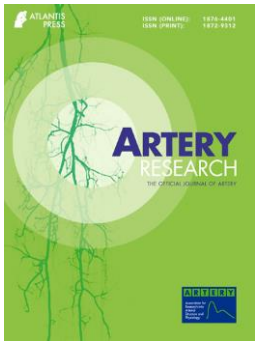

**Artery Research**

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

# 6.2: LARGE ARTERY STIFFNESS ASSESSMENT WITH ARTERIOGRAPH DEVICE

M. Alivon, K.T. Ong, H. Khettab, S. Yanes, J.F. Pruny, E. Bozec, J. Empana, B. Pannier, S. Laurent, H. Beaussier, P. Boutouyrie

**To cite this article**: M. Alivon, K.T. Ong, H. Khettab, S. Yanes, J.F. Pruny, E. Bozec, J. Empana, B. Pannier, S. Laurent, H. Beaussier, P. Boutouyrie (2010) 6.2: LARGE ARTERY STIFFNESS ASSESSMENT WITH ARTERIOGRAPH DEVICE, Artery Research 4:4, 149–150, DOI: https://doi.org/10.1016/j.artres.2010.10.179

**To link to this article**: https://doi.org/10.1016/j.artres.2010.10.179

Published online: 21 December 2019

## 5.5
## WHY DO PATIENTS WITH AORTIC STENOSIS AND UNOBSTRUCTED CORONARY ARTERIES SUFFER FROM ANGINA? INSIGHTS FROM TRANSCATHETER AORTIC VALVE INSERTION (TAVI)

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**Introduction:** It is unclear how aortic stenosis causes angina despite unobstructed coronary arteries. Transcatheter Aortic Valve Implantation (TAVI), permitting the instantaneous abolition of the stenosis, allows quantification of the direct physiological impact of the stenosis independent of associated pathologies such as left ventricular hypertrophy.
**Methods:** Intracoronary pressure and flow velocity were measured immediately before and after TAVI in six patients with unobstructed coronary arteries. We calculated the intra-coronary diastolic suction wave (the principal accelerator of coronary blood flow). To test physiological reserve to increased myocardial demand, we measured pressure and flow velocity at rest and during pacing at 90 and 120 beats per minute.
**Results:** Prior to TAVI the basal myocardial suction wave intensity was $2.2 \pm 1x10^{-5}$ $Wm^{-2}s^{-2}$, and increased in magnitude with increasing severity of aortic stenosis ($r = 0.82$, $p = 0.04$). This wave decreased markedly with pacing at higher heart rate ($\beta$ coefficient $= -0.19$ $x10^{-4}$ $Wm^{-2}s^{-2}$, $p = 0.003$). After TAVI despite a fall in basal suction wave ($2.2 \pm 1$ v $1.0 \pm 0.4x10^{-5}$ $Wm^{-2}s^{-2}$, $p < 0.004$), there was an immediate improvement in coronary physiological reserve as assessed with pacing ($\beta$ coefficient $= 0.12$ $x10^{-4}$ $Wm^{-2}s^{-2}$, $p = 0.014$).
**Conclusions:** In aortic stenosis, the coronary physiological reserve is reversed: instead of increasing with increased myocardial demand, the coronary diastolic suction wave paradoxically decreases. Immediately after TAVI, this physiological reserve returns to a normal positive pattern. This may explain why patients with aortic stenosis suffer from angina despite unobstructed coronaries and the prompt relief of angina after TAVI.

## 5.6
## CENTRAL BUT NOT PERIPHERAL FAT MASS IS ASSOCIATED WITH BLOOD PRESSURE COMPONENTS

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**Aim:** Both obesity and arterial stiffness are associated with cardiovascular disease. In the present study we investigated the possible associations between fat mass, measured at different locations, and measures of arterial stiffness in a geriatric outpatient's population.
**Methods:** Cross-sectional study. Fat mass was measured at different locations with a dual-energy X-ray absorptiometry (DEXA). Blood pressure was measured with Dynamap®, central blood pressure and augmentation index were calculated with Sphygmocor®. Associations were tested by regression analysis.
**Results:** 216 subjects were included. Mean age was 77.3 years. Central fat mass was associated with pulse pressure (PP) [0.579 (95CI% 0.177;0.981)], systolic blood pressure (SPB) [0.581 (95CI% 0.196;0.966)] and negatively with diastolic blood pressure (DBP) [−0.215 (95CI% −0.365;−0.064)], whereas peripheral fat mass was not (table 1). No association was found between measures of obesity and the AIx.
**Conclusion:** In the elderly, central but not peripheral fat mass is associated with blood pressure levels. The present study suggests the pathophysiological role of central fat mass in determining blood pressure levels.

