



## Artery Research

ISSN (Online): 1876-4401

ISSN (Print): 1872-9312

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

### **5.6: ASSOCIATION BETWEEN ENDOGENOUS SERUM TESTOSTERONE CONCENTRATIONS AND AORTIC PRESSURES AND PULSE WAVE AMPLIFICATION INDICES IN ERECTILE DYSFUNCTION PATIENTS**

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**To cite this article:** Dimitrios Terentes-Printzios\*, Charalambos Vlachopoulos, Nikolaos Ioakeimidis, Panagiota Pietri, Athanassios Angelis, Ioanna Gourgouli, Christos Georgakopoulos, Christodoulos Stefanadis, Dimitrios Tousoulis (2015) 5.6: ASSOCIATION BETWEEN ENDOGENOUS SERUM TESTOSTERONE CONCENTRATIONS AND AORTIC PRESSURES AND PULSE WAVE AMPLIFICATION INDICES IN ERECTILE DYSFUNCTION PATIENTS, Artery Research 12:C, 46–47, DOI: <https://doi.org/10.1016/j.artres.2015.10.031>

**To link to this article:** <https://doi.org/10.1016/j.artres.2015.10.031>

Published online: 7 December 2019

In a cross-sectional design, we analyzed 1077 subjects from the Czech population-based study ("Post-MONICA"). Aortic pulse wave velocity (aPWV) was measured using a Sphygmocor device. sRAGE concentrations were assessed in frozen samples by ELISA methods (R&D Systems).

Aortic PWV significantly ( $p < 0.0001$ ) increased across the sRAGE quartiles. After adjustment for all potential confounders, non-diabetic subjects in the bottom quartile of sRAGE ( $< 918$  pg/mL) had odds ratio of raised aortic PWV ( $\geq 9$  m/sec, top quartile), 1.8 (95% CI: 1.19–2.72) with  $p = 0.006$ ; the association was stronger when only hypertensive non-diabetic individuals were included: odds ratio 2.05 (95% CI: 1.26–3.32) with  $p = 0.004$ . In contrast, using similar regression models, low sRAGE was rejected as an independent predictor of raised aortic aPWV in diabetic or in normotensive subjects.

In conclusion, low circulating sRAGE was independently associated with increased arterial stiffness in a general population-based sample, but mainly in hypertensive non-diabetic patients. The lack of association in diabetics was probably due to low dispersion of sRAGE values and relatively small number of subjects (9% of the sample).

### 5.3

#### THE INFLUENCE OF SEX AND AGE ON ARTERIAL FUNCTION IN RESPONSE TO AN ACUTE INFLAMMATORY STIMULUS

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**Background:** Aging is associated with increased arterial stiffness and chronic low-grade inflammation. Acute inflammatory stimulus in the presence of low-grade chronic inflammation briefly increases the risk of cardiovascular events. The risk of cardiovascular events also increases substantially in older compared to younger women, therefore the relationship between sex and aging is important to understand.

**Purpose:** To describe the differential effects of age following induced systemic inflammation on arterial function, endothelial function, and wave reflection.

**Method:** Healthy volunteers aged 18–35 yrs ( $n = 18$ ,  $\approx 26$ yr, male = 6) or 55–75 yrs ( $n = 21$ ,  $\approx 64$ yr, male = 9) participated. Ultrasound of the common carotid and brachial artery was performed, Beta-stiffness ( $\beta$ ) and flow mediated dilation (FMD) were calculated. Aortic mean arterial (aMAP), pulse wave analysis with wave separation, pulse wave velocity (PWV) measurements were obtained in the supine position at rest using applanation tonometry. Participants received an influenza vaccine to induce acute inflammation following baseline measurements and returned for 24-hour follow-up.

**Results:** C-reactive protein and interleukin-6 increased pre-to-post similar in all groups ( $p < 0.05$ ).  $\beta$  was higher for older adults pre/post. ( $p < 0.05$ ). Older males exhibited decreased MAP and reflected wave pressure (RP), but increased PWV following vaccination ( $p < 0.05$ ). However, FMD significantly decreased only in young males.

**Conclusion:** The results suggest that differential responses occur between young and older adults and between males and females in response to acute inflammation. Although inflammation increased similarly, inflammation had limited effects on vascular function in both young and old females, suggesting there are significant sex effects for arterial function in response to acute inflammation.

### 5.4

#### MATRIX GLA PROTEIN IN RELATION TO LEFT VENTRICULAR DIASTOLIC FUNCTION

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**Introduction:** Matrix Gla Protein (MGP) is highly expressed in cardiomyocytes and is upregulated after acute and chronic pressure overload and in myocardial hypertrophy in mice and humans. However, no study addressed the relation between cardiac function and MGP in humans.

