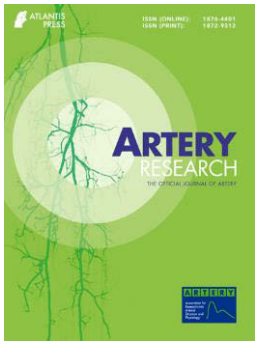

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2.6: BLOOD PRESSURE-INDEPENDENCE OF AORTIC-TO-BRACHIAL ARTERY STIFFNESS RATIO IS DEPENDENT ON DISEASE STATUS

Matthew K. Armstrong, Martin G. Schultz, Dean S. Picone, James E. Sharman

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2.4
BRACHIAL CUFF RESERVOIR CHARACTERISTICS AND END-ORGAN MARKERS OF CARDIOVASCULAR RISK IN AUSTRALIAN ADULTS: A CROSS-SECTIONAL STUDY

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Objective: Reservoir-excess pressure measured using tonometry methods predicts cardiovascular events, but the operator-dependency of tonometry is an impediment to widespread use. A cuff-based blood pressure device has been developed to derive reservoir-excess pressure from measured brachial pressure waveforms, but whether this method is independently associated with cardiovascular risk has never been investigated and this was the aim of this study.
Methods: 1874 adult participants (age 43.7 ± 5.2 years, 11% male) from the Longitudinal Study of Australian Children's Child Health CheckPoint study had reservoir pressure (RP) and excess pressure (XSP) derived from the brachial pressure waveform measured using cuff oscillometry (SphygmoCor XCEL, AtCor Medical, Sydney).
Central hemodynamics (augmentation index and central blood pressure) were estimated from the central pressure waveform. Carotid intima-media thickness (cIMT, n = 1467) and carotid-to-femoral pulse wave velocity (cf-PWV, n = 1674) were measured as end-organ markers of cardiovascular risk.
Results: XSP and RP were associated with cIMT after adjusting for age, sex, waist-to-hip ratio, heart rate (HR) and central hemodynamic indices ($\beta = 0.070$, $p = 0.027$ and $\beta = 0.052$, $p = 0.047$). RP was also significantly associated with cf-PWV after adjusting for the same variables as above ($\beta = 0.128$, $p < 0.001$). The additional reservoir-excess pressure variables in a model that originally included the Framingham risk score and HR strengthened the evidence for associations with cIMT and cf-PWV ($p < 0.001$ for all R^2 changes).
Conclusion: Cuff-based measures of reservoir-excess pressure are significantly associated with end-organ markers of cardiovascular risk independent of traditional risk factors. This cuff method may provide additional information to improve cardiovascular risk stratification.

2.5
NON-INVASIVE WAVE INTENSITY ANALYSIS IN THE AORTA AND INTERNAL CAROTID USING PHASE-CONTRAST MR ANGIOGRAPHY: THE EFFECT OF HYPERTENSION

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Introduction: Hypertension is associated with stiffening of blood vessels, reduced arterial lumen and reduced cerebral blood flow; however, it is not known how lower cerebral blood flow relates to arterial structure or impacts on wave dynamics. We hypothesise increased backward wave energy and faster wave speed in the hypertensive internal carotid artery as an indication of increased resistance to flow.
Methods: Normotensive, controlled and uncontrolled hypertensive participants were recruited (daytime ambulatory BP < 135/85 mmHg and >135/85 mmHg, respectively; n = 11 per group). Wave intensity analysis was performed on left internal carotid and ascending aorta phase-contrast magnetic resonance angiography.
Results: While ascending aortic wave speed increased significantly in the uncontrolled hypertensive compared to normotensive ($p < 0.001$) and controlled hypertensive participants ($p = 0.038$), no significant difference was observed in the internal carotid. Carotid forward and backward wave intensity increased in uncontrolled hypertensives compared to normotensives ($p = 0.036$ and $p = 0.033$, respectively), and backward wave energy increased in the controlled hypertensives compared to normotensives ($p = 0.041$). There was no significant difference between uncontrolled and controlled hypertensives.

