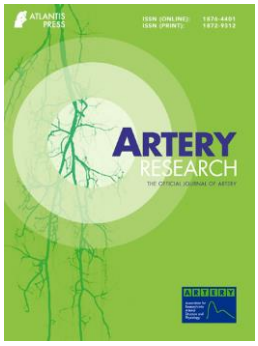

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1.5: AORTIC STIFFNESS IS INDEPENDENTLY ASSOCIATED WITH FATAL AND NON-FATAL CARDIOVASCULAR EVENTS IN CHRONIC KIDNEY DISEASE STAGE 2-5

A. Karras, J.P. Haymann, S. Laurent, E. Bozec, B. Stengel, C. Jacquot, P. Houillier, M. Froissart, P. Boutouyrie, M. Briet

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We have undertaken an individual participant data (IPD) meta-analysis of carotid-femoral pulse wave velocity (cf-PWV) with all cause mortality, CHD, stroke and combined CVD events using data from 14 studies (2 unpublished). Unlike a previous report, which only used published data, we were able to undertake standardised analyses with and without adjustment for cardiovascular risk factors and test, a priori, for potential interactions between cf-PWV and age group, gender, diabetic or hypertensive status on the various outcomes. We calculated discrimination statistics for models with and without cf-PWV, specifically focussing on individuals at intermediate (25-75th percentile) risk of CVD after adjustment for conventional Framingham risk factors. Fourteen studies provided data on 16,358 subjects with 1700 combined CVD events. We derived within study z-scores of log transformed cf-PWV (pooled SD = 3.3m/s). Risk of all outcomes was associated with increased cf-PWV (Table 1) and was linear across the range of cf-PWV values with no evidence of interaction except for age group (see Figure, p-value for trend = 0.0095). The additional benefit of measuring cf-PWV to reclassify intermediate risk individuals was assessed using the net reclassification index. 18.6% ($p<0.001$) and 22.4% ($p<0.001$) were appropriately reclassified into higher or lower quartiles of risk for CHD and stroke outcomes respectively. These findings highlight the added value of cf-PWV as an independent predictor, over and above existing risk factors, in intermediate risk groups and for younger subjects. Assessment of PWV should better identify high risk populations that may benefit from more aggressive risk factor management.

Table 1: Cox Proportional Hazards Models for cf-PWV as Predictor of an Outcome Event During the Follow-Up Period.

Outcome	Model 1*		Model 2*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
All cause mortality	1.21 (1.16, 1.27)	<0.001	1.16 (1.11, 1.23)	<0.001
CHD	1.33 (1.19, 1.48)	<0.001	1.22 (1.09, 1.36)	<0.001
CVD	1.42 (1.27, 1.59)	<0.001	1.28 (1.16, 1.41)	<0.001
Stroke	1.52 (1.30, 1.78)	<0.001	1.25 (1.14, 1.39)	<0.001

*Hazard ratio per 1 SD of log-transformed cf-PWV adjusted for age and sex
*As model 1, further adjustment for Framingham risk factors (systolic blood pressure, cholesterol, HDL-cholesterol, smoking status, baseline diabetes and baseline hypertension, where available).

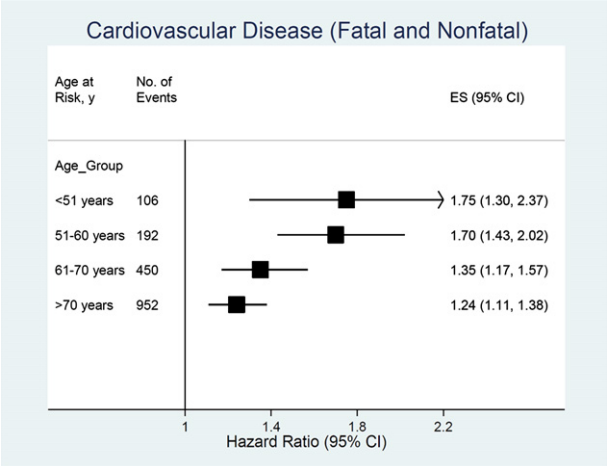

Figure: Pooled hazard ratios for cardiovascular disease for a one standard deviation increase in pulse wave velocity (log transformed) stratified by age group.

