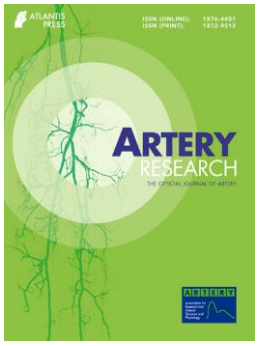

Artery Research

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

4.2: GENETIC VARIATIONS ON CHROMOSOME 14 INFLUENCE BCL11B GENE EXPRESSION LEVELS AND AORTIC STIFFNESS

R. Al Maskari, S. Cleary, Y. Li, A. Khir, G. Mitchell, I. Wilkinson, K. O'Shaughnessy, Yasmin

To cite this article: R. Al Maskari, S. Cleary, Y. Li, A. Khir, G. Mitchell, I. Wilkinson, K. O'Shaughnessy, Yasmin (2014) 4.2: GENETIC VARIATIONS ON CHROMOSOME 14 INFLUENCE BCL11B GENE EXPRESSION LEVELS AND AORTIC STIFFNESS, Artery Research 8:4, 126–127, DOI: https://doi.org/10.1016/j.artres.2014.09.070

To link to this article: https://doi.org/10.1016/j.artres.2014.09.070

Published online: 7 December 2019

(0.16±1.9 vs -0.12±2.2 m/s; P=0.4), or any other haemodynamic variable relative to control at six or 12 months (all P > 0.05).
Conclusions: Despite many observational studies to suggest that vitamin D supplementation could be a useful therapy for improving aortic stiffness and associated haemodynamic indices, 12-months intervention yielded no improvement in older people with vitamin D deficiency. These results do not support use of vitamin D supplementation to improve cardiovascular health in this patient population.

3.5
EFFECTS OF BETA-BLOCKERS WITH OR WITHOUT VASODILATING PROPERTIES ON CENTRAL BLOOD PRESSURE: A META-ANALYSIS OF RANDOMIZED TRIALS IN HYPERTENSION

G. Pucci [a], M. Ranalli [b], F. Battista [a], F. Anastasio [a], M. Crapa [a], G. Schillaci [a]
[a]*University of Perugia and Internal Medicine, Terni, Italy*
[b]*University of Perugia, Perugia, Italy*

Beta-blockers are effective in reducing peripheral blood pressure (pBP), but less effective than other drugs in reducing central blood pressure (cBP). It is controversial whether vasodilating (VB) beta-blockers may be more effective in reducing cBP compared to non-vasodilating (NVB) beta-blockers.
Methods: a meta-analysis was conducted by selecting randomized trials exploring the effect of beta-blockers on cBP. Twenty-two studies were selected. Comparisons were made between 33 trial arms (NVB=22,VB=11). In a random-effect meta-regression model, the following covariates were introduced: treatment (0=baseline, 1=treatment), drug class (VB vs NVB), interaction term: (treatment x drug class), mean age, study duration, study design, treatment-induced heart rate changes.
Results: 1225 subjects (NVB=908, VB=317) were included in the analysis. Mean pSBP was 147 mmHg for NVB and 148 mmHg for VB at baseline, and 133 mmHg for NVB and 134 mmHg for VB after treatment. The difference between pSBP and cSBP at baseline (pSBP - cSBP) was 12.9 mmHg for NVB and 13.4 mmHg for VB. Treatment with either VB or NVB determined a reduction of the above difference to 8.6 mmHg for NVB and 11.3 mmHg for VB (both p<0.01). In the final model, the effect of drug class on the difference between pSBP and cSBP (after treatment - baseline) was not significantly smaller for VB (-2.1 mmHg) than for NVB (-4.3 mmHg; p=0.09).
Conclusions: VB have a marginally, although not significantly, less unfavourable effects on cSBP than NVB. The blood pressure-lowering effect of beta-blockers is more pronounced for pSBP than for cSBP.

3.6
GENE EXPRESSION ANALYSIS IDENTIFY GENES ASSOCIATED WITH ARTERIAL STIFFNESS AND CAROTID DIAMETER IN THE TWINS UK COHORT

