholesterol, smoking or body mass index. Aortic calcification was greater (median 450 vs. 63 units, $P=0.001$) in the highest compared to lowest tertile of PWV and was independently association with PWV in regression analysis ($\beta = 0.48$; $P < 0.01$). Heritability of PWV was 0.54 and when corrected for MAP and heart rate 0.51.
Conclusion: In women aortic stiffness is heritable and relates to age, blood pressure and aortic calcification but not to other conventional cardiovascular risk factors. Genes involved in aortic calcification may be important determinants of PWV.

3.2
IS AORTIC STIFFNESS READY FOR CLINICAL PRACTICE? RESULTS FROM THE ROTTERDAM STUDY

G. C. Verwoert [1], S. E. Elias-Smale [1], D. Rizopoulos [1], E. W. Steyerberg [1], A. Hofman [1], M. Kavousi [1], E. J. G. Sijbrands [1], A. P. G. Hoeks [2], R. S. Reneman [2], F. U. S. Mattace-Raso [1], J. C. M. Witteman [1].
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Background: It has been demonstrated that aortic stiffness, as determined by the carotid-femoral pulse wave velocity, is an independent predictor of cardiovascular disease. Whether this measure is of use in cardiovascular risk stratification in clinical practice needs to be determined. We investigated whether aortic stiffness had an additional predictive value beyond traditional risk factors in older subjects.
Methods: Within the framework of the Rotterdam Study, a population-based prospective study, we stratified subjects free of cardiovascular disease at baseline into categories of low (<10%), intermediate (10-20%) and high (>20%) 10-year risk of cardiovascular disease based on Framingham risk factors. Within each risk category, we determined the percentages of subjects moving into a higher or lower risk category using a model that included prior risk and pulse wave velocity. Reclassification percentages and corresponding pulse wave velocity cut-off values are presented for the midpoint of prior risk within each risk category.
Results: Among 2855 participants, 304 cardiovascular events occurred during a median follow-up of 5.9 years. In subjects in the intermediate risk group (prior 10-year risk probability of 15%), 1.5% was reclassified to the high-risk group. Reclassified subjects had pulse wave velocity levels of above 19.7 m/s. In the low and high-risk groups additional measurements of pulse wave velocity did not result in reclassification to another risk category.
Conclusion: In an elderly population, addition of aortic stiffness measurement to traditional cardiovascular risk factors does not seem to be a powerful clinical tool for classification of subjects in 10-year cardiovascular disease risk categories.

3.3
EFFECT OF CELIPROLOL ON PREVENTION OF CARDIOVASCULAR EVENTS IN VASCULAR EHLERS-DANLOS SYNDROME

K. T. Ong [1], J. Perdu [2], H. Plauchu [3], J. De Backer [4], A. De Paepe [4], J. Emmerich [2], X. Jeunemaitre [5], D. Germain [6], P. Collignon [7], G. Georgesco [8], E. Bozec [1], J. S. Hulot [9], S. Laurent [1], P. Boutouyrie [1].
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Background: Vascular Ehlers-Danlos syndrome (vEDS) is a rare severe genetic disease which results from mutations in the gene encoding type III procollagen (COL3A1), characterized by vascular and/or hollow organic ruptures. No treatment is yet validated. We tested the ability of celiprolol, a beta1-adrenoceptor antagonist with a beta2-adrenoceptor agonist action, for preventing the complications of vEDS in a prospective, randomized, open, blinded endpoints trial.
Methods: Fifty three previously untreated vEDS patients were randomized to a 5-year treatment with either celiprolol ($n = 25$) or no treatment ($n = 28$). The two groups were matched for demographic, medical historic and clinical characteristics. Celiprolol was up-titrated from 100 to 400 mg by steps of 100 mg every 6 months. The primary end-point was an arterial event (rupture or dissection, fatal or not) occurring during follow-up. Secondary endpoints were intestinal or uterine rupture or major clinical events, related to vEDS, judged by the event committee.
Results: Mean duration of follow-up was 47 ($\pm$ 15) months. The study was ended prematurely by the safety monitoring board since significant differences were reached between two groups. The primary endpoint was reached by 5 patients (20%) in the celiprolol group and by 14 patients (50%) in the control group (hazard ratio, 0.36; 95% CI, 0.15 to 0.88; $P = 0.04$). Primary

plus secondary endpoints occurred in 6 patients (24%) in the celiprolol group and in 17 patient (61%) in the control group (hazard ratio, 0.31; 95% CI, 0.14 to 0.71; P = 0.0097).
Conclusions: Celiprolol effectively reduced both vascular complications and organic ruptures in vEDS patients.

