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

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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

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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

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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)

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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

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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.