

Selected Abstracts from the National Congress of the Italian Society of Hypertension (SIIA 2011)

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Atherosclerosis and Inflammation (and Cerebrovascular Disease)

1.1 Effect of Olmesartan on Oxidative Stress in Hypertensive Patients: Mechanistic Support to Clinical Trials Derived Evidence

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Introduction: The role of oxidative stress in the pathophysiology of hypertension and target organ damage is widely recognized. Using a molecular biology approach, we report, in essential hypertensive patients, the effect of the angiotensin II type 1 receptor blocker olmesartan on the mononuclear cell (PBMC) protein expression of major elements in the oxidative stress and vascular remodelling-related pathways, p22phox and HO-1, along with the phosphorylation state of ERK1/2 and plasma oxidized LDL (oxLDL).

Methods: Twenty untreated essential hypertensive patients (blood pressure range: 142–156/94–98 mmHg) were treated with olmesartan medoxomil (20 mg/day for 6 months) and blood samples collected at baseline, 3 and 6 months for PBMC p22phox and HO-1 protein expression, phosphorylation state of ERK1/2 (western blot) and oxLDL level (ELISA) evaluations.

Results: Olmesartan normalized blood pressure since the third month ($149 \pm 4.7/94.88 \pm 1.9$ mmHg vs $137.89 \pm 2.08/88.44 \pm 2.0$ at 3 months and vs $135.44 \pm 2.18/85.78 \pm 1.2$ at 6 months, ANOVA: $p < 0.001$). p22phox protein level declined at 3 months (7.10 ± 2.61 vs 9.32 ± 2.43 d.u., $p < 0.001$), further declining at 6 months (4.55 ± 1.26 d.u., $p < 0.001$). HO-1 levels increased at 3 months (10.87 ± 1.92 vs 7.70 ± 0.71 d.u., $p = 0.001$) and remained elevated (11.11 ± 1.89 d.u., $p = 0.001$), without further increase at 6 months. Phosphorylated ERK1/2 declined at 3 months (3.94 ± 1.44 vs 5.62 ± 1.11 d.u., $p = 0.001$), further declining at 6 months (1.94 ± 0.87 , $p < 0.001$). oxLDL significantly declined at 3 and 6 months.

Conclusions: These results demonstrate that olmesartan inhibits oxidative stress. Given the involvement of oxidative stress and its signalling in atherogenesis and the available evidence of olmesartan's vasoprotective, anti-inflammatory and antiatherosclerotic effects derived from clinical trials in humans (EUTOPIA, VIOS, MORE and OLIVUS), the results of our study provide a mechanistic rationale for the olmesartan's antioxidant and anti-inflammatory potential translation, in the long term, toward the antiatherosclerotic and antiremodelling effects reported on the clinical ground.

1.2 T-Lymphocyte RAS Activation is Modulated by Hypertensive Target Organ Damage

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Introduction: In these last years, human T-lymphocytes were shown to be endowed with a functional active renin-angiotensin system (RAS), independent to the circulating system, and to have a role in the development of hypertensive target organ damage (TOD). To date, findings on the possible T-lymphocyte-RAS involvement in modulation of TOD are discordant.

Methods: T-lymphocytes were obtained from peripheral blood samples of 7 hypertensive patients (I-II WHO class; 5 males, 2 females; 56 ± 5 years) without TOD and 5 hypertensive patients (I-II WHO class; 4 males, 1 female; 57 ± 8 years) with carotid and peripheral arterial atherosclerotic disease. No patients were in therapy with ACE inhibitors and/or angiotensin receptor blockers. Seven healthy subjects formed the age- and sex-matched control group. After T-lymphocytes isolation, mRNAs for ACE and AT1-R were quantified by RT-PCR under baseline conditions and after 0.1 pmol/L AngII addition to T-cell cultures at 6, 18 and 24 hours. Cell pellet and supernatant ACE activity and AT1-R cell content were measured.

Results: Both in controls and hypertensive patients, plasma renin activity was normal. AngII stimulation significantly increased ACE and AT1-R mRNA levels ($p < 0.05$) in controls. In hypertensive patients without TOD T-lymphocyte ACE and AT1-R mRNA basal levels were higher and showed a higher increase than controls after Ang II-stimulation ($p < 0.01$). In hypertensive patients with TOD, T-lymphocyte-RAS was activated in basal condition. Ang II stimulation did not determine further increase in ACE and AT1-R mRNA levels. T-lymphocyte of hypertensive patients with TOD had higher basal ACE activity and intracellular Ang II concentration than hypertensive patients without TOD and controls, even after Ang II-stimulation ($p < 0.01$).

Conclusions: A progressive increase in T-lymphocyte-RAS activation is present in hypertensive patients. In patients with TOD, RAS appears at the maximum activation. T-lymphocyte RAS could be considered as a new marker of early atherosclerotic damage, allowing an optimization of both cardiovascular risk definition and antihypertensive therapy.

1.3 Mitral Annular Calcification and Incident Embolic Stroke in Treated Hypertensive Patients: The Life ECHO-Substudy

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Introduction: Mitral annular calcification (MAC) has been associated with increased risk of embolic stroke. Whether MAC is an independent predictor of incident embolic stroke in treated hypertensive patients with target organ damage, independently of significant confounders, including LV mass has not been established in a prospective study.

Methods and Results: Baseline clinical and echocardiographic parameters were assessed in 929 hypertensive participants of the LIFE echo-substudy (66 ± 7 years, 42% women, 11% with diabetes) with ECG criteria of left ventricular hypertrophy (LVH), but without prevalent CV disease or significant mitral or aortic valve disease. At the time of the initial echo exam, MAC of any degree was detected in 450 hypertensive participants (48% of the total population). Participants with MAC were more often women (47 vs 36%), diabetic (13% vs 9%), older (67 ± 7 vs 64 ± 7 years), had higher systolic BP (176 ± 22 vs 171 ± 20 mmHg), heart rate (69 ± 12 vs 67 ± 12 bpm), had more often albuminuria (29% vs 22%) and LVH (78% vs 69%) compared to those without MAC (all $p < 0.01$), without significant differences for diastolic BP, BMI, cholesterol levels or smoking status between groups. Over a mean follow-up of 5 years, 56 participants (or 6%) had embolic stroke. Risk of incident embolic stroke was significantly associated with presence of baseline MAC (log Rank = 11, $p = 0.001$). In multivariate Cox-regression analysis, baseline MAC resulted to be a strong predictor of incident stroke (HR = 2.00; 95% CI 1.02, 3.92), independently of age, gender, baseline systolic BP, heart rate, presence of diabetes, initial LV mass index, left atrial dimension, urinary albumin/creatinine ratio and antihypertensive treatment.

Conclusions: In a population of treated hypertensive adults with ECG LVH, MAC was frequent (48%) and was a strong predictor of incident embolic stroke, independently of significant confounders.

1.4 Role of Aliskiren in Long-Term Brachial and Central Blood Pressure Control in Elderly Hypertensive Patients before and after Carotid Endarterectomy

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Introduction: Many elderly cerebrovascular patients with indication for carotid endarterectomy do not have controlled blood pressure levels at the time of surgery and thereafter.

Aim: To evaluate the central and brachial blood pressure in hypertensive patients on the waiting list for endarterectomy, and estimate the effects of adjunctive therapy with aliskiren or lercanidipine on blood pressure control and cognitive function.

Methods: Prospective study of 66 elderly hypertensive patients treated with at least two anti-hypertensive drugs (40 males, mean age 71.8 years) candidates for endarterectomy for carotid stenosis (>70% of the vessel lumen). Patients were divided into three groups: optimal blood pressure control ($n = 36$), and uncontrolled blood pressure, the latter further divided to added aliskiren therapy ($n = 15$, aliskiren group) or added lercanidipine therapy ($n = 15$, group lercanidipine). Exclusion criteria were: emergency endarterectomy, glomerular filtration rate < 30 mL/min, heart failure NYHA class III-IV or recent exacerbation, major cardiovascular events in previous 6 months. Measurements of brachial and central pressure (the latter obtained by SphygmoCor) were obtained at baseline, 2 months and 6 months. A Mini Mental State Examination (MMSE) was conducted by trained personnel at 2 and 6 months. All patients underwent endarterectomy around 2 months after first visit.

Results: In both groups with additional treatment brachial systolic pressure (SBP) and central (cSBP) decreased from 0 to 2 months. However, only patients treated with aliskiren have a further significant reduction of the SBP and cSBP at 6 months ($p = 0.005$ and $p = 0.006$). At 6 months follow-up the patients treated with aliskiren had a greater reduction in SBP and cSBP than the group treated with lercanidipine (SBP: -20.8 ± 12.7 to 140.0 ± 13.8 mmHg vs -6.8 ± 12.1 to 148.7 ± 17.1 mmHg; cSBP: -21.2 ± 10.3 to 129.0 ± 14.6 mmHg vs -4.8 ± 12.1 to 139.8 ± 15.2 mmHg, all $p < 0.01$). The reductions in diastolic blood pressure were similar in both groups. No significant differences were

found in MMSE between 2 and 6 months follow-up in the general population as well as in the three subgroups.

Conclusions: Aliskiren seems to be more effective than lercanidipine as adjunctive therapy in reducing the brachial and central systolic blood pressure in elderly candidates to carotid endarterectomy. The improved blood pressure control did not worsen cognitive function in elderly cerebrovascular patients.

1.5 Hypertension Modulates MIR-145 Expression in Human Atherosclerotic Plaques

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Introduction: MicroRNAs (miRNAs) are endogenous, noncoding, short, single-stranded RNAs and represent a new class of gene regulators. Recent evidences support a role for miRNAs in

cardiovascular pathophysiology and atherosclerosis development. We have previously demonstrated that miR-145 is widely expressed in vessel wall and in atherosclerotic lesions. Its down-regulation has been correlated with transition of vascular smooth muscle cells (VSMCs) from a differentiated phenotype to a dedifferentiated state, a cardinal step in the development of atherosclerosis. However, no evidences are available at this time about modulation of miR-145 in the setting of hypertension.

Aim: To investigate the expression of miR-145 in complicated hypertension.

Methods: atherosclerotic plaques were obtained from 21 patients undergoing carotid endarterectomy for high grade internal carotid artery stenosis. Plaques were subdivided into hypertension (n = 14) and control (n = 7) groups according to presence or absence of hypertension (as defined by PA >140/90 mmHg or current antihypertensive therapy). In study plaques, miR-145 values were evaluated using real-time PCR.

Results: We found that miR-145 was significantly more expressed in atherosclerotic plaques of hypertensive patients (1.22 ± 0.28 vs 0.40 ± 0.16 , fold induction \pm SEM; $p = 0.02$). Moreover, a *post hoc* analysis showed that treatment with angiotensin receptor blockers (ARBs) is associated with further increase in miR-145 levels, although ARB-treated patients were few and therefore not statistically significant ($p = 0.263$) for the limited sample size.

Conclusions: This study suggests for the first time that hypertension may upregulate miR-145 expression in human atherosclerotic plaques. Future investigations are focusing on the effects of miR-145 upregulation in established atherosclerotic lesions.

Blood Pressure Monitoring

2.1 Nocturnal Hypertension and Organ Damage in Dippers versus Non-Dippers

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Introduction: The relationship between high nocturnal blood pressure (BP), organ damage and the dipping/non-dipping status is poorly defined.

Aim: We investigated whether the dipping/non-dipping pattern defined on the basis of two 24-hour ambulatory BP monitoring (ABPM) is associated with subclinical organ damage in untreated hypertensive patients with elevated night-time BP.

Methods: All subjects underwent the following procedures: cardiac and carotid ultrasonography, 24-hour urine collection for microalbuminuria, and ABPM over two 24-h periods within 4 weeks. Nocturnal hypertension was defined according to current guidelines (i.e. night-time BP >120/70 mmHg) and non-dipping status as a reduction in average systolic and diastolic BP at night less than 10% compared with day-time values.

Results: Among 343 subjects, 199 were dippers and 144 non-dippers in both ABPM sessions. No differences were found in clinical variables, average 48-h BP, left ventricular mass, carotid intima-media and urinary albumin excretion between the groups. This was also the case for prevalence rates of left ventricular hypertrophy, carotid intima-media thickening or plaque and microalbuminuria. Finally, no relationship was found between the markers of organ damage and BP fall at night.

Conclusions: In the presence of nocturnal hypertension, dippers have similar subclinical cardiac and extra-cardiac organ damage as their non-dipper counterparts. These data suggest that therapeutic strategies only addressing the non-dipper pattern may be insufficient to protect hypertensive subjects against the dangerous effects of elevated nocturnal BP.

2.2 Nocturnal Blood Pressure in Untreated Essential Hypertensive Patients

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Introduction: Prevalence, correlates and reproducibility of nocturnal hypertension (NH) as defined by fixed cut-off limits in uncomplicated essential hypertension are poorly defined. Therefore, we assessed such issue in a cohort of 658 untreated hypertensive patients.

Methods: All subjects underwent procedures including cardiac and carotid ultrasonography, 24-h urine collection for microalbuminuria, ambulatory blood pressure monitoring (ABPM), over two 24-h periods within 4 weeks. NH was defined according to current guidelines (i.e. night-time BP

>120/70 mmHg) and non-dipping status as a reduction in average SBP and DBP at night lower than 10% compared with day-time values.

Results: A total of 477 subjects showed NH during the first and second ABPM period; 62 subjects had normal nocturnal BP (NN) in both ABPM sessions. Finally, 119 subjects changed their pattern from one ABPM session to the other. Overall, 72.5% of subjects had reproducible NH, 18% variable pattern (VP) and 9.5% reproducible NN. In the same group, figures of reproducible non-dipping, variable dipping and reproducible dipping pattern were 24%, 24% and 52%, respectively. Among NH patients, 56% of whom were dippers, subclinical cardiac organ damage was more pronounced than in their NN counterparts.

Conclusions: In uncomplicated essential hypertensive patients, NH is a more frequent pattern than non-dipping; NH is associated with organ damage, independently of dipping/non-dipping status. This suggests that options aimed at restoring a blunted nocturnal BP fall may be insufficient to prevent cardiovascular complications unless night-time BP values are fully normalized.

2.3 Blood Pressure/Height Ratio as Test Screening for Hypertension in Caucasian Adolescents

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Introduction: Diagnosis of hypertension in adolescence is difficult because of the need of several percentile grids. Recently, Lu and co-workers found that blood pressure/height ratio (BPHR) was a simple and accurate index for screening hypertension in adolescents. However, they suggested that this index had to be validated in other ethnic groups.

Aim: To test the applicability of this index on a population of Caucasian adolescents in order to consider its use also in this ethnic group.

Methods: Cross-sectional population-based study of 1413 Caucasian adolescents (705 females and 698 males, age range 12–15 years) among students of public junior high schools of Turin, Italy. Hypertension was defined according 2004 Guidelines. Obesity was defined by BMI \geq 95th percentiles. BPHR was calculated as follows: SBPHR = SBP (mmHg)/height (cm) and DBPHR = DBP (mmHg)/height (cm). Specificity and sensitivity of the index applied in our population against the gold standard were calculated.

Results: Regarding blood pressure, we observed mean values of 113 ± 11 (110 ± 11) and 54 ± 27 (57 ± 24), respectively, for systolic and diastolic value in boys (girls). Boys have significantly higher height (159 ± 9), weight (51 ± 11) and SBP than girls ($p < 0.01$) who had higher DBP values ($p < 0.04$). 24% of males and 19% of females were obese. The prevalence of hypertension was 15.32% (0.96% stage 2) in boys and 14.95% (2.05% stage 2) in girls. SBPHR (0.71 in both groups) and DBPHR (0.34 and 0.37 in males and females, respectively) were not correlated with age and height in both sexes but positively correlated with BP values. According to cut-off points provided by Lu and co-workers and considering stage 1 hypertension, sensitivity and specificity $\geq 90\%$ was found in both sexes. For stage 2, sensitivity was about 1 in both sexes and specificity was 1 for SBP, for DBP sensitivity was 1 and specificity was unavailable.

Conclusions: Our analysis adds a confirmation about the validity of BPHR as a simple and accurate index for hypertension diagnosis also in Caucasian adolescents.

2.4 Blood Pressure and Heart Rate Variability in Relation to Rage Expression in Primary Hypertensive Subjects

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Introduction: It is well known that psychological factors connected to persistent depression, anxiety and rage may increase the risk of developing hypertension. The first psychosomatic hypothesis dates back to the 1930s when Alexander suggested that chronic inhibition of rage may induce stable hypertension, whereas rage expression could decrease blood pressure (BP) at rest. Most studies addressing this possible relationship deal with the different expressions of rage, whether or not it is externalized (rage out, rage in). A meta-analysis shows that rage-in attitude is correlated with increased BP values at rest, whereas rage-out attitude is with lower BP rest values.

Aim: To evaluate BP and heart rate (HR) variability at rest, both in terms of time and frequency domains, in primary hypertensive subjects.

Methods: From our pool of 50 patients with essential hypertension, we selected 20 newly diagnosed, yet untreated males with a mean age of 43.14 ± 6.2 years. The latter were subdivided in two groups: Group A consisting of rage-out subjects and Group B with rage-in patients, on the basis of the Defense Mechanism Inventory (DMI) self-evaluation test created by Glesere and Ihilivech. BP was continuously assessed at rest for an hour by FinAPRES on 512 consecutive stabilized beats. Data obtained from the time domain were assessed using the Student t-test with a cut-off of $p < 0.05$ for significance. The evaluation of the frequency domain data was performed by spectrum analysis using the Fourier transform.

Results: Three frequency bands were identified within the spectrum: Low Frequency (0.025, 0.07 Hz), Mid Frequency (0.07, 0.14 Hz) and High Frequency (0.14, 0.35 Hz). Results obtained in the time domain showed significantly higher systolic and diastolic BP values in Group B compared with Group A, thereby confirming results from previous studies. No difference was found as far as HR. Analogous trends were observed for BP in LF in both groups. Pulse interval, instead, showed a significant LF increase in group A and a noteworthy decrease in group B. The latter trend was maintained in HF, with a significant decrease in the rage-out group with respect to the rage-in subjects.

Conclusions: The LF/HF ratio, which represents the sympathetic-vagal balance, revealed a higher sympathetic tone in group A, thus indicating a higher risk for secondary damage in the rage-out subjects, despite normal BP values at rest.

2.5 Comparison of Standing Blood Pressure Changes after Supine- versus Seated-Rest in Essential Hypertensive Patients

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Introduction: Orthostatic hypotension (OH) in patients with essential hypertension (EH) is hardly detectable in clinical practice, as the procedure is time-consuming.

Methods: In EH subjects we measured blood pressure (BP) changes from seated to active standing (UP/seated) and from supine to standing (UP/supine) during an office visit in order to detect OH (systolic and/or diastolic BP decline $>20/10$ mmHg, respectively, within 3 minutes of standing from the supine position) and evaluate the corresponding BP falls in the UP/seated posture. In 462 treated EH (age 61 ± 0.6 years, M/F = 230/232, BMI 27 ± 0.2 kg/m², drugs $n = 2.2 \pm 0.1$, diabetics $n = 42$), BP (sphygmo) and heart rate (HR, pulse rate) were measured within 3 minutes of active standing after a 5 minutes rest both in the seated (UP/seated) and supine position (UP/supine), in a random sequence, during a morning visit.

Results: The main findings of our study are reported in the table. Data are expressed as means \pm SEM; * $p < 0.05$ versus UP/seated values in subjects with OH ($n = 103$, Δ SBP -27 ± 1 and Δ DBP -4.5 ± 0.6 mmHg from supine to standing), SBP and DBP changes from seated to standing were -9.5 ± 1.0 and $+1.8 \pm 0.6$ mmHg, respectively. In subjects without OH ($n = 359$, Δ SBP -5.7 ± 0.5 and Δ DBP $+3.0 \pm 0.3$ mmHg from supine to standing), SBP and DBP changes from seated to standing were -3.0 ± 0.4 and $+3.7 \pm 0.3$ mmHg, respectively ($p < 0.01$ for both vs the corresponding changes in OH patients). A correlation was present between BP changes in both standing positions, for systolic ($r = 0.40$) and for diastolic changes ($r = 0.25$, $p < 0.01$ for both).

	Seated	Standing UP/seated	Supine	Standing UP/supine
Systolic BP (mmHg)	136.8 \pm 0.9	132.4 \pm 0.9	143.0 \pm 0.9	132.7 \pm 1.0
Diastolic BP (mmHg)	82.4 \pm 0.5	85.7 \pm 0.6	83.2 \pm 0.5	84.5 \pm 0.6*
HR (bt/min)	70.2 \pm 0.5	75.3 \pm 0.5	68.9 \pm 0.5	77.2 \pm 0.6*

Conclusions: Standing BP changes after a seated rest may largely identify OH in treated EH subjects during a clinic visit; thus, the procedure should be implemented in clinical practice.

2.6 Acetazolamide Counteracts Ambulatory Blood Pressure Increase Under Acute Exposure to High Altitude

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Introduction: We have shown that exposure to high altitude (HA) induces an increase in blood pressure (BP), only partly counteracted by β -blockers or angiotensin receptor antagonists.

Aim: To assess the effect of acetazolamide (AC), a drug used in acute mountain sickness, on ambulatory BP under acute exposure to hypoxia at HA.

Methods: 43 healthy normotensive subjects were randomized in double-blind design to receive AC 250 mg bid or placebo (PL). Study tests including ambulatory BP monitoring (ABPM; AND TM2430) were performed at sea level (SL) before (BAS-SL) and after 2 days of treatment (T-SL); and on the second full day of acute exposure to HA (Monte Rosa, 4559 m). 24-h, day and night BP and HR mean levels and nocturnal fall (%) were computed in each condition.

Results: All subjects (age 36.8 ± 8.9 y, 22M/21F, BMI 21.8 ± 2.6 kg/m²) but one completed the study. There were no significant differences between groups at BAS-SL. BP and HR increased at HA in PL while a minor increase in diastolic (D)BP and HR but not in systolic (S)BP occurred in AC group (see table). AC had little influence on study variables at T-SL except for an increase in daytime HR.

Variable	AC BAS-SL	PL BAS-SL	ACT-SL	PLT-SL	AC HA	PL HA	p AC vs PL at HA
24 h SBP	116.0 \pm 10.8	120.1 \pm 10.1	116.7 \pm 10.1	119.1 \pm 7.6	118.3 \pm 8.8	130.0 \pm 8.9	0.001
24 h DBP	72.5 \pm 6.1	73.3 \pm 6.0	73.2 \pm 5.4	72.7 \pm 4.5	76.2 \pm 6.2	80.8 \pm 5.8	0.077
24 h HR	68.9 \pm 6.1	68.6 \pm 7.7	72.8 \pm 6.3	70.3 \pm 7.0	75.4 \pm 8.4	80.8 \pm 8.4	0.141
Day SBP	121.6 \pm 11.1	127.2 \pm 12.2	123.4 \pm 10.7	126.8 \pm 8.1	122.9 \pm 11.0	135.2 \pm 10.0	0.002
Day DBP	77.1 \pm 6.5	79.1 \pm 7.2	79.4 \pm 7.2	78.9 \pm 4.9	79.5 \pm 7.2	84.1 \pm 6.2	0.022
Day HR	73.2 \pm 7.5	73.5 \pm 10.8	79.2 \pm 7.2	76.0 \pm 8.9	79.2 \pm 8.8	84.0 \pm 9.4	0.055
Night SBP	101.2 \pm 13.2	106.4 \pm 11.3	101.1 \pm 11.0	107.3 \pm 10.0	104.4 \pm 9.0	118.1 \pm 12.1	0.001
Night DBP	60.6 \pm 7.5	61.6 \pm 6.9	60.7 \pm 5.3	62.4 \pm 6.4	66.0 \pm 7.4	72.7 \pm 7.8	0.002
Night HR	58.9 \pm 7.0	58.9 \pm 6.3	60.0 \pm 7.4	61.6 \pm 7.2	66.4 \pm 9.1	73.4 \pm 9.3	0.006
SBP dip	16.7 \pm 8.6	16.7 \pm 5.9	17.7 \pm 6.5	15.3 \pm 7.0	14.9 \pm 5.5	12.5 \pm 7.6	0.276
HBP dip	22.3 \pm 6.9	22.5 \pm 4.8	23.3 \pm 7.8	20.8 \pm 8.2	16.9 \pm 7.3	13.5 \pm 7.8	0.138
HR dip	20.0 \pm 10.2	20.4 \pm 11.8	24.5 \pm 7.2	18.2 \pm 11.2	16.2 \pm 6.3	12.5 \pm 7.9	0.264

Conclusions: Acetazolamide almost completely counteracted ambulatory BP increase at HA in healthy subjects. This might contribute to the beneficial role of this drug in subjects prone to mountain sickness. Further research is needed to demonstrate its usefulness in preventing BP increase also in hypertensive patients exposed to HA.

2.7 Tronco-Conical Cuffs Can Provide More Accurate Blood Pressure Measurements than Cylindrical Cuffs in People with Large Arms

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Introduction: Cylindrical cuffs and bladders are currently used for blood pressure (BP) measurement at the upper arm. However, large arms often have a tronco-conical shape.

Aim: To evaluate whether cylindrical and tronco-conical cuffs provide different readings according to arm size and shape.

Methods: In 349 subjects (180 men) aged 56 ± 18 years, with arm mid-circumference ranging from 22 to 42.5 cm, proximal, middle, and distal arm circumferences and arm length were measured to calculate the frustum slant angle. Four different cylindrical and four different tronco-conical bladders of appropriate size were constructed, for arm circumferences ranging from 22.0 to 27.0 cm, for circumferences ranging from 27.5 to 32.0 cm, for circumferences ranging from 32.5 to 37.0 cm, and for circumferences ranging from 37.5 to 42.0 cm. Tronco-conical cuff and bladder slant angles for each arm-size group were derived from the anthropometric measures in the 349 subjects and were 87.0°, 86.5°, 86.0° and 85.0°, respectively, in the four groups. The validation test was conducted in 120 subjects. Sequential same-arm measurements were performed with the subject in the sitting position. In each subject, BP was measured in triplicate by two observers using the two cuffs in a random order.

Results: In all of the subjects, upper-arm shape was tronco-conical with slant angles ranging from 89.5° to 82.2° (mean = 86.2°). Conicity was highly correlated to arm mid-circumference (Bonferroni corrected $p < 0.001$), skinfold thicknesses ($p < 0.001$), body mass index (BMI, $p < 0.001$), and was inversely correlated to arm length ($p = 0.03$). In the 120 subjects who underwent the validation test, similar results to those obtained in the larger population were found. BMI progressively increased on going from the smallest (BMI, $21.5 \pm 3.0 \text{ kg/m}^2$) to the largest (BMI, $39.2 \pm 6.6 \text{ kg/m}^2$) arm size group ($p < 0.001$). Arm slant angle was correlated to the between-cuff systolic BP discrepancy ($p < 0.001$). Arm size was a significant predictor of the between-cuff systolic BP discrepancy (p for trend = 0.008) and diastolic BP discrepancy ($p = 0.018$). In comparison with the group with arm circumference between 22 and 27 cm, in the group with circumference 37.5–42 cm the cylindrical cuff overestimated BP measured with the tronco-conical cuff by $2.4/1.8 \text{ mmHg}$ ($p = 0.004/0.016$).

Conclusions: In obese people, the upper arm may have a pronounced tronco-conical shape and cylindrical cuffs may overestimate BP. Tronco-conical cuffs should be preferred for BP measurement in subjects with large arms.

2.8 Effects of Daily Sessions of Music-Guided Slow Breathing on Baroreflex Sensitivity and Renal Resistive Index in Hypertensive Patients

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Introduction: Daily sessions (30 min) of music-guided slow breathing (6 breaths/min) induced a significant reduction of 24-hour ambulatory blood pressure. In particular, the antihypertensive effect persisted at 6 months after session interruption so that a stable change of autonomic cardiovascular regulation can be hypothesized.

Aim: To investigate the effects of daily sessions of music-guided slow breathing exercises on baroreflex sensitivity and on renal resistive index in hypertensive patients.

Methods: Twenty-four patients with essential hypertension grade I (32–75 years) untreated or treated with stable medication from at least 3 months, were requested to perform daily sessions (30 min) of slow breathing (4–6 breaths/min; inspiration:expiration = 1:2) synchronized with music listening. At baseline, and after 1, 4 and 8 weeks, subjects underwent 24-hour ambulatory blood pressure monitoring (SpaceLabs 90207) and measurement of the baroreflex sensitivity in supine position using two validated standard methods: beat-sequence and spectral analysis with α -index evaluated in high- (HF) and low-frequency (LF) band. Renal resistive index was investigated by Doppler Sonography in the subgroup of untreated patients ($n = 10$). A linear mixed-effect model (SPSS version 17) was fitted to explore the effect of time.

Results: The significant reduction of 24-hour systolic BP at the 2-month visit (120 ± 8 vs 128 ± 8 , $p = 0.02$) was found to be associated with a significant increase of baroreflex gain at both beat-sequence method (12 ± 3.5 vs $9.3 \pm 3.6 \text{ ms/mmHg}$, $p < 0.05$) and spectral analysis (13.9 ± 4.9 vs 9.9 ± 3.8 for α -HF, $p < 0.001$ and 7.4 ± 2.8 vs 5.5 ± 3.7 for α -LF, $p < 0.05$). At the same time, a mild although significant reduction of renal resistive index was observed in patients not treated with antihypertensive drugs ($p < 0.05$).

Conclusions: Daily sessions of slow-breathing exercises induce an important stable change of autonomic cardiovascular regulation with significant enhancement of the baroreflex gain and reduction of renal resistive index.

2.9 Seasonality of 24-hour, Daytime and Night-Time Blood Pressure: Summer does not Always Mean Lower

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Introduction: We analysed 24-hour blood pressure monitoring (ABPM) data from 4701 patients referred to our Hypertension Center between September 2002 and January 2011 to evaluate the effects of coldest periods compared with hottest ones on blood pressure (BP).

Methods: ABPM were performed using Spacelabs 90207. Isolated nocturnal hypertension (INH) was defined as night-time BP $\geq 120/70 \text{ mmHg}$ in untreated patients with normal daytime and 24-hour BP. We considered as dippers those patients whose mean night-time SBP was at least 10% below the mean daytime values. A patient was defined as a non-dipper if the difference between night-time and daytime SBP was $< 10\%$. We considered the hottest and the coldest months in the Ancona area using the average daily temperature. We considered July and August (mean temperature: $24.4 \pm 1.3^\circ\text{C}$) as 'summer' while we considered January and February (mean temperature: $5.9 \pm 2.0^\circ\text{C}$) as 'winter'.