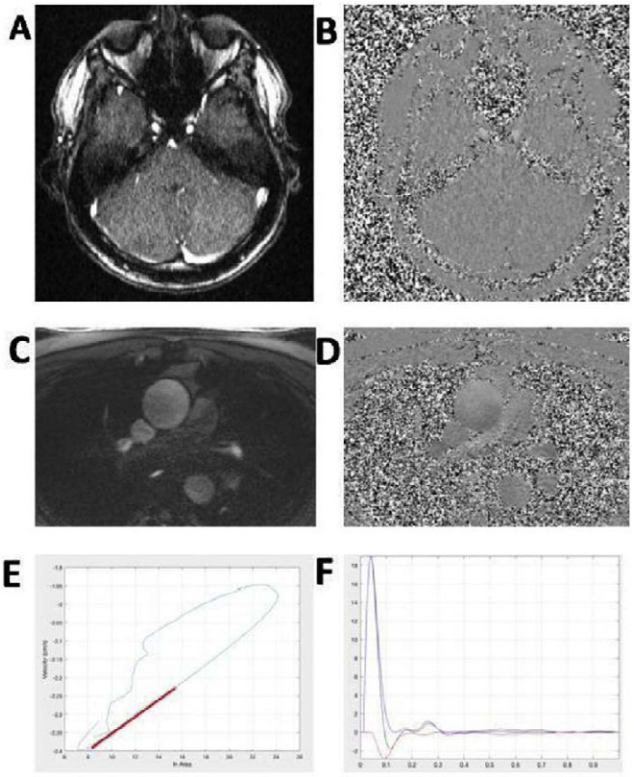

Figure 1 Analysis of the phase contrast MR angiography data. A) Magnitude image B) Phase image of the internal carotid arteries C) Magnitude image and D) Phase image of the ascending aorta E) example of log(Area)-Velocity loop. Red line indicates the slope from which wave speed is calculated in early systole F) Example of the wave Intensity components, where blue is the forward wave energy, red is the backward wave energy and black is the net wave intensity.

Conclusion: Wave intensity in the internal carotid artery is altered in uncontrolled hypertension. This is partly rescued when blood pressure is controlled by medication, although greater backward wave energy persists. This supports the hypothesis of increased resistance to flow in the cerebral circulation of the hypertensives. Whilst increased aortic wave speed confirmed an expected increase in stiffness, this was not observed in the internal carotid. This might suggest a protective mechanism in the cerebral circulation, in conjunction with the effect of vessel tortuosity.

2.6
BLOOD PRESSURE-INDEPENDENCE OF AORTIC-TO-BRACHIAL ARTERY STIFFNESS RATIO IS DEPENDENT ON DISEASE STATUS

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Introduction: Aortic stiffness predicts cardiovascular mortality but is limited as a risk marker because it is dependent on blood pressure (BP). A potential solution is provided from the ratio of aortic-to-brachial artery stiffness (ab-ratio), which is purported to be a BP-independent risk marker among patients with renal dysfunction (RD). We sought to determine the BP-independence of the ab-ratio in patients with disease (including RD) and healthy populations.
Methods: The ab-ratio (aortic/brachial pulse wave velocity; PWV) and mean arterial pressure (MAP) were recorded in patients with RD (n = 119, aged 65 ± 7 years), hypertension (n = 140, aged 62 ± 9 years), type 2 diabetes (n = 77, aged 60 ± 9 years) and healthy individuals (n = 99, aged 51 ± 8 years). Multiple-regression analysis was performed to test the independent association of MAP with the ab-ratio adjusted for age, sex, body-mass index and blood glucose.
Results: There was no significant relationship between the ab-ratio and MAP in patients with RD ($\beta = 0.002$, 95% CI 0.002, 0.006, $p = 0.34$), hypertension ($\beta = 0.001$, 95% CI 0.003, 0.006, $p = 0.62$) or diabetes ($\beta = 0.006$, 95% CI 0.002, 0.014, $p = 0.11$). However, in healthy individuals the ab-ratio was

significantly and independently associated with MAP ($\beta = 0.008$, 95% CI 0.003, 0.013, $p = 0.003$). There was a significant difference in the strength of association between the ab-ratio and MAP between patients with disease and healthy individuals ($z > 2.2$, $p < 0.05$ for all).
Conclusion: Although ab-ratio is purported to be a risk marker that is independent of BP, this was observed only among patient populations, and not in healthy individuals. Therefore, the ab-ratio is influenced by disease status and may have restricted value as a BP-independent risk marker.

2.7
THE GUT-DERIVED METABOLITE TRIMETHYLAMINE N-OXIDE INDUCES LARGE ELASTIC ARTERY STIFFENING AND ENDOTHELIAL DYSFUNCTION IN YOUNG MICE

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The gut microbiome, an emerging mediator of host physiological function, is adversely altered by aging and many diseases, termed "gut dysbiosis." One consequence of gut dysbiosis is elevated circulating levels of the gut-derived metabolite trimethylamine N-oxide (TMAO), which has been directly linked to cardiovascular (CV) risk, including the development of atherosclerosis. However, it is unknown whether TMAO mediates arterial dysfunction that precedes the onset of clinical disease, and if so, the underlying mechanisms.
Purpose: To determine whether TMAO independently induces large elastic artery stiffening and endothelial dysfunction via increased superoxide-related oxidative stress.
Method: Twenty young (6 mo) male C57BL/6 mice were fed a chemically-defined choline (0.08–0.09%) diet supplemented without (Control; $N = 9$) or with ($N = 11$) 0.12% TMAO for 6 months. Arterial stiffness was assessed as aortic pulse wave velocity (aPWV). Endothelial function was evaluated *ex vivo* as carotid artery endothelium-dependent dilation (EDD) to increasing doses of acetylcholine (10^{-9} to 10^{-4}M) in the absence or presence of the superoxide dismutase mimetic TEMPOL.
Results: TMAO increased aPWV (Control: 392 ± 20 vs. TMAO: 483 ± 32 cm/sec, $p = 0.04$) and impaired EDD (peak dilation, Control: 93.7 ± 3.2 vs. TMAO: $79.9 \pm 3.4\%$, $p = 0.01$).
Suppression of oxidative stress with TEMPOL restored EDD in TMAO-treated animals (peak dilation: $92.1 \pm 4.7\%$, $p = 0.46$ vs. Control).
Conclusions: TMAO independently induces large elastic artery stiffening and endothelial dysfunction in mice. Dysfunction appears to occur through increases in oxidative stress. These data may explain, at least in part, why TMAO increases CV risk and provide a potential target for prevention/treatment of arterial dysfunction.
Supported by R01 HL134887 & T32 HL007822.