1.4
PULSE WAVE VELOCITY AND INCIDENT HEART FAILURE IN CHRONIC KIDNEY DISEASE

R. R. Townsend [1], A. Sheridan [1], J. Strelsin [1], M. J. Duckworth [1], J. A. Chirinos [1], V. Teal [1], A. Khan [1], J. Kusek [2], M. Schreiber [3], N. Bansal [4], A. Ojo [5], J. P. Lash [6], M. M. Joffe [1], C. R. I. C. Investigators [1]
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Heart failure (HF) complicates chronic kidney disease (CKD) despite improving medical therapy for co-morbidities like hypertension. We hypothesized that vascular stiffness, (aortic pulse wave velocity [PWV]), predicts incident HF in well controlled CKD participants free of HF at enrollment.
We performed aortic (i.e. carotid-femoral) PWV measurements (Sphygmocor) in 1889 participants enrolled in the multicenter Chronic Renal Insufficiency Cohort (CRIC) at their second year follow up visit and followed them prospectively (mean follow-up time of 1.4 years) for incident hospitalized HF events occurring before December 31, 2007 adjudicated by two independent Investigators. Mean age was 60 years, 44% women, 42% black, 6% Hispanic and 47% were Caucasian with mean(SD) blood pressure of 127(22)/70(13) mmHg (more than half of the participants were prescribed >3 antihypertensives) and a mean estimated glomerular filtration rate of 42.6 mL/min/1.73m2. Mean(SD) BMI was 31(6.6) kg/m2. Mean(SD) aortic PWV (adjusted for waist circumference) was 9.5(3.1) m/sec. There were 54 incident HF events. The unadjusted Cox proportional hazard ratio [95% CI] for incident HF for those with PWV >10m/s was 4.71 (2.59, 8.54; censored for deaths / withdrawals); adjusting for age, race, gender and mean arterial pressure it was 3.82[2.02,7.25]. We observed that for each 1 m/sec increase in aortic PWV there was a 11% (unadjusted) and 9% (after adjustment) increase in the hazard for HF.
In summary, aortic PWV independently predicted incident HF in CKD patients with well-controlled BP. Measures to better understand and improve PWV may compliment standard BP control to prevent HF in CKD.

1.5
AORTIC STIFFNESS IS INDEPENDENTLY ASSOCIATED WITH FATAL AND NON-FATAL CARDIOVASCULAR EVENTS IN CHRONIC KIDNEY DISEASE STAGE 2-5

A. Karras [1], J. P. Haymann [2], S. Laurent [3], E. Bozec [3], B. Stengel [4], C. Jacquot [1], P. Houillier [5], M. Froissart [5], P. Boutouyrie [3], M. Briet [3]
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Objective: Chronic kidney disease (CKD) is characterized by a high cardiovascular risk. Subclinical damage to large arteries has been largely described in CKD and is mostly characterized by an increase in arterial stiffness and an outward remodeling of the carotid artery. However, the predictive value of arterial remodeling and stiffening for cardiovascular events and mortality is still debated in pre-dialysed CKD (stage 2-5).
Methods: 180 patients (mean age 59.6 ± 14 years) with CKD (mean mGFR 32 mL/min/1.73m^2) were included in this longitudinal study. Patients underwent a yearly check-up including arterial evaluation (carotid-femoral pulse wave velocity (SphygmoCor®), carotid thickness, diameter and stiffness (Art-Lab system®) and GFR measurement with the ^{51}Cr-EDTA clearance.
Results: During an average follow-up of 49 ± 16 months, 36 fatal or not fatal cardiovascular events occurred. In COX regression analyses, PWV was significantly associated with fatal and non fatal cardiovascular events (risk ratio for 1 SD 1.46 [1.04-2.04], $P=0.02$) independently of age, body mass index, proteinuria, measured glomerular filtration rate and mean blood pressure. By contrast carotid intima-media thickness and circumferential wall stress were not significantly associated with fatal and non fatal cardiovascular events.