**Methods and results:** In 767 participants randomly recruited from the Flemish population (51.5% women, mean age 50.6 years), we measured circulating levels of nonphosphorylated and uncarboxylated MGP (dp-ucMGP) and recorded early and late diastolic peak velocities of mitral inflow (E and A) by conventional Doppler and the mitral annular velocities (e' and a') by tissue Doppler imaging. Using principal component analysis, we summarized 7 Doppler indexes - namely, E, A, e' and a' velocities, and their ratios (E/A, e'/a', and E/e') - into a single diastolic score. According to published definitions, 73 (9.5%) participants had impaired relaxation and 114 (14.9%) had elevated LV filling pressure. In the continuous analysis, a doubling of dp-ucMGP is associated with a 6.9% increase in the diastolic score (95% CI 2.7–10.6,  $P < 0.001$ ). No association was seen between systolic function and dp-ucMGP. Multivariable-adjusted odds ratio for a doubling of dp-ucMGP was 0.70 (95% CI 0.50–0.98;  $P = 0.038$ ) for having elevated LV filling pressure. No significant association was seen between impaired relaxation and dp-ucMGP.

**Conclusion:** Higher circulating levels of dp-ucMGP are associated with better LV diastolic function. Pending confirmation in other cohorts and further experimental studies are required to translate our epidemiological findings into underlying molecular mechanisms.

### 5.5

#### MEASUREMENT OF ARTERIAL STIFFNESS BY ULTRAFAST ECHO: COMPARISON WITH ECHOTRACKING IN NORMOTENSIVE SUBJECTS AND HYPERTENSIVE PATIENTS

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Because measurement of arterial stiffness is highly dependent on blood pressure (BP), methods independent of BP are required. Ultrafast echography (UFE, Supersonic Imagine, Aix en Provence, France) makes use of very fast sampling rate (up to 10 kHz), so transient events such as pressure wave arrival can be tracked. This method has never been tested against classical echotracking (Artlab, Esaote, Maastricht, NL) and carotid-femoral pulse wave velocity (cf-PWV, Sphygmocor, AtCor, Sydney, Australia).

We included 56 subjects, 27 normotensives (NT) and 29 essential hypertensives (HT), matched for age and sex. We optimized UFE algorithms for pressure wave detection and tracking, for both foot of the wave (FW) and dicrotic notch (DN) PWV.

Feasibility appears good (FW: 78%, DN: 96%). The relations of arterial stiffness with age and blood pressure were stronger for echotracking and cf-PWV than for UFE. DN wave fronts appeared better associated with cf-PWV ( $r = 0.32$ ,  $p < 0.001$ ) and carotid PWV ( $r = 0.47$ ,  $p < 0.001$ ). FW was not associated with cf-PWV nor with carotid PWV. The residuals between DN and carotid PWV were not associated with BP or age. Similar associations between DN and cf-PWV/carotid PWV were found in NT and HT.

**Conclusion:** After optimizing algorithms for wave front identification and tracking, UFE appears as a promising technique for assessing arterial stiffness. DN showed the best associations with echotracking, whereas FW did not provide meaningful data. As previously shown by Hermeling et al (J Hypertens 2008 and 2009), FW is not appropriate for local stiffness measurement likely because of very early wave reflections.

### 5.6

#### ASSOCIATION BETWEEN ENDOGENOUS SERUM TESTOSTERONE CONCENTRATIONS AND AORTIC PRESSURES AND PULSE WAVE AMPLIFICATION INDICES IN ERECTILE DYSFUNCTION PATIENTS

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**Purpose:** Erectile dysfunction (ED) is an independent predictor of future cardiovascular (CV) events. Aortic pressures (central) and low testosterone independently predict future CV events and mortality. The relationship

between testosterone, central pressures and wave reflection indices in ED patients is unknown.

**Methods:** Total testosterone (TT) levels were measured in 407 consecutive ED patients ( $55 \pm 8$  y/o) without CVD. Central (aortic) systolic and pulse pressure, augmentation index (Alx) and augmented pressure (AP) as indices of pulse wave amplification across the arterial tree were measured with SphygmoCor device (AtCor Medical).

**Results:** TT levels were inversely correlated with systolic and pulse central pressures ( $r = -0.195$  and  $r = -0.249$ , respectively) and wave reflection indices (Alx:  $r = -0.208$  and AP:  $r = -0.168$ ) (all  $P < 0.001$ ). In multivariate regression models adjusting for age and risk factors, TT was an independent predictor of central pressures and wave reflection indices (all  $P < 0.001$ ).

The combination of low TT level ( $<4.0$  ng/ml) with higher central pulse pressure ( $>40$  mmHg) and Alx ( $>27\%$ ) values showed greater effect on 10-year risk of a CV event (figure).

**Conclusions:** Our study is the first, to the best of our knowledge, to demonstrate in ED patients the independent association of low testosterone with central pressures and indices of pulse wave amplification across the arterial tree. This observation highlights the role of testosterone as a marker of arterial disease and predictor of CV events and imply a pathophysiological contribution of testosterone deficiency to age and blood pressure-related processes associated with generalized arterial disease.