M. Cecelja, B. Jiang, K. McNeill, T. Spector, P. Chowienczyk
King's College London, London, UK

Background: Previous studies have identified several genetic variants associated with arterial stiffness. The aim of this study was to investigate whether expression profiles of these genes associate with measures of aortic stiffness and diameter.
Method and Results: In a cross-sectional study of 2092 women aged 21-84 years from the TwinsUK cohort, measures of aortic stiffness (carotid-femoral pulse wave velocity [PWV], carotid distensibility), carotid diameter and heritability were made. In a subsample (n=470), gene expression levels of 62 genes previously associated with PWV were measured in leukocytes with Affymetrix microarrays. PWV and carotid diameter increased by 75% and 18%, respectively, from the second to seventh decade. Carotid distensibility decreased by 73%. Pleiotropic genetic effects accounted for 53% of the phenotypic correlation between carotid distensibility and diameter. Leukocyte-derived transcript ENPP1 significantly correlated with PWV. In 121 women that had repeat vascular measures over a follow-up period of 4.3±1.4 years, leukocyte-derived ENPP1 expression and COL4A1 strongly related to PWV progression in multivariable regression (beta=0.19, p<0.01 and beta=0.32, p<0.0001; respectively). For carotid distensibility, leukocyte-derived transcript for angiotensin converting enzyme (ACE) most strongly associated with a reduction in carotid distensibility (beta=-0.20, p<0.001). Expression levels of ACE gene also associated with progression in carotid diameter (beta=0.21, p<0.05).
Conclusion: This study demonstrates that expression levels of ENPP1, which associated with arterial calcification, and COL4A1, associated with collagen formation, relate to progression in PWV. In addition, our findings suggest that ACE gene expression may exert pleiotropic effects on reduced carotid distensibility and dilation.

4.1
NORMAL VALUES AND DETERMINANTS OF FEMORAL ARTERY STIFFNESS

J. Bossuyt [a,c], L. Engelen [a,b,c], I. Ferreira [b,c], C. Stehouwer [a,b,c], P. Boutouyrie [d,c], S. Laurent [d,c], P. Segers [a,c], K. Reesink [b,c], L. Van Bortel [a,c]
[1]*Ghent University, Ghent, Belgium*
[2]*Maastricht University Medical Centre, Maastricht, The Netherlands*
[3]*Top Institute Food and Nutrition, Wageningen, The Netherlands*
[4]*Hôpital Européen Georges Pompidou, Paris, France*

Aims: Carotid-femoral pulse wave velocity (PWV) is considered the gold standard measure of arterial stiffness, representing mainly aortic stiffness. As compared to the elastic carotid and aorta, the more muscular femoral artery may be differently associated with cardiovascular risk factors (CV-RFs), or provide additional predictive information beyond carotid-femoral PWV. Still, clinical application is hampered by the absence of reference values. Therefore, our aim was (1) to establish age- and sex-specific reference values for femoral artery stiffness in healthy subjects and (2) investigate the associations with CV-RFs.
Methods: femoral artery distensibility coefficient (DC), the inverse of stiffness, was calculated as the ratio of relative diastolic-systolic distension (obtained from ultrasound echo-tracking) and pulse pressure among 5,069 individuals (49.5% men, age range: 15-87 year). Individuals without cardiovascular disease (CVD), CV-RFs and medication use (n=1,489; 43% men) constituted a healthy sub-population used to establish sex-specific equations for percentiles of femoral artery DC across age.
Results: In the total population, femoral artery DC Z-scores were independently associated with body mass index (BMI), mean arterial pressure (MAP), and total-to-HDL cholesterol ratio. Standardized βs, in men and women respectively, were -0.18 (95% CI: -0.23;-0.13) and -0.19 (-0.23; -0.14) for BMI; -0.13 (-0.18; -0.08) and -0.05 (-0.10; -0.01) for MAP; and -0.07 (-0.11; -0.02) and -0.16 (-0.20; -0.11) for total-to-HDL cholesterol ratio.
Conclusion: In young and middle-aged men and women, normal femoral artery stiffness does not change substantially with age up to the 6th decade. CV-RFs related to metabolic disease are associated with increased femoral artery stiffness.

4.2
GENETIC VARIATIONS ON CHROMOSOME 14 INFLUENCE BCL11B GENE EXPRESSION LEVELS AND AORTIC STIFFNESS

R. Al Maskari [a], S. Cleary [a], Y. Li [b], A. Khir [b], G. Mitchell [c], I. Wilkinson [a], K. O'Shaughnessy [a], Yasmin [a]
[a]*University of Cambridge, Cambridge, UK*
[b]*Brunel University, Middlesex, UK*
[c]*Cardiovascular Engineering, MA, USA*