## 6.1
## GENETIC VARIATIONS IN FIBULIN 1 AND AGGRECAN GENES ASSOCIATED WITH ARTERIAL STIFFNESS IN YOUNG HEALTHY ADULTS

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**Background:** Cardiovascular disease is the commonest cause of death worldwide and premature arterial stiffening is a key contributor to this risk. Stiffness is highly heritable, but despite a clear genetic basis, the precise molecular pathways regulating stiffness are poorly understood. We aimed to identify the possible genetic risk loci that associated with arterial stiffness in young healthy adults who have little evidence of atherosclerosis or other confounding factors.
**Methods:** In this candidate gene based association study, the most important tagging SNPs which influenced arterial stiffness were investigated in ENIGMA study. Genotyping was performed in two-stages. First, participants were selected for top and bottom deciles of PWV ($n = 480$) and genotyping carried out using Illumina Golden Gate assays. Significant tSNPs were subsequently tested in additional ENIGMA participants ($n = 1400$) using ABI Taqman assays.
**Results:** In primary analyses, a number of tSNPs were identified with a significance level of $<0.001$. However, only those tSNPs pertaining to extracellular matrix (ECM) are presented. Two tSNPs in Fibulin 1 (rs2018279, rs2238823) and three in Aggrecan (rs3743399, rs2882676, rs2293087) genes associated significantly with PWV after adjusting for confounding factors (adjusted $R^2 = 0.38$; $p < 0.001$) when subjects were selected for deciles of PWV. Similar findings were replicated when data was analysed including the whole cohort (adjusted $R^2 = 0.28$; $p < 0.005$).
**Conclusions:** These data demonstrate that genetic variants of key ECM proteins were significantly associated with increased risk of large artery stiffening in young healthy adults. However, additional studies are needed to determine whether variation in these marker genes is associated with other measures of arterial stiffness.

## 6.2
## LARGE ARTERY STIFFNESS ASSESSMENT WITH ARTERIOGRAPH DEVICE

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**Introduction:** Large artery stiffness is recognized as a strong, independent marker of cardiovascular risk, mainly through aortic pulse wave velocity (PWV). Carotid stiffness (CS), directly measured from echo tracking is correlated with PWV and has been associated with CV risk. Arteriograph is a new non-invasive oscillometric method, which estimates aortic PWV through brachial pressure wave analysis and provides an aortic stiffness index (ASI).
**Aim:** To compare CS with echotracking to ASI with arteriograph and define their determinants and discrepancies in a large unselected middle age population.
**Methods:** CS was assessed by echotracking system (ArtLab®) and central pulse pressure by calibrated distension waveforms, ASI by Arteriograph. R-squared Pearson's correlation coefficient ($R^2$) between the methods was calculated.
**Results:** 682 patients were included: 68 healthy control subjects (CTL), 412 patients with "non treated risk factors" (NTRF) and 202 with "treated risk factors" (TRF). Among NTRF and CTL patients, correlation between CS and ASI were weak ($R^2 = 0.019$ and 0.016 respectively, $p < 0.01$). In a robust multiple stepwise regression analysis, ASI was determined by mean blood

Table 1 Associations between central and peripheral fat mass percentages (FM) and blood pressure components.