3.4
A PRESSURE-INDEPENDENT ARTERIAL REMODELLING AND AORTA DILATATION IN TREATED PATIENTS WITH FABRY DISEASE

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Purpose: Fabry disease is a deficiency of lysosomal enzyme α-galactosidase A leading to accumulation of glycosphyngolipids in cardiac and vascular tissues. After long-term enzyme replacement treatment, we described a continuous vascular hypertrophy whereas the aortic stiffness was paradoxically decreasing. Preliminary results reported aorta dilatation in treated patients. The objective of this study was to determine the prevalence of aortic dilatation, and the relationship between aorta dilatation, aortic stiffness and arterial remodeling in treated Fabry patients.
Methods: Case-control study in 34 Fabry males patients (38 ± 12 yrs) receiving enzyme infusions every other week (3.5 ± 1.5 yrs), age-matched with 34 controls. All patients and subjects had arterial measurements of a) carotid IMT and diameter, pulse pressure (PP) and stiffness obtained with echotracking; b) aortic stiffness obtained through carotid-femoral PWV and c) aorta diameters (sinus, ascending and descending tubule, arch aortic) assessed by MRI examinations.
Results: Aorta root dilatation (>40 mm at sinus) was observed in 13 FD patients (35%), but not at others segments. In controls, sinus diameter was positively correlated with age, aortic and carotid stiffness in univariate analysis ($R = 0.59$, $P < 0.005$; $R = 0.53$, $P < 0.005$ and $R = 0.68$, $P > 0.0001$ respectively) and with both age and CPP in multivariate analysis ($R = 0.59$, $P < 0.005$; $R = 0.53$, $P < 0.005$, respectively).No relationship in Fabry patients were found in the same univariate and multivariate analysis. Carotid IMT is positively correlated with PP in controls, but not in Fabry patients.
Conclusion: This study highlight the pressure-independent arterial hypertrophy and aorta dilatation in treated Fabry patients.

3.5
IMPROVEMENT IN AORTIC STIFFNESS AFTER ONE YEAR OF ANTI-TUMOR NECROSIS FACTOR- THERAPY IN PATIENTS WITH INFLAMMATORY ARTHROPATHIES IS ASSOCIATED WITH REDUCTION IN CALPROTECTIN (A PROINFLAMMATORY S100 PROTEIN)

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Background: Chronic inflammatory arthropathies such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are associated with an increased risk of cardiovascular disease. TNF-α antagonists are previously reported to improve vascular function in these patients and thus be beneficial with regard to cardiovascular disease.
Aims: To examine the effect of one year treatment with Tumor Necrosis Factor (TNF)-α antagonists on arterial stiffness and carotid intima media thickness (cIMT) in patients with inflammatory arthropathies, and furthermore to explore possible associations between changes in the vascular measurements and Calprotectin which is a proinflammatory protein (S100A8/S100A9) associated with both inflammatory arthropathies, endothelial dysfunction and acute coronary events.
Methods and Results: A total of 53 patients with RA, AS or PsA and clinical indication for anti-TNF-α therapy were included. 36 patients started with anti-TNF-α therapy and were compared with a non-treatment group of 17 patients. Aortic pulse wave velocity (aPWV), augmentation index (AIx) (Sphygmocor), cIMT (ArtLab) and Calprotectin were measured at baseline and after one year. aPWV (mean $\pm$ SD) was reduced in the treatment group, but not in the control group (-0.51 ± 0.80 m/s versus 0.11 ± 0.48 m/s, respectively; $P = 0.001$). AIx and cIMT did not change in any of the groups. In the treatment group, change in aPWV correlated with change in Calprotectin ($r = 0.36$, $P = 0.04$).
Conclusion: These findings indicate that long term anti-TNF-α therapy improves aortic stiffness in patients with inflammatory arthropathies, and that the improvement is correlated with reduction in the proinflammatory protein Calprotectin.

3.6
OSTEOPROTEGERIN IS ASSOCIATED INDEPENDENTLY WITH AORTIC STIFFNESS IN PATIENTS WITH ATHEROSCLEROSIS AND IN HEALTHY SUBJECTS

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Background: Arterial stiffening is an independent predictor for cardiovascular mortality. Preliminary studies have shown that arterial calcification may have impact on increased vascular stiffness. However, little is known about the role of calcification inhibitor osteoprotegerin (OPG) as an independent predictor of arterial stiffness in patients with peripheral arterial disease (PAD) and in healthy subjects.
Aim: To evaluate the association between OPG level and arterial stiffness parameters in patients with PAD and in healthy subjects.
Materials and methods: We studied 59 males with PAD (age 63 ± 7 years) and 44 healthy subjects (age 54 ± 7 years). Serum OPG level was measured using ELISA kit. Arterial stiffness parameters, such as aortic pulse wave velocity aPWV and augmentation index, were determined by applanation tonometry using the Sphygmocor device.
Results: OPG level (5.40 ± 1.77 *vs* 4.19 ± 1.14 (pmol/L); $p < 0.001$) and aPWV (9.86 ± 2.31 *vs* 7.69 ± 1.66 (m/s); $p < 0.001$) were different for the patients and for the controls. There was linear relationship between OPG level and aPWV in patients with PAD ($R = 0.51$, $p = 0.0001$) as well as in healthy individuals ($R = 0.47$; $p = 0.002$). In multiple regression models, OPG level was independently associated with aPWV along with age and mean arterial pressure in the patient group ($R^2 = 0.34$; $p = 0.034$) as well as in the controls ($R^2 = 0.49$; $p = 0.037$)
Conclusion: The independent association between OPG level and aPWV in patients with PAD and in controls suggests that calcification inhibitor OPG may be important in the process of aortic stiffening in atherosclerosis and in healthy subjects.