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8.4: SYSTEMATIC REVIEW OF THE EFFECT OF ANTI-HYPERTENSIVE DRUG THERAPY ON ARTERIAL STIFFNESS

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50–00 mg daily for one year. Endothelial function (Salbutamol-induced vasodilation), wave reflection (Augmentation index (AI_x)), carotid-femoral pulse wave velocity (PWV), carotid artery intima-media thickness (IMT) and left ventricular wall thickness were measured at baseline, 6 months, and 12 months of treatment.

Results: NEB and MET decreased equally brachial blood pressure (BP), whereas reduction in central pulse pressure and left ventricular wall thickness was significant only in the NEB group. Left ventricular wall thickness change was significantly related to central systolic BP change ($r = 0.41$; $P = 0.001$) and central pulse pressure change ($r = 0.32$; $P = 0.01$). No significant changes in AI_x, PWV and IMT were detected in either treatment group. Endothelial function improved significantly after 6 months in the NEB treatment group.

Conclusion: Our study expands earlier observations with vasodilating BB and shows that nebivolol has a stronger impact on central blood pressure and left ventricular wall thickness reduction than metoprolol. Thus, β -blockers with vasodilating properties may offer a clear advantage over a conventional β -blocker in antihypertensive therapy.

8.1

BLOOD PRESSURE INCREASE AND DEVELOPMENT OF TARGET ORGAN DAMAGE IN SUBJECTS WITH HIGH NORMAL BLOOD PRESSURE IN A GENERAL POPULATION SAMPLE. A 9 YEARS FOLLOW-UP

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Background: Subjects with high-normal (HN) blood pressure (BP) may be at increased risk of progression to hypertension (HT) and of cardiovascular events, in comparison with normotensives (NT). Aim of our study was to evaluate the progression to hypertension and the development of target organ damage in a general population in Northern Italy.

Methods: In 585 subjects (age 50 ± 8 years, 46% males) a baseline visit and laboratory examinations were performed. Subjects were divided into 3 groups according to systolic (SBP) and diastolic blood pressure (DBP) values: NT (SBP/DBP < 130/85 mmHg); HN (SBP/DBP > 130/85 and < 140/90 mmHg) and HT (SBP/DBP > 140/90 mmHg). In 478 subjects a follow-up (FU) visit, laboratory examinations, measurement of carotid-femoral PWV and carotid IMT were performed after 8.7 ± 2.3 years.

Results: at baseline 30% of patients were NT, 25% were HN and 45% were HT. Among patients classified as HN at baseline, 71% developed hypertension at FU, 18% had HN BP, 11% were NT. Among subjects classified as NT at baseline, 34% developed hypertension at FU, 23% were classified as HN and 43% were NT. Mean BP values at FU were $129 \pm 13/82 \pm 7$ in NT, $139 \pm 13/87 \pm 6$ in HN, $146 \pm 15/89 \pm 8$ mmHg in HT, respectively (ANOVA $p < 0.001$). At FU in HN and in HT, as compared with NT, a significant increase of PWV (11.2 ± 2.1 and 12.4 ± 3.3 vs 10.1 ± 1.9 m/sec, ANOVA $p < 0.01$) and of common carotid IMT (1.00 ± 0.19 and 1.09 ± 0.27 vs 0.93 ± 0.15 mm, ANOVA $p < 0.01$) was observed.

Conclusions: In a general population in Northern Italy a large proportion of subjects with high normal BP developed hypertension and vascular target organ damage during a 9 years follow up.

8.2

(SHEAR) STRAIN IMAGING OF THE COMMON CAROTID ARTERY

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The primary trigger for myocardial infarction and stroke is destabilization of atherosclerotic plaques. The chance of a plaque to rupture is related to its composition and geometry. Ultrasound (shear) strain imaging allows assessment of local tissue mechanics and possible risk assessment of vulnerable plaques.

To non-invasively assess the local tissue mechanics of the common carotid artery radiofrequency data were acquired using a linear array ultrasound transducer (Philips 11-3L, $f_c = 7.5$ MHz) in longitudinal and in transverse direction. In transverse direction we used multiple beam steered angles. Simultaneously the ECG-signal was recorded. Axial and lateral displacement of the local tissue were estimated using a 2D coarse-to-fine cross-correlation based strain algorithm [1]. And from these displacements we derived the radial strain [2] and the longitudinal shear strain [3].

Both strains showed a cyclic pattern with an increase during the systolic and a decrease during the diastolic phase. The first *in vivo* results of radial strain in a plaque show increased strain values in the core of the plaque that might be related to a fatty composition.

The first results of non-invasive ultrasound strain imaging using radio-frequency ultrasound demonstrate the potential of quantifying plaque mechanics. Further validation of these methods will open the door for clinical screening of vulnerable plaques.