2.8
INVASIVE STUDY FOR TESTING NON-INVASIVE METHODS OF AORTIC PRESSURE ESTIMATION

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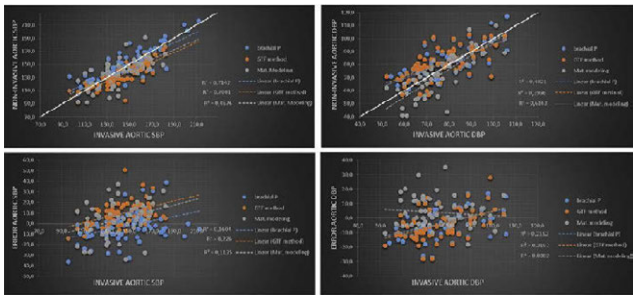
Purpose: Aortic blood pressure has a superior prognostic value with respect to the brachial pressure [1]. Nonetheless, the low efficacy of the most used non-invasive methods (i.e., approaches based on the generalized transfer function (GTF)) may hamper the detection of this superiority in population studies [2]. In this sense, low-order, patient-specific whole-body mathematical models might help to bridge brachial to aortic pressure waveforms. We aimed to compare (i) GTF, (ii) a patient-specific 1D-0D mathematical model, and (iii) brachial blood pressure in the estimation of invasive aortic pressure measured through catheter.
Method: One-hundred patients referred to diagnostic coronary angiography were included in this study. Brachial pressure was measured with a validated automatic oscillometric device simultaneously to invasive aortic pressure, which was measured with a calibrated fluid-filled catheter. End-systolic and end-diastolic left ventricular volumes, carotid-femoral pulse wave velocity and tonometric radial waveform were measured immediately prior to the invasive procedure and were used to set GTF and the mathematical model.
Results: Oscillometric brachial pressure overestimated both systolic (2.4 ± 12.6 mmHg, $R^2 = 0.71$) and diastolic (3.7 ± 9.8 mmHg, $R^2 = 0.48$) aortic pressure. GTF method underestimated systolic (9.4 ± 11 mmHg, $R^2 = 0.71$) and overestimated diastolic (4.5 ± 10.2 mmHg, $R^2 = 0.4$) aortic pressure. Mathematical model underestimated both systolic (4 ± 16.5 mmHg, $R^2 = 0.47$) and diastolic (3.9 ± 10.4 mmHg, $R^2 = 0.62$) aortic pressure. Brachial pressure and GTF methods presented trends toward systolic and diastolic pressure overestimation for higher aortic pressure, while mathematical modeling not.



Conclusions: Systolic and diastolic oscillometric brachial pressures give a better predictor of aortic pressure extremes with respect to both GTF- and mathematical model-based methods.
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Oral session III – Models and Technology
3.1
INTEGRATED CENTRAL PRESSURE-STIFFNESS RISK SCORE: A NEW OPPORTUNITY FOR CARDIOVASCULAR RISK STRATIFICATION. FIRST RESULTS ON CHRONIC KIDNEY DISEASE PATIENTS

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Background: The evaluation of arterial stiffness and central haemodynamics represent a new tool of cardiovascular (CV) risk stratification. Our aim was to create an integrated central pressure-stiffness risk score (ICPS score) which incorporate the predictive potential of identical parameters.
Methods: 100 chronic kidney disease patients on conservative therapy (CKD 1–5) were involved in our study. Pulse wave velocity (PWV), augmentation index (Aix), central systolic blood pressure (csys) and central pulse pressure (cPP) were measured.
Patients were followed for 59.7 months and CV morbidity and mortality were registered. Patients were classified into tertiles based on their PWV, Aix, csys and cPP values. After the analysis of the predictive values of the tertiles of the identical parameters, patients were scored. One score was given, when a patient had a third tertile value of PWV, csys or cPP or a second or third tertile value of Aix. Then the CV outcome was analyzed with Cox regression analysis of the groups of patients with different scores.
Results: During follow-up 37 CV events occurred. Compared with the zero-point group ($n = 21$), the one-point group ($n = 25$) did not have significantly