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### **5.5: RELATIONSHIP BETWEEN LARGE ARTERIES CHANGES, ANTIANGIOGENIC DRUGS PHARMACOKINETICS AND CANCER RESPONSE**

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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 $\pm$ 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<sup>®</sup>), and central blood pressure measurement (Sphygmocor<sup>®</sup>) plus platelet aggregation (AG) at 3 and 6 minutes and surface under the curve at 4 minutes (SD Innovation<sup>®</sup>), with collagen 2 and 20  $\mu$ g/mL, and ADP 5 and 10  $\mu$ M, just before one hemodialysis. Analysis included ANOVA, ANCOVA adjusted on age, gender, SBP, diabetes, treatments (hypertension, lipids), and multiple robust regression (NCSS<sup>®</sup>).

**Results:** 24 patients received anti-platelet treatment: age=72 $\pm$ 3 years, men/women=17/7, SBP/DBP=143 $\pm$ 4/73 $\pm$ 2 mmHg, PWV=12.1 $\pm$ 0.7 m/s, AI%=41 $\pm$ 2%, vs 26 patients without anti-platelet drugs: respectively 69 $\pm$ 3 years, m/w=7/19, 141 $\pm$ 5/75 $\pm$ 2 mmHg, 11.3 $\pm$ 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 90<sup>th</sup> 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.

**Methods:** In this prospective, single center observational study, 61 patients with cancer were included. Peripheral blood pressure and aortic pulse wave velocity (PWV) were performed at baseline and then every two weeks for two months after the initiation of treatment by sunitinib or sorafenib (V0 to V4). Blood samples were obtained from V1 to V4 for the pharmacokinetic study. Concentrations were determined by HPLC and standardized to combine both drugs (Z-score, mean=0, SD=1). Statistical analysis was performed through a robust stepwise regression analysis and Cox regression analysis.

**Results:** Mean age was 59(14), mean SBP 127(20) mmHg. At V2, mean BP increased by 5(14) mmHg. Determinants of PWV increase were high AAD blood concentration and mean BP increase (for 1 SD, +0.4 m/s and +0.3m/s respectively,  $p<0.01$ ). High concentration of AAD during follow-up was associated with a lesser cancer progression and mortality (for 1SD increase, HR: 0.60 [0.38-0.97] and HR: 0.38 [0.19-0.79] respectively,  $P<0.05$ , figure 1). High AAD and low PWV increase are associated with the lowest cancer progression.

**Conclusion:** Large arteries stiffening observed under AAD is proportional to the intensity of exposure to AAD independently of blood pressure increase. Patients under exposed to AAD are at higher risk of disease progression and mortality.

## 5.6

### AORTIC IS SUPERIOR TO BRACHIAL AMBULATORY BLOOD PRESSURE MONITORING FOR THE DETECTION OF EARLY DAMAGE AT THE HEART AND THE CAROTID ARTERY BUT NOT AT THE RETINAL MICROCIRCULATION: THE NON-INVASIVE AORTIC AMBULATORY BLOOD PRESSURE MONITORING FOR THE DETECTION OF TARGET ORGAN DAMAGE (SAFAR) STUDY

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**Introduction:** Preliminary evidence suggests the superiority of office aortic (a) blood pressure (BP) over brachial (b) in the management of arterial hypertension. The 24-hour ambulatory blood pressure monitoring (ABPM) is regarded as the optimal method for assessing cardiovascular (CV) risk. The non-invasive 24-hour aABPM is now feasible with validated operator independent brachial cuff-based oscillometric devices.

**Objective:** To examine whether aABPM is superior to bABPM for the early detection of cardiac and/or arterial damage in hypertensives.

**Design and method:** The SAFAR study is an ongoing cross-sectional observational study assessing heart function and structure, arterial (carotid, femoral and lower limb) atheromatosis, arterial stiffness (carotid and aortic), arterial hypertrophy (carotid) and retinal microcirculation in individuals' referred for BP evaluation.

**Results:** In consecutive individuals referred for BP evaluation the aABPM had greater ability than bABPM to detect both left ventricular hypertrophy and diastolic dysfunction (n=229, area under the curve: 0.74 versus 0.69,  $p=0.004$  and 0.69 versus 0.63,  $p=0.001$ , by c-statistics respectively), common carotid intimal-medial thickness greater than 0.9 mm (n=490, 0.69 versus 0.62,  $p=0.009$ ), but not narrowed retinal arteries assessed by central retinal arteriolar equivalent in fundus photography, (n=402 eyes, 0.62 versus 0.61,  $p=ns$ ).

**Conclusions:** aABPM is able to detect better than bABPM an early local damage at the heart and the nearby conduit arteries, but not at the distal retinal microcirculation.