| | SBP β (95% CI) | DBP β (95% CI) | PP β (95% CI) | $AI_x$ β (95% CI) |
|---|---|---|---|---|
| FM arms | 0.025 (−0.052;0.101) | −0.006 (−0.036;0.024) | 0.024 (−0.056;0.104) | −0.017 (−0.056;0.023) |
| FM legs | 0.307 (−0.124;0.738) | −0.132(−0.300;0.036) | 0.395 (−0.052;0.843) | 0.139 (−0.083;0.360) |
| FM trunk | 0.581 (0.196;0.966) | −0.215 (−0.365;−0.064) | 0.579 (0.177;0.981) | 0.148 (−0.053;0.349) |

Model is adjusted for age, gender, MAP, HR and BMI.

pressure (p-$R^2 = 0.066$, $p < 0.001$), independently of gender (p-$R^2 = 0.048$, $p < 0.001$) triglyceride (p-$R^2 = 0.044$, $p < 0.001$), whereas CS is associated with MBP (p-$R^2 = 0.093$, $p < 0.001$) and age (p-$R^2 = 0.043$, $p < 0.001$). CV drugs were associated with ASI (RAAS antagonists decreasing, calcium antagonists increasing), but not with CS.
**Conclusion:** ASI and CS are weakly correlated. Pressure and age, usually strong determinants of CS were modestly associated with ASI which appeared more sensitive to metabolic factors and drug treatments. Both techniques measure differently arterial stiffness and are not exchangeable.

### 6.3
### ASSESSING VENTRICULAR-VASCULAR INTERACTIONS IN OVERWEIGHT ADOLESCENTS

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**Introduction:** Overweight is associated with changes in vascular and myocardial structure and function. This study compared non-invasively determined ventricular-vascular interactions in overweight adolescents with healthy controls.
**Methods:** Ventricular assessment included M-mode, B-mode, pulse and tissue Doppler echocardiography. Vascular assessment included carotid ultrasound, brachial artery reactivity, applanation tonometry and echo-Doppler assessment of the biophysical properties of the aorta. Ventricular-arterial coupling assessed as the ratio between arterial elastance (Ea) and end-systolic ventricular elastance (Ees), was calculated using SBP, DBP, echo-derived stroke volume and the ratio between aortic pre-ejection time and total systolic time. Between groups comparisons were performed using parametric methods with p-values>0.05 considered significant.
**Results:** Twenty-one overweight (BMI $\geq 85^{th}$ percentile) adolescents (4 females; median age 14.6 years) and 27 healthy controls (4 females; median age 14.2 years) were studied. Resting heart rate, peripheral and centrally derived SBP, CIMT, aortic PWV, and radial augmentation index were higher in overweight adolescents compared with controls; carotid and aortic distensibility were lower; and flow-mediated endothelial dependent vasodilation was similar. LV mass was higher and diastolic parameters suggested abnormal relaxation in overweight adolescents. Ea was similar, but Ees and the ventricular-arterial coupling ratio Ea/Ees were both reduced in overweight adolescents.
**Conclusion:** Increased arterial stiffness, LV mass and abnormal ventricular relaxation in association with elevated resting heart rate and systolic blood pressure are already present in overweight adolescents. Lower end-systolic ventricular elastance may suggest an adaptive response of the ventricular-arterial coupling.

### 6.4
### SIMULTANEOUS MEASUREMENT OF WALL SHEAR RATE AND ARTERIAL DISTENSION IN FMD STUDIES BY MEANS OF A MULTIGATE DOPPLER SPECTRAL APPROACH

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Flow-mediated dilation (FMD) estimates endothelial function under the assumption that post-ischemic dilation represents a nitric-oxide mediated response to increase in wall shear stress, i.e. wall shear rate (WSR) times blood viscosity. Implementation of WSR measurements would expand the informative value of this technique.
Aim of the study was to provide preliminary clinical evaluation of a new ULtrasound Advanced Open Platform (ULA-OP, University of Florence) capable to record simultaneously arterial diameter and WSR based on a Multigate Spectral Doppler approach (Tortoli et al, UMB 2006).
**Methods:** The response of brachial artery diameter (FMD) and WSR to different forearm occlusion times was assessed by ULA-OP in twelve volunteers (age 25–29) undergoing two sequential exams (3 and 5-min occlusion) 30 min apart each other in random order. Time variant arterial distension curves and WSR were obtained at baseline and during post-ischemic reflow.
**Results:** Mean percent changes observed in peak WSR (far wall) and diameter (FMD) after 3 and 5 min ischemia are below reported in Table, together with the corresponding time lags between peak WSR and peak diameter (D). The post-ischemic WSR peaks always preceded peak diameter increase.