Conclusion: This study provides the first direct evidence that aortic stiffness not arterial remodeling is an independent predictor of fatal and non-fatal cardiovascular events in patients with CKD stage 2-5.

1.6
ARTERIAL STIFFNESS IS AN INDEPENDENT DETERMINANT OF COMPENSATORY HYPERFILTRATION AFTER KIDNEY DONATION

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After kidney donation, the remaining kidney tends to hyperfiltrate thus limiting the initial loss of renal function. However, the potential determinants of this compensative hyperfiltration (CHF) and the possible influence of arterial function are not known.
In 26 normotensive healthy kidney donors (51 +/- 9 yrs [mean+/-SD], 22 females), glomerular filtration rate (GFR) was measured by the clearance of continuously infused Tc99m-DTPA and timed urine collections at baseline -i.e. before donation- and 1 year after donation. CHF was computed as post-donation GFR minus half of baseline GFR. Arterial function was assessed at baseline through carotido-femoral pulse wave velocity (PWV) and carotid augmentation index (AIx).
After kidney donation, there were no significant changes in blood pressure (BP), but 2 subjects became hypertensive. GFR decreased from 104+/-17 to 71+/-11 mL/min/1.73m^2 and mean CHF was 19+/-9 mL/min/1.73m^2. In univariate analysis, CHF was inversely correlated to baseline age ($r^2=0.15$, $p=0.049$) and PWV ($r^2=0.23$, $p=0.012$), but not mean BP or AIx. In multivariate analysis, CHF remained inversely correlated to PWV ($p=0.020$), independently of baseline age, mean BP and GFR (model $r^2=0.45$, $p=0.002$).
In conclusion, in healthy subjects, increased arterial stiffness seems to be associated with a limited magnitude of post-donation hyperfiltration. This could reflect an influence of arterial function on renal reserve, providing further insights into the relationship between macrocirculation and renal microcirculation.

Oral Session 3
Young Investigators' Presentations

3.1
PRE-PREGNANCY CARDIOVASCULAR RISK IN WOMEN WITH PREVIOUS PREECLAMPSIA (PET)/INTRAUTERINE GROWTH RESTRICTION (IUGR)

A. A. Mahendru [1], C. C. Lees [1], T. R. Everett [1], C. M. McEniery [2], I. B. Wilkinson [2]
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Women with history of preeclampsia (PET) and delivery of intrauterine growth restriction (IUGR) babies are at increased risk of cardiovascular events later in life. This could be related to endothelial dysfunction, altered arterial stiffness or metabolic abnormalities resulting from pregnancy complications. Alternatively, pre-existing abnormalities in the cardiovascular system may predispose them to both pregnancy related complications and cardiovascular disease later in life. We compared pre-pregnancy arterial stiffness and central haemodynamics between women with previous PET/IUGR and those with previous uncomplicated pregnancies.
Method: 46 women planning to conceive were prospectively recruited in two groups: (1) 34 parous women with previous normal pregnancies (controls) (2) 12 women with previous PET (ISSHP guideline) requiring delivery at <34 weeks or requiring treatment for severe preeclampsia and/or who delivered an IUGR baby. Brachial and central blood pressures, pulse wave analysis (AIx), carotid-femoral pulse wave velocity (a PWV) and cardiac output were assessed along with routine biochemistry.
Results: Women with previous PET/IUGR had higher brachial diastolic blood pressure ($P=0.03$), central systolic blood pressure ($P=0.02$), MAP ($P=0.01$), and PVR ($P=0.03$) compared to controls but had lower PP amplification ($P=0.04$). There was no difference in the adjusted AIx, aPWV or in the cholesterol/lipid profile between the groups.
Conclusion: Vascular dysfunction as reflected by higher central blood pressure and peripheral resistance exists pre-pregnancy in women with previous PET/IUGR compared to normal healthy women. Further prospective pre-pregnancy studies prior to development of PET/IUGR are needed to assess the mechanism of the vascular dysfunction that persists following these pregnancy complications.