[1] Lopata RGP, *et al.* Ultrasound Med. Biol. 2009.

[2] Hansen HHG, *et al.* Phys. Med. Biol. 2010.

[3] Idzenga T, *et al.* Ultraschall in der Medizin 2010.

8.3

REDUCED SYSTEMIC ARTERIAL COMPLIANCE IN STABLE HEART TRANSPLANT PATIENTS

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Purpose: Despite high prevalence of cardiovascular diseases in heart transplanted patients (HTx), the global systemic arterial properties are not well described. Thus, the aim of this study was to evaluate arterial properties in HTx.

Methods: 26 stable heart transplanted patients (age 50 ± 17 years (mean \pm SD)) with no signs of rejection or cardiac failure were investigated 4.5 \pm 1.8 years after HTx and compared with healthy age-matched subjects with either normal blood pressure or similar brachial mean arterial blood pressure (MAP). Aortic root pressure and flow data were obtained by semi-simultaneous recordings of aortic root Doppler flow velocities, brachial arterial blood pressure and calibrated carotid arterial pulse trace. Systemic arterial properties were described by total arterial compliance (C), arterial elastance (Ea), characteristic impedance (Z₀), and peripheral vascular resistance (TVR). Parameters were estimated by Fourier analysis of central aortic pressure and flow data and methods based on the 2-element Windkessel model (pulse pressure method).

Results (Table): HTx patients had significantly higher Ea and lower C compared with the normotensive subjects. However, C tended lower ($p = 0.07$) in the MAP-matching group compared with the normotensive subjects.

Conclusion: Systemic arterial properties in HTx differ significantly from normotensive subjects; however only small variations were seen compared to the MAP-control group. Thus, the low compliance is likely due to a pressure-dependent effect.

	TxCor	MAP-control	Normotensive	P-ANOVA
Subjects (men/women)	26 (19/7)	22 (17/5)	24 (16/8)	
MAP (mmHg)	102 \pm 12	103 \pm 7 †	89 \pm 6 **	< 0.001
Heart rate (beats/s)	79 \pm 13	62 \pm 9 **	60 \pm 9 **	< 0.001
Cardiac output (l/min)	5.0 \pm 1.1	5.1 \pm 1.3	4.8 \pm 1.0	0.57
TVR (mmHg/(ml/s))	1.28 \pm 0.4	1.26 \pm 0.3	1.17 \pm 0.3	0.41
Z ₀ (103mmHg/(ml/s))	98 \pm 29	104 \pm 25	111 \pm 41	0.36
C (ml/mmHg)	0.88 \pm 0.3	0.95 \pm 0.2	1.12 \pm 0.2 **	0.005
Ea (mmHg/ml)	1.74 \pm 0.5	1.43 \pm 0.3 *	1.27 \pm 0.4 **	0.001

Mean \pm SD, * $p < 0.05$ and ** $p < 0.005$ compared with TxCor. † $p < 0.005$ compared with normotensive subjects.

8.4

SYSTEMATIC REVIEW OF THE EFFECT OF ANTI-HYPERTENSIVE DRUG THERAPY ON ARTERIAL STIFFNESS

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Background: Since arterial stiffness (AS) is one of the factors influencing prognosis in hypertensive patients, we performed a systematic review of studies testing the effect of anti-hypertensive therapy on AS.

Methods: We performed a systematic search of the literature using on-line databases (1966-Dec 2009). We included studies on Pulse Wave Velocity

(PWV, m/s -expression of AS) and blood pressure (BP-reported as continuous variable), measured at the beginning and at the end of study, carried out in adult populations after a run-in period. We found one placebo-controlled

(the arterial segment travelled in carotid-femoral PWV measurement) was compared to 7 tape measures commonly used in PWV measurement.

Results:

Comparison of aortic path lengths (APL) determined by MRI and tape measure.(cm)N = 98				
MRI travelled APL	TAPE estimated APL	MRI Mean (SD)	Tape-MRI Mean (SD)	MRI/Tape
(AA-FA)–(AA-CA)	(CA-FA)–(SSN-CA)	50.7(4.2)	2.32(3.8)*	0.957
	(CA-FA)–(SN-CA)		–2.35(3.8)*	1.050
	(SSN-Umb)+(Umb-FA)–(SSN-CA)		–3.51(4.1)*	1.074
	(SSN-FA)–(SSN-CA)		–5.11(3.5)*	1.114
	(CA-FA)		12.99(4.2)*	0.797
	(SN-FA)–(SN-CA)		–14.77(3.9)*	1.412
	(CA-FA) × 0.8. <i>The Reference Values for Arterial Stiffness' Collaboration, Eur Heart J. 2010.</i>		0.26(3.8)	0.996

* p < 0.001; AA = Ascending Aorta, CA = Carotid Artery, SSN = Suprasternal Notch, SN = Sternal Notch, Umb = Umbilicus, FA = Femoral Artery.

study (Mitchell, 2007) and 18 reporting a treatment effect in comparison with baseline. For each study, mean difference and 95%CI. were extracted and pooled using a random effect model.