Results: ABPM recorded in winter and summer were 1395: 742 men (53.2%) and 653 women (46.8%). The hypertensive patients were 1245 (89.3%), of which 795 (63.8%) under treatment. As expected, mean 24-h and daytime systolic (SBP) and diastolic blood pressure (DBP) were higher in winter and lower in summer ($p < 0.001$). The highest night-time mean SBP was recorded in summer and was significantly different versus the winter season ($p = 0.01$). In particular, uncontrolled hypertensive patients had the highest mean difference (about 4 mmHg) between winter and summer night-time SBP (127.1 ± 13.4 vs $131.0 \pm 12.6 \text{ mmHg}$; $p = 0.001$). In winter, a dipping pattern was prevalent (58.2% vs 41.8% of non-dippers), whereas in summer dippers were fewer and a non-dipping status prevailed (38.1% vs 61.9%) [$p < 0.001$]. INH was present in 9.8% of monitoring conducted in winter versus 15.2% of those carried out in summer ($p = 0.003$).

Conclusions: Our data on a very large ABPM sample confirm that hottest seasons were associated with lower BP compared with coldest ones, confirming the findings of previous studies. However, we show an inverse relationship between the hottest and coldest seasons regarding night-time BP, dipping status and INH. These associations are present in any subanalysis and are only less powerful in treated and controlled hypertensive patients. These data are quite unexpected and may be related to different sleeping behaviours between summer and winter or to an improper reduction and/or wrong timing of antihypertensive therapy. Our findings are especially important as night-time BP, strongly associated with organ damage, is becoming a new therapeutic target and may become the focus of interest in summer when daytime BP tends to fall and patients reduce treatment, sometimes with their own physician approval.

2.10 Effects of Outdoor and Indoor Air Temperature on Morning Blood Pressure Surge

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Introduction: Important climate-related variations of clinic and ambulatory blood pressure (BP) have been repeatedly reported. However, notwithstanding the wide use of indoor climate control systems, especially in winter, no information is available regarding the role of air temperature values measured proximally to the patient, in particular when focusing on specific components of the 24-hour BP profile, such as the morning BP surge (MBPS).

Methods: To investigate whether outdoor air temperature or the air temperature measured proximally to the patient influenced MBPS, 2120 hypertensive patients underwent 24-hour ambulatory blood pressure (ABP) monitoring with a battery-powered 'HOB0' temperature data logger fitted to the carrying pouch of the ABP monitor. Multivariate stepwise regression model, including age, gender, body mass index, office systolic BP, 24-hour average ABP, mean 24-hour outdoor atmospheric pressure and mean 24-hour air temperature measured both outdoor and by HOB0 as independent variables, investigated predictors of MBPS.

Results: Stepwise multiple regression analysis carried out in the 1728 subjects included in the final analysis selected outdoor air temperature ($\beta = -0.09$; $p < 0.0001$), 24-hour ABP ($\beta = -0.72$; $p < 0.0001$), and age ($\beta = -0.06$; $p < 0.002$) as negative independent predictors of MBPS, and systolic office BP as a positive independent predictor ($\beta = 1.04$; $p < 0.0001$) [$r = 0.610$]. No significant effect of HOB0 air temperature was observed. When subjects were stratified according to age, the effect on MBPS of outdoor air temperature was detectable in subjects > 65 years ($\beta = -0.086$; $p < 0.002$), whereas the only determinants of MBPS in subjects < 50 years were office SBP and 24-hour average SBP (positive and negative predictors, respectively).

Conclusions: These results confirm and extend previous observation on the occurrence of seasonal changes in 24-hour BP profiles, by providing new evidence that, in addition to office BP, 24-hour ABP and age, only air temperature measured outdoor affects BP morning surge, whereas no role seems to be played by air temperature measured proximally to the patient. The clinical implications of these findings for BP control would need to be further tested by *ad hoc* studies.

2.11 Acute Application of cPAP Lowers Blood Pressure without Reducing Plasma Renin Activity, Plasma Aldosterone and Overnight Urinary Catecholamines in Patients with Obstructive Sleep Apnoea Syndrome

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Introduction: Obstructive sleep apnoea syndrome (OSAS) is known to increase blood pressure (BP, mmHg) through numerous mechanisms including the activation of the sympathetic nervous system (SNS) and of the renin-angiotensin-aldosterone-system (RAAS). Continuous positive airway pressure (cPAP) lowers BP but its effects on SNS and RAAS are still debated.

Methods: We investigated the changes induced by the first night of application of cPAP on BP and those on plasma renin activity (PRA, ng/mL/h), plasma aldosterone (PA, pg/mL) and overnight

urinary catecholamines excretion (CAT, $\mu\text{g}/8$ hours) as indicators of RAAS and SNS activity, respectively. Studies were performed in 13 hypertensive patients with OSAS prior to and after the first night application of cPAP. Systolic and diastolic BP were evaluated with continuous BP recording. Blood for PRA and PA was collected in the morning while urine samples for CAT measurement were collected after the 8-hour sleeping period.

Results: 24-hour SBP and nocturnal SBP (mean \pm SD) were significantly lowered by cPAP (respectively, from 140 ± 17 to 135 ± 18 and from 138 ± 19 to 132 ± 20 $p < 0.05$). The equivalent reductions of DBP were from 82 ± 12 to 78 ± 11 and from 81 ± 13 to 75 ± 14 (NS). Diurnal SBP and DBP were also reduced but to a lesser, not significant, extent. PRA was slightly reduced by cPAP from 1.7 ± 2.5 to 1.4 ± 1.5 , while PA had a small increase from 67 ± 27 to 82 ± 47 ; urinary CAT decreased from 18 ± 7 to 15.5 (NS).

Conclusions: The first night application of cPAP effectively reduces 24 hours SBP mostly because of the fall in nocturnal SBP. However, these acute reductions in BP apparently are not attributable to concomitant decreases in the activity of RAAS and of SNS.

Epidemiology and Clinical Aspects

3.1 Psychopathological Aspects in Essential Hypertension

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Introduction: Many studies support the role of psychological factors in the natural history of essential hypertension. The assessment of psychological factors could have important implications in management of hypertensive patients.

Aim: To describe psychopathological aspects in hypertensive patients and the contribution of these factors on health-related quality of life (HRQL).

Methods: 62 hypertensive patients consecutively referred to the Hypertension Unit between January 2009 and March 2010, were recruited into the study. All participants, aged 18–65 years, were assessed by Symptom Checklist-90-R (SCL-90-R), that measures symptoms of psychological distress, and the Medical Outcomes Study Short Form-36 (SF-36), a generic instrument for rating HRQL.

Results: The mean age of patients was 47 ± 9 years, the mean drug treatment/patient was 1.42 ± 1.18 drug/patient. The mean blood pressure was 140 ± 17 mmHg for systolic values and 87 ± 8 mmHg for diastolic. Mean body mass index was 27 ± 5 kg/m^2 . The most representative symptom observed in hypertensive patients, using SCL-90-R was Somatization (SOM, 27.4%) and, in decreasing order, Depression (DEP, 25.9%), Anxiety (ANX, 24.2%), Obsessive-Compulsive (O-C, 21%), Interpersonal Sensitivity (11.3%), Paranoid Ideation (9.7%), Hostility (8.1%), Phobic Anxiety (8.1%) and Psychoticism (3.2%). Considering Physical Component Summary (PCS) the mean score was $72.7 (\pm 16.2)$ and $67.3 (\pm 18.6)$ for Mental Component Summary (MCS). The mean scores observed using SF-36, compared with standard scores from epidemiological study, were lower in the following domains Bodily pain (BP), General health perception (GH), Vitality (VT) and Social Functioning (SF). Patients who had simultaneously symptoms SOM, ANX, DEP and O-C showed statistically significantly lower scores in the following domains of SF-36 ([PCS $p = 0.004$] and MCS, BP, SF, Role Emotional, Mental Health [$p < 0.001$]) when compared with the other patients HBP.

Conclusions: Psychological symptoms have been found in the sample of hypertensive patients. In particular, most representative dimensions of SCL-90-R were SOM, DEP, ANX and O-C and patients who showed these aspects had a lower well being perceived, if compared with the other HBP patients and the general population. Preliminary data suggest the important role of psychological aspects in the subjective well being and health perception.

3.2 Traditional Factors and New Biomarkers on Cardiovascular Risk Determination

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Introduction: The assessment of patients cardiovascular risk is based on traditional, well studied factors: diabetes and hypertension. Additional biomarkers have been developed that may improve traditional factors efficiency.

Aim: To evaluate the effectiveness of these new biomarkers in combination with the traditional ones.

Methods: 138 patients (58% women, 62 years), examined for the first time on 2004; values of PCR, Lp a, pro-BNP were measured and follow-up monitoring continued until 2009. The resulted classification of patients was 0.758 of HR for conventional risk factors and 0.760 for coronary events.

Results: During follow-up phase 13 cardiovascular and 7 coronary events were recorded. The percentage of re-classification using the new biomarkers was minimal as being 8% for cardiovascular risk and 5% for coronary risk. This observed on those with medium risk factor mostly involving patients who did not go through episodes on the follow-up unlike those who actually experienced them.

Conclusions: These new biomarkers for cardiovascular risk assessment have proved to be valuable in the prediction of events, but their advantage over traditional one is minimal. Risk assessment classification has improved only on individuals with medium risk most of whom, however, are not likely to be subjected to cardiovascular disorders.

3.3 Retrospective Evaluation of Blood Pressure Changes after the 2009 L'Aquila Earthquake

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Introduction: Blood pressure (BP) is influenced by mental and/or physical stress, and we have shown that a major stressful event, such as the L'Aquila earthquake (April 6, 2009, Richter 5.8), induced acute blood pressure changes. Little is known on the follow-up of these patients, and on the possibility of long lasting BP effects.

Aim: To retrospectively evaluate the effects of the L'Aquila earthquake on 24-hour ambulatory blood pressure monitoring (ABPM), at variable time after the event.

Methods: All ABPMs (Spacelabs 90207) performed in the same patients before and after the earthquake (2008-2009-2010 years) were extracted from our database and then used for statistical evaluation, taking into account BP changes in patients with constant treatment and changes in drug treatment as a marker of changing severity of the hypertensive condition in those in whom therapy was up- or downgraded.

Results: We identified 47 patients (n=25 females, age 52±14 years) with an ABPM performed both before and after the earthquake. Patients were divided into 3 groups according to the changes in antihypertensive therapy observed after the earthquake: (i) unchanged therapy (UT) [n=24, 15 females, mean age 54±13 years]; (ii) increased therapy (IT) [n=17, 8 females, mean age 53±13 years]; and (iii) reduced therapy (RT) [n=6, 2 females, mean age 42±13 years]. In the UT group (first ABPM: 7±4 months before, second ABPM: 15±5 months after the earthquake) a marked increment of 24-hour (125.6±10.7 vs 132.1±13.5 mmHg, p=0.004), day-time (130.3±11.6 vs 136.4±13.5 mmHg, p=0.01) and night-time systolic BP (SBP) [118.3±11.9 vs 123.3±14.3 mmHg, p=0.02] as well as 24-hour (76.5±7.7 vs 80.6±9.8 mmHg, p=0.005), day-time (80.7±9.2 vs 84.5±10.1 mmHg, p=0.01) and night-time diastolic BP (DBP) [69.4±6.6 vs 73.8±9.7 mmHg, p=0.009] was observed. No difference in ABPM could obviously be observed in the IT group and RT groups because of the change in treatment (IT: first ABPM: 7±5 months before, second ABPM: 15±5 months after the earthquake; RT: first ABPM: 7±3 months before; second ABPM: 11±5 months after the earthquake), but the much higher number of patients in the IT as compared with the RT group is another indication of the occurrence of long-lasting BP effects after an earthquake.

Conclusions: The present data further support our previous report of marked acute increments in 24-hour, day-time and night-time BP levels immediately after the L'Aquila earthquake. Although, retrospectively, the current study also confirms this trend in the long term, at least in the UT group. The larger number of subjects in whom IT had to be upgraded rather than downgraded over a few months after the event is another indication that BP may increase after an earthquake, not only acutely, but also in the long term. Therefore, cardiovascular risk must be carefully evaluated and intensively controlled in patients surviving an earthquake.

3.4 Insulin Resistance, Pre-Hypertension, Hypertension and Blood Pressure Values in Paediatric Age

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Introduction: Hypertension risk is increased in childhood obesity, but it is not clear whether it is linked to obesity itself, fat distribution or insulin resistance. Moreover, the role of insulin resistance in determining hypertension risk in normal weight children has still to be ascertained.

Aim: to evaluate, in children of different weight categories, the effect of body mass index (BMI), HOMA index (as estimate of insulin resistance) and waist-to-height ratio (WtHr, as estimate of fat distribution) on pre-hypertension and hypertension risk. The relative contribution of BMI, WtHr, and HOMA index to determine left ventricular mass (LVM) was also evaluated.

Methods: We studied 377 children (age 6–16 years) referred for hypertension (n=289) or positive family history of cardiovascular disease (n=88). Hypertension and pre-hypertension were ascertained according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents and weight class was established according to International Obesity Task Force classification. HOMA index was calculated as plasma insulin (μU/mL)×plasma glucose (mmol/L)/22.5 and left ventricular mass was assessed according to American Society of Echocardiography and standardized to height (m^{2.7}).

Results: Ninety-four children (24.9%) were normal weight, 133 (35.3%) were overweight and 150 (39.8%) were obese. In both genders, frequency of pre-hypertension and hypertension was higher in overweight subjects (18.0% and 31.6%, respectively) and obese (22.5% and 39.7%) compared with normal weight (11.7% and 23.4%); p<0.05. Left ventricular mass tended to increase together with weight class (p<0.05). Multivariate logistic regression models showed an independent significant effect of HOMA index, in addition to BMI (Z-score) and WtHr effect, on the risk of pre-hypertension and hypertension and on continuous systolic blood pressure values, while only BMI (Z-score) and WtHr had an effect on LVM.

Conclusions: Our data strongly suggest that insulin resistance adds an impact to the predictive power of BMI and WtHr in determining hypertension risk and blood pressure values in paediatric age. This finding is evident not only in hypertensive and/or obese children but also in normotensive and/or normal weight peers.

3.5 High Prevalence of Undiagnosed Hypertension in Young Male Subjects: Data from the Brisighella Heart Study

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Introduction: An early diagnosis of hypertension is very relevant for preventive purposes, in particular in young subjects who will be exposed to the risk factor for a longer life time.

Methods: The Brisighella Heart Study is an epidemiological investigation on the main cardiovascular disease risk determinants, active from the 1972. At each survey a complete medical examination of a cohort, representative of the whole Brisighella population. The following parameters are usually sampled: family and personal history, lifestyle habits, anthropometric data, haemodynamic data, full metabolic evaluation, drug use.

Aim: To evaluate the hypertension prevalence in newly enrolled younger subjects and describe the characteristics of the newly diagnosed hypertensive patients.

Results: In the 2008 survey we visited 1638 subjects (M: 789, W: 849; mean age: 53±18 years, body mass index: 26±4 kg/m², TC=203±39 mg/dL, LDL-C=135±34 mg/dL, TG=113±68 mg/dL, HDL-C=46±10 mg/dL, apoB=88±21 mg/dL, apoAI=143±28, glycaemia=105±18 mg/dL). The 18% of the population habitually smokes, while 26% interrupted the habit. Overall, the prevalence of hypertension was 42%. In the group of subjects aged less than 30 years, the hypertension prevalence was 14%, 23% among men and 7% among women. Comparing men and women aged less than 30, men appeared to have significantly higher body mass index (25±4 kg/m² vs 22±4 kg/m²) and lower HDL-cholesterol (43±7 mg/dL vs 50±11 mg/dL), and consequently a higher prevalence of metabolic syndrome.

Conclusions: In a representative sample of general population participating in the Brisighella Heart Study, we observed a relatively high prevalence of hypertension in male subjects aged less than 30 years, in particular in men.

3.6 Prevalence and Main Features of Resistant Hypertension in Central and Eastern Europe: Data of the BP-CARE Study

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Introduction: Very little information is available on the prevalence of resistant hypertension in Europe, particularly in countries of Central and Eastern Europe. Data collected in the observational study BP-CARE (Blood Pressure control rate and Cardiovascular Risk profile) enabled assessment of the prevalence of resistant hypertension, defined according to the European Guidelines as the condition in which blood pressure is ≥140/90 mmHg despite the documented use of at least three antihypertensive drugs at full dosage, including a diuretic, and its main clinical features.

Methods: The study was conducted in over 7200 hypertensive patients in 9 countries of Central and of Eastern Europe (Albania, Belarus, Bosnia, Lithuania, Czech Republic, Romania, Serbia, Slovakia, Ukraine).

Results: 1031 patients, representing 14.2% of the sample studied, were resistant hypertensive patients, showing clinical blood pressure (mean±SD of 3 measurements) values of 168.6±17.0/100.6±12.6 mmHg despite the median use of 3.6±0.5 tablets of antihypertensive agents daily (diuretics [100%], ACE inhibitor [79.9%], β-blocker [71.9%], calcium channel blocker [66.4%], ARB [17.7%] and others [22.6%]). Compared to controlled (n=1996, 27.6%) and uncontrolled hypertensive patients (n=4220, 58.2%) resistant hypertensive patients had similar age (59.9±10.3 years) and gender distribution, and showed a higher rate of previous cardiovascular event, especially heart failure, stroke and cerebral transient ischaemic attack. The resistant hypertensive patients also had a body mass index (30.9±5.3 kg/m²) and waist circumference (100.0±14.3 cm) significantly greater (p<0.01) than the other two populations, with a higher prevalence of obesity (20%). The mean values of plasma total cholesterol (224.8±47.4 mg/dL), triglycerides (188.2±81.8 mg/dL), glucose (111.9±39.5 mg/dL) were in the group of resistant hypertensive patients significantly greater (p<0.01) than in the other 2 groups, whereas the values of glomerular filtration rate (71.9±23.6 mL/min/1.73 m²) significantly lower (p<0.01).

Conclusions: These data provide the first large-scale epidemiological evidence on the main characteristics of resistant hypertension in Central and Eastern Europe, showing a prevalence slightly higher than that found in Western Europe and the US. The data also show a high association of this condition with overweight, obesity, diabetes, renal failure and a history of previous cardiovascular events.

3.7 Adrenal Vein Sampling for Identification of the Subtypes of Primary Aldosteronism: Results of the First Phase of the AVIS (Adrenal Vein Sampling International Study)

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Introduction: Primary aldosteronism (PA) is the most common cause of endocrine hypertension. To distinguish the surgically curable causes from those that need pharmacological treatment the Endocrine Society Guidelines recommend use of adrenal venous sampling (AVS), which is held to be invasive, risky, technically challenging and difficult to interpret.

Aim: to determine the rate of use and major complications of AVS, and how this test is being performed and interpreted at major referral centres worldwide.

Methods: AVIS is an observational, retrospective, multicentre international study. Eligible centres were identified through a literature search of those published in English on AVERSUS between 2005 and 2010. The study entails 2 phases, the goal of the first phase was collect summary AVERSUS data, and in the second phase data on individual AVERSUS studies will be gathered.

Results: The first phase of study was completed on November 2010 and provided data on a total of 2635 AVERSUS studies performed in the last 5 years at 83% of 24 centres in Asia, Europe, North America and Australia. The overall rate of adrenal vein rupture was 0.6% and was inversely related to the number of AVERSUS performed by each radiologist ($b = -0.683$; $p = 0.007$) and the number of AVERSUS performed at a particular centre ($b = 0.831$; $p = 0.002$). The median percentage of PA patients systematically submitted to AVERSUS was 80% but there was a wide variability across the centres (range 40% to 100%). The majority of centres used the sequential catheterization technique (65%) and only 35% used bilateral simultaneous AVS. In spite of the lack of any theoretical basis, some centres continue to use absolute hormonal values instead of established indexes for the interpretation of test. Moreover, analysis of the cut-off values used for assessment of indices of selectivity, lateralization and contralateral suppression showed a wide variability and across the centres.

Conclusions: At variance with common belief, AVERSUS is being performed with a very low complication rate at most referral centres worldwide. Despite the Endocrine Society guidelines, there is a high variability of the rate with which AVERSUS is offered to patients to be selected for adrenalectomy. Finally, notwithstanding the lack of any theoretical basis, some centres continue to use absolute hormonal values for diagnosing PA.

3.8 Relationship between Blood Pressure and Lipid Profile in Europe: The EURIKA Study

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Introduction: Hypertension and lipid abnormalities are the most prevalent risk factors and a relationship between lipid profile and blood pressure (BP) has been previously described in single-population surveys (e.g. Tromso Study, Brisighella Heart Study).

Aim: The relationship between lipid profile and BP values across the Europe has been investigated in the EURIKA (European Study on Cardiovascular Risk Prevention and Management in Daily Practice [NCT00882336]) study.

Methods: EURIKA was a cross-sectional study conducted in 12 countries. We collected information on risk factor prevalence and control from 806 randomly selected physicians enrolling 7641 patients ≥ 50 years, free of clinical CVD, and with at least one major CVD risk factor. Individual BP values (in mmHg) have been linearly correlated as continuous variables with lipid parameters including: Total- (TC), LDL- (LDL-C), non-HDL- (non-HDL-C) and HDL-cholesterol (HDL-C). We also included in the analysis the plasma levels of both Apo-A1 and Apo-B lipoproteins. Pearson's correlation coefficient with correspondent p-value has been calculated.

Results: In the EURIKA population 68.5% were treated with antihypertensive and lipid-lowering drugs. Systolic BP was linearly correlated with TC (0.030; $p = 0.009$), non-HDL-C (0.044, $p = 0.0001$), HDL-C (-0.035 ; $p = 0.001$) but not with LDL-C (0.019; $p = 0.09$). Diastolic BP values correlated with all the components of the lipid profile including TC (0.09; $p = 0.0001$), non-HDL-C (0.125, $p = 0.0001$), HDL-C (-0.083 ; $p = 0.0001$) and LDL-C (0.095; $p = 0.0001$). Plasma Apo-A1 levels were significantly correlated with both systolic (0.023; $p = 0.04$) and diastolic BP (0.03; $p = 0.01$) while Apo-B was only related to diastolic BP. The relationship between systolic BP and lipid profile was abolished in statin-treated patients and confirmed for diastolic BP ($p = 0.0001$ for TC, LDL-C, non-HDL-C and $p = 0.002$ for HDL-C).

Conclusions: The results of the EURIKA study largely confirm previous studies demonstrating a correlation between BP values and lipid profile. The correlation is significant despite the intrinsic heterogeneity of the population and the use of antihypertensive and lipid-lowering drugs and is partially abolished by statin treatment. This might reflect some pathogenetic linking between lipid profile and blood pressure that might contribute to the development of hypertension and the atherosclerotic disease and could be effectively prevented by an early management of lipid profile.

3.9 Left Ventricular Structure and ABPM Correlation in Very Very Old People

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Introduction: Few studies report the correlation between 24-hour blood pressure profile and left ventricular structure in very elderly (over 90 years).

Aim: To evaluate left ventricular mass (LVM) and 24-hour ambulatory blood pressure monitoring (ABPM) in a group of very elderly.

Methods: We studied 106 patients (90 females and 16 males) hospitalized in our Geriatric Institute (Pio Albergo Trivulzio of Milan) over 90 years old (mean age 95 years; range 90–106 years). They underwent a clinical visit including BP and HR values, blood samples, ECG, echocardiogram and 24-hour ambulatory BP. Clinic blood pressure was the mean of three measurements and ambulatory blood pressure monitoring was performed with Spacelab device. Left ventricular hypertrophy (LVH) was defined by two gender-specific criteria (LVMI >125 g/m² in men and 110 g/m² in women, LVMI >51 g/h^{2.7} in men and 47 g/h^{2.7} in women). We considered dipping status as a fall in blood pressure during night-time period $>10\%$ for both SBP and DBP; reduced dipping and non dipping profile as 5–10% and $<5\%$, respectively. During the study, 20 patients died or did not give their consensus at the execution of instrumental exams, and therefore they did not undergo echocardiogram and/or ABPM.

Results: We observed that prevalence of hypertension and cognitive impairment were, respectively, 57% (61 patients) and 68% (72 patients). 64% of subjects with a history of hypertension (39 patients) was affected by cognitive impairment, and 54% (39 patients) of patients with cognitive impairment showed an anamnesis of hypertension. 69% of patients (59 patients) showed LVH (mean LVMI: 125 ± 41 g/m²; 55.9 ± 19.5 g/h^{2.7}); 63% (37 patients) of these had a history of hypertension. 75% of total patients (64 patients) had diastolic dysfunction (E/A <1); 58% of these (37 patients) were hypertensive patients. With regard to left ventricular geometry, 53% (46 patients) and 15% (13 patients) of total patients had concentric and eccentric LVH, respectively; 19% (16 patients) had a concentric remodelling and 13% (11 patients) showed a normal pattern. Among the hypertensive patients, the great majority (59%) showed concentric LVH, while the other patterns were equally distributed (16% eccentric LVH, 14% concentric remodelling, 12% normal pattern). With regard to ABPM profile, we found a reverse pattern in 49% and 29% of patients for SBP and DBP, respectively; a non dipping profile in 21% (SBP) and 40% (DBP); a reduced dipping in 10% (SBP) and 17% (DBP); a dipping profile in 20% (SBP) and 14% (DBP), respectively.

Conclusions: Our results suggest that the great majority of very elderly have a LVH, especially with a concentric pattern, and show a non-dipping or even a reverse pattern of 24-h blood pressure profile.

3.10 Blood Pressure Monitoring and LVM in Centenarians

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Introduction: Few studies report the correlation between 24-hour blood pressure profile and left ventricular structure in very elderly (over 100 years).

Aim: To evaluate left ventricular mass (LVM) and 24-hour ambulatory blood pressure monitoring (ABPM) in a group of centenarians.

Methods: We studied 17 patients (16 females and 1 male) hospitalized in our Geriatric Institute (Pio Albergo Trivulzio of Milan) aged over 100 years (mean age 103 years; range 100–106 years). They underwent a clinical visit including BP and HR values, blood samples, ECG, echocardiogram and 24-hour ambulatory BP. Clinic blood pressure was the mean of three measurements and ambulatory blood pressure monitoring was performed with a Spacelab device. Left ventricular hypertrophy (LVH) was defined by two gender-specific criteria (LVMI >125 g/m² in men and 110 g/m² in women, LVMI >51 g/h^{2.7} in men and 47 g/h^{2.7} in women). During the study, 4 patients died and therefore they did not undergo echocardiogram.

Results: We observed that prevalence of hypertension and cognitive impairment were, respectively, 71% (12 patients) and 53% (9 patients). 50% of subjects with a history of hypertension was affected by cognitive impairment, and 67% of patients with cognitive impairment showed an anamnesis of hypertension. 85% of patients (11 patients), both with a history of hypertension and without, showed a concentric LVH and the others (2 patients, 15%) had a concentric remodelling (mean LVMI: 131.9 ± 28 g/m²; 58.8 ± 13.2 g/h^{2.7}). Mean clinic blood pressure, day-time BP and night-time BP were $115.3 \pm 17.6/76.6 \pm 8.3$ mmHg, $124.9 \pm 14.3/66.6 \pm 7.5$ mmHg, $120.3 \pm 17.2/60.4 \pm 5.4$ mmHg, respectively. Mean clinic HR, day-time HR and night time HR were 75.2 ± 11.2 , 77.9 ± 12.1 , 72.9 ± 13.3 bpm. Clinic pulse pressure was 47.6 ± 13.5 mmHg; all patients showed a non-dipping profile, especially for systolic blood pressure, and a low HR variability.

Conclusions: Our results suggest that centenarians, as with those aged between the seventh and ninth decades of life, are characterized by concentric LVH/remodelling and reduction of HR and BP variability, according to well known parapsychological modifications of the cardiovascular system with aging. Instead, we observed a normalization of pulse pressure. Finally, in our study we did not find a correlation with history of hypertension and development of cognitive impairment.

3.11 Plasma Levels of Matrix Metalloproteinases and their Inhibitors in Hypertension: A Systematic Review and Meta-Analysis

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Introduction: The remodelling of the extracellular matrix is controlled by the matrix metalloproteinases (MMPs) and the tissue inhibitors of MMPs (TIMPs). Hypertension is a major cause of cardiovascular (CV) remodelling.

Aim: To elucidate the behaviour of plasma MMP and TIMP levels in hypertension and their relationship to CV remodelling.

Methods: MEDLINE and EMBASE databases were searched up to June 2010. Studies were considered eligible if they provided values of plasma MMPs and TIMPs in hypertensive subjects. Given the high variability of the plasma biomarker values among studies, the standardized mean difference (SMD) was calculated.

Results: Thirteen studies provided data of plasma TIMP-1 and three of TIMP-2. For plasma TIMP-1, the SMD between 901 hypertensive patients and 395 normotensive subjects was 1.36 units (95% CI 0.41, 2.31; $p < 0.01$). For TIMP-2, the SMD between 274 hypertensive patients and 165 normotensive subjects was 0.3 units (95% CI 0.1, 0.51; $p < 0.01$). The heterogeneity was high for TIMP-1 and low for TIMP-2. Three studies investigated whether plasma TIMP-1 predicted left ventricular (LV) remodelling: the SMD between 92 hypertensive patients with and 88 hypertensive patients without LV hypertrophy was 5.81 units (95% CI 0.92, 10.69; $p < 0.05$). The heterogeneity was high. Differences in plasma MMP-1, -2 or -9 between hypertensive patients and normotensive subjects were not significant.

Conclusions: These results suggest that whereas MMPs do not appear to be biomarkers of hypertension and cardiac hypertrophy, plasma TIMPs are. If these results are confirmed in prospective clinical studies, they could provide new tools to stratify CV risk in hypertensive patients.

3.12 Effect of Cigarette Smoking on Risk Profile of Patients with Optimally Controlled Hypertension

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Introduction: Cardiovascular (CV) disease is one of the most important causes of morbidity and mortality in industrialized countries. Several studies analysed the relationship between behaviour at risk (alcohol, smoking, lack of physical activity, inappropriate dietary habits, etc.) and development of CV disease. However, there is still lack of information about their combined effect on CV target organ damage in hypertensive subjects with optimal antihypertensive therapeutic control.

