



Artery Research

ISSN (Online): 1876-4401

ISSN (Print): 1872-9312

Journal Home Page: <https://www.atlantis-press.com/journals/artres>

04.03: AORTIC STIFFNESS, CENTRAL PULSE PRESSURE AND THE RISK OF PRIMARY CORONARY HEART DISEASE IN OLDER ADULTS. THE ROTTERDAM STUDY

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To cite this article: F.U.S. Mattace-Raso*, W.J. Bos, T.J.M. van der Cammen, B.E. Westerhof, R. Asmar, A. Hofman, J.C.M. Witteman (2006) 04.03: AORTIC STIFFNESS, CENTRAL PULSE PRESSURE AND THE RISK OF PRIMARY CORONARY HEART DISEASE IN OLDER ADULTS. THE ROTTERDAM STUDY, Artery Research 1:S1, S24–S25, DOI: [https://doi.org/10.1016/S1872-9312\(07\)70010-8](https://doi.org/10.1016/S1872-9312(07)70010-8)

To link to this article: [https://doi.org/10.1016/S1872-9312\(07\)70010-8](https://doi.org/10.1016/S1872-9312(07)70010-8)

Published online: 21 December 2019

02.04

DETERMINANTS OF ARTERIAL STIFFNESS IN PATIENTS WITH CORONARY ARTERY DISEASE

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Purpose: Arterial stiffness (AS) is associated with, and a predictor of, outcome in patients with renal and cardiovascular disease. In this study we measured different indices of arterial stiffness, and determinants of these, in subjects with various degrees of coronary artery disease (CAD). We also assessed their predictive value, and that of renal function, for cardiovascular morbidity and mortality.

Methods: Subjects were included following evaluation of CAD at coronary angiography. AS was measured using pulse wave velocity (PWV), pulse wave analysis (PWA) and digital volume pulse (DVP) analysis. Renal function was assessed using serum creatinine concentration [creat]_{sr} and estimated glomerular filtration rate (eGFR) using the Cockcroft & Gault equation. Subjects with a history of renal disease were excluded. The primary-endpoint was a composite of hospitalisation due to cardiovascular causes and all-cause mortality.

Results: 284 subjects (210 males), with a mean age of 62 years, were included. Compared with PWV, the augmentation, reflection and stiffness indices did not confer similar information. PWV was determined by age, heart rate, systolic BP, body mass index and [creat]_{sr} ($R^2 = 0.38$, $p < 0.001$), and negatively associated with eGFR ($R^2 = 0.30$, $p < 0.001$). Follow-up was for a mean of 1.5 years. A lower eGFR ($p < 0.01$), PWVs above the median ($p < 0.05$) and degree of CAD ($p < 0.001$) predicted a shorter time to a composite endpoint.

Conclusion: In our study renal function rather than traditional cardiovascular risk factors determined AS. EGFR, PWV and degree of CAD were predictive of cardiovascular outcome.

Free Communications

04.01

ENHANCED EXTERNAL COUNTERPULSATION TREATMENT IMPROVES ARTERIAL WALL PROPERTIES AND WAVE REFLECTION CHARACTERISTICS IN PATIENTS WITH REFRACTORY ANGINA

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Background: Early return of reflected pressure waves from the lower body, resulting from increased arterial stiffness, augments central aortic pressure and increases left ventricular (LV) afterload and myocardial oxygen demand. Enhanced external counterpulsation (EECP) acutely enhances coronary perfusion (supply) and reduces LV afterload (demand). However, the mechanism(s) responsible for the sustained beneficial effects of EECP treatment are unclear.

Objectives: To determine if arterial properties and wave reflection characteristics are favourably altered after EECP treatment in patients with refractory angina.

Methods: Radial artery pressure waveforms were recorded by applanation tonometry and central aortic pressure waveforms generated using a mathematical transfer function in 20 patients with stable refractory angina. Data were collected before and after 34 one-hour EECP sessions. Augmentation index (AI_a) and timing of the reflected pressure wave were calculated from the aortic waveform.

Results: EECP treatment caused a decline in AI_a and an increase in reflected wave travel time. These modifications in wave reflection characteristics caused a decrease in aortic systolic pressure and wasted LV pressure energy. The average number of angina episodes and Canadian Cardiovascular Society (CCS) class, both decreased in concordance with the physiologic changes due to EECP treatment.

Conclusions: EECP treatment reduces arterial stiffness and improves wave reflection characteristics in patients with refractory angina. These changes decrease LV afterload and myocardial oxygen demand and reduce the number of angina episodes and therefore, enables patients to participate in continuous exercise programs which in turn may provide long term benefits and sustained improved quality of life.