Table 1 Pre-pregnancy haemodynamics in two groups:

Cardiovascular parameter	Previous normal pregnancies (n=34)	Previous PET/IUGR (n=12)	P*
Age (yrs)	37 ± 4	34 ± 5	0.07
Brachial SBP (mm Hg)	108 ± 8	114 ± 9	0.07
Brachial DBP (mm Hg)	71 ± 7	77 ± 8	0.03*
Brachial PP (mm Hg)	37 ± 6	37 ± 4	0.7
Central SBP (mm Hg)	100 ± 9	107 ± 9	0.02*
PP (mm Hg)	28 ± 5	29 ± 5	0.4
PP amplification	1.4 ± 0.1	1.3 ± 0.1	0.04*
MAP (mm Hg)	84 ± 9	92 ± 9	0.01*
Heart rate (beats/min)	67 ± 9	67 ± 13	0.9
CO (L/min)	5.5 ± 1.0	5.1 ± 1.1	0.3
SV (ml)	77 ± 13	64 ± 25	0.1
PVR (dynes.s^{-1}.cm^{-5})	1258 ± 239	1508 ± 334	0.03*
AIX_a (%)	23 ± 6	27 ± 7	0.06
$aPWV_b$ (m/sec)	5.4 ± 0.1	5.5 ± 0.2	0.8

Data are means ± S.D. a=adjusted for age, height and heart rate. b=adjusted for MAP. *P <0.05 is statistically significant. (SBP= Systolic blood pressure, DBP= Diastolic blood pressure, PP= pulse pressure, MAP=Mean arterial pressure, CO=cardiac output, SV= stroke volume, PVR= peripheral vascular resistance)

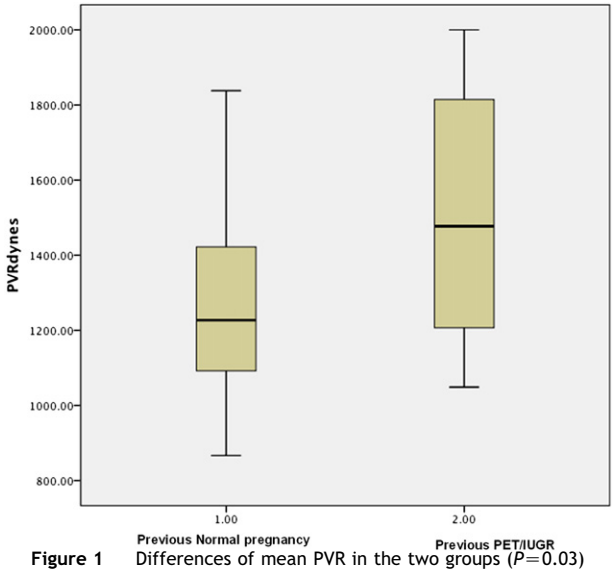

Figure 1 Differences of mean PVR in the two groups ($P=0.03$)

3.2
SPECTRAL ANALYSIS OF CAROTID DISTENSION RATE AND R–R INTERVAL (SPONTANEOUS BAROREFLEX ACTIVITY) PREDICTS CORONARY HEART DISEASE RISK IN PATIENTS WITH MODERATE CHRONIC KIDNEY DISEASE AND IN THOSE WITH NORMAL RENAL FUNCTION: THE EPP3 STUDY

L. Zanoli [1,2], M. Alivon [1], J. P. Empana [1], N. Estrugo [1], G. Ecriou [1], H. Ketthab [1], J. F. Pruny [1], P. Castellino [2], S. Yanes [1], D. Laude [1], K. Bean [1], F. Thomas [3], X. Jouven [1], S. Laurent [1], P. Boutouyrie [1]
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The classic technique to evaluate the spontaneous baroreflex is the spectral analysis of finger blood pressure and heart rate. However, baroreceptors respond to deformation and not to pressure per se and the results obtained with this technique can be influenced by the vascular component of the baroreflex. Recently, the spectral analysis of carotid distension rate has been used to study the neural baroreflex. The aim of this study is to test this new technique to predict the coronary heart disease (CHD) risk in patients with moderate chronic kidney disease (CKD) and in those with normal renal function.