| | FMD (%) | Δ Peak WSR (%) | Time to peak D (s) |
|---|---|---|---|
| 3 min occlusion | $6.14 \pm 3.5$ | $80 \pm 28$ | $41 \pm 10$ |
| 5 min occlusion | $7.13 \pm 3.1$ | $101 \pm 31$ | $35 \pm 9$ |

**Conclusions:** WSR and D can be simultaneously measured during FMD studies by ultrasound. Compared to the standard 5-min occlusion, the post-ischemic response to a 3-min occlusion appears slightly delayed and lower, for both diameter and shear.Simultaneous recording of WSR and arterial distension may expand knowledge of the mechanisms regulating vascular responses to hemorheologic changes.

### 6.5
### HEMOGLOBIN A1C IS ASSOCIATED WITH PULSE WAVE VELOCITY IN NEVER-TREATED HYPERTENSIVES: THE IMPACT OF THE AMERICAN DIABETES ASSOCIATION 2010 POSITION STATEMENT DEFINITIONS

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**Introduction:** Hypertension is associated with increased arterial stiffness. Arterial stiffness, which is a predictor of cardiovascular risk, has been shown to correlate with glycemic control in diabetics. However, it is unclear what is the impact of the recent American Diabetes Association (ADA) 2010 position statement definitions for hemoglobin A1c (HbA1c) on the prediction of arterial stiffness.
**Methods:** We enrolled 1225 consecutive essential hypertensives (mean age $52.9 \pm 11.7$ years, 728 males, 86 diabetics). Arterial stiffness was determined with carotid-femoral pulse wave velocity (PWV) using the Complior® device. HbA1c was measured in venous blood samples.
**Results:** In multivariable regression analysis, HbA1c exhibited significant positive association with PWV, which was independent of age, gender, mean blood pressure, smoking, body-mass index, blood glucose, LDL and CRP ($p < 0.001$, adjusted R2 of model = 0.418). In further analyses we employed dichotomous outcome variable (PWV $\geq$50th percentile [7.8 m/s]). Subjects were divided into 3 groups according to HbA1c levels, based on ADA definitions (Normal group: HbA1c<5.7, Pre-diabetes group: 5.7≤HbA1c≤6.4, Diabetes group: HbA1c≥6.5). In multivariable logistic regression models adjusting for the abovementioned confounders, compared to subjects in the normal group, both the subjects in the pre-diabetes and diabetes group had a significantly elevated odds risk of PWV≥50th percentile (OR = 1.653, 95% CI:1.215–2.249, $p = 0.001$ and OR = 6.518, 95% CI:1.742–24.381, $p = 0.005$, respectively).
**Conclusion:** Higher HbA1c is an independent predictor of increased arterial stiffness in never-treated essential hypertensives. Furthermore, our findings support the significance of the cut-off points of the ADA definitions, as they are able to predict increased arterial stiffness and eventually increased cardiovascular risk.

### 6.6
### COMPARING THE EFFECTS OF NEBIVOLOL VERSUS METOPROLOL SUCCINATE ON CENTRAL HAEMODYNAMICS, FUNCTIONAL-STRUCTURAL CHANGES OF ARTERIES, AND LEFT VENTRICULAR WALL THICKNESS: THE NEMENDAS STUDY

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**Aims:** The vasodilating β-blockers (BB) have several advantages over conventional cardioselective BB atenolol in the treatment of hypertension. However, metoprolol (MET) is the most widely used cardioselective BB in Northern and Eastern European countries. The aim of the present study was to investigate the long-term effects of nebivolol (NEB) and MET on central haemodynamics, structural and functional changes of arteries, and left ventricular wall thickness.
**Methods:** We conducted a randomized, double-blind study in 80 hypertensive patients, who received either nebivolol 5 mg or metoprolol succinate