Results: We identified 19 studies(37cohorts), which included 1,291 participants. The mean observation time was 17 weeks. In the pooled analysis, there was a significant decrease of PWV after treatment (–1.17; 95% C.I. = –1.51,–0.83). In separate analyses the significant PWV reduction was evident with ACE-I (n = 12, –1.39; –1.97,–0.82), ARBs (n = 7, –1.56; –3.00,–0.12) and Beta-blockers (n = 7, –1.03; –1.23,–0.82). While PWV changes with Ca-channel-blockers (n = 7, –0.88; –1.84,0.08) and Diuretics (n = 3, 0.13; –0.26,0.52) were not significant. There was no publication bias but significant heterogeneity between studies. Meta-regression analysis showed that significant sources of heterogeneity were basal age and BP and BP changes after therapy.

Conclusions: This systematic review suggests that anti-hypertensive treatment improves AS probably with a drug related effect. However the lack of placebo controlled as well as comparative treatment trials do not allows us to reach definite conclusions.

8.5

CAROTID TO FEMORAL PULSE WAVE VELOCITY: WHICH DISTANCE, OBTAINED BY TAPE MEASURE, CORRESPONDS BEST WITH THE REAL TRAVELLED AORTIC PATH LENGTH?

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Objective: Carotid-femoral pulse wave velocity (PWV) is the gold standard method for determination of arterial stiffness. Path lengths are commonly determined by tape measure, which may not correspond to anatomical path lengths. This study investigates the correspondence between the travelled arterial length obtained from magnetic resonance imaging (MRI) images with commonly used body-surface distances obtained by tape measure.

Design and method: 98 healthy males/females were included (50% men, age 21–76). Exclusion criteria: heart disease, pacemaker, implant or clip, large tattoo, pregnant or breastfeeding, claustrophobia, significant obesity.

MRI path lengths were obtained through centrelines reconstructed from the centerpoints determined manually in each slice. The MRI-measured length

Conclusions: In the present population sample the distance (CA-FA) × 0.8, which is the distance from the carotid artery to the femoral artery multiplied by 0.8, provides the best approximation of the real travelled aortic path length.

8.6

PLASMA OSTEOPROTEGERIN AND PROTEINURIA ARE INDEPENDENTLY ASSOCIATED WITH HIGHLY SENSITIVE TROPONIN T IN CHRONIC KIDNEY DISEASE (CKD) STAGES 3 & 4

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Background: Highly sensitive cardiac troponin-T (hs-cTropT) is a predictor of mortality in dialysis dependent renal failure patients. Vascular calcification is also associated with adverse outcome in CKD. Osteoprotegerin (OPG) is a mediator of the bone-vascular axis and has been associated with adverse cardiovascular outcomes.

Aims: We investigated the relationship of hs-cTrop T with OPG and other clinical and biochemical parameters in a cohort of patients with CKD stages 3 & 4.

Method: ELISA kits were used to measure hs-cTropT (Roche, UK) and OPG (Biovendor, CZ).

Results: 122 patients were studied, 95 M:27F. Age 69 ± 11 years (mean ± SD). Diabetic:Non-Diabetic 28:94. Systolic BP 154 ± 21mmHg, DBP 104 ± 21mmHg, eGFR 32 ± 11 ml/min/1.73 m², PO₄ 1.08 ± 0.20 mmol/l. uPCR* 35.8 (14.9–75.2 mg/mmol) (*Geometric Mean (25th–75th centile), *iPTH 79.1 (49–127ng/l),* OPG 9.41(7.4–12.1pmol/l), *hs-cTropT 0.174 (0.010–0.283 µg/l).

Significant univariate correlation was found between hs-cTropT, Age, eGFR, uPCR, iPTH, OPG.

After stepwise multivariate analysis age (β = 0.420, p < 0.001), loguPCR (β = 0.290, p < 0.001), eGFR (β = –0.281, p < 0.001) and logOPG (β = 0.184, p = 0.011) were independently associated with loghs-cTropT. Model adjusted R² = 0.491. The other variables were excluded from the model.

Conclusion: In addition to the recognised cardiovascular risk factors age and eGFR, proteinuria and plasma osteoprotegerin are independently associated with hs-cTropT in CKD stages 3 & 4. This suggests involvement in the pathogenesis of cardiovascular disease in pre-dialysis CKD.