



Artery Research

ISSN (Online): 1876-4401

ISSN (Print): 1872-9312

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

5.1: EPOXYEICOSATRIENOIC ACIDS IN THE REGULATION OF VASCULAR TONE

L. Yang, J. Cheriyan, C. McEniery, I. Wilkinson

To cite this article: L. Yang, J. Cheriyan, C. McEniery, I. Wilkinson (2014) 5.1: EPOXYEICOSATRIENOIC ACIDS IN THE REGULATION OF VASCULAR TONE, Artery Research 8:4, 127–128, DOI: <https://doi.org/10.1016/j.artres.2014.09.075>

To link to this article: <https://doi.org/10.1016/j.artres.2014.09.075>

Published online: 7 December 2019

BCL11B gene expression levels among those with different genotypes. In addition, rs1461587G>T and rs1773233G>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

^aUniversity of Cambridge, Cambridge, UK

^bCardiff Metropolitan University, Cardiff, UK

^cCardiff 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

^aErasmus MC, Rotterdam, The Netherlands

^bVU University Medical Center, Amsterdam, The Netherlands

^cWageningen 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 (≥ 65 years), with hyperhomocysteinemia ($12-50 \mu\text{mol/L}$), 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 $3.6 \mu\text{mol/L}$ ($p < 0.001$). 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. Chowieniczky
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 $\mu\text{g/Kg/min}$), norepinephrine (12.5 - 50 ng/Kg/min), phentolamine (10 - 40 $\mu\text{g/min}$) and nitroglycerin (0.03 - 0.30 $\mu\text{g/min}$). 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}

^aAarhus University, Aarhus, Denmark

^bImperial College London, London, UK

^cUniversity 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 ($17 \pm 3 \text{ mmHg}$) 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 $2.64 \pm 1.39 \text{ m/s}$. 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

hyperpolarising factor. EETs are synthesised from arachidonic acids by cytochrome P450 enzymes, and soluble epoxide hydrolase (SEH) inhibition may up-regulate EETs. EETs signaling may be implicated in cardiovascular risk groups. The effects of two agonists in stimulating EETs release were compared, and the best agonist was chosen to investigate this pathway in cardiovascular patient groups, and to confirm target engagement in a first in human clinical trial of a novel SEH inhibitor.

Methods: Healthy volunteers (12 male, 12 female) underwent 4 forearm venous occlusion plethysmography studies to compare the effects of intra-arterial bradykinin and acetylcholine co-infused with saline, fluconazole (cytochrome P450 inhibitor), L-monomethylarginine (nitric oxide synthase inhibitor) plus aspirin (cyclo-oxygenase inhibitor) (LNMMA+ASA), or with all three inhibitors (Triple). Data were analysed by repeated measures analysis of variance. Mean±SEM are presented.

Results: Fluconazole had no effect on basal tone ($p=0.25$). Bradykinin and acetylcholine both caused dose related vasodilatation ($p<0.0001$ vs. $p<0.001$). Fluconazole inhibited bradykinin-induced flow, but not acetylcholine ($p<0.0001$ vs. $p=0.86$). LNMMA+ASA inhibited bradykinin and acetylcholine induced vasodilatation ($p<0.0001$ vs. $p<0.0001$). There was no additive effect with triple inhibition. At top agonist doses, fluconazole inhibited bradykinin-induced flow, but not acetylcholine ($-18.84\pm 5.08\%$ vs. $3.36\pm 9.07\%$; $p=0.01$). LNMMA+ASA inhibited bradykinin and acetylcholine induced flow ($-35.74\pm 7.57\%$ vs. $-32.78\pm 10.60\%$ $p=0.74$). There were no gender differences.

Conclusions: Basal tone is not dependent on EETs signaling. Bradykinin-induced flow is EETs dependent, therefore bradykinin was chosen to probe EETs in cardiovascular patient groups.

5.2

A NEW PRESSURE-WAVEFORM DERIVED VASCULAR STIFFNESS INDEX AND ITS COMPARISON TO PRESSURE-DEPENDENT ARTERIAL COMPLIANCE

T. S. Phan, J. Li

Rutgers University, Piscataway, NJ, USA

Background: Vascular stiffness increases with age and is accelerated by disease. The arterial system also becomes more amenable to a Windkessel with increased pulse wave velocity and altered vascular structure and function with age. Pressure waveform derived indices of stiffness such as pulse wave velocity do not explicitly account for pressure dependence of stiffness, but depend on statistical means for comparisons. We present a new stiffness index, termed CPI, derived from a modified Windkessel model with pressure-dependent compliance $C(P)$, that requires pressure waveform only and can explicitly account for pressure-dependence to permit isobaric comparisons.

Methods: A modified Windkessel model incorporating pressure-dependent compliance was used to analyze 19 pairs of aortic pressure and flow waveforms experimentally obtained from dogs. Various vasoactive states were induced using pharmacological interventions. Cardiac properties were altered by brief occlusion of LAD coronary artery. CPI was compared against $C(P)$ normalized by stroke volume for each dataset.

Results: CPI evaluated at various pressures (range 49-177 mmHg) presented the same inverse exponential shape as $C(P)$ values (range 0.194-1.31 mL/mmHg) obtained using both aortic pressure and flow waveforms. There was strong positive correlation between CPI and $C(P)$ ($r=0.981$, $p<0.001$).

Conclusion: As with $C(P)$, CPI evaluated at corresponding pressure levels in different conditions revealed how compliance was passively affected by changes in pressure and cardiac parameters, rather than a change in arterial wall property. Thus, comparing stiffness between and within subjects when pressure or cardiac properties are altered should be made at common pressure ranges and stroke volumes.