## 5.7

### AORTIC PULSE WAVE VELOCITY INCREASES AFTER 2 YEARS IN PATIENTS WITH COPD: DATA FROM THE ARCADE STUDY

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**Objectives:** Patients with COPD have increased risk of cardiovascular (CV) events and mortality beyond that attributable to smoking. However, there have been no longitudinal studies of arterial stiffness in COPD. The Assessment of Risk in Chronic Airways Disease Evaluation (ARCADE) aims to study CV risk factors in COPD and controls, free from respiratory disease, longitudinally. We hypothesised that patients with COPD would have increased Aortic pulse wave velocity (AoPWV) over 2 years.

**Methods:** At baseline, AoPWV was measured using the SphygmoCor device in 525 patients with COPD and 150 controls. Lung function (Forced expiratory

volume in 1 second (FEV1) and Forced vital capacity (FVC)), BMI, blood pressure (BP) and systemic inflammation (HsCRP) was also measured. These were repeated after 2 years.

**Results:** At baseline, patients and controls were similar in age, gender and BMI, but patients had greater PWV, systolic and mean arterial BP, heart rate and HsCRP (all  $p<0.05$ ). Thus far 200 patients with COPD have completed the 2 year follow-up assessment. Patients had a mean AoPWV increase of 0.5 m/s (95%CI 0.25-0.71,  $p<0.001$ ), despite no change in central mean arterial BP. In addition, lung function declined ( $p<0.05$ ) and HsCRP remained high.

**Conclusions:** The 2 year AoPWV increase in COPD was independent of traditional risk factors suggesting an alternative mechanism for aortic stiffness in COPD. Further longitudinal assessments of a control group will inform the understanding of the development of arterial stiffness and may indicate possible therapeutic targets.

# Poster Abstract Presentations

## P1.1

### ANTI-ANGIOGENIC TREATMENT IN CANCER PATIENTS CAUSES ARTERIAL DILATION AND STIFFENING BEYOND THE BLOOD PRESSURE EFFECT

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**Introduction:** Anti-angiogenic treatment (AAT) prescribed in cancer patients often induces hypertension and is associated with increased pulse wave velocity (PWV). PWV is known to depend on blood pressure (BP). Therefore, we assessed whether AAT changes PWV beyond an estimated first-order BP effect.

**Methods:** We obtained carotid artery systolic and diastolic cross-sectional areas (echo-tracking) and corresponding BPs in 17 cancer patients with metastatic solid tumours at baseline, and after 3 weeks of treatment ( $22.1 \pm 3.2$  days) with sorafenib, sunitinib or bevacizumab. For each patient, we derived local PWV (Bramwell-Hill) and a single-exponential P-A curve. Based on baseline P-A curves and measured follow-up pressures, we estimated the BP-induced PWV change at follow-up. By comparing estimated and measured changes in PWV at follow-up, we assessed the PWV increase beyond the BP effect. In the same way, we assessed whether diastolic cross-sectional area ( $A_d$ ) changed beyond the BP-induced amount.

**Results:** Based on the increase in SBP/DBP from (mean $\pm$ SD)  $115 \pm 15/70 \pm 8$  mmHg at baseline to  $126 \pm 13/78 \pm 10$  mmHg at follow-up, follow-up PWV was an estimated  $7.2 \pm 1.0$  m/s, whereas measured PWV was higher at  $7.8 \pm 1.7$  m/s ( $p=0.068$ ). Measured follow-up  $A_d$  markedly increased beyond the estimated pressure dilation (from  $38.1 \pm 9.5$  mm<sup>2</sup> to  $41.1 \pm 10.6$  mm<sup>2</sup>,  $p=0.034$ ).

**Conclusion:** AAT increases carotid PWV and cross-sectional area beyond the BP effect. While AAT is known to cause peripheral arterial vasoconstriction, this is not the case in the carotid artery. This finding may be explained by the deleterious influence of AAT on carotid vasa vasorum, possibly causing smooth muscle cell hypoxia and thereby wall stiffening (Stefanadis et al., Circulation 1995).

## P1.2

### ATHEROMATOSIS, ARTERIOSCLEROSIS AND DETERIORATION OF CARDIAC STRUCTURE AND PERFORMANCE; THE PIVOTAL CONTRIBUTION OF MEDITERRANEAN DIET IN CARDIOVASCULAR HEALTH

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**Purpose:** Atheromatosis and arteriosclerosis applied to changes in the intima and media vessel wall respectively, as part of the atherosclerotic process. Mediterranean diet, promoting olive oil and fruits consumption, contributes to cardiovascular disease prevention. Aim of our study is to investigate whether left ventricular (LV) and peripheral vascular parameters associate to adherence to the Mediterranean dietary pattern.

**Methods:** 75 males ( $56 \pm 11$  years) underwent cardiac ultrasound examination. Doppler diastolic parameters (E/A, E' / E'), LV mass (LVM) and LV mass index (LVMI) were obtained. Diameter of the ascending aorta was assessed and aortic distensibility was calculated. All patients underwent carotid-