Background: Genetic variants in the 3'-BCL11B gene desert on 14q32.3 were recently shown to associate with aortic pulse wave velocity in the *AortaGen Consortium* GWAS meta-analysis. This region is believed to harbour a gene enhancer targeting BCL11B. We investigated the influence of 5 polymorphisms from this study (rs1381289C>T, rs6485690G>A, rs10782490C>T, rs1461587G>T and rs17773233G>T) on BCL11B mRNA levels and stiffness measured as Young's Elastic Modulus (EM) in 167 donor aortic tissue samples.
Methods: Demographic and other data were obtained, and EM was measured using Instron. SNP genotyping and BCL11B gene expression levels were determined using ABI assays.
Results: Mean age of sample was 57 ± 15 years. As expected, EM correlated significantly with age (r= 0.47, P<0.001). BCL11B gene expression levels were higher in subjects carrying rs1381289 T and rs10782490 C alleles (P <0.05). rs1461587G>T and rs17773233G>T polymorphisms showed genotype specific higher EM values (P<0.05); subjects homozygous for the risk allele had stiffer arteries compared to those who were heterozygous or those who did not carry the allele. Multiple regression adjusted for confounders showed rs1461587G>T and rs17773233G>T associated with increased EM (beta=-0.15, P<0.05) and (beta=0.17, P<0.05) respectively.
Conclusions: We have demonstrated for the first time that rs1381289 and rs10782490 have an effect on BCL11B transcription, resulting in different

BCL11B gene expression levels among those with different genotypes. In addition, rs1461587G>T and rs17773233G>T polymorphisms influence aortic stiffness measured ex vivo, confirming previous observations. Further functional studies are required to elucidate the role of this locus on aortic stiffness.

4.3
IMPACT OF AGE AND GENDER ON THE HAEMODYNAMIC DETERMINANTS OF BLOOD PRESSURE ACROSS THE ADULT AGE-SPAN

A. Cocks [a], J. Smith [a], J. Woodcock-Smith [a], K. Miles [a], K. Maki-Petaja [a], B. McDonnell [b], J. Cockcroft [c], I. Wilkinson [a], C. McEniery [a]
[a]*University of Cambridge, Cambridge, UK*
[b]*Cardiff Metropolitan University, Cardiff, UK*
[c]*Cardiff University, Cardiff, UK*

Background: Systolic and diastolic blood pressure (BP) oscillate around the mean arterial pressure (MAP), which is determined, physiologically, by the cardiac output (CO) and peripheral vascular resistance (PVR). Although data describing the influence of age and gender on BP are widely available, few studies have examined the normal age-related changes in CO and PVR and the impact of gender on these changes, in a sufficiently large cohort of healthy individuals.
Methods: Detailed haemodynamic data including blood pressure (BP), CO and PVR were available in 5580 individuals (2518 males), aged between 18-92 years. Data were stratified according to gender and decade of age.
Results: As expected, MAP increased progressively with age in both males and females ($P<0.001$ for both). PVR was significantly higher in females at all ages and increased significantly with age in both sexes ($P<0.001$ for both). In contrast, CO was significantly higher in males at all ages and declined significantly with age in both sexes ($P<0.001$ for both). The decline in CO was due to a decline in stroke volume (SV) ($P<0.001$ for both), since there was no effect of age on heart rate. Adjusting CO and SV for body size abolished the gender-related differences but the age-related differences remained.
Conclusion: These data indicate that the physiological determinants of blood pressure vary between genders and with ageing, supporting the need for differential approaches in understanding, and treating high BP across the adult age-span.

4.4
THE EFFECT OF B-VITAMIN SUPPLEMENTATION ON ARTERIAL STIFFNESS IN ELDERLY

S. Van Dijk [a], Y. Smulders [b], A. Enneman [a], K. Swart [b], J. Van Wijngaarden [c], A. Ham [a], N. Van Schoor [b], R. Dhonukshe-Rutten [c], L. De Groot [c], P. Lips [b], A. Uitterlinden [a], H. Blom [b], J. Geleijnse [c], E. Feskens [c], T. Van den Meiracker [a], F. Mattace-Raso [a], N. Van der Velde [a]
[a]*Erasmus MC, Rotterdam, The Netherlands*
[b]*VU University Medical Center, Amsterdam, The Netherlands*
[c]*Wageningen University, Wageningen, The Netherlands*

Background: Hyperhomocysteinemia is an important cardiovascular risk indicator in the oldest old and is also associated with elevated arterial stiffness in this age group. Several intervention trials reported a lack of benefit of B-vitamin supplementation on cardiovascular outcomes, therefore we aimed to investigate the effect of B-vitamin supplementation on arterial stiffness and cardiovascular events in hyperhomocysteinemic elderly subjects.
Methods and Results: The B-PROOF study is a double-blind randomized-controlled trial, including 2919 elderly ($\geq$ 65 years), with hyperhomocysteinemia (12-50 μmol/l), treated with B-vitamins (500 μg vitamin B12 and 400 μg folic acid) or placebo for 2 years. In a subgroup ($n = 569$) the effect of B-vitamins on pulse wave velocity (PWV) was investigated. In the total B-PROOF population, incidents of cardiovascular and cerebrovascular events were determined via structured questionnaires and also blood pressure was measured. Compared to placebo, B-vitamins lowered serum homocysteine by 3.6 μmol/L ($p<0.001$). Analysis of covariance showed no effect of B-vitamins supplementation on PWV levels, but aortic pulse pressure was higher in the intervention than in the placebo group (49.6 mmHg vs. 47.2 mmHg; $p = 0.02$). Furthermore, a significant reduction of cerebrovascular events in females (OR 0.33 95%CI [0.15 ; 0.71]), but not in males was observed.
Conclusions: B-vitamins supplementation in hyperhomocysteinemic elderly has no effect on PWV and caused a modest increase in aortic pressure, but also a reduction in cerebrovascular events in females. Arterial stiffness is not likely to be the underlying pathway of the negative trial outcomes.