5.3

PLATELET AGGREGATION IS MODULATED BY ARTERIAL STIFFNESS IN END STAGE RENAL DISEASE

L. Tran^{a,b}, T. Serrato^a, P. Lacolley^b, Y. Bezie^c, S. Marchais^a, V. Regnault^b, B. Pannier^a

^a*Manhès Hospital, Fleury-Merogis, France*

^b*INSERM Unit 1116, Vandoeuvre-les-Nancy, France*

^c*Saint Joseph Hospital, Paris, France*

Cardiovascular diseases are the main cause of mortality in end stage renal disease (ESRD) and arterial stiffness is major determinant of mortality. Platelet aggregation contributes to thrombosis. We tested it in ESRD according to aortic pulse wave velocity (PWV, measure of aortic stiffness) and augmentation index (AI, index of central wave reflections).

Methods: 50 ESRD were explored with aortic PWV (Complior Analyse[®]), and central blood pressure measurement (Sphygmocor[®]) plus platelet aggregation (AG) at 3 and 6 minutes and surface under the curve at 4 minutes (SD Innovation[®]), with collagen 2 and 20 $\mu\text{g/mL}$, and ADP 5 and 10 μM , just before one hemodialysis. Analysis included ANOVA, ANCOVA adjusted on age, gender, SBP, diabetes, treatments (hypertension, lipids), and multiple robust regression (NCSS[®]).

Results: 24 patients received anti-platelet treatment: age= 72 ± 3 years, men/women= $17/7$, SBP/DBP= $143\pm 4/73\pm 2$ mmHg, PWV= 12.1 ± 0.7 m/s, AI= $41\pm 2\%$, vs 26 patients without anti-platelet drugs: respectively 69 ± 3 years, m/w= $7/19$, $141\pm 5/75\pm 2$ mmHg, 11.3 ± 0.4 m/s, $42\pm 2\%$ (all comparisons: NS).

Aggregation with the low concentration of ADP was positively correlated with PWV for the whole population as for both groups.

Aggregation with the high concentration of collagen (independent of the thromboxane pathway) was correlated with AI for all. Different parameters of the aggregation curves with the low concentration of ADP or collagen were correlated with AI for each group.

Conclusion: PWV and AI were associated with platelet aggregation characteristics in ESRD independently of anti-platelet drugs. Interface vascular wall-platelet, at the level of macrocirculation and microcirculation, may impact the cardiovascular risk of mortality in ESRD.

5.4

PULSE WAVE VELOCITY DISTRIBUTION IN A COHORT STUDY—FROM ARTERIAL STIFFNESS TO EARLY VASCULAR AGEING (EVA)

P. Cunha^{a,b}, J. Cotter^{a,b}, P. Oliveira^d, I. Vila^{a,b}, P. Boutouyrie^e, S. Laurent^e, P. Nilsson^f, A. Scuteri^g, N. Sousa^{b,c}

^a*Centro Hospitalar do Alto Ave / Minho University, Guimarães, Portugal*

^b*University of Minho, Braga, Portugal*

^c*ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal*

^d*Universidade do Porto, Oporto, Portugal*

^e*Université Paris Descartes, Paris, France*

^f*Lund University, Skane University Hospital, Malmö, Sweden*

^g*San Raffaele Pisana IRCCS, Rome, Italy*

By contrast with other southern European people, north Portuguese population registers an especially high prevalence of hypertension and stroke incidence. We designed a cohort study to identify subjects presenting accelerated and premature arterial ageing in the Portuguese population. Pulse Wave Velocity (PWV) was measured in randomly sampled population dwellers aged 18 - 96 years from northern Portugal, and used as a marker of early vascular ageing (EVA). Of the 3038 subjects enrolled, 2542 completed the evaluation. Mean PWV value for the entire population was 8.4 m/s (men: 8.6 m/s; women: 8.2 m/s; $p<0.02$). Subjects were classified with EVA if their PWV was $\geq 97.5^{\text{th}}$ percentile of z-score for mean PWV values adjusted for age (using normal European Reference values as comparators). The overall prevalence of EVA was 12.5%; 26.1% of individuals below 30 years presented this feature, and 40.2% of subjects in that same age strata were placed above the 90th percentile of PWV. 18.7% of the population exhibited PWV values above 10 m/s, with male predominance (17.2% of men aged 40-49 years had PWV>10m/s). Logistic regression models indicated gender differences concerning the risk of developing large artery damage, with women having the same odds of PWV>10m/s 10 years later than men. Conclusions: population PWV values were higher than expected in a low CV risk area (Portugal). High prevalence rates of EVA and noteworthy large artery damage in young ages were found.

5.5

RELATIONSHIP BETWEEN LARGE ARTERIES CHANGES, ANTIANGIOGENIC DRUGS PHARMACOKINETICS AND CANCER RESPONSE

M. Alivon^{a,b}, B. Blanchet^c, M. Vidal^c, F. Goldwasser^d, S. Laurent^{a,b}, P. Boutouyrie^{a,b}

^a*Inserm U970, Paris, France*

^b*Paris Descartes University, Paris, France*

^c*Cochin Hospital Pharmacology Department, Paris, France*

^d*Cochin Hospital Oncology Department, Paris, France*

Introduction: Antiangiogenic drugs (AAD) are indicated in various solid tumors and induce hypertension. We previously reported a pressure-independent large arteries stiffening under AAD. We hypothesized that large arteries stiffening could be related to the intensity of AAD exposure and that exposure to AAD is related to cancer progression.