Aim: To analyse the effect of lifestyle, studied through a specific questionnaire on development and progression of CV disease.

Methods: 617 non-diabetic subjects with essential hypertension (age 53.1 ± 7.6 years, 44.9% men), without prevalent CV disease, cancer, chronic liver disease and with GFR >30 mL/mmHg/1.73 m², were studied. Metabolic syndrome (MetS) was diagnosed according to the ATP III guidelines. Presence of left ventricular hypertrophy was determined by values of LV mass index ≥ 51 g/m². Carotid atherosclerosis (CA) was determined by measuring the intima-media thickness (IMT). IMT values between 0.9 and 1.3 were defined as 'thickening' and values >1.3 mm as 'plaque'.

Results: Among the 617 studied patients, 288 were smokers (S). Compared with non-smokers (NS), S exhibited lower values of BMI (27.54 ± 4.0 vs 28.28 ± 4.3 ; $p = 0.029$), HDL-cholesterol (48.14 ± 12.6 mg/dL vs 51.39 ± 14.1 ; $p < 0.006$) and more often CA (93.9% vs 86.1%; $\chi^2 < 0.002$). When dietary habits were studied, patients reporting a lower number of daily meals and snacks (<2 meals/day) showed more often CA (96.6% vs 85.7%; $\chi^2 < 0.001$), with no difference in anti-hypertensive therapy. Moreover, comparing subjects with or without CA, only the number of smoked cigarettes calculated as the number of packets/year (391 ± 165 vs 208 ± 136 ; $p < 0.0001$) and the age of initiation of smoking habit (21.53 ± 10.2 years vs 17.58 ± 6.3 years; $p = 0.018$) were statistically associated with CA. In a binary logistic model, including BMI, HDL-cholesterol, cigarette smoking and number of daily meals, only smoking confirmed to be strongly associated with higher values of IMS ($p < 0.03$).

Conclusions: In a group of patients with essential hypertension, under optimal antihypertensive treatment, smoking habit is independently associated with CA. In particular, increased IMS is associated with the number of smoked cigarettes and age of onset of smoking habit.

3.13 Identification of Phenotypes at Risk of Transition from Systo-Diastolic Hypertension to Isolated Systolic Hypertension

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Introduction: Isolated Systolic Hypertension (ISH) is the most frequent subtype of uncontrolled hypertension in elderly patients and is associated with higher cardiovascular (CV) risk, even compared with systo-diastolic hypertension (SDH). Very little information is available about the natural evolution towards this type of hypertension and about the phenotype associated with its appearance.

Aim: To detect predictors of evolution towards ISH in subjects with initial SDH.

Methods: 6027 individuals with SDH (age 52.52 ± 11.3 years, 56.5% men, systolic blood pressure (SBP) 159.4 ± 20.5 , diastolic blood pressure (DBP) 99.2 ± 10.3), without prevalent CV disease, glomerular filtrate ratio (GFR) >30 mL/mmHg/1.73 m², and with at least a 6-month follow-up were selected from the CampaniaSalute registry. The diagnosis of ISH was made at end of follow up according to the European Guidelines (SBP ≥ 140 mmHg with DBP < 90 mmHg).

Results: After a mean follow-up period of 55 ± 44 months, 19% of the study population showed ISH ($n = 1122$). Patients with ISH were older and more often women. At baseline, they were more often women and diabetic, and exhibited higher values of SBP, HDL cholesterolaemia, left ventricular (LV) mass, relative wall thickness, pulse pressure/stroke index ratio (PP/stroke index), more severe carotid atherosclerosis and lower values of GFR (all $p < 0.001$). These differences were studied in relation to the follow-up period, using a multivariate proportional hazard model (Cox) including all variables that were found different at the descriptive analysis. Presence of ISH at follow-up was independently predicted by older age at baseline ($p < 0.0001$; HR = 1.20/5 years; CI = 1.20, 1.28), female gender ($p < 0.004$; HR = 1.22; CI = 1.06, 1.40), higher LV mass index ($p = 0.04$; HR = 1.04/5g*m^{-2.7}; CI = 1.01, 1.05), higher carotid intima-media thickness ($p = 0.02$; HR = 1.12/mm; CI = 1.02, 1.22) and higher PP/stroke index ($p < 0.0001$; HR = 1.35/mmHg* mL*m^{2.04}; CI = 1.23, 1.48) at the time of initial visit.

Conclusions: Factors influencing the transition from SDH to ISH are older age, female gender and signs of CV target organ damage. As recently stated by guidelines, a prompt and aggressive therapy for arterial hypertension before the onset of target organ damage could be desirable to help lowering the prevalence of ISH especially in elderly female patients.

3.14 Identification of Phenotypes at Risk of Resistant Hypertension

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Introduction: The presence of elevated blood pressure values despite the use of at least three different medications, including a diuretic, is defined as resistant hypertension (RH). RH is associated with a high risk of stroke, myocardial infarction and arrhythmia. Detection of high-risk phenotypes for RH could be of great help in better addressing and graduating initial therapy.

Aim: In the present study, predictors of RH were identified in a large population of subjects with essential hypertension, after a period of at least 12 months' follow-up.

Methods: 6215 subjects with essential hypertension have been prospectively studied (age 52.8 ± 11.3 years, 56.6% men, systolic blood pressure [SBP]: 158.1 ± 19.8 , diastolic blood pressure [DBP]: 99.3 ± 9.9), without prevalent cardiovascular disease, glomerular filtrate ratio (GFR) >30 mL/mmHg/1.73 m².

Results: After a mean follow-up time of 61 ± 43 months, 12% of the studied population showed RH ($n = 744$). Patients with RH were older (56.5 ± 10.4 vs 52.3 ± 11.3 , $p < 0.0001$), and more often women ($p < 0.0001$). At baseline, patients with RH were more often diabetics, with metabolic syndrome (MetS), they were less frequently smokers and showed higher values of SBP, DBP, BMI, fasting plasma triglycerides and glucose, left ventricular (LV) mass, carotid intima-media thickness, duration of hypertensive disease, pulse pressure/stroke index (PP/stroke index), relative wall thickness and lower values of GFR and serum potassium (all $p < 0.001$). These differences were studied also in relation to duration of follow-up, by a proportional hazard model (Cox) including the variables that were different in the descriptive analysis. Evidence of RH during follow-up was independently predicted by: female sex ($p = 0.015$; HR = 1.22; CI = 1.04, 1.42), age ($p < 0.0001$; HR = 1.03/year; CI = 1.02, 1.04) left ventricular mass index ($p = 0.001$; HR = 1.02/g*m^{2.7}; CI = 1.02, 1.03) SBP ($p < 0.0001$; HR = 1.01/mmHg; CI 1.00, 1.02), reported duration of hypertension ($p < 0.0001$; HR = 1.02/year; CI 1.01, 1.03) and MetS ($p = 0.003$; HR = 1.36; CI 1.11, 1.67), at baseline.

Conclusions: In essential hypertensive patients, resistance to maximal antihypertensive therapy is more frequent in women with MetS and is predicted by older age, higher initial values of SABB, longer presence of hypertensive disease and presence of cardiovascular target organ damage.

3.15 Psoriatic Arthritis is Associated with Increased Arterial Stiffness in the Absence of Known Cardiovascular Risk Factors

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Introduction: Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis. Recent evidence suggests that psoriatic disease is also associated with an increased cardiovascular risk similar to other rheumatic conditions such as rheumatoid arthritis and systemic lupus erythematosus, in both of which accelerated atherosclerosis and increased cardiovascular risk have been described.

Aim: To evaluate of arterial stiffness in patients with PsA.

Methods: Twenty PsA patients classified on the basis of the CASPAR criteria (F/M: 6/14; mean age 38.7 years; range 22–53), attending our out-patient clinic, and 20 healthy control subjects (F/M: 6/14; mean age 38.6 years; range 22–53) matched for age, weight, height and with similar cardiometabolic profile, entered the study. Exclusion criteria were the presence of known cardiovascular risk factors. Central haemodynamic parameters and aortic pulse wave velocity (aPWV) were assessed non-invasively by Sphygmocor device.

Results: A significantly higher aPWV was detected in PsA patients compared with controls. The difference remained statistically significant after adjustment for age, weight, height, heart rate (HR) and central mean pressure (mean±SE; PsA: 8.29 ± 0.23 vs control: 6.76 ± 0.23 m/s; $p < 0.0001$). Among PsA patients, aPWV was related to known duration of disease ($r = 0.63$; $p = 0.003$). These results were confirmed after adjustment for the main confounders ($\beta = 0.011$; $p = 0.013$).

Conclusions: PsA patients without known cardiovascular risk factors had an increased arterial stiffness when compared with healthy control subjects. These results support the concept of psoriatic disease as a systemic condition involving not only skin, joints and gastrointestinal tract but also arterial vessels. The involvement of the vascular system points to pathogenetic mechanisms that could accelerate the atherosclerotic process in this condition.

3.16 Systematic Review of the Effect of Antihypertensive Drug Therapy on Arterial Stiffness

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Introduction: Several studies investigated the effect of anti-hypertensive therapy on arterial stiffness (AS) and their results were not univocal.

Aim: We performed a systematic search of the literature using on-line databases (1966–December 2010) to assess the effect of different classes of anti-hypertensive drugs on arterial stiffness through a meta-analysis of the available studies.

Methods: Criteria for inclusion were adult population study, measures of Pulse Wave Velocity (PWV, m/s - expression of AS) and blood pressure (BP-reported as a continuous variable) obtained at the beginning and at the end of study, time of run-in, outcome expressed as difference between the effects of single drug versus baseline or placebo. For each study, mean difference in PWV and 95% confidence intervals were extracted and pooled using a random effect model. Heterogeneity, publication bias, subgroup, and meta-regression analyses were performed.

Results: Twenty-one studies were identified providing 40 cohorts that included 1375 male and female participants. Only one study was a randomized controlled trial, in all the others the effect of therapy being evaluated versus baseline. The mean time of observation was 17 weeks (range 3–208). Arterial stiffness was assessed by different devices: Sphygmocor ($n = 18$), Complior ($n = 9$), Colin ($n = 9$), and Doppler methods ($n = 4$). In the pooled analysis, there was a significant mean difference (MD) in PWV after therapy with renin-angiotensin system (RAAS) blockers = -1.27 m/s (95% CI: $-1.85, -0.69$; $p < 0.001$), in particular with ACEI = -1.39 ($-1.97, -0.82$; $p < 0.001$) and ARBs = -1.46 ($-2.68, -0.25$; $p = 0.02$); β -blockers = -1.03 ($-1.23, -0.82$; $p < 0.001$). The pooled analysis of Ca-antagonist and diuretic therapy showed a nonsignificant decrease MD = -0.88 ($-1.84, 0.08$; $p = 0.07$) and -0.62 ($-1.56, 0.33$), respectively. There was significant between-studies heterogeneity, but no evidence of publication bias. In meta-regression analysis, blood pressure at baseline, changes in blood pressure, age and different device utilized, were significant sources of heterogeneity. The comparison between drug classes did not show significantly different effects (heterogeneity $p > 0.10$).

Conclusions: This systematic review showed in the first place that there is a lack of randomized controlled trials of the effect of anti-hypertensive therapy on arterial stiffness. Based on the available methodologically faulted studies, our meta-analysis suggests that anti-hypertensive treatment might improve arterial stiffness probably in relation to the effect on blood pressure. Possible differences in the effect of different drug classes were not apparent.

3.17 A New Sodium-Sensitivity Index from 24-hour Ambulatory Blood Pressure Recordings during Habitual Diet

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Introduction: It has been shown that the nocturnal dipping pattern of pulse pressure (PP) tends to disappear while the heart rate (HR) increases in sodium sensitive hypertensive subjects during high sodium diet.

Aim: To evaluate whether an index of sodium sensitivity risk (SSIABPM) can be derived from HR and PP measured from an ambulatory BP monitoring (ABPM) performed during habitual diet, avoiding the challenging protocol for conventional SSI assessment.

Methods: We performed 24-hour ABPM in 46 mild hypertensive subjects during usual diet. PP was averaged over day-time (8am–10pm) and night-time (0am–6am) and its night/day ratio (PPN/D) was calculated. The HR was averaged over the 24-h and normalized by dividing it by a reference level of 70 bpm (HR^{24H}). SSIABPM was defined as PPN/D \times HR^{24H}. Then subjects underwent the traditional assessment of sodium sensitivity. They were classified as sodium sensitive (SS) or sodium resistant (SR) and the sodium sensitivity index (SSI) was calculated as ratio between difference in mean arterial pressure (mmHg) and difference in urinary sodium excretion rates (mol/day) at the end of a high-sodium and a low-sodium diet. Correlation between traditional SSI and the proposed SSIABPM was assessed by Spearman's rank R.

Results: Correlation with SSI was not significant for PPN/D ($R = 0.20$, $p = 0.19$) while reached the significance level for HR^{24H} ($R = 0.36$, $p = 0.02$). However, a much higher rank-correlation was found when PPN/D and HR^{24H} were combined in SSIABPM, and the correlation was highly significant ($R = 0.40$, $p = 0.006$).

Conclusions: SSIABPM obtained under habitual diet appears a reliable tool for identifying the cardiovascular risk associated to salt sensitivity without requiring complex procedures for sodium intake control.

3.18 Dietary Sodium Intake of Hypertensive Subjects in Italy: Preliminary Results of MINISAL-SIIA Study

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Introduction: The main aim of MINISAL-SIIA study is to evaluate dietary sodium intake in a representative sample of the Italian hypertensive population, through the analysis of 24 hours urinary sodium excretion (Na_{24h}), and its association with the relevant anthropometric characteristics.

Methods: 1200 hypertensive patients were recruited, between January 2010 and May 2011 (1), by the 49 Italian centres recognized by the Italian Society of Hypertension. All subjects were on stable antihypertensive treatment and previously submitted to the diagnostic screening and evaluation of the organ damage. Main anthropometric indexes, blood pressure (BP) and Na_{24h} were measured. The population was made of 586 male (52%) and 547 women (48%) and was divided in three macro-areas: North ($n = 405$), Centre ($n = 438$) and South ($n = 290$), according to the geographical localization of the centres.

Results: The population sample had a mean age (mean±SD) of 59.4 ± 13.3 , 59.9 ± 12.8 and 58.9 ± 12.9 years respectively for South, Centre and North ($p = 0.482$). Blood pressure was not controlled (PA $> 140/90$) in 671 (59%) participants. The three areas significantly differ for BP and BMI values, with the central regions with the highest values. The Na_{24h} (at moment available in 622 patients) was not significantly different between the three macro-areas, even though the North showed higher values ($n = 216: 164 \pm 71$ mmol/24h) in comparison to the Centre ($n = 312: 150 \pm 64$) and the South ($n = 94: 154 \pm 65$). Men had a higher Na_{24h} than women (170 ± 70 vs 139 ± 58 ; $p < 0.001$) in the whole population, as well as dividing for macro-areas.

Conclusions: This preliminary analysis of the MINISAL-SIIA point out that in this representative sample of the Italian hypertensive population, the dietary salt consumption is about 9 grams/day, almost double the 5 grams recommended by the OMS. Furthermore this analysis showed a significant higher sodium intake in men, independently of the geographical area.

3.19 Olivetti Heart Study: Cigarette Smoking Provokes Increases of Albumin Urinary Excretion

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Introduction: A significant positive association between cigarette smoking and urinary excretion of albumin (UA) has been demonstrated recently in cross-sectional studies.

Aim: to evaluate the association between cigarette smoking, blood pressure (BP) and UA, in an 8 years of follow-up in a sample of adult male population (The Olivetti Heart Study).

Methods: The population sample included 682 individuals examined in 1994-95 (baseline) and after 8 years (end of the study) with normal renal function (GFR >60 mL/min) at baseline and without changes in their smoking habit during the follow-up. We stratified the sample in two subgroups: smokers (S; n=238) and not-smokers (NS; n=444), both at baseline and at last examination.

Results: At baseline the prevalence of hypertension and obesity were 42% and 17%, respectively. There were a statically significant difference in Systolic BP (SBP) [S vs NS: 126.0±14.8 vs 132.3±17.1 mmHg; p<0.001], Diastolic BP (DBP) [81.9±9.2 vs 86.0±9.5 mmHg; p<0.001] and BMI (26.2±3.1 vs 27.4±2.9 kg/m²; p<0.001), but not in UA, GFR and metabolic profile. After 8-year of follow-up, in S there was a significant increase (Δ) in SBP (Δ±SD; S vs NS: 10.9±16.7 vs 6.34±16.5 mmHg; p=0.001) and DBP (6.4±10.7 vs 4.0±10.8 mmHg; p=0.006), but not in GFR (-15.1±11.2 vs -16.0±13.4 mL/min; p=0.3) and BMI (0.37±1.6 vs 0.32±1.6 kg/m²; p=0.6). Moreover, UA at the end of the study was higher in S than NS (alb/crea 0.26±0.91 vs 0.15±0.47 p=0.036). This association was also confirmed after adjustment for the main confounders (β±ES; 18.4±8.3; p=0.026). Then, we stratified the sample according to the median of UA in low UA (lUA) and high UA (hUA) subjects. A higher prevalence of S was found in hUA (S vs NS; 54% vs 43%; p=0.009). The difference was also confirmed in a logistic regression analysis after adjustment for age, ΔBMI, ΔSBP, ΔGFR and antihypertensive therapy (OR=1.68, 95% CI: 1.21, 2.35; p=0.002). Similar results were observed also replacing smoking with the number of cigarettes smoked per day (OR=1.03, 95% CI: 1.01, 1.06; p=0.032).

Conclusions: In this selected sample of adult male population, smoking and daily cigarette number were associated with higher UA together with higher BP, as previously demonstrated.

3.20 Analysis of Physical Activity in the Elderly Affected by Diabetes Mellitus and Hypertension

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Introduction: Physical activity is relevant in the prevention of cardiovascular diseases. The main guidelines recommend daily or 3 times/week mild exercise. The training programme must be thoroughly evaluated in order to propose activities suited to the movement capacity of the subject.

Aim: To investigate the average level of physical exercise in elderly people living in urban areas through the so-called 'International Questionnaire on Physical Activity'. Elderly subjects affected by both non-insulin-dependant diabetes mellitus and mild/moderate hypertension, still active and sedentary, have been proposed an adapted physical activity (APA) programme.

Methods: 43 elderly people (M 18, F 25, mean age 72±6 y) affected by non-insulin-dependant diabetes mellitus (NIDDM) and mild/moderate hypertension were included. They were all treated with hypoglycaemic oral drugs for diabetes mellitus (DM) and mono/combined therapy for hypertension. Through the International Questionnaire on Physical Activity we detected that 22 subjects (M 9, F 13, mean age 70±3 y) had a mild physical activity which was mostly walking. 21 subjects (M 9, F 12, mean age 71±5 y) were mostly sedentary. The design of this study included the evaluation of: (i) glycaemia, HbA1c; (ii) bodyweight, body mass index (BMI); (iii) ABPM; and (iv) echocardiogram. We also recorded data concerning atrial fibrillation, cigarette smoking, cholesterol, lipid and creatinine.

Results: In active elderly people we detected: (i) HbA1c 6.0±0.3; (ii) bodyweight 72±7 kg (p<0.01), BMI 27±10 kg/m² (p<0.05); (iii) SBP 137±15 mmHg (p<0.01), DBP 86±15 mmHg (p<0.01); (iv) MVSI 130/110 gr/m², MVS/h >56/47 gr/h 2.7 (0.01). Therefore in active subjects we recorded lower values of HbA1c, BMI, BP, PP and LVM compared with those recorded in the sedentary patients: (i) HbA1c 7.3±0.5; (ii) bodyweight 75±11 kg (p<0.01, BMI 31±6 kg/m² (p<0.05); (iii) SBP 157±22 mmHg (p<0.01), DBP 95±14 mmHg (p<0.01); (iv) MVSI 132/110 gr/m², MVS/h >58/47 gr/h 2.7 (0.01). After these results we proposed to the 2 different groups an activity programme consisting of 3 day/week aerobic exercise for 6 months whose schedule was: 15 minutes warm up; 30 minutes indoor aerobic exercise. This programme is still going.

Conclusions: A mild physical activity in aging people affected by non-insulin-dependant diabetes mellitus and mild/moderate hypertension can induce an improvement in both the metabolic and cardiovascular functions.

3.21 Predictive Value of ABPM-Derived Vascular Indices in Different Age Strata: Results of the Dublin Outcome Study

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Introduction: Several indices derived from the relationship between systolic (S) and diastolic (D) blood pressure (BP) measured with ambulatory BP monitoring (ABPM) have been shown to have prognostic relevance.

Aim: To assess the prognostic value of the ambulatory arterial stiffness index (AASI), the BP variability ratio (BPVR) and 24 h pulse pressure (PP) in a large cohort of previously untreated subjects stratified by age.

Methods: The study included 10,499 untreated subjects (age 54.4±14.5 years, 47% male) assessed of hypertension in Dublin, Ireland, in whom 24 h ABPM of adequate quality was obtained. AASI was computed as 1-slope of regression of SBP on DBP; BPVR as the ratio of 24 h SBP SD to 24 h DBP SD; 24 h PP as the mean 24 h difference between SBP and DBP. The association of these variables with cardiovascular (CV) mortality was assessed in Cox regression models adjusted for sex, BMI, smoking status, diabetes, previous CV disease, 24 h mean arterial pressure (MAP) and MAP nocturnal fall, and obtained separately for age strata <50, 50-65 and >65 years.

Results: 498 CV deaths occurred in the study population over the average follow-up period of 5.8 years. The main findings of our study are reported in the table.

	50 y (n=3775)			50-65 y (n=4176)			≥65 y (n=2548)		
	24h PP	AASI	BPVR	24h PP	AASI	BPVR	24h PP	AASI	BPVR
Unadjusted									
HR	1.054	14.9	6.5	1.032	4.5	0.91	1.019	2.54	0.80
Wald	16.3	9.9	15.0	22.5	6.7	0.1	23.6	5.7	1.6
P-Value	<0.001	0.002	<0.001	<0.001	0.01	NS	<0.001	0.02	NS
Adjusted									
HR	1.036	8.19	5.0	1.038	4.0	0.92	1.018	1.8	0.75
Wald	4.49	4.8	9.5	21.3	5.0	0.1	14.9	2.0	2.5
P-Value	0.03	0.03	0.002	<0.001	0.03	NS	<0.001	NS	NS

Conclusions: BP-derived vascular indices differ importantly in terms of predictive power in different age strata. PP is more predictive in elderly subjects, while AASI and BPVR better predict outcome in younger subjects. The differences in the prognostic power of these indices are probably due to varying underlying pathophysiological characteristics to be identified by future studies.

3.22 Prevalence, Associated Cardiovascular Risk Factors and Target Organ Damage in Patients with Resistant Hypertension: The Vobarno Study

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Introduction: Resistant hypertension (RH) is defined by most guidelines as blood pressure that remains above goal despite use of at least 3 antihypertensive agents of different classes, including a diuretic, prescribed at optimal doses. Few data are available on the clinical characteristics and on the prevalence of different forms of organ damage in these patients.

Aim: To evaluate the prevalence of RH and the presence of associated cardiovascular (CV) risk factors and target organ damage (TOD) in a group of hypertensive patients selected from a general population sample in Northern Italy (Vobarno Study).

Methods: 478 subjects (mean age 58±3 years, 44% males, 66% hypertensive patients) underwent laboratory examinations and both clinic and 24 hours BP measurement (Spacelabs 90207). Left ventricular (LV) and carotid artery structure were assessed by ultrasound and carotid-femoral PWV was measured using Complior SP (Artech, Pantin, France).

Results: Among treated hypertensive patients 9.5% were defined as resistant. Patients with RH were older (mean age 69±4 vs 60±9 years, p<0.01), had higher glucose values (115±47 vs 103±24 mg/dL, p<0.05) and were more often of female gender (female 73% vs male 27%, p<0.05); no difference in BMI and lipid levels was observed. Estimated glomerular filtration rate (MDRD) was lower in RH (72±17 mL/min/1.73 m² vs 82±16, p<0.01). Patients with RH had greater LV mass index (47.7±10.5 vs 40.7±10.0 gr/m², p<0.001), LV relative wall thickness (0.42±0.08 vs 0.38±0.05 p<0.001), intima media thickness (Mean max 1.47±0.42 vs 1.18±0.30 mm, p=0.01) and PWV (13.3±2.8 vs 11.8±2.8 m/sec, p<0.05).

Conclusions: In a group of hypertensive patients selected from a general population in Northern Italy the prevalence of RH was relatively high. Patients with RH were older, had higher glucose values and a higher prevalence of cardiac, vascular and renal organ damage.

3.23 Cardiovascular Prognosis in Patients Admitted to an ED with Hypertensive Emergencies and Urgencies

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Introduction: At present, few data are available on the prognostic significance of hypertensive emergencies and urgencies admitted to Emergency Departments (EDs).

Aim: To evaluate the incidence of total and cardiovascular events (CV) during follow-up in hypertensive patients admitted to an ED of the Brescia Hospital (Northern Italy) with hypertensive emergencies (HE) or urgencies (HU).

Methods: Between January and December 2008, medical records of patients aged >18 years, admitted to the ED of the Spedali Civili di Brescia with blood pressure values >180 mmHg (SBP) and/or >120 mmHg (DBP) were collected and analysed (328 patients were classified as 'hypertensive emergency', 890 patients as 'hypertensive urgency', 380 patients as 'pseudo hypertensive urgency' and 38 patients with 'hypertensive urgency and a first diagnosis of hypertension'). Data on 947 patients were analysed; the mean duration of follow-up after admission to the ED was 2 years.

Results: A first fatal or non fatal CV event occurred in 226 patients (62 cardiovascular events, 45 cerebrovascular events, 42 hospital admissions for heart failure, 46 cases of new onset kidney failure and 31 cases of new-onset diabetes). Patients with CV events were older, more frequently males, with a higher prevalence of diabetes mellitus and previous CV disease, and a greater proportion of inadequate BP control. During the follow-up a new episode of 'hypertensive crisis' was recorded in 203 patients (24%). The incidence of hypertensive crises was significantly higher in patients with hypertensive emergency in comparison with hypertensive urgency ($p=0.03$). The incidence of fatal and non fatal events was 14.8, 5.1, 5.3, 2.5 per 100 patient-year in patients with hypertensive emergency, urgency, pseudo-urgency and first diagnosis of hypertension, respectively ($p<0.001$ emergency vs others, by the log-rank test). Similar results were obtained when we considered separately the occurrence of cardiovascular, cerebrovascular or renal events.

Conclusions: Admission to the ED for hypertensive emergencies identifies hypertensive patients at increased risk for fatal and nonfatal cardiovascular events. Our results underline the need for a strict and accurate follow-up in patients with hypertensive crises.

3.24 Prevalence and Associated Cardiovascular Risk Factors of Renal Damage in Hypertensive Women in Italy: The I-DEMAND Study

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Aim: To evaluate the differences in the prevalence of chronic kidney disease (CKD) and of associated cardiovascular risk factors and diseases between men and women participating in the Italy Developing Education and awareness on MicroAlbuminuria in patients with hypertensive Disease (I-DEMAND).

Methods: This is an observational, cross-sectional, multicentre study aimed at determining prevalence and correlates of among Italian hypertensive patients attending out-patient referral clinics. CKD was defined as glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m (Modification of Diet in Renal Disease equation) or urine albumin to creatinine ratio of at least 2.5 mg/mmol in men and of at least 3.5 mg/mmol in women or both.

Results: A total of 3559 study patients with renal data available were considered for this analysis: mean age was 61 ± 4 years and 37% had diabetes mellitus. Female patients ($n=1636$, 46%) were older, with a greater prevalence of obesity and lower prevalence of smoking. The prevalence of concomitant coronary artery and peripheral artery diseases, but not of hypertension, diabetes mellitus, or heart failure, was lower in women than in men. A higher proportion of patients were treated among women than men (94% vs 91% chi square $p=0.0001$), while adequate blood pressure (BP) control (SBP <140/90 and <130/80 mmHg in diabetics) was similar in men and women (42% vs 44%). The overall prevalence of microalbuminuria was lower (16% vs 23%, chi-square $p=0.001$), while the prevalence of reduced GFR was higher (33% vs 21%, chi-square $p=0.001$) in women than in men. CKD was similar in women and men (44% vs 41%, respectively, chi-square $p=0.095$). The prevalence of LVH (diagnosed by either ECG or LVH) was similar in men and women (18% vs 20%, chi-square $p=ns$). In men age, smoking, glycaemia, uraemia and pulse pressure, while in women age, BMI, glycaemia, uraemia and pulse pressure were the independent predictors of CKD.

Conclusions: Renal abnormalities are found in a significant number of female hypertensive patients. In women, a decrease in eGFR is more frequently observed than microalbuminuria, in respect to men. Associated risk factors and clinical conditions seem to differ between men and women, suggesting the need to develop specific therapeutic strategies to prevent renal dysfunction and reduce associated morbidity and mortality.

3.25 Resistant Hypertension Prevalence and Associated Cardiovascular Risk Factors and Renal Disease: The I-DEMAND Study

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Introduction: Resistant hypertension (RH) is defined by most guidelines as blood pressure that remains above goal despite use of at least 3 antihypertensive agents of different classes, including a diuretic, prescribed at optimal doses. Few data are available on the clinical characteristics and on the prevalence of different forms of organ damage in these patients.

Aim: To evaluate the prevalence of RH and the prevalence of associated chronic kidney disease (CKD) and cardiovascular risk factors and diseases, participating to the Italy Developing Education and awareness on MicroAlbuminuria in patients with hypertensive Disease (I-DEMAND).

Methods: this is an observational, cross-sectional, multicentre study aimed at determining prevalence and correlates of among Italian hypertensive patients attending out-patient referral clinics. CKD was defined as glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m (Modification of Diet in Renal Disease equation) or urine albumin to creatinine ratio of at least 2.5 mg/mmol in men and of at least 3.5 mg/mmol in women or both.

Results: A total of 3754 study treated patients with renal data available were considered for this analysis: 47% women, mean age 62 ± 11 years and 38% had diabetes mellitus. Resistant hypertension was observed in 271 patients (7.1%). Patients with RH were older (mean age 67 ± 9 vs 61 ± 11 years, $p<0.01$), had higher glucose values (129 ± 41 vs 117 ± 39 mg/dL, $p<0.001$), BMI (29 ± 45 vs 28.5 ± 5 mg/dL, $p<0.005$) and triglycerides (169 ± 107 vs 145 ± 94 mg/dL, $p<0.001$). Estimated glomerular filtration rate (MDRD) was lower in RH (59 ± 23 mL/min/1.73 m² vs 74 ± 24, $p<0.001$), while albuminuria was higher; in addition the prevalence of CKD and of LVH (diagnosed by either ECG or echocardiography) was greater in patients with resistant hypertension.