4.5
DO BACKWARD PRESSURE WAVES ARISE FROM "REFLECTIONS" OR FROM A "RESERVOIR"?

Y. Li, H. Fok, B. Jiang, S. Epstein, J. Alastruey, P. Chowienczyk
King's College London, London, UK

Objective: Pressure waves in the aorta can be described as the summation of forward pressure wave generated by ventricular contraction and backward wave. Backward wave is usually regarded as being due to reflections from discontinuities in the arterial tree but could arise as a result of wave emptying backwards from "reservoir". We examined these possibilities in numerical models and with clinical data obtained during modulation of ventricular and arterial function using inotropic, vasodilator and vasopressor drugs.
Methods: Numerical models included simple Windkessel models with no wave propagation and a distributed single tube model terminated with impedance which allows wave propagation. Clinical data was obtained by carotid tonometry and Doppler sonography during modulation of cardiovascular function in healthy volunteers with dobutamine (2.5 - 7.5 μg/Kg/min), norepinephrine (12.5 - 50 ng/Kg/min), phentolamine (10 - 40 μg/min) and nitroglycerin (0.03 - 0.30 μg/min). Wave intensity analysis and arterial reservoir theory were applied to numerical models and clinical data.
Results: For numerical modelling, backward pressure over a range 0 - 50 mmHg was highly correlated with reservoir pressure both in Windkessel ($R=0.958$, $P<0.001$) and single tube models ($R=0.990$, $P<0.001$). For clinical data, there was a linear relationship between backward pressure over a range 5 - 20 mmHg and reservoir pressure ($R=0.911$, $P<0.001$) for all the subjects at rest and after inotropic/vasomotor stimulation. Augmentation pressure was neither related to the reflected pressure, nor to the reservoir pressure.
Conclusion: This study shows that the backward pressure wave may arise in large part from an arterial reservoir.

4.6
WAVE INTENSITY ANALYSIS IN THE PULMONARY ARTERY

J. Su [a,b], C. Manisty [c], K. Parker [b], A. Hughes [b,c]
[a]*Aarhus University, Aarhus, Denmark*
[b]*Imperial College London, London, UK*
[c]*University College London, London, UK*

Introduction: Little is known about the roles of wave travel and wave reflection in the development of right ventricular dysfunction. The objective of this study is to apply wave intensity analysis (WIA) in the pulmonary artery to assess right ventriculo-arterial function and coupling in man.
Methods: Right heart catheterisation was performed using a pressure and Doppler flow sensor tipped catheter to obtain simultaneous pressure and flow velocity measurements in the pulmonary artery (PA). Recordings were made at rest as well as during a modified Valsalva manoeuvre and handgrip exercise. WIA was subsequently applied to the acquired data.
Results: 7 patients (48 ± 14 years, 5 male) undergoing cardiac catheterisation and with normal mean pulmonary arterial pressure (17 ± 3 mmHg) and without significant cardiovascular disease or lung disease were studied. In the main PA, WIA showed a forward (proximally originating) compression wave in early systole caused by right ventricular ejection and a forward expansion wave prior to closure of the pulmonary valve that decreased the arterial pressure and flow in late systole. Backward (reflecting) waves were minimal. Wave speed was 2.64 ± 1.39 m/s. The wave pattern was unchanged by respiration and handgrip exercise, however, during Valsalva manoeuvre the magnitude of the waves reduced.
Conclusion: Contrary to previous work in animals, our data show that minimal backward waves are present in the pulmonary artery indicating well matched ventriculo-arterial coupling in individuals without pulmonary artery disease. Patients with pulmonary hypertension will be assessed in the continuation of this study.

5.1
EPOXYEICOSATRIENOIC ACIDS IN THE REGULATION OF VASCULAR TONE

L. Yang, J. Cheriyan, C. McEniery, I. Wilkinson
University of Cambridge, Cambridge, UK

Background: Epoxyeicosatrienoic acids (EETs) are released from the endothelium and regulate vascular tone as an endothelium-derived