04.02

THE METABOLIC SYNDROME IS ASSOCIATED WITH CENTRAL AND PERIPHERAL ARTERIAL STIFFNESS IN YOUNG WOMEN BUT NOT IN MEN: THE MEDIATING ROLE OF INSULIN RESISTANCE AND LOW-GRADE INFLAMMATION. THE NORTHERN IRELAND YOUNG HEARTS PROJECT (NIYHP)

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Increased arterial stiffness may explain, at least in part, the increased cardiovascular and diabetes risk associated with the metabolic syndrome (MetS). However, the mechanisms linking the MetS to an increased (central and/or peripheral) arterial stiffness are incompletely understood and gender differences may exist. We therefore examined whether: (1) the (clustering of the) risk factors (RFs) of the MetS is associated with stiffness of central and peripheral arterial segments; (2) these associations were similar in men and women; and (3) insulin resistance and low-grade inflammation mediated any such associations.

Subjects were 313 young men and women (mean age of 23), participating in an ongoing longitudinal study (NIYHP). Subjects were categorized according to the number of RFs of the MetS; in addition, a continuous MetS score was calculated. Arterial stiffness was assessed by measuring pulse wave velocity (PWV) in three arterial segments (non-invasive optical method).

The prevalence of the MetS was similar for men (10.6%) and women (10.5%). After adjustment for potential confounders and other RFs, PWV of the three arterial segments investigated increased with increasing traits of the MetS in women only. Women with the MetS, as compared to those without RFs of the syndrome, had greater PWV of the aorto-iliac (+14.0%, $p = 0.016$), the aortic-radial (+13.2%, $p = 0.010$) and aorto-dorsalis pedis (+11.8%, $p = 0.011$) segments. A great deal of the association (up to 75%) between the MetS and aortic-iliac PWV was mediated by heart rate, inflammation markers (CRP and fibrinogen) and insulin resistance (HOMA-IR), whereas these variables did not explain much of the association between the MetS and PWV of the peripheral segments.

Young women with the MetS show increased stiffness of peripheral and central arteries, a mechanism that may explain their increased cardiovascular risk. Low grade inflammation, insulin resistance and sympathetic activation explain much of the adverse impact of the MetS on central, but not peripheral, arterial stiffness.

04.03

AORTIC STIFFNESS, CENTRAL PULSE PRESSURE AND THE RISK OF PRIMARY CORONARY HEART DISEASE IN OLDER ADULTS. THE ROTTERDAM STUDY

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Aim: We investigated whether aortic stiffness and central pulse pressure were predictors of coronary heart disease in apparently healthy subjects.

Methods and Results: We included 2024 subjects participating the third examination phase of the Rotterdam Study, a large ongoing population-based study. Aortic stiffness was measured as the carotid-femoral pulse wave velocity. Finger blood pressure was measured (Finapres) and central pulse pressure was calculated using upper arm level correction and a generalized transfer function. Information on smoking habits and previous cardiovascular disease were obtained. Body mass index was calculated. Serum total cholesterol and HDL cholesterol values were determined and diabetes mellitus was defined. The carotid IMT was assessed. Subjects with previous coronary heart disease were excluded from the analyses. Cox's proportional hazard regression analysis, adjusted for cardiovascular risk factors was carried out. To facilitate comparisons among central pulse pressure and aortic stiffness each measure was divided by its standard deviation. The mean age of the participants was 71.4 years, 39.5% were men. During a mean follow-up time of 6.1 years, 109 subjects developed coronary heart disease. Hazard ratios and corresponding 95% CI of coronary heart disease for change of 1 standard deviation of aortic stiffness and central pulse pressure were 1.27 (1.06-1.51) and 1.20 (1.00-1.44), respectively. When both measures were included in the same statistical model, the prognostic value of aortic

stiffness remained significant [1.22 (1.02-1.47)] whereas estimates of pulse pressure were slightly decreased [1.13 (0.93-1.37)].

Conclusions: Aortic stiffness is an independent predictor of coronary heart disease in apparently healthy subjects.

04.04

AMBULATORY ARTERIAL STIFFNESS INDEX (AASI) PREDICTS STROKE IN A GENERAL POPULATION

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Background: The ambulatory arterial stiffness index (AASI), defined as one minus the regression slope of diastolic on systolic blood pressure in individual subjects, can be computed from 24-h ambulatory blood pressure recordings and predicted stroke in a large cohort of referred patients.

Methods: We investigated the prognostic value of AASI and 24-h pulse pressure (PP) in a sex- and age-stratified random sample of 1829 Danes, aged 40-70 years. We used Cox regression to adjust for sex, age, body mass index, mean arterial pressure, smoking, diabetes mellitus, and a history of cardiovascular disease. We also adjusted AASI for PP and vice versa.

Results: Over a median follow-up of 9.4 years, the incidence of fatal and nonfatal endpoints amounted to 40 for stroke, 150 for coronary heart disease, and 212 for cardiovascular events. In fully adjusted models, the relative hazard ratios associated with a 1 SD increase (0.14 units) in AASI were 1.61 (95% confidence interval, 1.14 to 2.27; $P=0.007$) for stroke, 0.94 (0.78 to 1.12; $P=0.46$) for coronary heart disease, and 1.04 (0.89 to 1.20; $P=0.64$) for cardiovascular events. For PP, none of the fully adjusted ratios reached significance ($P>0.45$). AASI still predicted stroke after excluding subjects with previous cardiovascular disease or after adjustment for systolic blood pressure instead of mean arterial pressure.