Conclusions: In groups of treated hypertensive patients participating in the I-DEMAND study, the prevalence of RH was relatively high. Patients with RH were older, had higher glucose values and a higher prevalence of cardiac and renal organ damage.

3.26 Cardiovascular Complications and Predictive Value of the Ankle-Brachial Index in Diabetic Patients

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Introduction: Peripheral arterial disease (PAD), demonstrated by altered ankle-brachial index (ABI), is associated with increased incidence of cardiovascular events (up to 20% in 10 years), but the value of ABI in risk stratification of diabetic patients is still controversial.

Aim: To evaluate the reliability of ABI as a prognostic indicator of global cardiovascular risk, prevalence of the diabetic foot, need for revascularization and amputation due to PAD in diabetic patients.

Methods: ABI was measured using the standard method in 94 diabetic patients (aged 77 ± 8.3 years). We used the average value of right and left ABI for statistical analysis. In 58 patients ABI was less than 0.9 (the lower normal limit) and were referred to as group 1; in the remaining 36 patients ABI was >0.9 and were named group 2.

Results: At enrolment the patients with reduced ABI (group 1) were significantly different from group 2 patients for HbA1c, total and LDL cholesterol plasma levels, urinary albumin excretion and systolic blood pressure. The two groups also significantly differed in prevalence of diabetic nephropathy (73% in group 1 and 47% in group 2) and in prevalence of clinically evident PAD (respectively 89% and 41%). The diabetic foot prevalence was not significantly different between the groups. During a mean follow-up period of 6 years, 30 patients died (32%) without differences between group 1 and group 2. No differences were found in serum creatinine increase (from 1.02 ± 0.26 to 1.32 ± 0.64 mg/dL in group 1, and from 1.02 ± 0.28 to 1.25 ± 0.52 mg/dL in group 2). Albuminuria levels increased from 108 to 375 mg/24h in group 1 and from 57 to 214 mg/24h in group 2 without a statistically significant difference. A statistically significant difference in clinically evident PAD prevalence between the two groups was found also during follow-up period (96% and 79%, respectively).

Conclusions: ABI correlates with the presence of kidney and vascular disease in diabetic patients. ABI is a good predictor of vascular complications (need for revascularization and amputation) but not for the progression of kidney disease, in diabetic patients.

3.27 Prevalence and Determinants of Resistant Hypertension in a Hypertension Unit

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Introduction: The diagnosis of resistant hypertension allows identifying patients with higher cardiovascular risk and in which different diagnostic and therapeutic options should be considered. However, the prevalence of this condition is still a matter of debate.

Aim: To investigate the prevalence of resistant hypertension, using ESC/ESH definition, in an Outpatient Hypertension Unit, and to identify clinical parameters characterizing this condition.

Methods: 541 consecutive hypertensive patients were enrolled. Medical history, anthropometric parameters, and routine blood exams were collected. Resistant hypertension was identified according to the following criteria: office blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes, including a diuretic, at full dose.

Results: 93 patients (17.2%) resulted to be resistant to antihypertensive treatment. Among resistant hypertensive patients the following conditions were significantly more represented: older age (62.3 ± 10.5 vs 55.9 ± 13.1 years, $p < 0.0001$), sedentary status (91.1% vs 81.5% $p < 0.05$), previous cardiovascular events (31.8% vs 15.2%, $p < 0.001$), diabetes (36.9% vs 14.5%, $p < 0.001$), hypercholesterolaemia (22.7% vs 14.5%, $p < 0.05$), obesity (27.2% vs 14.3%, $p < 0.0001$), chronic kidney disease (28.3 vs 16.0%, $p < 0.05$). In a logistic regression model adjusted for confounders, only obesity ($p = 0.02$) and diabetes mellitus ($p = 0.002$) were associated with an increased probability to have resistant hypertension.

Conclusions: Resistant hypertension affects about 1 of 6 patients seen by a hypertension specialist. Though all classical cardiovascular risk factors were more frequent in resistant hypertensive patients, only obesity and diabetes mellitus were independently associated with this condition.

3.28 Obesity Increases Prevalence of Cardiovascular Target Organ Damage in Hypertension (The Campania Salute Network)

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Introduction: Whether concomitant obesity in hypertension is associated with increased prevalence of vascular as well as cardiac target organ damage needs further clarification.

Methods: Data from carotid ultrasound and echocardiography in 10 800 hypertensive patients free of prevalent CV disease, participating in the CampaniaSalute Project were used. The population was grouped into body mass index (BMI) classes. Vascular and cardiac target organ damage was defined as plaque in >1 of the common or internal carotid arteries and left ventricular hypertrophy (LVH), respectively.

Results: A majority of the patients were either overweight or obese, as reported in the table (in the table, data are expressed as percentage or as mean \pm SD; * $p < 0.01$ versus normal weight group). In spite of more use of combination therapy, the obese group had slightly higher blood pressure (BP) and included more patients with carotid plaques and LVH. In multivariate logistic analyses, concomitant obesity was associated with a 21% (95% CI 7, 36) increased prevalence of carotid plaques, a 3.7 times higher prevalence of LVH (95% CI 3.32, 4.18) and a 2.4 times higher prevalence of combined vascular and cardiac target organ damage (95% CI 2.12, 2.78, all $p < 0.01$) independent of significant associations with gender, age, diabetes mellitus, clinic systolic BP and antihypertensive treatment.

Variable	Normal BMI (n=2708)	Overweight (n=5252)	Obesity (n=2840)
Women (%)	53.1	36.7*	45.5
Diabetes mellitus (%)	3.7	5.3*	8.1*
Clinic systolic BP (mmHg)	144 + 19	144 + 18	146 + 19*
Clinic diastolic BP (mmHg)	88 + 12	89 + 11*	90 + 12*
Carotid plaque (%)	55.4	59.3*	61.6*
LVH (%)	22.6	40.1*	60.2*
Combined carotid plaque and LVH (%)	17.4	28.3*	42.6*
Combination therapy (%)	49.3	60.0*	65.3*

Conclusions: In hypertensive patients participating in the Campania Salute Project, concomitant obesity is associated with a highly increased prevalence of LVH, and a modest increased prevalence of carotid plaques, independent of high BP.

3.29 The Burden of the Arterial Hypertension in the Genesis of the Heart Failure

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Introduction: Heart failure (HF) is a major cause of mortality in the elderly population, often to the point of being regarded as a true epidemic. Hypertension is a major cause, especially in the elderly population. The treatment of this disease through a programme of outpatient management specialist-integrated (GSI) is intended to provide greater efficacy and better control of cardiovascular risk factors.

Aim: To evaluate the clinical characteristics and the burden of cardiovascular risk factors of patients with hypertensive heart disease and heart failure followed through a programme of GSI.

Methods: 100 patients with clinical and instrumental signs of HF enrolled in 2006 after at least 1 hospitalization for clinical HF (55 M and 45 F, mean age 73 years, range 43–96). At enrolment, a clinical and laboratory evaluation, with determination of NYHA class, BNP, and an echocardiographic assessment were performed.

Results: Between cardiovascular risk factors, 23% of the population had diabetes mellitus, 12% had had a cerebral ischaemic event, 29% suffered from chronic renal failure, 45% had atrial fibrillation and 53% of the population was hypercholesterolaemic. The ejection fraction (EF%) was 61 ± 8 , diastolic volume (EDV/mL) was 93 ± 24 , the end-systolic volume (ESV/mL) was 30 ± 14 , left atrium diameter was of 4.2 ± 0.6 , the diameter of the ascending aorta (cm) was 2.5 ± 0.8 , the E/A ratio was 0.83 ± 0.21 and finally the baseline BNP (pg/mL) were 353 ± 261 .

Conclusions: The clinical characteristics of our population once again support the role of hypertension and cardiovascular risk factors in the genesis of the HF and put more attention to the shape of diastolic heart failure-type with an increased incidence in the elderly population. In our experience, the GSI approach remains the cornerstone for the prevention and treatment of cardiovascular risk factors.

3.30 Vitamin D and Cardiovascular Risk in Obese Women

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Introduction: recent epidemiological studies have indicated a strong, inverse correlation, between serum vitamin D values and cardiovascular (CV) risk, thus suggesting that vitamin D deficiency might be a CV risk factor. Obesity is associated with an increased CV risk and with a vitamin D deficiency, due to a reduced bioavailability of vitamin D, which is accumulated in the adipose tissue.

Aim: To evaluate whether serum vitamin D levels were associated with coronary heart (CH) disease risk, as evaluated by Framingham score, and CV risk, as assessed by Progetto Cuore, in a population of severely obese women.

Methods: Serum vitamin D levels were measured by RIA (16.9 ± 9.6 ng/mL) in 176 severely obese women with age 45.9 ± 8.6 years (mean \pm SD), bodyweight 110.7 ± 18.5 kg, body mass index (BMI) 43.3 ± 6.7 kg/m², waist circumference (WC) 123.1 ± 14.9 cm, hip circumference 129.7 ± 14 cm and waist to hip ratio (WHR) 0.95 ± 0.09 . Visceral fat (VF), measured by ultrasound, was 85.7 ± 24.4 mm. CHD risk assessed with Framingham score was 9.6 ± 6.3 , CV while risk assessed with Progetto Cuore score was 1.8 ± 2.04 .

Results: univariate analysis showed that vitamin D was inversely and significantly ($p < 0.05$) associated with CHD risk ($r = -0.183$) and CV risk ($r = -0.189$). In the multivariate analysis, using CHD and CV risk as dependent variables, and anthropometric parameters and vitamin D as independent variables, vitamin D together with VF and bodyweight, was still inversely and significantly associated with CHD and CV risk (R2 for these 3 variables 0.25 and 0.15, respectively). When vitamin D was correlated with each parameter of risk used in the Framingham and Progetto Cuore algorithms, it was found significantly and inversely correlated with systolic blood pressure ($r = 0.23$) and age ($r = 0.18$).

Conclusions: In a cohort of severely obese women, serum vitamin D levels were inversely and significantly associated with CHD and CV risk, a finding that can be at least partially explained by the inverse association with systolic blood pressure and age. Controlled studies evaluating whether vitamin D supplementation can reduce CHD and CV risk are needed.

3.31 Cardiovascular Risk and Polycystic Ovary Syndrome

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Introduction: Polycystic ovary syndrome (PCOS) is the most common endocrine disease in women of reproductive age (5–10%). Some data show that PCOS is associated with an increased cardiovascular risk but it is unclear whether this risk profile is simply determined by hyperandrogenism. **Aim:** To assess the main cardiovascular risk factors and in particular the blood pressure (BP) values and lipid profile in women with PCOS compared with a control group.

Methods: 269 Caucasian PCOS and 169 controls women, well matched for age and body mass index (BMI) were studied (age mean±SD, 25±6 vs 27±8 years, BMI 28.66±7.98 vs 30.36±9.23 kg/m², respectively). PCOS was diagnosed according to Rotterdam criteria. We evaluated BP values, triglycerides (TGs), total cholesterol (TC), high-density lipoprotein (HDL)-

cholesterol, low-density lipoprotein (LDL)-cholesterol, fasting insulin, HOMA-index, testosterone (T), free-androgen index (FAI).

Results: No significant difference between the 2 groups both in BP values and in lipid profile were found. All values were within normal range (PCOS group: systolic blood pressure (SBP) 120±12 mmHg, diastolic BP 77±9 mmHg; TC 179±31 mg/dL, LDL 110±28 mg/dL, HDL 62±16 mg/dL, TGs 88±54 mg/dL; control group: SBP 121±12 mmHg, DBP 78±9 mmHg; TC 174±28 mg/dL, LDL 107±26 mg/dL, HDL 61±15 mg/dL; TGs 82±39 mg/dL). Dividing our population according to insulin resistance, assessed by HOMA, whereas insulin resistance (IR) subjects with HOMA-index ≥2.5, we found in the PCOS group 24% IR subjects versus 26% in controls (p=ns). Individuals with IR show a mean of LDL-cholesterol (120±30 vs 108±27, p<0.05) and triglycerides (120±69 vs 77±41, p<0.05) significantly increased compared to non-IR women. Moreover IR women showed HDL-cholesterol values significantly lower (54±14 vs 64±15, p<0.05) than N-IR. Instead no significant difference in BP values were found. In the PCOS group, in a multivariate analysis, the only parameters independently and directly correlated with lipid profile parameters were BMI and HOMA index.

Conclusions: These data suggest that in young PCOS women hyperandrogenism didn't influence blood pressure values and lipid profile.

Genetics and Pharmacogenomics

4.1 Single Nucleotide Polymorphisms and Arterial Stiffness:

Preliminary Analysis in a Cohort of Hypertensive Subjects

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Introduction: The association between SNPs on 9p21 region and coronary artery disease is well known; however, only few studies have evaluated the influence of this region on intermediate phenotypes, like arterial stiffness.

Aim: To evaluate the association between 384 SNPs (located in ENDR, ELN, MMP9 and 300 SNPs on short arm of 9 chromosome) and carotid-femoral PWV in a cohort of hypertensive patients.

Methods: In 821 hypertensive patients (age 53.9±13.7, mean±SD) we assessed, along with body mass index (BMI), biochemical values, blood pressure (BP), echocardiographic and carotid ultrasound variables, cf-PWV via the Complior method. DNA was extracted from blood samples (Promega kit) and the selected SNPs were screened with a custom-made chip on Illumina BeadXpress Reader platform. C-f PWV was considered a quantitative trait; age, systolic blood pressure, sex and BMI was used for the multivariate analysis (PLINK). We adopted False Discovery rate (FDR) to account for multiple testing.

Results: Our data showed a trend of association between PWV and rs300622 and rs2381640. The C allele of rs300622 was associated with a higher cf-PWV value (11.190±2.95 m/sec vs 10.717±2.68 m/sec, p=0.003); while the C allele of rs2381640 was associated with a higher cf-PWV value (10.904±2.81 m/sec vs 10.522±2.49 m/sec, p=0.003). However, this two SNPs did not pass correction for multiple testing (FDR 0.6). In the same population sample rs300622 showed a significant association with IMTdx.

Conclusions: The association signals for cf-PWV did not pass multiple testing correction, probably due to the small sample. However, our data suggest that genes located on chromosome 9p21 may regulate arterial stiffness.

4.2 Null Phenotype of GSTT1 Gene as Gender-Related Marker of Essential Hypertension

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Introduction: Glutathione S-transferase enzymes (GSTs) constitute the principal phase II superfamily, which plays a key role in cellular detoxification. Different studies have successfully investigated the role of several GST gene polymorphisms in relation to the expression and development of complex diseases. Regarding the arterial hypertension, to date few studies have been conducted on GST gene variability, but the results of these studies are in some cases conflicting.

Aim: To analyse the possible involvement of GST gene variants in essential hypertensive subjects. In particular, we focused our attention on functional polymorphisms of GST genes (GSTA1*69C/T, GSTM1 null, GSTP1*1105V, GSTT1 null) that had been previously studied in relation to blood pressure, and on two functional GSTO gene polymorphisms (GSTO1*A140D, GSTO2*N142D) not yet studied in relation to hypertension.

Methods: The study population consisted of 403 adult people (193 patients with history of essential hypertension and 210 healthy individuals) who were not relatives. GST SNPs were determined using the PCR-RFLP method while GST null polymorphisms were determined using a Multiplex PCR.

Results: Among GST polymorphisms, only the frequency of the GSTT1 null phenotype was significantly higher in hypertensive patients than in normotensive participants (p<0.001; adjusted OR=2.24 [1.43, 3.50]). In sex-based analysis, the risk was significantly higher in female hypertensive patients (p<0.001; adjusted OR=3.25 [1.78–5.95]) but not in male subjects.

Conclusions: Our outcome suggests that the null phenotype of the GSTT1 gene could be a sex-specific marker for essential hypertension. One potential mechanism by which the GSTT1 null phenotype might contribute to essential hypertension in females is that this variant could increase the sensibility of cells to xenobiotics (i.e. contraceptive agents) and to oxidative stress (i.e. menopause effects). Exploration of the physiological roles of GSTT1 will lead to a clearer understanding of the significance of GST gene polymorphisms in the development of essential hypertension. To date our research group is involved in studies to investigate the association between GST and hypertension in pregnancy, and to analyse the genetic variability of theta class, where the GSTT1 gene is located.

4.3 Oxidative Stress and Baroreflex Sensitivity after Omega-3 Diet Supplementation, in an Experimental Model of Menopause in Rats

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Introduction: Menopause decreases the sensitivity of baroreceptor reflex (SBR) in women and in experimental models of surgical menopause. Exercise and estrogen therapy improves SBR by reducing oxidative stress (OS).

Aim: To investigate if a diet supplementation with omega-3 fatty acids is effective in reducing OS and improving SBR, in an experimental model of menopause in rats.

Methods: Twenty one, 6-month-old, Wistar-Kyoto rats were equally divided into 3 groups: (a) control: sham surgery, normal diet (CTRL), (b) ovariectomy, normal diet (OVX) and (c) ovariectomy, + omega-3 (0.8 g/kg/day daily gavages administration) supplementation diet (OVX+ omega3). Two months after surgery, arterial pressure and heart rate were directly measured by femoral catheter; Superoxide anion generation in aorta rings (SOD-inhibitable cytochrome C reduction assay) assessed VOS. Erythrocyte membranes omega-3 were measured by gas-chromatography. The SBR was calculated as the slope of the correlation between pressure and heart rate.

Results: The main findings are reported in the table.

Variables	CTRL	p-Value	OVX	p-Value	OVX+Ω3
BRS (msec/mmHg)	8.49±0.1 n=7	<0.0001	2.5±0.05 n=7	<0.05	5.2±0.3 n=7
Superoxide (nmol/min/mm ²)	97.4±8.3 n=9	0.01	142.3±14.6 n=7	0.04	105±9.8 n=9
Membrane omega-3 index	3.19±0.14 n=10	0.01	2.54±0.076 n=10	<0.0001 vs OVX, CTRL	5.18±0.24 n=10

Conclusions: Omega-3 diet supplementation improves the SBR, likely by reducing the reactive oxygen species (ROS), key molecules in the regulation of central and peripheral sympathetic transmission.

4.4 High Amino-Terminal Natriuretic Peptide Plasma Levels are Markers of Cardiovascular Risk

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4.8 A Quantitative Trait Locus on Chromosome 18 of the Spontaneously Hypertensive Rat (SHR) Influences the Response to Sodium Load of Autonomic Indexes of Blood Pressure and Pulse Interval Variability

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4.10 Clinical Follow-Up for Pheochromocytoma/Paraganglioma in a Population of Susceptible Subjects Identified by Genetic Analysis

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Introduction: Over the last few years, the genetic screening of patients with pheochromocytoma/paraganglioma (PHEO/PGL), either syndromic, as in multiple endocrine neoplasia type 2, von Hippel-Lindau disease (VHL) and neurofibromatosis type 1 (NF1) or isolated, has led to the identification of mutation-carrier index cases, as well as of their relatives with the same genetic susceptibility.

Aim: To evaluate the impact of a targeted clinical follow-up in the early detection of PHEO/PGL in subjects carrying known gene mutations predisposing to such disease.

Methods: Study population involved 193 subjects: 59 index cases (INDEX) affected by PHEO/PGL and 134 apparently asymptomatic mutation-carrier relatives (FAM). Overall, 54 subjects had mutation in SDHB/SDHD genes (11/2 INDEX and 41/0 FAM), 10 in VHL (9 INDEX, 1 FAM), 7 in NF1 (all INDEX), 123 RET (31 INDEX, 92 FAM). At the time of first

recognition of the genetic predisposition all subjects underwent a clinical assessment protocol including biochemical and imaging investigation, aimed to detect any manifestation of disease; in addition, they were submitted to annual or biannual follow-up re-evaluation.

Results: PHEO/

5.4 Differential Expression of MicroRNA in the Heart of Diabetic Rats

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Introduction: MicroRNA (miRNAs), non-coding single-strand RNA molecules, play an important role in the regulation of gene expression. Each miRNA regulates many genes, suggesting that miRNAs may play a role in many biological processes.

Aim: To evaluate the effect of diabetes on myocardial microRNA expression profiles in streptozotocin-induced diabetic rats.

Methods: Diabetes was induced in 8 Sprague Dawley rats by streptozotocin injection (i.p). Control rats (n=6) underwent only buffer injection. Three months after the onset of diabetes, microRNAs were extracted (Mirvana, Applied Biosystems) and TaqMan Low-Density Array system (Applied Biosystems) was used to investigate miRNA expression profiles in the heart. MiRNA expression differences between the control and diabetic rats were confirmed with real time PCR. Target genes for differentially expressed miRNAs were predicted by using two different algorithms (TargetScan and Miranda) and classified in intracellular pathways (Kegg). Myocardial fibrosis was evaluated by histomorphometric analysis, previous serious red stain.

Results: During the experimental period, diabetic rats showed a significant increase in blood glucose level (p<0.01). In diabetic rats histomorphometric analysis showed an increase in myocardial fibrosis (p<0.01) as compared with control rats. Differential expression (upregulation) was confirmed by real time PCR for miR-296-5p and miR-342-5p. Gene Ontology analyses of the putative target genes of miR-296-5p and miR-342-5p identified these specific miRNAs in TGF- β signalling pathways, Jak-STAT, MAPK and WNT signalling, and in extracellular matrix interaction networks.

Conclusions: These data suggest a role of miR-296-5p and miR-342-5p in different pathways involved in remodelling processes and in myocardial fibrosis in diabetes.

5.5 Fasting Glucose Levels are Associated with an Early Diastolic Dysfunction in Non-Diabetic Hypertensive Patients: A Tissue Doppler Imaging Study

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Introduction: It is known that diabetes mellitus is associated with diastolic dysfunction of the left ventricle (LV), but a relationship between early changes in plasma glucose and LV diastolic function has never been investigated.

Aim: To evaluate the relationships between glucose metabolism parameters and LV diastolic function in non-diabetic hypertensive patients.

Methods: In 82 non-diabetic untreated essential hypertensive patients (age 48 \pm 13 yr; 43M/39F), we measured BMI and waist circumference, fasting glucose (Gluc), insulin (INS), and C-peptide levels, and calculated HOMA-index. In a subset of 52 patients we evaluated glycaemic and insulinaemic response to an oral glucose tolerance test (OGTT). By standard echocardiography we assessed cardiac morphological and functional variables and LV mass indexed (LVMI; g/m^{2.7}) and by Tissue Doppler Imaging (TDI) we measured myocardial early-diastolic velocities at septal and lateral portions of the mitral annulus (Esept and Elat, respectively), myocardial end-diastolic velocities in the same segments (Asept and Alat, respectively), and we calculated E/Esept, Esept/Asept, E/Elat and Elat/Alat ratios.

Results: The E/A trans-mitral ratio was directly and significantly related with age, waist circumference, Gluc, and HOMA-index. Esept velocity was significantly lower in patients with impaired fasting glucose (p=0.031) and reduced glucose tolerance at OGTT (p=0.012) than in patients with normal glucose levels, thus suggesting an impaired diastolic function in patients with early changes of glucose metabolism. Esept, Elat, Esept/Asept and Elat/Alat were inversely related with age, waist circumference, Gluc and LVMI. Multivariate analysis included demographic and anthropometric variables and LVMI and showed that Esept and Elat were independent related with fasting glucose levels (p=0.010 and p=0.016, respectively).

Conclusions: Diastolic dysfunction is detected by TDI in non-diabetic hypertensive patients with impaired fasting glucose or impaired glucose tolerance. In these patients diastolic dysfunction is independent of age, body mass and LVMI. This observation suggests the opportunity of early correction of glucose levels in hypertensive patients even before the development of overt diabetes.

5.6 Demographic, Anthropometric, Haemodynamic and Metabolic Determinants of Left Atrial Size in the General Population: Data from the Pamela Study

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Introduction: Left atrium enlargement is associated with an increased cardiovascular morbidity and mortality. No data, however, are available on whether and to what extent demographic, anthropometric, haemodynamic and metabolic variables, affect left atrium size and prevalence of left atrial enlargement in the general population.

Methods: A sample of 3200 subjects was randomly selected from the general population of Monza (Italy), aged 25–74 years, stratified for sex and decades of age. The participation rate was 64%. In each subject we obtained: height and weight for calculation of body surface area (BSA); office systolic (S) and diastolic (D) blood pressure (BP); home SBP and DBP (mean of 2 self measurements); 24-hour SBP and DBP; office, home and 24-hour heart rate (HR); left ventricular mass index (LVMI) and left atrial diameter (LAD) by echocardiography. The full set of data (which also included blood glucose, total and HDL-cholesterol (C) and serum triglycerides) was available in 1785 subjects. 339 of them were treated hypertensive patients (TH). Controlled hypertensive patients (CH) for each type of BP measurement were TH in whom SBP was <140 mmHg, <132 mmHg and <125 mmHg, respectively for office, home and 24-hour measurement. Pathological left atrial enlargement was defined as LAD \geq 3.9 cm in women and \geq 4.1 cm in men, while left ventricular hypertrophy (LVH) was defined as LVMI \geq 106 g/m² and \geq 111 g/m², respectively.

Results: Mean LAD was 3.51 cm (3.35 in females, 3.66 in males). In the population as a whole prevalence of LAD abnormality amounted to 12.4%, increasing significantly in presence of LVH (34.8% vs 8.5%, p<0.0001). After adjustments for age and BSA, we found a significant direct relationship between LAD and LVMI, office, home and 24-hour SBP and DBP; and an inverse one with office and 24-hour HR and HDL-C. Similar results were found excluding TH from the analysis. In the normotensive subjects (NT, n=971) only the direct relationships with LVMI, office and home SBP and the negative relationships with office and 24-hour HR remained significant. In linear regression model, age, BSA, LVMI and office SBP were independently and directly associated with LAD, while an independent inverse association was found between HDL-C and LAD. Similar results were found excluding from the analysis TH. In NT only the independent positive association of LAD with age, BSA and LVMI remained significant. Adjusting for age, gender and BSA, LAD in TH was higher than in NT but also than in not-treated hypertensive patients (NTH). In CH, LAD remained higher than in N and in NTH.

Conclusions: These data provide evidence that in the general population age, BSA, LVMI and office SBP are important independent determinants of left atrial size. They also show that TH patients show a LAD value higher than NT and NTH and that this is the case even in treated and well controlled hypertensive patients, suggesting that this structural alteration is only partially affected by treatment.

5.7 New-Onset Left Atrial Enlargement in a General Population: Data from the Pamela Study

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Introduction: Left atrium enlargement is associated with an increased cardiovascular morbidity and mortality.

Aim: To assess the factors involved in the development of left atrial enlargement in a general population.

Methods: A sample of 3200 subjects was randomly selected from the general population of Monza (Italy), aged 25–74 years, stratified for sex and decades of age. The participation rate was 64%. In each subject we obtained: office systolic (S) and diastolic (D) blood pressure (BP); home SBP and DBP (mean of 2 self measurements); 24-hour SBP and DBP; office, home and 24-hour heart rate (HR); left ventricular mass index (LVMI) and left atrial diameter (LAD) by echocardiography; height and weight for calculation of body surface area (BSA) and body mass index (BMI). Pathological left atrial enlargement (LAE) was defined as LAD \geq 3.9 cm in women and \geq 4.1 cm in men, while left ventricular hypertrophy (LVH) was defined as LVMI \geq 106 g/m² and \geq 111 g/m², respectively. Reference values for office, home and 24-hour BP (SBP/DBP) were 140/90 mmHg, 132/83 mmHg and 125/79 mmHg, respectively. All variables (including blood glucose, total and HDL-cholesterol and serum triglycerides) were collected twice, the first at the beginning of the nineties, and the second ten years later. The analysis was carried out on the individuals without atrial enlargement at the first examination, which accepted to take part in the second survey 10 years later (n=1045).

Results: Among the 1045 subjects without LAE at the first examination, 123 developed LAE during the 10-year time interval (11.8%). The incidence of a new onset LAE was progressively greater from the lowest to the highest tertile of office, home and 24-hour SBP (p<0.0001 for trend), and it was also progressively more frequent in subjects with no BP elevation those with 1, 2 and 3 blood pressures (office, home and 24-hour BP) [p for trend <0.0001] increase. The incidence of a new onset LAE was progressively greater from the lowest to the highest tertile of LVMI (p<0.0001 for trend), and from the lowest to the highest tertile of BMI, plasma total cholesterol and blood glucose (p<0.001 for trend). The factors independently involved with new onset LAE, identified by stepwise selection model, were office SBP, LVMI, age, BSA and female gender.

Conclusions: In the general population, among subjects with a normal sized left atrium, 11.8% developed LAE in ten year. The factors that independently increase the risk of left atrium enlargement are age, female gender, office SBP, LVMI and BSA.

5.8 Plasma Neutrophils are Increased in Overweight/Obese Patients and are Associated with Early Impairment of Cardiac Diastolic Function

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Introduction: Experimental findings suggested that neutrophils contribute to left ventricular (LV) remodelling due to volume and pressure overload, through pro-oxidant mediators released in the myocardium. Obesity is associated with increased airway polynuclear cell infiltration, LV remodelling and systemic oxidative stress.

Aim: We questioned whether plasma neutrophil levels are increased in overweight/obese patients and correlate with LV remodelling and function.

Methods: We consecutively enrolled patients attending our out-patient clinic for cardiovascular (CV) disease: 40 patients with body mass index (BMI) >25 kg/m² and 21 patients with BMI <25 kg/m² (mean BMI: 29.5±3.7 g/m² vs 23.1±1.2 g/m², p<0.0001). All the patients were non-smokers, never treated with antihypertensive drugs or statins and without overt CV disease. All patients underwent: echocardiography, ambulatory blood pressure (BP) monitoring and plasma measurement of white cell count.

