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


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

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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=treatment, 1=control), drug class (VB vs NVB), interaction term: (treatment x drug class), mean age, study duration, introduced: treatment (0=0 years from the TwinsUK cohort, measures of aortic stiffness and diameter.

**Previous studies have identified several genetic variants associated with measures of aortic stiffness, relating 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**

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**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 to establish age- and sex-specific reference values for femoral artery stiffness in healthy subjects and investigate the correlations 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 Zs, 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 correlated 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**

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**Background:** Genetic variants in the 3′-BCL11B gene desert on 1q43.2 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 (rs1318298C>T, rs4685690G>A, rs10782490C>T, rs461587G>T and rs7773233G>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 inson. 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 rs1318298 T and rs10782490 C alleles (P <0.05). rs1461587G>T and rs7773233G>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 rs7773233G>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 rs1318298 and rs10782490 have an effect on BCL11B transcription, resulting in different 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.
BCL11B gene expression levels among those with different genotypes. In addition, rs1461587 was associated with a reduction in cerebrovascular events in females. Arterial stiffness in the oldest old 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”?

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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), phen tolamine (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

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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 ventricular-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 EPOXYEICOSATRIENIOIC ACIDS IN THE REGULATION OF VASCULAR TONE

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Background: Epoxyeicosatrienoic acids (EETs) are released from the endothelium and regulate vascular tone as an endothelium-derived factor. The role of EETs in the regulation of vascular tone is not well understood.

Methods: Young adult and old age C57Bl6 mice were treated with vehicle or HMB 7 mg/kg for 2 weeks. One group (n=6) of young adult mice and one group (n=6) of old age mice were treated with vehicle for 2 weeks. The mice were anesthetized with pentobarbital sodium and the thoracic aorta was cannulated and perfused with Tyrode solution at 37°C. The aortic ring was placed in an organ bath containing Tyrode solution at 37°C and stimulated with 1 μM phenylephrine (PE) for 10 min. The contractile response to PE was measured in parallel with the RP2000 isometric force displacement transducer. The baseline tone was applied for 10 min before the addition of PE and the contractile responses were recorded for 10 min. The results were expressed as the percentage change in force compared to baseline tone. Statistical analysis was performed using one-way ANOVA followed by Dunnett’s post-hoc test.

Results: The contractile response to PE was significantly increased in old age mice compared to young adult mice. The contractile response to PE was significantly decreased in old age mice treated with HMB compared to young adult mice treated with vehicle. The contractile response to PE was significantly increased in young adult mice treated with HMB compared to young adult mice treated with vehicle. The contractile response to PE was significantly decreased in old age mice treated with HMB compared to old age mice treated with vehicle.

Conclusion: These results suggest that EETs play a role in the regulation of vascular tone in young adult and old age mice. The role of EETs in the regulation of vascular tone may be modulated by aging and hormone treatment.

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

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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

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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 (≥ 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 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 a likely to be the underlying pathway of the negative trial outcomes.

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