Conclusions: In middle-aged and older individuals randomly recruited from a European population, AASI was a strong predictor of stroke over and beyond traditional cardiovascular risk factors, including mean arterial pressure and PP.

07.01

REDUCING ARTERIAL STIFFNESS AND WAVE REFLECTION - QUEST FOR THE HOLY GRAIL?

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Arterial stiffness and wave reflection are fast emerging as therapeutic targets in their own right. While thiazide diuretics have little or no effect on either arterial stiffness or wave reflection, vasodilators including nitrates and phosphodiesterase type-5 inhibitors e.g., sildenafil, reduce wave reflections and aortic pressures but not aortic stiffness. β -blockers have the opposite effect; they reduce aortic stiffness but increase aortic pulse pressure and wave reflections while calcium antagonists and α -blockers show varying effects on the vascular wall. Drugs targeting the renin-angiotensin-aldosterone system, namely angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs) and aldosterone antagonists have been shown as the most effective in reducing both arterial stiffness and wave reflection, and in some cases, to a greater extent than predicted from the extent of blood pressure (BP) reduction. Also, there is evidence of an additive effect on arterial stiffness with combined ACEI and ARBs. Exploring further the synergistic effects of anti-hypertensive drugs on arterial stiffness, a poly-pill containing a low-dose combination of a thiazide diuretic, calcium antagonist, β -blocker and an ACEI, decreased arterial stiffness more than the individual drugs in standard doses. However, beyond the dynamic effects of anti-hypertensive drugs, future therapies may directly target vascular structural alterations including collagen degradation, advanced glycation end-products, the matrix metalloproteinases and vascular inflammation. Finally, one can speculate about the role of pharmacogenomics which may help tailor "de-stiffening therapy" in individuals with stiff arteries.

07.02

INFLAMMATION AND ARTERIAL FUNCTION

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During the last decade, several studies have documented the unfavorable effects of inflammation on cardiovascular function and its role in the pathophysiology of atherosclerotic disease. The interplay between inflammation and arterial system is multifaceted. On the one hand, the arterial endothelium contributes to the initiation and the perpetuation of inflammation. On the other hand, the inflammatory cascade affects adversely the endothelium-dependent processes and the mechanical properties of the arteries. These effects give rise to impaired vasomotion, arterial stiffening and increased wave reflections and thus result in an unfavorable hemodynamic loading of the heart. Chronic inflammatory diseases (such as rheumatoid arthritis, and others) as well as acute inflammatory stimuli (such as acute infections) may adversely influence the arterial performance. Moreover, systemic subclinical low-grade inflammation, as expressed by high blood levels of inflammatory markers/mediators, is a common denominator of most cardiovascular risk factors (hypertension, diabetes, etc.) and importantly, it is closely related to impaired arterial elastic properties. In addition, vasculogenic erectile dysfunction, which comprises an alternative phenotype of arterial dysfunction and an emerging cardiovascular risk predictor, is accompanied by low-grade inflammatory activation. Among the several inflammatory markers/mediators, C-reactive protein level has been consistently associated with indices of arterial function in several populations. However, data regarding a possible direct etiological role of CRP in arterial dysfunction and atherosclerosis, if any, are yet inconclusive. Current evidence suggests that anti-inflammatory strategies benefit arterial function in several clinical settings. Further research is needed to elucidate whether inflammation may comprise a worthwhile treatment target regarding the cardiovascular system.

07.03

SODIUM EXCRETION AS A MODULATOR OF GENETIC INFLUENCE ON ARTERIAL STIFFNESS AND OTHER CARDIOVASCULAR PHENOTYPES

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Hypertension is a chronic age-related disorder, affecting nearly 20% of all adult Europeans. This disease entails debilitating cardiovascular complications and is the leading cause for drug prescriptions in Europeans older than 50 years. Intensive research over the past two decades has so far failed to identify common genetic polymorphisms with a major impact on blood pressure or associated cardiovascular phenotypes, suggesting that multiple genes each with a minor impact, along with gene-gene and gene-environment interactions, play a role. The European Project on Genes in Hypertension (EPOGH) is a large-scale, family-based study in which participants from seven different populations were phenotyped and genotyped according to standardized procedures. The EPOGH demonstrated that phenotype-genotype relations strongly depend on host factors such as gender and lifestyle, in particular salt intake as reflected by the 24-h urinary excretion of sodium. Individuals with the same genetic predisposition had different vascular stiffness, left ventricular mass or heart rate variability, depending on whether they ate a high-sodium or a low-sodium diet. The EPOGH therefore highlights the concept that phenotype-genotype relations can only be studied within a defined ecogenetic context.

Free Communications (Young Investigators)

09.01

EZETIMIBE AND SIMVASTATIN BOTH REDUCE INFLAMMATION, DISEASE ACTIVITY, AORTIC STIFFNESS AND IMPROVE ENDOTHELIAL FUNCTION IN RHEUMATOID ARTHRITIS

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Background and Aims: HMG-CoA reductase inhibitors (statins) have been shown to have anti-inflammatory and disease modifying properties in patients