Results: The two groups were similar for mean age, gender, systolic and diastolic BP throughout the 24 hours. LV mass, indexed for height^{2.7} (h)^{2.7}, was normal in all the patients and higher in the overweight/obese ones (37.6±7.2 vs 30.4±5.8 g/h^{2.7}, p<0.0001). Relative wall thickness was not different between groups. With regard to LV diastolic function, overweight/obese patients showed higher left atrial diameter and volume (35.5±2.8 mm vs 33.1±2.9 mm, p<0.01 and 46.4±11.3 mL vs 37.5±13.2 mL, p<0.01), lower Em/Am (0.73±0.19 vs 0.89±0.32, p<0.05) and E'/A' (1.1±0.4 vs 1.2±0.4, ns) from septal and lateral Tissue Doppler Imaging, and higher E/Em (7.56±1.59 vs 6.26±1.27, p<0.01) and E/E' (4.90±0.91 vs 4.36±1.03, p<0.05). Plasma absolute neutrophil count was normal in all the patients, but higher in overweight/obese patients (p<0.01), and positively correlated with BMI (r=0.24, p=0.06), left atrial diameter (r=0.26, p<0.05) and volume (r=0.27, p<0.05), E/Em (r=0.35, p<0.01) and E/E' (r=0.28, p<0.05).

Conclusions: We found that plasma neutrophil levels are higher in overweight/obese patients and are associated with early impairment of LV diastolic function. Our preliminary results suggest a potential role for plasma neutrophils as markers/mediators of cardiac remodelling in obesity.

5.9 Glycaemic Control in Type 2 Diabetes Mellitus: Relationship with Left Ventricular Diastolic Function and Matrix Metalloproteinases

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Introduction: A good glycaemic control reduces the risk of vascular complications in type 2 diabetes mellitus, whereas the influence of glycaemic control on the development of diabetic cardiomyopathy is still under evaluation.

Aim: To evaluate the relationship of glycaemic control with left ventricular (LV) morpho-functional characteristics and plasma levels of matrix metalloproteinases (MMPs) in type 2 diabetic patients without overt cardiovascular disease.

Methods: Diabetic patients were consecutively enrolled and divided into two groups, according to glycaemic control: HbA1c <7% and HbA1c >7%. The patients underwent: 24-hour blood pressure (BP) monitoring, echocardiography and plasma measurement of MMP-9 and -2, markers of collagen metabolism.

Results: Forty-eight patients were enrolled (28 men, mean age 55±9 years): 17 with HbA1c <7% and 31 with HbA1c >7%. The 2 groups were not different for age, gender, duration of diabetes, BMI and systolic and diastolic BP throughout the 24 hours. LV mass index was normal in all the patients and similar between the 2 groups (80±18 g/m² vs 86±20 g/m², ns). With regard to LV diastolic function, patients with HbA1c >7% showed lower transmitral E/A ratio (0.9±0.2 vs 1.1±0.2, p<0.05) and Em/Am ratio (from Tissue Doppler Imaging) [0.9±0.3 vs 1.1±0.3, p<0.05] and higher E/E' (6.6±2.1 vs 4.7±0.9, p<0.01). E/E' ratio was significantly correlated with HbA1c (p<0.05). Plasma MMP-9 was detected in 77% of patients with HbA1c >7% and in 35% of patients with HbA1c <7% (p<0.05); few patients had detectable levels of plasma MMP-2 (23% of patients with HbA1c >7% and 6% of patients with HbA1c <7%, ns).

Conclusions: In type 2 diabetic patients a poor glycaemic control is associated with a greater impairment of LV diastolic function and a higher prevalence of plasma MMP-9 expression. The latter finding indicates a potential role of plasma MMP-9 as marker of preclinical cardiac dysfunction in diabetic cardiomyopathy.

5.10 Predictors of Left Ventricular Hypertrophy in Hypertensive Patients with Normal ECG

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Introduction: Early identification of left ventricular hypertrophy (LVH) in hypertensive patients is of great importance for correct stratification of cardiovascular (CV) risk. It is well known that ECG has low sensibility in detecting LVH, while echocardiography, for organizational difficulties, cannot be performed routinely.

Aim: To evaluate the prevalence of LVH and of anomalies of diastolic function in a group of hypertensive patients free of diabetes, CV diseases, and with normal ECG.

Methods: We excluded patients with CV diseases, diabetes, chronic kidney disease (CKD), or having ECG-LVH or other ECG anomalies. Then, we enrolled 310 hypertensive patients (mean age 48 years). All enrolled subjects underwent echocardiographic examination (Acuson Sequoia 512). LV mass was indexed by body surface area (LVMI) and LVH was defined as LVMI >125 g/m² in men and >110 g/m² in women. Diastolic function was evaluated by mitral inflow and Tissue Doppler Imaging (TDI).

Results: Patients with LVH had higher age and duration of hypertension when compared with patients without LVH (p=0.002 and <0.0001, respectively). Prevalence of LVH in the whole sample was 8.18%; among these patients, 77.7% had concentric LVH. The analysis was then repeated in each sex: 6% of males and 11.6% of females had LVH. Concentric geometry was highly prevalent both in males (75%) and females (80%). Mean value of LVMI was 91.48±19.19 g/m² in the whole sample and 129±10.79 g/m² in the subgroup with LVH (135.5±7.84 g/m² in males and 123.8±10.1 g/m² in females with LVH). Further, we evaluated the mean difference of LVMI from the cut-off value for LVH: it was 12.3±9.19 g/m² in the whole group, 10.5±7.84 g/m² in males and 13.8±10.1 g/m² in females. Multiple regression analysis showed that the variables independently associated with the presence of LVH were age and duration of hypertension (p<0.001). Diastolic dysfunction, defined as early diastolic myocardial velocity (Em) <0.08 m/sec, was found only in 3.2% of patients.

Conclusions: The prevalence of LVH among hypertensive patients with normal ECG, and free of diabetes, CV diseases and CKD is low (8.18%); further, patients with echocardiographic LVH had LVMI values that generally identified mild forms of LVH, accompanied only in very few cases by anomalies of diastolic function. In hypertensive patients with such characteristics, the echocardiographic examination should probably be reserved to older patients or with higher duration of hypertension.

5.11 Increased Left Ventricle Apical Rotation Under Exposure to Hypobaric Hypoxia at Very High Altitude: A Sign of Subendocardial Ischaemia? Data from the HIGHCARE Project

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Introduction: Exposure to hypobaric hypoxia at high altitude (HA) was shown to be associated with an increase in global left ventricle (LV) function in healthy subjects. However, in cultured myocytes a reduced contractility has been described with low levels of oxygen pressure. The discrepancy between *in vivo* and *in vitro* results could be explained by a different behaviour of LV subepicardial and subendocardial layers. Occurrence of an increased LV torsion could unveil even small alterations of subendocardial LV contractility.

Aim: To explore possible subendocardial LV contraction abnormalities in subjects exposed to HA through analysis of LV apical rotation patterns.

Methods: In 46 healthy volunteers (31 males, age 39.9±10) participating in the HIGHCARE project, 2D cross-sectional echocardiographic images at apical level were repeatedly recorded at sea level (SL); during acute exposure to HA (3500 m a.s.l., HA); at very HA (Mt Everest Base Camp, 5400 m a.s.l.) both after 1–3 days (VHA1) and 7–9 days (VHA2); after return to SL (SLR). 2D echo images were analysed by using speckle tracking technique to evaluate the apical rotation. For each step systolic (S), diastolic (D) blood pressure (BP), heart rate (HR), oxygen saturation (SpO2) and plasma norepinephrine were assessed.

Results: HR, SBP, DBP and plasma noradrenaline increased progressively with altitude, whereas SpO2 decreased (p<0.01). The corresponding values of apical LV rotation and its values corrected for concomitant LV radius changes are shown in the table. A strong inverse linear correlation was found between SpO2 and LV apical rotation (p<0.002).

	SL	HA	VHA1	VHA2	SLR
Rot max °	9 (1.06)	10.4 (1.05)	11.7 (1.07)	11.4 (1.08)	9.8 (1.05)
Rot/delta r °/cm	19.2 (1.37)	19.7 (1.62)	22 (2.62)	22.4 (2.747)	18.8 (1.23)

Rot max ° = maximum value of systolic LV apical rotation in degrees (°); Rot/delta r °/cm = systolic apical rotation divided by the systo-diastolic change of radius degrees/centimetre; ** p<0.01.

Conclusions: These data suggest a depressant effect of HA hypobaric hypoxia on subendocardial LV fibre contractility, possibly related to hypoxia-induced sympathetic activation, unveiled by a significant increase in LV apical rotation and confirmed by its inverse relationship with SpO₂.

5.12 Renal Haemodynamic Changes after Major Heart Surgery: An Echo-Doppler Study

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Introduction: Acute kidney injury (AKI) is a frequent complication after major heart surgery (MHS), and is associated with high morbidity and mortality. Renal haemodynamic changes play an important pathogenetic role.

Aim: We investigated if early changes in Doppler indexes reflecting intrarenal haemodynamics may predict the development of AKI after MHS.

Methods: We studied renal haemodynamics by transgastric echo-Doppler in 60 consecutive patients (mean age 69.5 years, range 30–88 years; 41 m) undergoing MHS. Measurements were taken before (anaesthesia induction), and after (at 2 and 4 hours) cardiopulmonary bypass (CPB) start. Resistance (RI) and pulsatility indexes (PI) were derived both at renal sinus at the level of the left renal artery trunk (rsRI and rsPI, respectively), and intraparenchymally at the level of the interlobular/arcuate arteries (intraRI and intraPI, respectively). Serum creatinine was measured at baseline, 6 hours after surgery, and daily for the subsequent 7 days. Statistical analyses were based on linear mixed models for repeated measures and least-square regression.

Results: AKI developed in 27/60 patients (45%); two required dialysis. Systemic haemodynamic parameters (Swan-Ganz catheter) were similar in patients who did and who did not develop AKI. rsRI increased significantly at 2 and 4 hours in both groups ($p=0.04$), with higher absolute values in AKI patients (average difference between groups, $p=0.02$). intraRI values were also significantly higher at all timepoints in the AKI patients ($p<0.001$), although no clear-cut intraoperative increase was observed (mean rate of change $p=0.91$). rsPI and intraPI displayed similar changes, though with greater variability. On the other hand, the first clinically significant difference in serum creatinine in AKI patients was observed only after 24 hours ($1.53+0.03$ vs $0.96+0.04$ mg/dL, AKI vs no AKI, $p<0.001$).

Conclusions: Early intraoperative changes in renal Doppler indexes may help identify the patients with the highest risk of developing AKI after MHS.

5.13 Prevalence of Atrial Septal Abnormalities, Hypertension and Concentric Geometry in Patients with Transient Ischaemic Attack

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Introduction: Atrial septal abnormalities are found with relatively high frequency in subjects with ischaemic stroke. Most data are regarding atrial septal aneurysm (ASA) or patent foramen ovale (PFO), whilst less are about simple atrial septal bulging without proper ASA (B).

Aim: To assess the association between ASA or B and transient ischaemic attack (TIA), assessing also the prevalence of hypertension (HBP) and concentric geometry.

Methods: We examined 1651 consecutive patients submitted to echocardiography in 1 year (778 M, 873 F). Of them, 97 patients had TIA (6%, 43 M, 54 F, mean age 68.5 years, range 27–99 years), whilst ASA/B or TIA were present in 178 patients.

Results: The main findings of our study are reported in the table. In the general population, 1122 patients (68%) had HBP, and 129 (8%) had ASA (93 patients, 6%) or B (36 patients, 2%) (51 M, 78 F, age 69.1 years, 27–99 years). Seventy-eight of ASA/B patients (60%) did not have TIA and 52 of them (67%) had HBP. Among TIA patients, 73 had HBP ($p<0.05$ vs general population), 21 (21.6%) had a history of atrial fibrillation, and 35 (36%) had a cardiomyopathy, which could have potentially been responsible for TIA. ASA was found in 38 TIA patients (39.2%), B in

	General population, (G) [1651 pts] (%)	TIA [97 pts] (%)	No TIA but ASA/B (N) [81 pts] (%)	p-Value
ASA	93 (6)	38 (39.2)		<0.001
B	36 (2)	13 (13.4)		<0.001
PFO	10 (0.06)	12 (12.4)	5 (3)	<0.001 vs G
HBP	1122 (68)	73 (75)	52 (64)	<0.05 vs G,N
Concentric hypertrophy		36 (37.1)	22 (27.2)	<0.05
Concentric remodelling		26 (26.8)	24 (29.6)	NS

13 (13.4%). Therefore, globally ASA or B were found in 51 TIA patients (52.6%; $p<0.001$ vs ASA/B in general population), of which 12 had documented PFO (45 patients underwent microwaves or transoesophageal echocardiography). HBP was present in 36 patients with TIA/ASA/B (70%), concentric hypertrophy in 16 (31.3%), concentric remodelling in 14 patients (27.4%, while no patients had eccentric hypertrophy).

Conclusions: Not only ASA and PFO, but also simple atrial septal bulging without proper criteria for ASA diagnosis, are found with higher frequency in patients with TIA than in the general population. Mean age of our TIA patients with ASA/B suggests that these atrial septal abnormalities are not only a prevalent finding in young TIA patients but are a frequent association in older ones as well. Moreover the high prevalence of HBP and concentric hypertrophy in TIA patients with such abnormalities suggests how all these aspects could be together considered risk factors for cerebral ischaemic events.

5.14 Assessment of Haemodynamic Hypertensive Patterns by Interaction between Peripheral Resistance and Arterial Stiffness

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Introduction: Different combinations of pressure and volume overload result in high blood pressure (BP) with different characteristics. Peripheral resistance (TPR) and arterial stiffness interact leading to different haemodynamic patterns potentially addressing to different therapies.

Methods: Low, normal and high tertiles of TPR measured by echocardiogram (mean BP/cardiac index [COi]) and arterial stiffness (pulse pressure [PP]/systolic index [SVi]) were crossed in 10 069 hypertensive participants in the Campania Salute Network.

Results: Combination of high TPR with high PP/SVi is associated with the lowest volume dependence and the low HR. The highest HR is associated with low TPR and high PP/SVi. (all $p<0.0001$, adjusted for age and sex).

Conclusions: Different loads are identifiable in the nine models and could be useful in helping defining therapy.

5.15 Development and Validation of a Predictive Index for Acute Mountain Sickness

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Introduction: Acute mountain sickness (AMS), a clinical condition that shows a combination of headache and other symptoms, can affect hikers rapidly ascending and staying at altitudes above 2500 m. It is usually reversible, but the most severe forms, characterized on the basis of the score collected after administration of a standardized questionnaire (Lake Louise AMS scores, LLS), may progress to high-altitude cerebral oedema. The main form of treatment is to descent to lower altitudes, but this decision could be hampered by adverse weather conditions. Currently, no predictors able to identify subjects at risk during an expedition are available.

Methods: The first phase was performed on 47 subjects during an expedition to Mount Everest Base Camp (5400 m). The clinical and instrumental evaluations and the assessment of LLS were carried out at different altitudes during the expedition. Parameters independently associated to LLS and the coefficients estimated from the model obtained through stepwise multiple regression analysis were used to create the predictive index. The cut-off for LLS ≥ 4 was determined by ROC curves. In a second phase, conducted on the Italian Alps, the predictive value of the index was investigated by making measurements at an intermediate altitude (3600 m) on 44 subjects who participated in a climb to Monte Rosa (Capanna Margherita, 4559 m).

Results: During the expedition to Mount Everest Base Camp, oxygen saturation, haematocrit, the day of expedition, maximum velocity of clot formation and a thromboelastographic index of coagulation activation, were selected as variables independently associated with LLS and included in the predictive index (estimated cut-off 5.92). During the second expedition, the index had a sensitivity of 85% and a specificity of 59% to predict the onset of AMS within 48 hours after reaching Capanna Margherita (odds ratio 8.1; 95% CI 1.7, 38.6), while no isolated parameters showed a sufficient predictive value.

Conclusions: The combination in a single index of more clinical and haematological parameters, measured with point of care instruments at an intermediate step on the way to the top, may provide information on impending AMS and supports the possibility to screen who can take advantage from waiting before continuing the trip.

5.16 Pressure-Independent Association between Aortic Stiffness and Left Ventricular Concentric Geometry

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Introduction: Systolic blood pressure (BP) is the main pressure determinant of left ventricular (LV) mass in hypertension. It is uncertain whether arterial stiffness and central haemodynamics are related to LV mass and geometry independently of brachial, central or 24-hour BP level.

Methods: 744 consecutive never-treated subjects with uncomplicated essential hypertension (men 59%, age 49 ± 11 years, BP $149/93 \pm 16/10$ mmHg) underwent M-mode echocardiography and 24-hour BP monitoring. Carotid-femoral pulse wave velocity (cfPWV), aortic augmentation and aortic BP were evaluated by applanation tonometry.

Results: The main findings of our study are reported in the table. Women with LV hypertrophy (LV mass >51 g/m^{2.7}) had a higher cfPWV (10.5 ± 3 vs 9.3 ± 2 m/s, $p < 0.001$), augmentation (21 ± 7 vs 16 ± 7 mmHg, $p < 0.001$) and heart rate-corrected augmentation index (0.37 ± 0.08 vs

	cfPWV/LV mass		cfPWV/RWT		augm/LV mass		augm/RWT	
	women	men	women	men	women	men	women	men
Unadjusted	0.30**	0.14**	0.26**	0.20**	0.33**	0.11*	0.09	0.09
Age- and brachial SBP-adjusted	0.10	0.03	0.15*	0.12*	0.15*	0.02	-0.04	0.04
Age- and aortic SBP-adjusted	0.07	0.05	0.15*	0.14*	0.02	-0.05	-0.10	0.00
Age- and 24h SBP-adjusted	0.07	0.01	0.15*	0.11*	0.14*	-0.02	-0.03	0.01

* $p < 0.05$; ** $p < 0.005$.

0.34 ± 0.12 , $p = 0.04$). Similar data were found in men. LV relative wall thickness (RWT) but not LV mass index was significantly associated with cfPWV independent of age and brachial, central or 24h systolic BP (see table). The association of aortic augmentation with LV mass and RWT was no longer significant after adjustment for age and systolic BP. In a multiple regression model, 24h systolic BP, LV mass and cfPWV (all $p < 0.05$) independently predicted LV-RWT when a consistent number of risk factors was simultaneously controlled for.

Conclusions: The impact of aortic PWV on LV concentric geometry is independent and additional to that of peripheral, central or 24h BP.

5.17 Epicardial Fat Thickness is an Independent Predictor of Left Ventricular Repolarization Changes

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Introduction: Obesity is strongly linked to the development of cardiovascular diseases, and body fat distribution may play a key role in this association. Epicardial fat tissue has been related to an

increased cardiovascular risk in different settings and populations independently from the effect of total body fat mass, and has a significant relation with reduced coronary flow reserve in women. In hypertensive patients, minor ST-T abnormalities on the resting ECG may reflect an initial impairment in coronary circulation and are independent predictors of coronary morbidity and mortality.

Aim: To evaluate the association of echocardiographic epicardial fat thickness with minor ST-T alterations in a population of untreated hypertensive adults.

Methods: 203 untreated hypertensive subjects (48 ± 10 years, 63% males) underwent 12-lead ECG and 2D-echocardiography. Patients with prevalent cardiovascular disease, complete bundle branch block, poor-quality echocardiographic images or digoxin use were excluded. ST-T repolarization changes at ECG were defined according to Minnesota coding as the presence in >1 of leads I, II, aVL or V2-V6 of: (i) horizontal or downsloping ST-J depression <0.05 mV; (ii) upsloping ST-J depression ≥ 0.1 mV; (iii) flat, negative or diphasic (negative-positive type only) T wave; or (iv) T-R wave amplitude ratio $<1:20$. Epicardial fat thickness was assessed by echocardiography by midventricular parasternal short-axis, as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium, measured perpendicularly on the free wall of the right ventricle at end-systole (average of three cardiac cycles).

Results: Subjects with minor ST-T changes (22%) were older (54 ± 12 vs 46 ± 9 years, $p < 0.001$) than subjects with normal repolarization; sex distribution, blood pressure values, body mass index, waist circumference and left ventricular mass did not differ. Epicardial fat thickness was greater in the subjects with ST-T changes (4.9 ± 2 vs 4.0 ± 2 mm, $p = 0.026$), and had a significant direct relation with body mass index ($r = 0.45$), waist circumference ($r = 0.36$), and left ventricular mass ($r = 0.19$, all $p < 0.001$), but not with age, sex or blood pressure. In a multivariable logistic regression analysis, epicardial fat thickness (odds ratio for each 1-SD increase, 1.53, 95% CI 1.08, 2.28), and age (OR 1.75; 95% CI 1.21, 2.54) were the only independent predictors of minor repolarization changes.

Conclusions: Epicardial fat thickness at echocardiography is an independent predictor of prognostically adverse left ventricular repolarization changes in untreated subjects with uncomplicated hypertension. Epicardial fat may have a detrimental effect on coronary circulation.

5.18 Doppler Ultrasonography in Arterial Hypertension

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Clinical Case: A 28-year-old man came to the hospital because of severe hypertension and headache. His first pathological value of blood pressure was found when he was 21 years old during a medical examination at work; since then he began therapy with ACE inhibitor and after a while changed to a calcium antagonist. Clinical examination demonstrated a harsh systolic murmur over the precordium with normal upper-limb pulses, whereas leg pulses were little palpable. Echocardiography showed mild left ventricular hypertrophy with good systolic function. Blood pressure was 170/100 mmHg in both arms and 105/95 mmHg in the left and right leg. Abdominal aortic Doppler and renal artery Doppler showed demodulated flow and high diastolic flow on these arteries. CT angiography confirmed the diagnosis of aortic coarctation that was distal to left subclavian artery. The patient was referred for percutaneous balloon dilatation of the aorta.

Conclusions: Aortic coarctation is a rare disorder accounting for approximately 2% of congenital heart disease. The diagnosis should be considered in patients with hypertension and diminished leg pulses. Because untreated coarctation of the aorta may carry a poor prognosis, early intervention is advised.

Hormonal Mechanisms Endocrine Hypertension

6.1 Changes of Blood Pressure Profile in Hypertensive Patients with Surgically Treated Hyperparathyroidism

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Introduction: Hyperparathyroidism (PHPT) is characterized by excessive secretion of parathyroid hormone and persistent hypocalcaemia. Besides the typical clinical features of PHPT, there is an increased prevalence of hypertension, atherosclerosis and endothelial dysfunction.

Aim: To investigate the behaviour of arterial blood pressure and cardiovascular damage, before and after surgical treatment.

Methods: We enrolled 21 consecutive patients with PHPT (3 M, 18 F; mean age 56 ± 6 years) and 20 NS (4 M, 16 F; mean age 55 ± 6 years), evaluating blood pressure profile, echocardiography and IMT.

Results: 81% of patients with PHPT were affected by hypertension and ABPM showed the lack of normal circadian rhythm ('non-dipping pattern'), in almost 57% PHPT patients, compared

with 10% of NS. PHPT patients also had a significant cardiovascular remodelling respect to NS, such as interventricular septum (10.7 ± 8.8 vs 8.8 ± 1.1 mm/m²; $p < 0.001$), systolic and diastolic end-stage diameter of left ventricle (46 ± 5 vs 29.3 ± 1.9 mm/m²; $p < 0.001$; and 30 ± 2.0 vs 18.3 ± 1.9 mm/m²; $p < 0.001$, respectively), mass of left ventricle (182 ± 30.4 vs 125 ± 26 mm/m²; $p < 0.001$), IMT (0.76 ± 0.15 vs 0.57 ± 0.07 mm/m²; $p < 0.05$). We showed in PHPT patients a positive correlation between serum PTH levels and SBP values, and a negative correlation between serum PTH levels and LVESD-LVDD. The evaluation 1 year after parathyroidectomy showed a decrease of number of patients affected by hypertension (81% vs 62%, $p = 0.012$), and patients with the 'no-dipping pattern' (57% vs 42%, $p = 0.003$), and decrease of mean number of antihypertensive drugs (1.7 vs 1.05, $p = 0.001$); moreover, 17% of patients did not take any antihypertensive drug and 48% reduces the number and dose of antihypertensive drugs.

Conclusions: Surgical treatment of PHPT normalizes calcium-phosphorus metabolism, and can reduce blood pressure profile, restore circadian rhythm of blood pressure and reduce cardiovascular remodelling.

6.2 Low Levels of 25-Hydroxyvitamin D are Associated with Left Ventricular Hypertrophy in Essential Hypertension

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Introduction: Low serum 25-hydroxyvitamin D [25(OH)D] levels may have an important role in predisposing to hypertension and myocardial disease.

Aim: To investigate the relationship between 25(OH)D and left ventricular (LV) structure and function, assessed by echocardiography, in a series of patients with essential hypertension (EH).

Methods: Sixty-two newly diagnosed never-treated patients (32 M/30F), aged 18 to 65 years, with grade 1–2 hypertension, no diabetes mellitus, no obesity, no hyperlipidaemia, and no cardiopulmonary, renal, or hepatic disease, were studied. Twenty-four healthy normotensive age/sex/BMI matched subjects served as controls.

Results: Hypertensive patients with 25(OH)D deficiency ($n=28$), defined as serum 25(OH)D levels <50 nmol/L, had higher prevalence of LV hypertrophy (LVH) than their 25(OH)D-sufficient counterparts ($n=34$), i.e. 57.1 versus 17.6%, $p=0.02$; no difference between the two groups were found in blood pressure levels as well as in other biochemical and hormone parameters. There was an inverse correlation between LV mass index and 25(OH)D levels ($r=0.366$, $p<0.0003$) and a direct correlation between LV mass index and BMI ($r=0.333$, $p<0.006$) in the entire hypertensive population. The two variables remained independently associated with LVH at multivariable logistic regression analysis (OR 1.05, $p<0.005$ and OR 1.25, $p=0.03$, respectively). Prevalence of 25(OH)D deficiency was similar in EH patients and controls (45.1% vs 41.6%, $p=0.89$), where no correlation between any echocardiographic parameter and hormone levels was found.

Conclusions: In the absence of major cardiovascular risk factors, 25(OH)D deficiency is a frequent finding in EH patients and is independently associated with LVH.

6.3 Concurrent Primary Aldosteronism and Subclinical Cortisol Hypersecretion: a Prospective Study

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Introduction: Cortisol hypersecretion from an aldosterone-producing adenoma has been reported anecdotally. In the absence of overt Cushing's syndrome, the true prevalence of concurrent aldosterone and subclinical cortisol hypersecretion may be underestimated since hypercortisolism is not routinely investigated in primary aldosteronism.

Aim: To prospectively estimate the occurrence of subclinical hypercortisolism in patients with primary aldosteronism.

Methods: Within a large population of hypertensive patients studied over the last 2 years, 76 had primary aldosteronism and were further investigated. No patient had clinical signs of hypercortisolism. Differential diagnosis between unilateral and bilateral aldosterone hypersecretion was made by CT/MRI and/or by adrenal venous sampling (AVS) with aldosterone/cortisol ratio. Subclinical hypercortisolism was defined by failure to suppress plasma cortisol to <50 nmol/L after 1 mg overnight dexamethasone (dex), initially used as screening test, and at least one of two abnormal tests, i.e. ACTH <2 pmol/L and urine cortisol >694 nmol/d.

Results: Unilateral adrenal disease was found in 34 patients (micronodular hyperplasia, $n=2$; adenoma, $n=32$). Three out of these patients had plasma cortisol >50 nmol/L after dex. Only one (M, 71 y.o.) showed low-normal ACTH (1.7 pmol/L) and mildly elevated urine cortisol (894 nmol/d) in addition to no suppression of plasma cortisol by dex (104 nmol/L). The patient had a right 4 cm adrenal mass at CT scan, and no AVERSUS was performed. Laparoscopic adrenalectomy was followed by short-term steroid replacement to prevent adrenal insufficiency. All criteria for adrenocortical adenoma were fulfilled at histology, with a marked prevalence of zona-fasciculata-like cells in the tumour. *In situ* hybridization showed expression of CYP11B1 only in temporal tissue and CYP11B2 expression only in the peri-tumoural area, suggesting the co-existence of a cortisol-producing adenoma and an aldosterone-producing hyperplasia in the same adrenal. Restoration to normal of ACTH, urinary cortisol and plasma cortisol response to dex, as well as serum potassium and aldosterone normalization, was seen at 6 months after surgery.

Conclusions: Concurrent aldosterone and subclinical cortisol hypersecretion is a rare event in patients with primary aldosteronism. In case of unilateral adrenal disease, there are important implications for the perioperative management.

6.4 Aldosterone does not Modify Gene Expression in Human Endothelial Cells

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Introduction: The toxic effects of aldosterone on the vasculature, and in particular on the endothelial layer, have been proposed as having an important role in the cardiovascular pathology observed in mineralocorticoid-excess states.

Methods: In order to characterize the genomic molecular mechanisms driving the aldosterone-induced endothelial dysfunction, we performed an expression microarray on transcripts obtained from both human umbilical vein endothelial cells (HUVEC) and human coronary artery endothelial cells (HCAEC) stimulated with aldosterone 10^{-7} M for 18 hours.

Results: We found that aldosterone did not determine any significant changes in gene expression in either cell type. These results were confirmed by a time-course qRT-PCR analysis on transcripts obtained from HCAEC targeting a group of genes known to be involved in the control of the endothelial function or previously described as regulated by aldosterone. A luciferase-reporter assay using a plasmid encoding a mineralocorticoid and glucocorticoid-sensitive promoter showed no activation of the mineralocorticoid receptor (MR) following aldosterone stimulation.

Conclusions: Our data indicate that the status of non-functionality of the MR expressed in cultured HUVEC and HCAEC does not allow aldosterone to modify gene expression and provide evidence against either a beneficial or a harmful genomic effect of aldosterone on healthy endothelial cells.

6.5 Urinary Prostaglandin N, a Serin-Protease Activating ENaC, is Physiologically Modulated by Natriuresis in Normotensive Individuals

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Introduction: Proteolysis removing inhibitory peptides on fx -chain is considered an important step of Epithelial Na Channel (ENaC) activation. Prostaglandin, a GPIIb/IIIc anchored serin-protease co-expressed in all tissues with ENaC, activates the channel and it is then secreted in extracellular fluids (including urine). Previous data in humans showed overexpression of prostasin in urine of patients with Conn's adenoma and its modulation by Na in hypertensive patients with raised aldosterone to renin ratio (ARR). However, being based on immunoblotting methods, these reports did not provide a precise quantification of the absolute concentration of the protein. As in very recent time a new ELISA method to assay prostasin has been settled.

Methods: We evaluated prostasin concentrations in normotensive males and females of similar age, possible variations in women during the menstrual cycle and after oral estrogen-progestins (OC) therapy, and possible relationships of prostasin concentration with natriuresis.

Results: Urinary prostasin presented a wide range of values (from 1 to 40 ng/mL) with no difference by gender (8.25 ± 9.3 ng/mL in males and 11 ± 11 ng/mL in females). Urinary prostasin was positively correlated with ARR ($r=0.363$; $p=0.02$) but not with circulating aldosterone or renin individually considered. Urinary prostasin increased linearly up to the limit of about 200 mmol U-Na/L concentration (under this value both variables were linearly correlated with $r=0.40$, $p<0.05$), whereas it decreased for more elevated U-Na concentration in fertile women, in spite of aldosterone, renin and ARR variations, no significant changes of prostasin concentration were observed during menstrual phases. After OC therapy urinary prostasin increased to a relevant extent (5.03 to 10.3 ng/mL) that was, however, only near the statistical significance ($p=0.07$).

Conclusions: Urinary prostasin is physiologically modulated by natriuresis in normotensive individuals. It remains to clarify if this modulation is abnormally regulated in hypertensive patients.

6.6 18-Hydroxycorticosterone, 18-Hydroxycortisol and 18-Oxocortisol in the Diagnosis of Primary Aldosteronism and its Subtypes

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Introduction: The diagnosis of primary aldosteronism (PA) is made following a three-step flow-chart comprising screening, confirmation testing and subtype diagnosis (aldosterone-producing adenomas, APAs, and bilateral adrenal hyperplasia, BAH) with CT scan and adrenal vein sampling (AVS). However, there is no agreement on which confirmatory test should be performed and AVERSUS is highly costly and not available in most hospitals. 18-hydroxycorticosterone (18OHB), 18-hydroxycortisol (18OHF) and 18-oxocortisol (18oxoF) may be of help in the diagnosis of PA.

Aim: To evaluate the role of serum 18OHB and urinary and serum 18OHF and 18oxoF in the diagnosis of PA and its subtypes.

Methods: We studied 62 patients with low-renin essential hypertension (LREH), 81 PA (20 APA, 61 BAH), 24 patients with glucocorticoid-remediable aldosteronism (GRA), 16 patients with non-secreting adrenal tumours (NSAT) and 30 normotensive subjects.

Results: We observed a significant correlation between urinary levels of 18OHF and 18oxoF ($p < 0.01$). Urinary levels of 18OHF and 18oxoF were significantly higher in GRA patients compared with all other groups of patients ($p < 0.001$). Patients with PA displayed significantly higher levels of urinary 18OHF and 18oxoF compared with LREH and normal subjects ($p < 0.001$ for all comparisons); considering PA subgroups, patients with APA displayed 18OHF and 18oxoF levels significantly higher than patients with BAH ($p < 0.001$ for both hormones). Interestingly, only 3% of LREH had 18OHF higher than 190 $\mu\text{g}/\text{day}$, compared with 53% of PA patients. The highest measured level of 18OHF in LREH was 329 $\mu\text{g}/\text{day}$, whereas 26% of PA patients displayed values greater than 330 $\mu\text{g}/\text{day}$. The highest value of 18OHF measured in BAH patients was 507 $\mu\text{g}/\text{day}$, whereas 30% of patients with APA displayed values higher than 510 $\mu\text{g}/\text{day}$. Furthermore, 65% of APA patients displayed values higher than 330 $\mu\text{g}/\text{day}$. Finally, the lowest value of 18OHF in APA patients was 133 $\mu\text{g}/\text{day}$, whereas 83% of LREH patients had values lower than 130 $\mu\text{g}/\text{day}$. We also observed a significant correlation between serum 18OHB, 18OHF, 18oxoF and aldosterone levels ($p < 0.01$ for all comparisons). PA patients displayed higher levels of serum 18OHB compared to LREH patients ($p < 0.01$) and APA patients display higher levels compared with BAH patients ($p < 0.01$). Saline infusion significantly reduced 18OHB, 18OHF and 18oxoF in all groups of patients, but steroid reduction was much lower for APA patients compared with BAH and LREH and the 18OHB/aldosterone ratio after SLT increased more than twice in LREH, whereas remained unchanged in PA patients, particularly for the APA subgroup. Also the measurement of urinary 18oxoF and serum 18OHB could be of help in some patients.

Conclusions: Our hypothesis confirms the use of urinary 18OHF and 18oxoF and serum 18OHB assay in the diagnostic work-up for PA.

6.7 Under-Expression of the Twik-Related Acid-Sensitive K+ 2 Channel (TASK-2) in Aldosterone-Producing Adenoma: Genetic and Epigenetic Mechanisms

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Introduction: Primary aldosteronism is highly prevalent cause of arterial hypertension, but its underlying molecular mechanisms are unknown. K⁺ is a key regulator of aldosterone secretion and interacts with physiological secretagogues of aldosterone as angiotensin II (Ang II). The Twik-related Acid-Sensitive K (TASK) channels are a widely distributed class of channels that generate introduction or 'leak' potassium (K⁺) currents. Noteworthy, *in vivo* genetic manipulation of two such channels created a phenotype that closely mimics human primary aldosteronism.

Methods: We therefore investigated the gene expression of K⁺ channels, including those of the TASK family, and the microRNA profiles of a large series (n=32) of aldosterone-producing adenoma (APA). TASK-2 subcellular localization was assessed by immunohistochemistry, confocal microscopy and co-immunoprecipitation experiments. Finally, mutation analysis of TASK-2 promoter sequence was performed by direct sequencing.

Results: By whole transcriptome analysis we found a marked under-expression of TASK-2 channel in all APA (n=32) compared with the normal adrenal cortex. At variance TASK-1 and TASK-3 were heterogeneously expressed. Moreover, immunocytochemistry, confocal microscopy and co-immunoprecipitation experiments disclosed the subcellular localization of TASK-2 and its heterodimerization with TASK-1 and TASK-3. Moreover, with a regression analysis we identified 25 microRNA negatively correlated with TASK-2 expression. A putative binding site for TASK-2 3' UTR was found in 4 of them. Finally, with a promoter analysis of the TASK-2 gene in 101 patients with primary aldosteronism we identified three novel mutations, two of which were germinal and one somatic, which can predispose to blunting the TASK-2 expression.

Conclusions: Thus, a reduced expression of TASK-2 channels is a feature of APA that can be important pathophysiologically as a blunted activity of TASK-2 through cell depolarization increases the opening state probability of voltage-gated T-type calcium channels, thus rendering adrenocortical cells more sensitive to aldosterone secretagogues and stimulating cell proliferation. These data suggest some genetic and epigenetic mechanisms involved in TASK-2 expression modulation in APA.

6.8 Effects of Long-Term Cholecalciferol Administration on the Renin-Angiotensin System in Patients with Essential Hypertension and Hypovitaminosis D

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Introduction: It is well known that vitamin D plasma levels inversely correlate with cardiovascular mortality in humans and that vitamin D positively influences chronic renal disease progression. Suppression of the systemic and local renin-angiotensin system (RAS) by vitamin D seems to be involved in this association. Indeed, animal and *in vitro* studies suggest that vitamin D receptor activation inhibit mRNA levels and protein expression of key components of RAS (angiotensinogen, renin, renin receptors and angiotensin-II type 1 receptor), independently of calcium metabolism. However, to date, studies on the relationship between vitamin D receptor activation and RAS in humans are lacking.

Methods: The most important plasma components of RAS (PRA, active renin, angiotensin-II, and aldosterone) and blood pressure values have been evaluated in 10 essential hypertensive patients (5 males and 5 females; BMI 27.3 ± 0.8 kg/m²; SBP 155 ± 3.2 mmHg; DBP 97 ± 2.1 mmHg) with hypovitaminosis D (14.1 ± 3.2 ng/mL, normal values >30 ng/mL). The patients were submitted to a therapy with an angiotensin II receptor blocker (ARB) for 15 days (time -15) with the purpose of indirectly activating plasma renin and angiotensin-II to better detect the possibly inhibitory effect of vitamin D on RAS. On time 0, cholecalciferol (300.000 IU orally, once a day) was administered while ARB therapy were maintained for 2 months. Humoral and haemodynamic parameters were reassessed after 30 and 60 days.

Results: 25(OH)vitamin D levels statistically increased ($p < 0.001$) reaching the normal range (35.6 ± 3.2 vs 14.1 ± 3.2 ng/mL), while no suppression of the renin-angiotensin system was detected. Indeed, PRA (time 0: 2.56 ± 0.9 ng/mL/h; 1 month: 3.07 ± 0.9 ng/mL/h; 2 months: 3.04 ± 1.2 ng/mL/h), active renin (time 0: 23.9 ± 12.7 pg/mL; 1 month: 34.8 ± 12.7 pg/mL; 2 months: 28.76 ± 16.7 pg/mL), angiotensin-II (time 0: 9.0 ± 3.4 pg/mL; 1 month: 12.2 ± 3.4 pg/mL; 2 months: 11.69 ± 4.4 pg/mL) and aldosterone (time 0: 14.29 ± 2.1 ng/dL; 1 month 13.61 ± 2.1 pg/dL; 2 months: 12.7 ± 2.7 pg/dL) levels did not show significant changes during the study. PTH and 1,25(OH) vitamin D levels were also unmodified. Blood pressure showed a significant ($p < 0.001$) reduction after ARB administration (time -15: SBP 155 ± 3.2 mmHg, DBP 97 ± 2.1 mmHg; time 0: SBP 133 ± 3.2; DBP 80 ± 2.1 mmHg), while it remains unchanged during the study.

Conclusions: These data show that in patients with essential hypertension and hypovitaminosis D, the normalization of the vitamin D levels is not associated with RAS suppression.

6.9 Prorenin Receptor Activation Results in ERK 1/2 Phosphorylation in Human Adrenocortical Carcinoma Cell Lines

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Introduction: The detection of prorenin in plasma despite the suppression of renin in patients with primary aldosteronism (PA) along with the high expression of the pro-renin receptor (PRR) in the human zona glomerulosa (ZG) and in aldosterone-producing adenoma (APA) collectively suggest a pathophysiological role of prorenin acting via the PRR in PA.

Aim: We investigated the effect of PRR activation with pro-renin on ERK 1/2 phosphorylation in human adrenocortical carcinoma cell lines.

Methods: After confirming the presence of the PRR mRNA with Real time RT-PCR in the adrenocortical carcinoma cell lines H295R and HAC15, we sought for the expression of the PRR at the protein level with immunoblotting, confocal microscopy, and immuno-gold electron microscopy. These cell lines were found to highly expressed the PRR at the protein level, thus indicating that they represent a good model for functional experiments involving PRR activation. Stimulation experiments were then performed with angiotensin II (100 nM) and pro-renin (50 nM) in presence or absence of the angiotensin II receptor type 1 (AT-R1) antagonist irbesartan (5 μM) in H295R and HAC15 to investigate the functional relevance of this receptor.

Results: Both prorenin and angiotensin II stimulation induced ERK 1/2 phosphorylation in H295R and HAC15 cells. The angiotensin II-induced phosphorylation was abolished by preincubation with irbesartan in both cell lines. The prorenin-induced phosphorylation was abolished by preincubation with irbesartan only in the H295R and not in the HAC15 cells, which is consistent with the higher expression of ACE-1 in the former.

Conclusions: Prorenin induced ERK 1/2 phosphorylation, a response that is associated with cell proliferation, differentiation, and apoptosis, in two adrenocortical carcinoma cell lines, albeit with different mechanisms. Therefore these results are consistent with a functional role of PRR in the pathophysiology of primary aldosteronism.

6.10 Subtle Hyperparathyroidism: A Novel Feature of Primary Aldosteronism that is Corrected by Adrenalectomy

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Introduction: The pathophysiological mechanisms underlying primary aldosteronism (PA) are unknown. *In vitro* studies showed that PTH concentration-dependently increases aldosterone secretion from human adrenocortical cells; hence, hyperparathyroidism could be a mechanism driving aldosterone excess in PA.

Methods: To test this hypothesis we measured prospectively the plasma levels of intact (1-84)-PTH, total and ionized calcium, inorganic phosphorus, magnesium, potassium, PRA, aldosterone (PAC), 1,25(OH)₂D, 25 (OH)D and the 24-hour urinary excretion of deoxypridinoline (U-DPD), calcium and phosphorus in 112 consecutive hypertensive patients. Of them 49 had PA (due to aldosterone producing adenoma (APA) by the 'four corner criteria' in 40, and to idiopathic hyperaldosteronism (IHA) in 10); 62 had primary hypertension (PH). These indexes were measured again after adrenalectomy in APA patients. We also sought for the PTH receptor expression in APA tissue by immunohistochemistry and RT-PCR.

Results: As compared to PH, the PA patients showed lower potassium, higher PAC, ARR, and PTH (APA 114±66 vs PH 79±32 ng/L; p=0.001). 25(OH)D showed similarly deficient levels in both PA and PH; no between-group differences were found for all other biochemical indexes of calcium and phosphorus metabolism. Moreover, a significantly higher slope of the relation between PTH and ionized calcium was seen in PA than in PH patients. At follow-up post-adrenalectomy, besides the normalization of the biochemical pattern of PA a significant reduction of PTH (from 120±47 to 77±39 ng/L, p=0.003) with an increase of ionized calcium levels (from 1.16±0.04 to 1.22±0.03 mmol/L, p=0.002) was seen, while the slope of the relationship between Ca and PTH fell to values similar to PH patients. RT-PCR and immunohistochemistry showed the transcript and protein of the type 1 PTH receptor in APA.

Conclusions: Mild hyperparathyroidism can contribute to maintaining hyperaldosteronism acting on type 1 PTH receptor in APA despite suppression of the renin-angiotensin system.

The higher slope of the relation between PTH and calcium in PA than in PH patients points to an alteration in calcium sensing of the parathyroid cells.

6.11 Polycystic Ovary Syndrome: Implications of Measurement of Plasma Aldosterone, Renin Activity and Progesterone

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Introduction: Polycystic ovary syndrome (PCOS) is considered an endocrine-metabolic disease with future cardiovascular complications, diabetes and hypertension. In a previous report a positive correlation between aldosterone, inflammatory parameters, blood pressure and metabolic abnormalities was reported.

Aim: To measure plasma aldosterone, plasma renin activity (PRA) and progesterone in women with polycystic ovary syndrome (PCOS) and to consider the interrelationships between these hormones.

Methods: The study population consisted of 66 women with PCOS and 53 age- and body mass index-matched controls. The Rotterdam criteria were used to diagnose PCOS. We chose to study only women with normal BMI to avoid the interference of obesity on the parameters evaluated and to limit the rate of anovulation. In addition to diagnostic and metabolic tests, plasma aldosterone, renin activity (PRA) and progesterone were measured at day 21st of the cycle. The results are reported for all cases and also grouped by progesterone level (group A: progesterone >10 nmol/L; group B: progesterone <10 nmol/L).

Results: Considering all the patients together, we found significantly higher values of aldosterone (726±403 pmol/L in PCOS and 354±102 pmol/L in controls, p<0.0001) and aldosterone (pmol/L)/PRA (ng/mL/h) ratio (ARR) [336.4±207.1 in PCOS and 130.6±77.8 in controls, p<0.0001] in patients compared with controls. Aldosterone was significantly higher in group A PCOS patients compared with group B PCOS, while no difference was observed in controls. Progesterone/aldosterone ratio was lower (p<0.0001) in group A PCOS compared with group A controls. Mean blood pressure was normal but significantly higher in PCOS than in controls.

Conclusions: The increase of plasma aldosterone, ARR and mean blood pressure could be an index of an increased mineralocorticoid activity in PCOS compared with controls, which could be involved in the increased cardiovascular risk. A prolonged therapy with spironolactone associated with appropriate dietary measures and physical activity could counteract both the hyperandrogenism and reduce the future cardiovascular risk.

6.12 Opposite Changes of Plasma Renin Activity and Aldosterone Induced by Sunitinib Treatment in Neoplastic Patients

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Introduction: Hypertension is a frequent adverse effect of treatment with angiogenesis inhibitors in malignancies.

Aim: To evaluate the role of the renin-aldosterone system in the blood pressure (BP) increase, we assessed plasma renin activity (PRA) and aldosterone (Aldo) before and after treatment with sunitinib, a blocker of vascular endothelial growth factor (VEGF)-mediated signalling, in patients with metastatic renal cell carcinoma.

Methods: In 5 patients (age 56±2 years, M/F 3/2, BMI 29±2 kg/m², estimated glomerular filtration rate, eGFR, 64±7 mL/min/1.73 m²), 24-hour BP and heart rate (HR) were monitored, supine PRA and Aldo were measured and Aldo to renin ratio (ARR) was calculated at baseline, after the first cycle of Sunitinib (50 mg/day for 4 weeks) and after 2 weeks recovery.

Results: The main findings of our study are reported in the table (data are expressed as means ± SEM; in the table: * p<0.05 vs baseline) Renal function was unchanged after sunitinib (eGFR = 63 ± 10 mL/min/1.73 m²). Overall, ARR was related to systolic and diastolic BP values (r = 0.68 and 0.60, respectively, p < 0.05).

	24h BP (mmHg)	24h HR (beats/min)	Serum K ⁺ (mEq/L)	PRA (ng/mL/h)	Aldo (ng/dL)	ARR
Baseline	119/80±6/4	78±4	4.7±0.4	0.9±0.4	6.9±1.8	13±5
Sunitinib	141/99±6/4*	73±3	4.4±0.2	0.2±0.1*	11.3±3.5	73±25*
Recovery	125/83±6/3	81±3	4.5±0.2	0.6±0.3	9.2±3.2	19±8

Conclusions: Hypertension induced by chronic sunitinib treatment in neoplastic patients is associated with increased ARR; this humoral pattern of primary aldosteronism is reversed after sunitinib withdrawal.

6.13 Obesity, Pulse Pressure and Thyroid Hormones

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Introduction: Overweight and obesity are associated with elevated blood pressure. The Framingham Heart Study showed that 65–75% of overweight and obese patients are at risk for hypertension. Concerning the mechanism relating obesity to hypertension, most obese humans have increased sympathetic activity, hyperinsulinaemia and higher levels of the renin-angiotensin-aldosterone system. Some recent studies showed that obesity is associated to the tendency to higher systolic blood pressure and lower diastolic blood pressure, at least before that hypertension becomes stable; these studies seem to suggest that obesity is associated to higher pulse pressure. FT3 serum levels are higher in women with abdominal obesity and it may well be that these patients having higher FT3 serum levels have also higher pulse pressure.

Aim: We have examined whether TSH, FT3, FT4, have an independent effect on 24-hour mean systolic (SBP) and diastolic (DBP) blood pressure levels and 24-hour mean pulse pressure (24-hour mean SBP-24-hour mean DBP) in a cohort of euthyroid subjects, represented by overweight and obese patients.

Methods: A total of 231 euthyroid overweight and obese patients (103 women and 128 men) aged 18, 68 years, normotensive (69) or with recently developed hypertension (162), never treated with antihypertensive drugs, were investigated. Fasting insulin, TSH, FT3, FT4, glucose and lipid (cholesterol, HDL-cholesterol and triglyceride), serum concentrations were measured. Waist circumference was measured as an indirect parameter of central fat accumulation. Ambulatory blood pressure monitoring (ABPM) was performed.

Results: 24-hour mean SBP showed a direct significant association with waist circumference (p<0.01) and FT3 levels (p<0.05), whereas 24-hour mean DBP showed a significant relationship with age (positive, p<0.001) and with BMI (negative, p<0.05). 24-hour mean pulse pressure (PP) showed a significant positive correlation with BMI (p<0.001), waist circumference (p<0.001) and FT3 (p<0.001) and insulin serum levels (p<0.05). When a multivariate analysis was performed, and 24-hour PP was considered as the dependent variable, and waist circumference, FT3, insulin, mail sex and age as independent parameters, 24-hour mean PP maintained a significant association only with waist circumference (p<0.001) and FT3 levels (p<0.05).

Conclusions: Central obesity is associated with higher PP and FT3 levels are positively and independently related with daily mean PP. These results suggest that FT3 may contribute to haemodynamic changes in obese subjects before hypertensive state becomes stable.

6.14 Prevalence of Obstructive Sleep Apnoea Syndrome in Hypertensive Patients Referred to a Specialized Outpatient Clinic and Association with Primary Aldosteronism

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Introduction: Obstructive sleep apnoea syndrome (OSAS) is an established cause of resistant arterial hypertension and has been associated with increased levels of plasma aldosterone and with an increased prevalence of primary aldosteronism (PA).

Aim: We prospectively determined the prevalence of OSAS and its predictors, including its association with PA and resistance to treatment, in hypertensive patients referred to a specialized outpatient hypertension clinic.

Methods: We systematically investigated the occurrence of OSAS in 350 consecutive hypertensive patients (177 women and 173 men, age 57.7 ± 16.2 years) referred to the High Blood Pressure Centre of the University of Padova between April 2008 and August 2010. All underwent a protocol for the ascertainment of any secondary form of arterial hypertension, which included history, physical examination, a simplified sleepiness questionnaire, and measurement of plasma aldosterone concentration (PAC), renin activity (PRA), 24-hour urinary Na⁺ and K⁺ and metanephrine excretion. The patients were selected to undergo cardio-respiratory monitoring based on a higher probability of OSAS. The diagnosis of PA and aldosterone-producing adenoma was based on the PAPY study criteria and that of resistant hypertension was made according to the ESH/ESC guidelines.

Results: 20.1% of the patients had resistant hypertension and 7.1% had OSAS. In OSAS patients the average apnoea-hypopnoea index (AHI) was 33.3 ± 4.5 ; the total number of apnoeas was 136 ± 30 with a predominance of obstructive apnoeas (116 ± 24 , 85.3% of all apnoeas). As compared with the patients without OSAS, the OSAS patients were mostly male (76.0% vs 24.0% female, $p=0.007$), had a higher BMI (29.7 ± 3.8 vs 27.5 ± 3.5 , $p=0.002$) and a 20-fold increased rate of chronic obstructive pulmonary disease or asthma (COPD, 12.0% vs 0.6%, $p=0.003$). Unlike resistant hypertension that occurred similarly among the two groups, the prevalence of PA was higher among those with than without OSAS (20.0% vs 13.2%), but this difference did not achieve statistical significance. At regression analysis (backward) the predictors of OSAS were BMI, the presence of COPD, and PAC ($F=7.96$, $p<0.0001$); a model with these three variables accounted for 10% of OSAS variance.

Conclusions: OSAS is common among referred hypertensive patients and can be overlooked if not systematically searched for. The non-significant association with PA and resistant hypertension is at variance with some previous findings and might be due to insufficient statistical power and/or to a selection bias. The identification of predictors of OSAS can improve its detection thus opening the way to specific treatment.

6.15 Prospective Appraisal of the Prevalence of Primary Aldosteronism in Hypertensive Patients Presenting with Atrial Fibrillation or Flutter (PAPPHY) Study

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Introduction: A retrospective study showed a 12-fold increased risk of atrial fibrillation in patients with aldosteronism (PA) compared with the patients with essential hypertension. However, PA prevalence in hypertensive patients presenting with lone atrial fibrillation is unknown.

Aim: The Prospective Appraisal of the Prevalence of Primary aldosteronism in Hypertensive patients presenting with atrial flutter or fibrillation (PAPPHY) study is a multicentre study that has been registered at clinicaltrials.gov and was designed to prospectively ascertain the prevalence of primary aldosteronism and of its subtypes (aldosterone producing adenoma and idiopathic hyperaldosteronism) in the hypertensive patients referred for lone (not valvular) paroxysmal or permanent atrial fibrillation or flutter (FA). Secondary objectives are to (i) identify the clinical, echocardiographic and biochemical markers predicting FA risk; (ii) evaluate if FA may lower aldosterone/renin ratio (ARR) thereby preventing diagnosis of PA; (iii) prospectively determine the diagnostic usefulness of ARR calculated with direct renin (DRA); (iv) ascertain if FA and/or PA may affect the perception of quality of life; (v) evaluate if N-terminal propeptide collagen I PINP is increased in FA/PA compared with FA; (vi) establish if FA/PA is associated to higher arterial stiffness; (vii) determine the relative risk of cardiovascular events.

Methods: Case detection of PA and identification of subtypes will be performed following the criteria of the PAPY study; diagnosis of APA will use the '4 corners' criteria and cardioversion will follow AHA guidelines. Organ damage, cardiovascular events and recurrence of FA will be recorded at the follow-up.

Expected results and Conclusions: The demonstration of a higher prevalence of PA in FA patients could (i) modify the diagnostic strategy and therapeutic approach to the hypertensive patients with lone FA; (ii) clarify the pathogenic mechanisms underlying FA and define the cardiac damage in FA; (iii) identify patients with this potentially curable form of hypertension among patients with FA.

6.16 Sequential or Bilateral Simultaneous Adrenal Venous Sampling (AVS) in the Primary Aldosteronism: Effect on AVERSUS Selectivity

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Introduction: Adrenal venous sampling (AVS) is currently performed either with the simultaneous bilateral or with the sequential technique. Whether these different techniques affect the selectivity of AVERSUS is unknown. However, the stress reaction associated with AVS, which resolves in a few minutes, could impair the assessment of selectivity of catheterization by the selectivity index (SI) if time elapses between the first blood sample obtained from the right adrenal vein and the last obtained from the left adrenal vein with the sequential technique.

Aim: To prospectively investigate whether the simultaneous bilateral or sequential sampling technique differentially affect the assessment of the selectivity of AVS.

Methods: 52 patients with primary aldosteronism (PA) underwent simultaneous bilateral AVERSUS after proper pharmacological preparation and correction of hypokalaemia. Blood was collected simultaneously from the right and the left adrenal veins and from the inferior vena cava (IVC) within 1 minute, for the measurement of PCC and aldosterone. After 15 minutes blood drawings were performed again following the same procedure. To simulate the conditions occurring with the sequential AVERSUS technique the SI values were calculated as PCCside/PCCcivc by using the samples obtained simultaneously twice under basal conditions (at t-15 and t0 minutes), and also by combining PCCside and PCCcivc obtained at the different times (PCCside t-15/PCCcivc t0 and PCCside t0/PCCcivc t-15).

Results: Within-patient comparison showed that SI was lower at t0 than at t-15 (right -49%, left -48%, $p<0.001$), because PCCside fell on both sides from t-15 to (right -59%, left -49%, t0 vs t-15, $p<0.001$). The SI values calculated with PCCside and PCCcivc obtained at different times differed from those simultaneously obtained at both t-15 and t0 (PCCright t-15/PCCcivc t0 vs SIright t0: +500%; PCCleft t-15/PCCcivc t0 vs SI left t0: +610%; PCCleft t0/PCCcivc t-15 vs SI left t-15: -44%; $p<0.001$). The percentage of selective AVERSUS was lower at t0 than at t-15 when a SI=3 was used as cutoff. Moreover, when SI was calculated with PCCside and PCCcivc obtained non-simultaneously the percentage of selective AVERSUS was significantly lowered than with simultaneously obtained values.

Conclusions: Due to the stress reaction that occurs in many patients during AVERSUS the PCC values measured in the adrenal veins at different times during AVERSUS can differ significantly. Hence, the SI values obtained with either sequential or the simultaneous AVERSUS technique can be discordant, particularly when stringent cutoff values for the SI are used.

6.17 Primary Aldosteronism and Essential Hypertension: Assessment of the Global Cardiovascular Risk at Diagnosis and Follow-Up

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Introduction: High blood pressure represents the first cause of mortality in the general population worldwide.

Aim: To evaluate the cardiovascular risk according to the ESH/ESC 2007 guidelines for the treatment of hypertension, in patients with primary aldosteronism (PA) and with essential hypertension (EH), at diagnosis and at follow-up.

Methods: We studied 71 PA patients (29 with aldosterone producing adenoma-APA and 42 with idiopathic hyperaldosteronism-IHA, M/F 42/29, mean age 51 ± 12 years, BMI 27 ± 4 kg/m²) and 80 essential hypertensive patients (M/F 23/57, mean age 55 ± 11 years, BMI 31 ± 7 kg/m²), at basal and after surgical or medical treatment. After a mean follow-up period of 4.3 years for APA patients who underwent adrenalectomy, and 6.4 years for medically treated IHA, and 4 years for EH, patients were re-evaluated to assess the cardiovascular (CV) risk.

Results: The resolution of hypertension was observed in 48% of APA and 35% of IHA. According to the ESH/ESC 2007 guidelines the CV risk in PA was, respectively at diagnosis and follow-up: low in 0% and 7%, moderate in 11% and 25%, high in 55% and 47%, very high in 34% and 21%. Moreover, while 26% of patients had a grade 3 hypertension at diagnosis, only 1% had the same grade at follow-up. The reduction of global CV risk was more evident in APA patients than in IHA, in whom, anyway, a significant increase of HDL-cholesterol was observed, together with a reduction of left ventricular cardiac mass and posterior wall thickness ($p<0.05$). Considering the prevalence of the very high risk category, a marked reduction after treatment was observed in APA (41% vs 17%), while the reduction was less evident in IHA (30% vs 25%) and very modest in EH (16% vs 14%). As for EH, the CV risk was at diagnosis and follow-up, respectively: low 3% versus 12%, moderate 15% versus 25%, high 66% versus 49%, very high 16% versus 14% ($p<0.05$). Despite the same distribution of severity of hypertension among the three groups, the global CV risk was higher in PA than in EH patients, highlighting the deleterious effects of aldosterone excess on CV risk beyond blood pressure.

Conclusions: Patients with PA present a high CV risk, which is, however, in great part reversible after specific treatment, due both to the reduced blood pressure values and to the improvement of end-organ damage. EH patients display a less evident reduction of the CV risk after treatment due to less consistent reduction of blood pressure and to the small improvement of cardiovascular risk factors.

6.18 Cell-Mediated Autoimmune Mechanisms Involved in the Pathogenesis of Primary Aldosteronism

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Introduction: Primary aldosteronism (PA) is the most frequent endocrine cause of secondary hypertension. Even though the underlying causes remain unknown, the continuum between its two major subtypes, e.g. aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH), suggests a common pathogenetic mechanism that could involve autoimmunity.

Aim: To investigate the role of cell-mediated autoimmune mechanisms in the pathogenesis of PA.

Methods: We characterized the lymphocytic subpopulations infiltrating APA tissue and the adjacent adrenal cortex (n=37) by immunohistochemistry; normal adrenocortical tissues and autopsy cases

served as negative controls. We also performed a whole-transcriptome analysis of Th1, Th2, Th17 and Treg specific markers with oligomicroarray (n=23) followed by RT-PCR (n=12) to determine relative gene expression compared with normal adrenal tissue. T helper-CD4+ circulating lymphocytes were characterized in peripheral blood from patients with APA by flow cytometry (n=8).

Results: A scattered lymphocytes infiltration was consistently detected in the adrenals of PA patients by immunohistochemistry and flow cytometry, the major proportion of this population entailing non-toxicologically active CD8+ cells (TIA1, Perforin and Granzyme negative). B cells were scarce. A remarkable lymphocytic infiltration in the cortex closely surrounding the adenoma was detected in many patients, while was less present in APA or adrenocortical nodular lesions. Among T helpers CD4+ tissue-infiltrating lymphocytes, molecular studies showed a predominance of Treg phenotype: FoxP3 specific marker was 2.724 folds overexpressed in APA specimens than in normal adrenal tissue (p<0.01) and inversely correlated to the expression of T-BET (r=0.632, p=0.001) and other Th1-specific genes. Moreover, the proportion of Treg among circulating CD4+ lymphocytes was significantly higher in APA patients than in healthy controls (4.42±0.93 vs 2.52±1.33, p=0.0016).

Conclusions: Collectively these findings suggest an involvement of cell-mediated immunity in the pathogenesis of PA. The increase of Treg lymphocytes, a 'suppressive' population modulating immunotolerance, both in adrenals and peripheral blood might inhibit CD8-mediated response to a clone expansion and therefore allow the transition from a hyperplastic lesion to APA.

Imaging Techniques and Procedures

7.1 Initial Myocardial Impairments in Essential Hypertension: Evaluation Throughout Speckle Tracking Echocardiography

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Aim: To assess whether LV mechanics evaluation by means of speckle tracking echocardiography (STE) is able to reveal early systolic LV function changes in essential hypertension (EH). A further purpose was to determine whether STE may provide more insight into the remodelling process during the early stage of afterload increase.

Methods: 41 patients with EH (23 M, 56.5±14 years) and 41 age-matched healthy subjects (22 M, 52±13 years) were enrolled. LV dimensions, volumes, ejection fraction (EF), left atrial (LA) volume, mitral flow parameters, endocardial and mid-wall fractional shortening (e-FS%, m-FS%), circumferential end-systolic stress (c-ESS, 103 dynes/m²), LV mass index (g/m²), relative wall thickness (RWT, %) were measured. According to the presence of LV hypertrophy (LVH) patients were divided in 2 groups: LVH (+) [22 patients] and LVH (C) [19 patients]. By TDI, Sm and Em annular velocities were measured at the anterior, inferior, septal and lateral corner and the results were averaged. For LV strains and twist assessment, LV short axis and apical views were obtained.

Results: No difference among groups was observed concerning LV dimensions, EF and e-FS. In contrast, patients and controls differed for RWT, m-FS, LV mass index, c-ESS, LA size and diastolic function (p=0.001). Mean Sm and Em were reduced in LVH(-) patients (Sm=6.7±1.7 cm/s; Em=7.2±2.2 cm/s) with respect to controls (Sm=7±1.8 cm/s; Em=8.7±1.5 cm/s), and even more reduced in LVH(+) patients (Sm=4.8±0.9 cm/s; Em=5±1.6 cm/s); only the latter difference, however, was statistically significant. Longitudinal strain was lower both in LVH(-) [218±1.9%, p=0.02] and in LVH(+) patients (215.9±3.3%, p, 0.001) with respect to controls (220.4±2.5%); circumferential strain, in contrast, was normal in each of the 2 groups of patients independent of LV hypertrophy; radial strain (RS) was lower in LVH(+) [40±20%, p=0.02] than in controls (54.5±16%), while it was normal (56.6±18%, p=ns) in LVH(-) patients. LV twist was increased in LVH(+) patients (23.8±5.28, p=0.001), compared with controls (12.5±4.88, p=ns), but it was normal (13.5±4.98) in LVH(-) patients.

Conclusions: Hypertension is associated with a progressive cardiac involvement that starts even before the increase of LV mass. M-FS is the only conventional marker, sensitive in the early stage of the disease. TDI is useful to identify myocardial damage when changes in LV geometry occur. The evaluation by means of STE provides more detailed insight, revealing longitudinal dysfunction even before LV mass increase. Alterations in radial and circumferential direction, as well as twist changes occur only in advanced stages, when LV hypertrophy is evident.

Kidney

8.1 Glomerular Hyperfiltration is an Independent Predictor of Sub-Clinical Carotid Damage in Hypertensive Non-Diabetic Subjects

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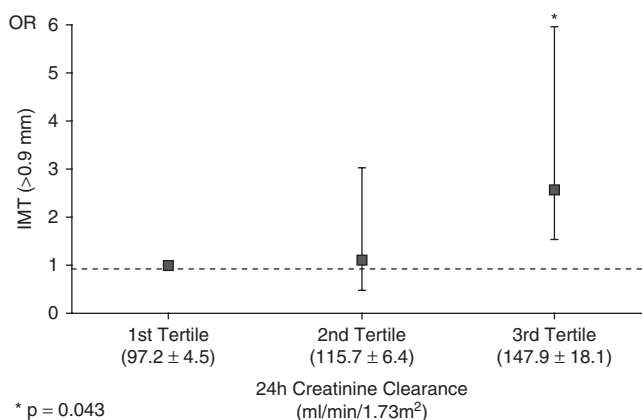
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Introduction: Glomerular hyperfiltration (GHF) is a common condition in hypertensive subjects (HTs), but whether GHF is a risk factor of sub-clinical organ damage (TOD), defined as carotid intima-media-thickness (IMT) >0.9mm and left ventricular mass index (LVMI) >110 g/m² in women and >126 g/m² in men, has not yet been clearly established.

Methods: In 202 non-diabetic HTs (mean age 54.7±11.3 years) with normal serum creatinine (Scr) and without associated clinical conditions, the creatinine clearance was measured using the Scr and a 24-hour urine collection (ClCr-24h). ClCr-24-hour was divided into tertiles and the HTs of the 3rd tertile were defined to have GHF. Office blood pressure (BP) and 24h-ambulatory BP (ABPM) were measured with Riva-Rocci sphygmomanometer and Takeda TM-2430 device, respectively. The differences between continuous variables were evaluated by ANOVA, while gender-specific odds ratio (OR) and 95% confidence intervals (CI 95%) of GHF were calculated for independent variables by logistic regression analysis.

Results: IMT and serum aldosterone (AP) values and the prevalence of non-dipper profile at the ABPM, were significantly higher in HTs of the 3rd compared with lower tertiles of GHF, respectively, 1.08±0.38 versus 0.93±0.29 and 0.807±0.28 (p=0.0001), 113.5±44.0 versus 93.8±43.7 and 91.4±50.3 (p=0.034) and 41.4 versus 32.6 and 22.4% (p=0.01). GHF predicted the carotid TOD independently of albuminuria (figure). No relationship was found between GHF and cardiac TOD in both genders.

Conclusions: In HTs with GHF the subclinical carotid TOD assessment should be recommended. The increased risk of TOD is in part due to the increase of 24-hour BP load and of the high levels of AP observed in HTs with than those without GHF.



8.2 The Medical and Endovascular Treatment of the Atherosclerotic Renal Artery Stenosis (METRAS) Study: Rationale and Study Design

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Introduction: It is unclear if revascularization of renal atherosclerotic stenosis (RAS) by means of percutaneous renal angioplasty and stenting (PTRAS) is advantageous over optimal medical therapy. Hence, we designed a randomized clinical trial based on an optimized patient selection strategy and hard experimental endpoints.

Study Design and Protocol: The protocol of a prospective, randomized, un-blinded, two-arm multicentre study 'The Medical and Endovascular Treatment of Atherosclerotic Renal Artery Stenosis (METRAS)' [clinicaltrials.gov, Identifier: NCT01208714] is presented. It enrolls patients with clinical and angio-CT evidence of RAS affecting the main renal artery or its major branches, performed in terms of percentage of area reduction, either between 70% and 90% or, if <70%, with post-stenotic dilatation. Renal function will be assessed with ^{99m}Tc-DTPA renal scintigraphy. Patients will be randomized to either arms considering the presence of unilateral/bilateral stenosis. Primary objective will be to determine if PTRAS is superior or equivalent to optimal medical treatment for preserving glomerular filtration rate (GFR) in the ischaemic kidney as assessed by ^{99m}TcDTPA sequential renal scintiscan. Secondary objectives will be to establish if the two treatments are equivalent in lowering blood pressure, preserving overall renal function as assessed by total estimated GFR, the reciprocal of serum creatinine, and indexes of Ca²⁺ and PO4³⁻ metabolism and regressing target organ damage, preventing cardiovascular events and improving quality of life.

The sample size is estimated in 60 patients per arm to achieve a 0.05 significance level and a 99% power to detect a difference in means of GFR in the vascularized (or control untreated kidney) of 7.5 mL/min, assuming a 16% drop-out rate and a common standard deviation of 8.0 mL/min. With its high power this study should clarify whether PTRAS on top of optimal medical therapy is superior or equivalent to the latter alone in preventing deterioration of GFR in the ischaemic kidney. Assessment of secondary endpoints will clear up some clinically relevant issues concerning BP lowering, rate of renal and major cardiovascular events, and changes in quality of life after PTRAS. The METRAS study will last for 5 years.

8.3 Association of Oxidative Stress with Aortic Stiffness in Hypertensive Patients with Chronic Kidney Disease

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Introduction: It is well known that arterial stiffness and oxidative stress are features of chronic kidney disease (CKD). Several studies have consistently demonstrated that arterial stiffness becomes progressively worse as CKD progresses and a negative correlation of oxidative stress with renal function has been described. There is also sound experimental evidence indicating that oxidative stress is involved in atherogenesis. The contribution of oxidative stress to aortic stiffness is less clear.

Aim: To analyse the relationship between plasma levels of 8-ISO-prostaglandin F_{2α} (8-ISO-PGF_{2α}), an index of lipid peroxidation, considered a reliable biomarker of oxidative stress, and aortic stiffness in a group of hypertensive patients with chronic kidney disease.

Methods: We enrolled 126 hypertensive patients (mean age 58 ± 13 years, males 56%) with CKD. In all the subjects 24-hour urine collection was performed to determine albuminuria and routine biochemical parameters and 8-ISO-PGF_{2α} plasma values, measured by an enzyme-linked immunosorbent assay, were obtained. Moreover, ambulatory blood pressure monitoring and measurement of c-f PWV, by a computerized automatic method (Arteriograph), were performed. The GFR was estimated by the four-variable MDRD study equation.

Results: The mean value of eGFR was 44 ± 26 mL/min/1.73 m². The patients with elevated values of c-f PWV (>12 m/sec) showed significantly higher 8-ISO-PGF_{2α} plasma levels than those of subjects with PWV <12 m/sec (p < 0.01). A statistical significant correlation was found between 8-ISO-PGF_{2α} and c-f PWV in the whole study population (r = 0.33; p = 0.001). This association held even after adjustment for age, gender, mean arterial pressure, smoking habit, glycaemia, total cholesterol, calcium phosphate product and eGFR (beta = 0.23; p = 0.006) in a stepwise multiple regression model.

Conclusions: Our results seem to suggest that in hypertensive subjects with CKD there is an independent relationship between oxidative stress and aortic stiffness and that the unfavourable influence of a reduced renal function on large artery elastic properties may be partly mediated by an increased oxidative stress.

8.4 Endothelin-1 (ET-1) Modulates Epithelial-Mesenchymal Transition (EMT) that is Involved in Kidney Tubulo-Interstitial Fibrosis of Angiotensin II-Dependent Hypertension

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Introduction: The origin of myofibroblasts that are responsible for collagen deposition and kidney fibrosis remains uncertain, but recent studies suggest that the epithelial cells can acquire a fibroblast-like phenotype via epithelial-mesenchymal transition (EMT).

Aim: To investigate whether EMT contributes to the development of kidney fibrosis in a model of angiotensin II-dependent hypertension and to identify the possible role of ET-1 via ETA and/or ETB receptors.

Methods: Transgenic rats (mRen2)27 [TGRen2] randomly received for 4 weeks one of the following treatments: (i) irbesartan (50 mg/kg); (ii) bosentan (non selective antagonist of ET-1 receptors, ETA and ETB, 100 mg/kg); (iii) BMS-182874 (BMS; selective antagonist of ETA receptors, 52 mg/kg); (iv) BMS (52 mg/kg) + irbesartan (50 mg/kg); (v) nifedipine (30 mg/kg); (vi) placebo. EMT was assessed by investigating coexpression, in the same cell, of a marker of epithelial cell (E-cadherin) and one of myofibroblast (S100A4 or alphaSMA) with double immunofluorescence. Immunohistochemistry (IHC) was performed with diaminobenzidine/horseshadish peroxidase, and specific immunoreactivity was measured in an operator-independent manner using QWin Standard Leica ImageTM software and specific routine.

Results: A reduction in blood pressure was found only with irbesartan (p < 0.001, vs placebo), whereas both bosentan (p < 0.01) and irbesartan (p < 0.01) lowered tubulo-interstitial fibrosis. Coexpression of E-cadherin and S100A4, or E-cadherin and alphaSMA markedly decreased in the kidney tubular cells of TGRen2 treated with irbesartan and bosentan. alphaSMA expression was reduced after treatments with irbesartan, bosentan, BMS + irbesartan and nifedipine (-76%, -61%, -70%, -58% vs placebo, respectively, p < 0.001), but not after BMS. S100A4 expression decreased after irbesartan, bosentan and BMS + irbesartan (-62%, -51%, -91%, vs placebo, respectively, p < 0.001). E-cadherin increased only after treatment with irbesartan (+11% vs placebo, p < 0.05).

Conclusions: The coexpression of the myofibroblasts and epithelial cells markers in the kidney tubular epithelial cells demonstrates the occurrence of EMT and suggests its crucial role in the pathogenesis of Ang II-mediated hypertension-induced renal fibrosis. The reduction of both markers of myofibroblasts not only after irbesartan, which lowered blood pressure, but also after blockade of ETA and ETB receptors, which did not affect hypertension in this model, suggests an involvement of ET-1 in the Ang II-mediated EMT via mechanisms partly independent from blood pressure lowering.

8.5 Relationship between Plasma Aldosterone and Left Ventricular Mass in Hypertensive Subjects with Mild-to-Moderate Chronic Kidney Disease

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Introduction: Plasma aldosterone (ALD) levels are generally increased in subjects with chronic kidney disease (CKD), especially in those with end-stage renal disease. Convincing clinical and experimental data indicate that aldosterone plays a fundamental role in determining functional and structural changes of the heart. On the other hand, it is known that hypertensive patients with renal dysfunction, also of mild degree, show an increased prevalence of cardiovascular organ damage. Little is known about the relationships between aldosteronaemia and left ventricular mass in subjects with mild-to-moderate CKD.

Aim: To analyse the relationships between ALD and left ventricular mass (LVM), in a group of hypertensive patients with stages I-III CKD.

Methods: We enrolled 194 hypertensive patients with stages I-III CKD (mean age 46 ± 12 years, males 70%). All the subjects performed 24-hour urine collection to assay albuminuria, and electrolytes, and underwent, where necessary after a wash-out pharmacological period of 2 weeks, blood collection to assay biochemical routine parameters, plasma renin-activity (PRA) ALD plasma levels, both by radioimmunological assay. Moreover, we also performed 24-hour ambulatory blood pressure monitoring (ABPM) and echocardiogram. Left ventricular mass (LVM), calculated according to the formula of the American Society of Echocardiography, was indexed for height^{2.7} (LVMH^{2.7}). Glomerular filtration rate (eGFR) was estimated by the 4-variables equation of the MDRD study.

Results: The patients with CKD and LV hypertrophy (LVH), [LVMH^{2.7} > 51 g/m^{2.7}] showed higher levels of ALD (p = 0.001), when compared to those without LVH; this difference held even after adjustment (p < 0.01) for age, gender, 24-hour systolic blood pressure (SBP), BMI and PRA. A statistically significant correlation was observed between ALD and LVMH^{2.7} (r = 0.26; p < 0.001). This association remained significant even taking into account various confounding factors, such as age, gender, 24-hour SBP, BMI, albuminuria, PRA and eGFR in multiple regression analysis (beta = 0.22; p = 0.001).

Conclusions: Our results seem to suggest that the increase of LVM, previously documented in patients with renal dysfunction, even of mild-to-moderate degree, may be mediated, at least in part, by increased levels of aldosterone.

Metabolic Aspects and Mechanisms

9.1 Overweight or Obesity are Strong Predictors of Hypertensive Complications in Young Subjects with Stage 1 Hypertension

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Introduction: The prevalence of obesity in young people has increased dramatically but little is known about the effect of obesity on the risk of end organ involvement in the early stage of hypertension.

Aim: To examine the impact of overweight or obesity on development of target organ damage (TOD) in young subjects screened for stage 1 hypertension.

Methods: Participants were 727 never-treated young adults (516 men) with a mean baseline age of 33.8 ± 8.4 years (range, 18–45 years), who were screened for stage 1 hypertension on at least two occasions two weeks apart. Patients were seen every 6 months for clinic blood pressure (BP), with 24-hour ambulatory BP and global risk assessment to determine which subjects needed drug therapy according to current guidelines. Albumin excretion rate (AER, ≥30 mg/24h) and left ventricular hypertrophy (LVH, ≥50 g/m^{2.7} in men and ≥47 g/m^{2.7} in women) were measured at entry, every 5 years, and/or just before starting treatment. Subjects were divided according to whether they had normal weight (NW, n = 364), overweight (OvW, n = 289) or obesity (Ob, n = 74) at the baseline.

Results: After a median of 8 years, hypertension needing treatment was developed by 54.7% of NW, 66.6% of OvW, and 73.0% of Ob subjects (p < 0.001). LVH and/or AER at study end was present in 10.7% of NW, 16.4% of OvW, and 31.1% of Ob (p < 0.001). These differences remained significant also when adjusted for baseline urinary albumin or left ventricular mass. In a multivariable logistic analysis, after adjusting for age, sex, lifestyle factors, parental hypertension, 24-hour BP, clinic BP and heart rate, overweight (p = 0.008) and obesity (p < 0.001) were significant predictors of TOD development with odds ratios (ORs) of 2.0 (95% CI 1.2, 3.3) and 4.2 (2.2, 8.2), respectively. When baseline TOD was included in the model, these associations remained highly significant with ORs = 3.1 (1.5, 6.2) and 4.9 (2.0, 12.1), respectively, the same was observed after inclusion of changes in 24-hour BP (ORs = 3.2 [1.6, 6.5] and 5.1 [2.1, 12.7], respectively) or changes in body weight (ORs = 3.4 [1.6, 7.6] and 5.9 [2.1, 16.0] respectively).

Conclusions: These data show that young stage 1 hypertensive subjects with increased body mass index have a much higher risk of target organ damage than NW subjects. This relationship is linear and suggests an early antihypertensive treatment if BMI is elevated.

9.2 Evaluation of Insulin Signalling in Adipose Tissue in Hypertensive Patients with Primary Hyperaldosteronism

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Introduction: Previously, we found no differences as to gene expression of various insulin signalling molecules in the *ex-vivo* visceral adipose tissue (VAT) of patients with aldosterone-producing adenoma (APA) and with non-functioning adrenal adenoma (NFA) as controls, not supporting an effect of aldosterone excess on fat insulin sensitivity. Only pharmacological aldosterone concentrations were able to reduce glucose uptake in human subcutaneous (sc) adipocytes, possibly acting on insulin signal distal to insulin receptor substrate (IRS) isoforms.

Aim: To evaluate the phosphorylation of IRS downstream molecules: (i) in the *ex vivo* VAT of patients with primary aldosteronism; and (ii) in human sc adipocytes pre-treated with pharmacological aldosterone concentrations.

Results: Visceral adipose tissue was obtained from APA (n = 7) and NFA patients (n = 7) undergoing laparoscopic adrenalectomy. Subcutaneous adipocytes were obtained from subjects who requested abdominoplasty after weight loss. Western blotting was used to detect phosphorylation of Akt and of extracellular signal-regulated kinase (ERK) 1/2 in VAT from APA and NFA patients, and in sc adipocytes pre-treated with different aldosterone concentrations. Phosphorylation of Akt and ERK1/2 was similar in VAT of patients with APA and NFA. Pre-treatment in sc adipocytes with both physiological (1 nM) or pharmacological (10 μM) doses of aldosterone did not affect basal or insulin-induced phosphorylation of Akt and ERK1/2.

Conclusions: Our data give further evidence that intracellular insulin signalling in human VAT is not affected by primary aldosterone overproduction. Inhibition of glucose transporter translocation to plasma membrane might be an alternative mechanism for previously reported impairment of glucose uptake in human sc adipocytes after pharmacological doses of aldosterone.

9.3 Serum Levels of Vitamin D in Grade 1 Hypertensive Patients

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Introduction: Hypovitaminosis D is common in the Italian population, probably due to insufficient exposure to ultraviolet B rays. Vitamin D regulates approximately 3% of the human genome and many observational studies support the hypothesis that it is also involved in the pathogenesis of cardiovascular disease and hypertension. In particular, vitamin D contributes to the determination of blood pressure by its ability to inhibit the renin-angiotensin-aldosterone system, to protect the vessel wall and obviously to contribute to the calcium homeostasis.

Aim: To evaluate serum levels of vitamin D in patients with recently diagnosed grade 1 essential hypertension.

Methods: We selected 35 patients (26 M and 9 F) with grade 1 essential hypertension and 35 age- and sex-matched normal controls. All patients were evaluated for anthropometric parameters, lipid profile, fasting glucose and insulin concentrations, and serum levels of vitamin D by standard laboratory methods.

Results: The group of patients (mean age ± SD: 47 ± 10.30 years) with grade 1 essential hypertension (mean sitting SBP ± SD = 141.64 ± 11.53 mmHg, mean sitting DBP ± SD = 91.85 ± 9.47 mmHg) had mean serum levels of vitamin D at the lower limits of the normal range and lower than the control group (34.97 ± 7.41 vs 50.10 ± 6.25 ng/mL, respectively, p = 0.007). Inverse correlations were found in the hypertensive group between serum levels of vitamin D and BMI (r = -0.538, p = 0.02), fasting insulin levels (r = -0.698, p = 0.007) and the index of insulin resistance HOMA-IR (r = -0.678, p = 0.0139). No correlations were found in normal subjects.

Conclusions: Our study shows that relatively young, recently diagnosed patients with grade 1 essential hypertension had decreased serum levels of vitamin D. This finding suggests that vitamin D is involved in the development of hypertension and its supplementation might be considered in these patients. Both of these hypotheses are markedly reinforced by the finding that patients with hypertension also manifest with inverse correlations between vitamin D levels and BMI, fasting insulin levels and HOMA-IR.

9.4 Metabolic and Adrenergic Effects of Bariatric Surgery in Obese Subjects

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Introduction: It has been recently reported that weight loss induced by restrictive bariatric surgery triggers an improvement of both insulin sensitivity and sympathovagal balance at the level of the heart. No data, however, are available on the effects of the procedure on a direct index of sympathetic cardiovascular function accurately reflecting more the whole cardiovascular adrenergic drive such as efferent postganglionic sympathetic nerve traffic and on the inter-relationships between sympathetic and insulin sensitivity changes induced by the intervention.

Methods: In 7 severely obese patients (age 49.8 ± 4.05 years, 3 male, 4 females) we measured clinic (sphygmomanometric) and beat-to-beat (Finapres) blood pressure (BP), heart rate (ECG), bodyweight, body mass index (BMI), waist-to-hip ratio (WHR), HOMA index and efferent postganglionic muscle sympathetic nerve traffic (MSNA, microneurography). Measurements were performed 3–4 days before bariatric surgery and repeated 6 and 12 months after the procedure. The same evaluations were performed in 8 age-, gender-, body mass index- and waist-hip ratio- matched normotensive obese subjects not undergoing the surgical procedure, thus serving as controls.

Results: Both MSNA and HOMA were significantly related before surgery to BMI and WHR but not to each other. Six months after bariatric surgery BMI and WHR values were significantly reduced (from 43.0 ± 1.9 to 35.3 ± 2.1 kg/m² and from 1.02 to 0.94, respectively, p < 0.05 for both), the weight loss being accompanied by a significant decrease in systolic BP (from 143 ± 2.4 to 134 ± 2.1 mmHg, p < 0.05). HOMA index was also significantly reduced (from 4.7 ± 0.3 to 2.5 ± 0.2, p < 0.05) and this was the case for MSNA (from 69.8 ± 4.0 to 54.3 ± 3.4 bs/100hb, p < 0.05). The weight loss and MSNA reduction were substantially maintained after 12 months from surgery (BMI: 35.9 ± 2.1 kg/m², 53.3 ± 3.1 bs/100hb), while HOMA index showed a tendency to increase again returning toward pre-surgery values (3.9 ± 0.4). No significant changes were observed in the various anthropometric, haemodynamic, metabolic and neural variables in the control group.

Conclusions: These data provide the first evidence that massive weight loss induced by bariatric surgery triggers profound sympatho-inhibitory and eumetabolic effects, which, however, appear to follow a different time-course, suggesting their independent behaviour. This is particularly the case in the long-term period, indicating that the sympatho-inhibition accompanying weight loss is more related to the bodyweight reduction *per se* rather than to changes in insulin sensitivity.

9.5 Neuroadrenergic and Metabolic Profile in Patients with Resistant Hypertension

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Introduction: Resistant hypertension is characterized by profound abnormalities in neurohumoral homeostatic control of circulation. Whether these include also metabolic and adrenergic cardiovascular influences is largely unknown.

Methods: In 8 patients (6 males, 2 females) with documented resistant hypertension (RHT, defined by blood pressure values not at goal and a systolic blood pressure ≥ 160 mmHg despite the use of 3 antihypertensive agents at full dosage, including a diuretic) without obstructive sleep apnoea and with a body mass index < 27 kg/m², we measured clinic (sphygmomanometric) and beat-to-beat (Finapres) blood pressure (BP), heart rate (ECG) and efferent postganglionic muscle sympathetic nerve traffic (MSNA, microneurography). Measurements, including plasma renin activity (RIA), plasma aldosterone (RIA) and HOMA-index. The same evaluations were performed in 13 hypertensive patients (HT) without resistant hypertension matched for BP values with RHT and in 9 age-matched control normotensive subjects (C). In both HT and RHT patients' antihypertensive drug treatment was withdrawn 7 days before the study.

Results: The two hypertensive groups displayed, as expected, blood pressure and MSNA values significantly greater than C. For similar age (61.8 ± 2.9 vs 59.7 ± 2.3 years), body mass index (25.2 ± 1.1 vs 24.1 ± 0.9 kg/m²) and clinic systolic and diastolic blood pressure ($171.2 \pm 2.9/98.4 \pm 2.0$ vs $169.7 \pm 2.5/97.4 \pm 1.9$ mmHg), RHT showed MSNA values significantly greater than HT both when expressed as bursts incidence over time and as bursts incidence corrected for heart rate (60.5 ± 2.9 vs 44.8 ± 2.2 beats/min; 86.1 ± 5.1 vs 70.3 ± 3.9 bs/100 hbs, $p < 0.05$ for both). Plasma aldosterone and HOMA index values were also significantly greater in RHT than in HT (13.8 ± 1.4 vs 9.1 ± 0.8 ng/dL and 2.31 ± 0.4 vs 1.43 ± 0.2 ; $p < 0.05$ for both), whereas plasma renin activity significantly lower (0.8 ± 0.2 vs 1.5 ± 0.3 ng/mL/h, $p < 0.05$). In RHT but not in HT plasma aldosterone and HOMA index values were significantly and directly correlated with MSNA.

Conclusions: These data provide the first evidence that resistant hypertension is a state of marked sympathetic activation, greater for magnitude than that seen in non-resistant essential hypertension. They also suggest that in resistant hypertension the adrenergic overdrive is independent on sleep apnoea and is likely related to metabolic (insulin resistance) and/or humoral (elevated aldosterone levels) factors with documented central sympatho-excitatory influences.

9.6 Adiponectin, Insulin Resistance and Blood Pressure in a Paediatric Population

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Introduction: Circulating levels of adiponectin are decreased in obesity-induced insulin resistance, and correlate negatively with visceral fat amount. In adults reduced levels of adiponectin are a predictor of the development of arterial hypertension. Few data are available on the relationship between adiponectin and blood pressure in children.

Aim: To evaluate in normal weight (NW) and obese (OB) children with (HT), and without hypertension (NT) the relationships among adiponectin, blood pressure and HOMA-index (as estimate of insulin resistance).

Methods: In 100 children (age 6.2–16.5 years, 39 females) systolic (SBP) and diastolic (DBP) blood pressure, body mass index (BMI), waist circumference (WC, as estimate of visceral fat), adiponectin and HOMA index were measured. Hypertension was ascertained according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, weight class according to the International Obesity Task Force classification and BMI percentile according to CDC charts. The study population was split into 4 groups: Group A (NW and NT, n=27), Group B (NW and HT, n=18), Group C (OB and NT, n=27), Group D (OB and HT; n=28). Differences among groups were calculated by ANOVA + Fisher's PLSD. Correlations between continuous variables were analysed by simple and multiple regression.

Results: Among OB subjects adiponectin was significantly lower (6562 ± 2558 vs 8359 ± 3426 ng/mL, $p = 0.04$), and HOMA-index higher (3.8 ± 3.8 vs 2.4 ± 1.7 , $p = 0.03$) in HT compared with NT subjects. In obese HT children, WC values (85.3 ± 10.7 vs 79.5 ± 7.9 cm, $p = 0.01$), but not BMI percentile (98.4 ± 1.0 vs 97.9 ± 1.0 , NS) were higher compared with NT. Among NW children, BMI percentile (59.1 ± 23.9 vs 46.7 ± 28.7 , $p = 0.03$), but not WC (64.7 ± 8.5 vs 62.2 ± 6.1 cm, NS), was higher in HT compared with NT. In the entire study population, SBP percentiles were inversely correlated with adiponectin, and positively correlated with HOMA-index values ($p = 0.015$ and 0.001 , respectively). Adiponectin and HOMA-index values correlated also with BMI percentiles ($p = 0.001$ and 0.003 , respectively) and with WC values ($p = 0.001$ for both). In a multiple regression model, only BMI percentiles ($p = 0.035$) and WC ($p = 0.011$) were independently associated with SBP values.

Conclusions: In OB children adiponectin levels and insulin resistance may play a role in determining systolic blood pressure values, presumably because of the greater accumulation of visceral fat in HT compared with NT subjects. In NW children SBP seems to be mostly determined by BMI.

9.7 Metabolic Syndrome and Microalbuminuria Predict Renal Outcome in Non-Diabetic Patients with Primary Hypertension: The Magic Study

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Introduction: Metabolic syndrome has recently been shown to be a forerunner of chronic kidney disease. Microalbuminuria is associated with both metabolic syndrome and chronic kidney disease.

Aim: To prospectively investigate the relationship between microalbuminuria, metabolic syndrome and renal outcome in non diabetic patients with primary hypertension.

Methods: A total of 790 hypertensive patients enrolled in the MAGIC study between 1993 and 1997 (mean age 49.3 ± 10.7 years) were included in the analysis. Renal outcome was defined as the first hospitalization with a diagnosis of chronic kidney disease.

Results: At baseline, 146 (19%) and 60 (7.6%) patients met metabolic syndrome and microalbuminuria criteria, respectively. After a median follow-up of 11.6 years (interquartile range 3.2 years), renal endpoint was reached in 15.8% of patients with metabolic syndrome and in 8.9% of those without it ($p = 0.0087$). The incidence of renal events increased progressively starting from patients with neither metabolic syndrome nor microalbuminuria, to patients with only one of these abnormalities, and then to those with both. Significant interaction was observed between metabolic syndrome and microalbuminuria. Patients with concomitant occurrence of metabolic syndrome and microalbuminuria at baseline showed a greater than 5-fold risk of renal outcome as compared to patients with neither of these two risk factors (HR 5.46; 95% CI, 2.34, 12.75). This risk became even higher when data were adjusted for potential confounders.

Conclusions: Metabolic syndrome and microalbuminuria are independent and interactive predictors of renal outcome in non diabetic patients with primary hypertension.

9.8 Plasma Aldosterone Levels are Associated to an Increased Left Ventricular Mass in Presence of Elevated Fibrinogen Levels in Essential Hypertension

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Introduction: Plasma aldosterone levels are independent determinants of left ventricular mass in both hypertensive patients and normotensive subjects. We have previously demonstrated that plasma aldosterone is directly related with some haemostatic variables, and this relationship could contribute to the development of target organ damage in hypertension.

Aim: To examine the relationships between plasma aldosterone, haemostatic variables and left ventricular mass in untreated essential hypertensive patients.

Methods: In 279 untreated essential hypertensive patients (age 49 ± 14 years, 164M/115F) we evaluated clinical characteristics, anthropometric variables, plasma aldosterone (PA) and active renin, aldosterone to renin ratio (ARR), urinary aldosterone excretion, and plasma levels of fibrinogen, D-dimer, prothrombin fragment 1+2, and PAI-1. Cardiac morphofunctional parameters were evaluated by echocardiography. For statistical purposes hypertensive patients were subdivided into tertiles of fibrinogen levels.

Results: Left ventricular mass (LVMI; g/m^{2.7}) was significantly greater in patients with PA levels above the median value (125 pg/mL) only in patients in the higher tertile of fibrinogen. LVMI was directly related to age ($p < 0.001$), systolic blood pressure ($p < 0.001$), BMI ($p < 0.001$), PA levels ($p = 0.022$), ARR ratio ($p = 0.017$), and fibrinogen levels ($p < 0.001$). Fibrinogen was significantly and directly related with age, systolic blood pressure, and PA. PA was also directly related with D-dimer and PAI-1 levels. No relationships were found between LVMI and other haemostatic parameters. Multivariate analysis including demographic and anthropometric variables, mean blood pressure, PA, and fibrinogen levels, showed that LVMI was independently associated to age ($p = 0.002$, $\beta = 0.213$), blood pressure ($p = 0.004$, $\beta = 0.189$), BMI ($p = 0.010$, $\beta = 0.166$), PA ($p = 0.03$ (1), $\beta = 0.141$) and fibrinogen ($p = 0.016$, $\beta = 0.166$).

Conclusions: In essential hypertension, plasma aldosterone levels are associated to an increase of left ventricular mass only in presence of high fibrinogen levels.

9.9 Relationships between Plasma Aldosterone Levels and Urinary Calcium Excretion in Hypertensive Patients

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Introduction: Experimental and clinical studies have demonstrated that low-renin hypertension and aldosteronism are associated with abnormalities of calcium metabolism. Although these studies suggest a potential role of mineralocorticoid hormones, a direct involvement of aldosterone in calcium metabolism has never been shown in hypertensive patients.

Aim: To investigate the relationship between aldosterone and calcium metabolism in essential hypertension.

Methods: In 129 patients (age 45 ± 12 years; 75 M/54 F) with untreated hypertension we measured anthropometric indexes, fasting plasma calcium levels and 24-h urinary calcium excretion, creatinine clearance, plasma renin activity, plasma aldosterone levels, and 24-h urinary cortisol excretion. For statistical analysis, patients were divided according to tertiles of plasma aldosterone levels.

Results: Plasma calcium and plasma phosphate levels decreased progressively and urinary calcium excretion increased progressively and significantly with raising tertiles of plasma aldosterone. Urinary sodium excretion and creatinine clearance did not differ among plasma aldosterone tertiles. Univariate regression analysis demonstrated a direct relationship between urinary calcium excretion and plasma aldosterone levels ($r=0.209$; $p=0.017$), urinary cortisol excretion ($r=0.243$; $p=0.008$), and urinary potassium excretion ($r=0.216$; $p=0.014$). Multivariate analysis including age, body mass index, creatinine clearance, plasma renin activity, urinary potassium and cortisol excretion indicated that urinary calcium excretion is independently associated to plasma aldosterone levels ($p=0.024$).

Conclusions: These results show that aldosterone might be a major player in the mechanisms leading to abnormal calcium metabolism in essential hypertension.

9.10 A Bioelectrical Impedance Analysis Assessment of Body Fluid Compartments and Insulin Sensitivity in Hypertension

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Introduction: Hyperinsulinaemia is associated with sodium and water retention and can therefore influence body water distribution. The bioelectrical impedance analysis (BIA) is a non-invasive and reproducible method that permits assessment of water distribution and has been validated in renal patients.

Aim: To investigate the relationships between glucose metabolism and total body water content and distribution by BIA in patients with hypertension.

Methods: In 72 untreated essential hypertensive patients (51 ± 14 years, 37M/35F) we measured anthropometric indexes (BMI, waist circumference), plasma glucose, insulin and C-peptide levels after fast and in response to an oral glucose load, and the HOMA-index was calculated. Body fluid composition was measured by BIA after calculation of total body water that was normalized for the body surface area (TBW/m²) and extra-to intracellular ratio of water distribution was subsequently determined.

Results: There was no difference in TBW/m² between patients with (HOMA >2.5) or without insulin-resistance (HOMA <2.5). TBW/m² had no relationship with the other metabolic variables. Patients with insulin-resistance had a higher extra-to-intracellular body water ratio (0.98 ± 0.27 vs 0.83 ± 0.16 , $p=0.004$). At univariate analysis extra-to-intracellular body water ratio was directly related to age ($r=0.480$, $p<0.001$), insulin level ($r=0.345$, $p=0.006$), and HOMA-index ($r=0.294$, $p=0.020$). In the multivariate analysis that included BMI as a potential confounder, age ($\beta=0.273$, $p=0.029$) and plasma insulin ($\beta=0.396$, $p=0.002$) were independently associated with extra-to-intracellular body water ratio. No relationships were found between body water distribution and blood pressure values, creatinine clearance, and blood glucose.

Conclusions: In untreated hypertensive patients, fasting plasma insulin levels are an independent determinant of body water distribution. These findings support a role for this hormone in the regulation of body fluid homeostasis.

9.11 Insulin Sensitivity and Lp(a) Levels in Hypertensive Patients

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Introduction: Lipoprotein(a) [Lp(a)] is an emergent cardiovascular risk factor that is related with the presence and severity of organ damage in hypertensive patients. In these patients, insulin-resistance and hyperinsulinaemia are frequently detected. Population studies have reported an inverse relationship between plasma Lp(a) and insulin levels.

Aim: To examine the relationships between Lp(a) and glucose metabolism variables in essential hypertension.

Methods: In 389 consecutive hypertensive patients (age 55 ± 12 years, 46% women), we measured the anthropometric indexes, lipid profile including Lp(a) levels, fasting glucose, insulin and C-peptide, we calculated the Homeostatic Model Assessment (HOMA index) to estimate insulin resistance, and assessed the renal function. For statistical analysis, patients were divided according to tertiles of the HOMA index.

Results: Age ($p<0.05$), BMI ($p<0.0001$), waist circumference ($p<0.0001$), fasting glucose ($p<0.0001$), insulin ($p<0.0001$), C-peptide ($p<0.0001$), triglycerides ($p<0.001$), and the LDL/HDL ratio ($p<0.01$) were progressively higher with increasing values of the HOMA. Conversely, plasma Lp(a) levels ($p<0.01$) decreased progressively with increasing HOMA. Univariate regression analysis showed that Lp(a) was significantly and inversely related to HOMA ($r=-0.145$; $p<0.01$), fasting glucose ($r=-0.144$; $p<0.01$), insulin ($r=-0.139$; $p<0.01$), C-peptide ($r=-0.102$; $p<0.05$), creatinine clearance ($r=-0.187$; $p<0.001$), and alcohol intake ($r=-0.131$; $p<0.05$). Multiple regression analysis adjusted for age, sex, BMI, creatinine clearance, triglycerides, HDL, and alcohol intake, showed that the HOMA ($\beta=-0.147$; $p<0.05$) and creatinine clearance ($\beta=-0.196$; $p<0.01$) were independently and inversely related to Lp(a) levels.

Conclusions: Lower Lp(a) levels are associated with insulin resistance and hyperinsulinaemia in hypertensive patients. This association should be considered in the assessment of cardiovascular risk in these patients.

9.12 Effect of Short-Term Treatment with Telmisartan or Nifedipine on Insulin Signalling in Lymphomonocytes of Essential Hypertensive Patients

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Introduction: It was previously demonstrated that metabolic syndrome in humans is associated with an impairment of insulin signalling in circulating mononuclear cells, in particular with reduced molecular concentrations of insulin receptor, of IRS-1 (insulin receptor substrate-1), mTOR (the mammalian target of rapamycin), and other downstream proteins. At least in animal models of hypertension, ACE inhibitors and angiotensin receptor blockers (ARBs) may correct alterations of insulin signalling in the skeletal muscle.

Aim: Therefore, we investigated the effects of a 3 month treatment with an ARB with additional PPAR-gamma agonist activity, telmisartan, or with a dihydropyridine calcium channel blocker, nifedipine, on insulin signalling in patients with mild-moderate essential hypertension.

Methods: Twelve patients were included in the study; six were treated with telmisartan (20–80 mg/day) and 6 with nifedipine in a slow-release formulation (20–60 mg/day). Insulin signalling was evaluated in mononuclear cells by Ficol-Paque density gradient centrifugation and Western-Blot.

Results: The main findings of our analysis are summarized in the table (Mean \pm SD, * = $p<0.05$, ** = $p<0.01$ vs Basal; # $p<0.05$ vs nifedipine). No difference between groups or versus baseline was observed in the expression of insulin receptor. An increased expression of mTOR and of phosphorylated (active) mTOR (pmTOR) was observed in patients treated with telmisartan, but not in those treated with nifedipine, while both treatments increased the cellular expression of glucose transporter type 4 (GLUT-4).

	BP (mmHg)	mTOR (units)	pmTOR (units)	GLUT-4 (units)
Basal telmisartan	146/85 \pm 10/9	2486 \pm 819	2174 \pm 1043	6980 \pm 1579
3mo telmisartan	129/78 \pm 14.5**/	5299 \pm 1869**	5232 \pm 626**	28 076 \pm 2896*
Basal nifedipine	141/92 \pm 10/6	8254 \pm 1508	4518 \pm 1431	5059 \pm 872
3mo nifedipine	127/87 \pm 10.6**/	6169 \pm 1522	2913 \pm 802	20 339 \pm 6817*

Conclusions: Telmisartan and nifedipine are both effective in improving insulin signalling in human hypertension; however, telmisartan seems to have broader effects. This effect might contribute to explain the reduction in the onset of new diabetes observed in clinical trials especially with ARBs.

9.13 Circulating Indices of Inflammation/Oxidative Stress in Normotensive and Hypertensive Obese Patients

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Introduction: Obesity is partly an inflammatory process, and an increased production of inflammatory markers was observed in fat tissue.

Methods: We investigated circulating indices of inflammation and oxidative stress in 27 patients with severe obesity. Twelve of them were normotensive and 15 hypertensive. All obese patients underwent bariatric surgery. We compared results obtained with those observed in 13 normotensive lean controls. Circulating levels of C-reactive protein (CRP), proinflammatory cytokines interleukin-6 (IL-6) and interleukin-18 (IL-18), macrophage chemotactic factor-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), soluble vascular cell adhesion molecule 1 (VCAM-1) and soluble inter-cellular adhesion molecule 1 (sICAM-1) have been measured in plasma by ELISA. Total antioxidant power, malonyldialdehyde (MDA) and lipid peroxidation (LPO) were measured in plasma using spectrophotometric assay.

Results: A statistically significant difference between normotensive lean subjects versus hypertensive and normotensive obese patients pooled together was observed for circulating levels of IL-6 (1.26 ± 0.64 vs 5.02 ± 0.71 pg/mL, $p=0.039$), sVCAM (941 ± 96.3 vs 1556 ± 139 ng/mL, $p=0.029$) and CRP (287 ± 87.9 vs 1114 ± 107 ng/mL, $p=0.000038$). No difference was observed for total antioxidant power, LPO, MDA, MCP-1, IL-18 sICAM and PAI-1. Similar data were obtained when normotensive lean subjects were separately compared with normotensive and hypertensive obese patients. The main findings of our study are reported on the table (data are expressed as mean \pm SEM; in the table: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ vs normotensive lean subjects).

	Normotensive lean subjects	Normotensive obese subjects	Hypertensive obese patients
Total antioxidant power (μ M)	317 \pm 34.3	335 \pm 42.9	371 \pm 24.2
LPO (μ mol/L)	1.42 \pm 0.12	1.15 \pm 0.09	1.27 \pm 0.11
MDA (μ mol/L)	1.29 \pm 0.24	1.44 \pm 0.34	1.12 \pm 0.35
MCP-1 (pg/mL)	163 \pm 15.2	164 \pm 13.3	183 \pm 24.8
IL-6 (pg/mL)	1.26 \pm 0.64	3.67 \pm 0.65*	5.73 \pm 0.84**
IL-18 (pg/mL)	403 \pm 36.7	413 \pm 18.9	480 \pm 33.6
sICAM-1 (ng/mL)	526 \pm 34.2	484 \pm 21.9	565 \pm 25.4
sVCAM-1 (ng/mL)	941 \pm 96.3	1521 \pm 214*	1668 \pm 197*
PAI-1 (ng/mL)	78.2 \pm 16.9	98.3 \pm 12.6	95.6 \pm 9.95
CRP (ng/mL)	287 \pm 87.9	921 \pm 196**	1287 \pm 128***

Conclusions: Our data suggest that the presence of obesity is associated with increased systemic inflammation.

9.14 Cardiovascular Remodelling in Patients with Abdominal Adiposity: Correlation with Central Arterial Blood Pressure and Aortic Stiffness

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Introduction: Previous studies demonstrated that obesity is associated with cardiovascular (CV) remodelling. Little evidence is available regarding the relation between central arterial blood pressure (BP) and cardiovascular remodelling in patients with abdominal obesity.

Aim: to evaluate the correlation between left ventricle (LV) morpho-functional characteristics, carotid intima-media thickness (IMT), central arterial BP and aortic stiffness in overweight/obese patients.

Methods: We consecutively enrolled 54 patients without active smoke, CV disease and diabetes, never treated with anti-hypertensive drugs or statins. Among them: 34 patients showed body mass index (BMI) >25 kg/m² and abdominal circumference (AC) >102 cm for men and >88 for women; 20 patients showed BMI <25 kg/m² and AC <102 cm for men and <88 for women (BMI: 30.2 ± 3.7 vs 22.7 ± 1.2 kg/m², $p < 0.001$; AC: 103.6 ± 8.9 vs 86 ± 4.6 cm, $p < 0.001$). Each patient underwent: ambulatory 24 hours BP monitoring, echocardiographic examination, carotid ultrasonography, tonometry and measurement of the carotid-femoral pulse wave velocity (PWV).

Results: The two groups did not differ for age (46 ± 6 vs 45 ± 7 years, ns), sex, systolic and diastolic 24 hours BP. Serum PCR values were higher in the overweight/obese group (3 ± 2.3 vs 1.2 ± 0.9 mg/dL, $p < 0.001$). LV mass index was higher in the overweight/obese group (37.7 ± 7.3 vs 31.2 ± 6.8 g/h^{2.7}, $p < 0.006$). There was no significant difference between the two groups regarding relative wall thickness, end-diastolic LV diameter and ejection fraction. As for diastolic function, the overweight/obese group showed lower E/A ratio (interventricular septum, Tissue Doppler Imaging, TDI) (0.72 ± 0.2 vs 0.91 ± 0.31 , $p < 0.04$), higher E/E' ratio

(7.5 ± 1.6 vs 5.9 ± 1 , $p < 0.001$) and E/Em ratio (lateral wall, TDI) [4.90 ± 0.91 vs 4 ± 0.8 , $p < 0.003$]. Carotid IMT was greater in the overweight/obese group (0.74 ± 0.13 vs 0.66 ± 0.16 mm, $p < 0.05$). There was no difference in the carotid-femoral PWV between the two groups (7.3 ± 2.7 vs 6.5 ± 1.15 m/s, ns). The systolic aortic BP was higher (124 ± 12 vs 110 ± 11.0 mmHg, $p < 0.001$) in the overweight/obese group. There was a positive correlation between the aortic central BP and the PWV with the LV mass ($r = 0.306$, $p = 0.02$, $r = 0.49$, $p = 0.001$) and the carotid IMT ($r = 0.271$, $p < 0.04$, $r = 0.457$, $p < 0.001$).

Conclusions: In overweight/obese patients with abdominal obesity, CV remodelling appears to be significantly influenced by central BP and arterial stiffness.

9.15 Age, Bodyweight and Usual Sodium Intake in a Sample of Italian Hypertensive Population: Preliminary Results of MINISAL-SIIA Study

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Introduction: The main aim of MINISAL-SIIA study is to evaluate dietary sodium intake in a representative sample of the Italian hypertensive population, through the analysis of 24 hours urinary sodium excretion (Na24h), and its association with the relevant anthropometric characteristics.

Results: 1200 hypertensive patients were recruited, between January 2010 and May 2011, by the 49 Italian centres recognized by the Italian Society of Hypertension. All subjects were on stable antihypertensive treatment and previously submitted to the diagnostic screening and evaluation of the organ damage. Main anthropometric indexes, blood pressure (BP) and Na24h were measured. The population was divided both, according to BMI, in normal weight (NWn = 331), overweight (OWn = 488) and obese (OB = 314) subjects, and by age in quartiles, (mean age: IT: 42.3 ± 6.7 , IIT: 56.3 ± 3.3 , IIT: 65.5 ± 2.4 and IVT: 75.6 ± 4.5 years).

Results: Na24h (at moment available in 622 individuals) was directly associated with BMI ($r = 0.218$, $p < 0.001$), umbilical circumference ($r = 0.199$, $p < 0.001$) and heart rate ($r = 0.146$, $p = 0.009$) but inversely with age ($r = -0.123$, $p < 0.05$). NW, OW and OB did not differ for age (59.2 ± 14.2 vs 60.1 ± 12.9 vs 58.7 ± 11.6), while as expected, they were different for BP, with the highest SBP in obese people ($p < 0.001$). Furthermore, the three groups were significantly different for Na24h levels, with a positive trend between the groups (NW = 160: 133 ± 59 , OW = 276: 159 ± 68 and OB = 186: 170 ± 66 mmol/24h, $p < 0.001$). In addition Na24h was significantly different also between the quartiles of age, with higher values in younger patients (quartile I, n = 172, 163 ± 72 ; II, n = 17 (I), 157 ± 64 , III, n = 15 (I), 156 ± 65 , IV, n = 128, 141 ± 61 ; $p < 0.001$). The quartile of age also differed for BMI, BP and HR ($p < 0.05$).

Conclusions: This preliminary analysis of the MINISAL-SIIA study showed that: (i) obesity is associated with a high sodium intake, about 1.6 g/day; and (ii) younger subjects have a salt intake higher than older individuals of about 0.9 g/day.

9.16 Visceral Obesity is a 'New' Marker of Endothelial Dysfunction among Subjects Affected by Chronic Kidney Disease

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Introduction: patients affected by chronic kidney disease (CKD) have an increased cardiovascular morbidity and mortality rate. Endothelial dysfunction is a precocious index of worse cardiovascular prognosis.

Aim: To evaluate the relationship between endothelial function and other possible cardiovascular risk factors in a population of subjects affected by CKD.

Methods: We evaluated 191 patients affected by CKD and free for previous cardiovascular (CV) events. We collected: (i) medical history and anthropometric parameters; (ii) blood and urinary samples; (iii) ultrasonographic evaluation of flow mediated dilation of the brachial artery (FMD). Renal function was assessed by means of measured creatinine clearance (mCrCl), MDRD (eGFR) and Cockcroft-Gault (eCrCl) formulae. Albuminuria was determined as the mean value of three first morning samples of albumin/creatinine ratio (A/C) and as a 24-hour urinary collection (ProtU).

Results: Characteristics of our cohort were: M/F 127/65; age 62 ± 14 years; diabetes 48%; hypertension 84%; SBP 137 ± 21 mmHg; DBP 79 ± 12 mmHg; MAP 99 ± 14 mmHg; PP 58 ± 17 mmHg; BMI 28 ± 4.9 kg/m²; waist circumference 100.4 ± 13.7 cm; total cholesterol 219 ± 83 mg/dL; HDL 53 ± 16 mg/dL; LDL 136 ± 74 mg/dL; triglycerides 144 ± 74 mg/dL; Patients were homogeneously distributed between CKD stages (Stage 1 18%; Stage 2 24%; Stage 3 40%; Stage 4 18%); mCrCl 64 ± 34 mL/min; eGFR 58 ± 23 mL/min; eCrCl 53 ± 31 ; logA/C 1.19 ± 0.91 ; ProtU 1.27 ± 2.24 ; FMD of brachial artery was $13 \pm 8.3\%$. At univariate analysis, FMD correlate with: age ($r = -0.153$; $p = 0.04$) and waist circumference ($r = -0.20$; $p = 0.00086$) while it was not significantly correlated with any renal index or CV risk factors. Furthermore, when FMD was considered as the dependent variable of a multivariate regression analysis in which main CV risk factors and indices of renal function were the independent variable, waist circumference was maintained as the only modifiable and independent variable associated with FMD impairment.

Conclusions: Our results indicate that in a population of subjects affected by CKD visceral obesity is an independent and modifiable risk factor associated with endothelial dysfunction and may be consequently associated with worse CV prognosis.

9.17 Insulin Resistance, but not the Metabolic Syndrome, Induces the Structural Microcirculatory Damage at Early Stages of Hypertension

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Introduction: The metabolic syndrome (MS) is considered a clinical outcome of insulin resistance (IR). **Aim:** To highlight if MS (ATP III), associated or not with IR (HOMA index >3), may induce a macro- and micro-vascular damage at the early stages of hypertension.

Methods: By medical exam, ABPM and routine blood chemistry, 513 hypertensive patients were divided in 231 without SM and IR (SM-IR-), 88 with SM (SM+IR-), 90 with IR (SM-IR+) and 104 with both SM and IR (SM+IR+). Carotid intima-media thickness (IMT) by echo-color-Doppler, a preclinical macro-vascular lesion, and the capillary density at baseline (CAP) and during venous congestion (CVC), by videocapillaroscopy, indices of structural and functional micro-vascular damage, were taken.

Results: The findings of our study are reported in the table (data are shown as mean ± SD; in the table: * p < 0.05, ** p < 0.01, *** p < 0.001 vs SM-IR-; ° p < 0.05, °° p < 0.01, °°° p < 0.001 vs SM+IR-; ^ p < 0.05, ^^ p < 0.01, ^^° p < 0.001 vs SM-IR+). Pearson analysis, adjusted for age, smoke and history of hypertension, showed a progressive association between HOMA and CAP and CVC in SM+IR- (-0.296 and -0.338; p < 0.05 for both comparisons), in SM-IR+ (-0.695 and -0.686; p < 0.001 for both comparisons) and in SM+IR+ (-0.727 and -0.783; p < 0.001 for both comparisons).

paz/var	SBP/DBP	Microalb.	HOMA	IMT	CAP	CVC
SM-IR-	131 ± 1/83 ± 1	15.1 ± 1.1	1.56 ± 0.04	0.87 ± 0.04	39.8 ± 0.9	47.9 ± 0.8
SM+IR-	137 ± 2/84 ± 1***	30.1 ± 9.4**	1.97 ± 0.08***	0.94 ± 0.03	37.5 ± 0.7*	45.8 ± 0.9
SM-IR+	130 ± 1/83 ± 1°°°	31.2 ± 2.7***	4.69 ± 0.21***°°°	0.95 ± 0.03	36.4 ± 0.7***	42.8 ± 0.9***°
SM+IR+	135 ± 2/84 ± 1***^	38.1 ± 3.4***	6.17 ± 0.35***°°°^	0.98 ± 0.03	35.7 ± 0.8***	41.4 ± 0.9***°°°

Conclusions: The findings show that SM induces a functional microcirculatory rarefaction while IR, independently of SM, may cause the structural microcirculatory damage, since the early phases of hypertension, before the onset of preclinical macro-vascular lesion.

9.18 Insulin Resistance and Beat-to-Beat Cardiovascular Dynamics: A Continuous Relationship across Different Body Mass Index Categories

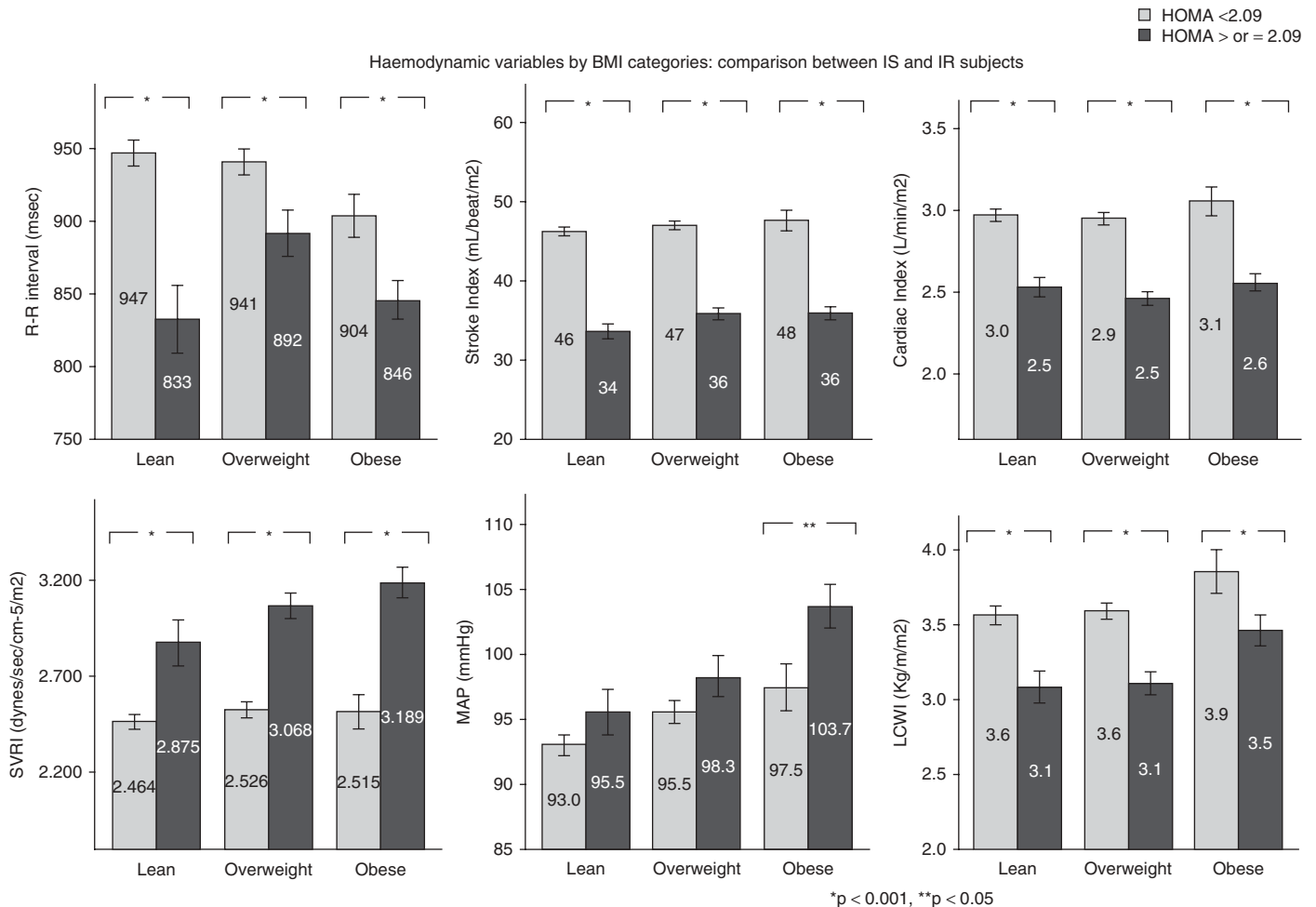
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Introduction: Haemodynamic effects of insulin are thought to be largely dependent on its association with bodyweight.

Aim: To assess whether insulin resistance (IR) is independently associated with blood pressure (BP) levels and haemodynamic indices of cardiovascular (CV) function across different categories of BMI.

Methods: For the present analysis a total of 731 non-diabetic subjects from the general population of Medellín Colombia were included. A value of HOMA-IR index of 2.09 (75th percentile of distribution curve) was considered as the threshold to classify subjects as insulin-sensitive (IS, HOMA < 2.09) or insulin-resistant (HOMA ≥ 2.09). Subjects were further classified according to their BMI as lean (< 25 kg/m²), overweight (25–29.9 kg/m²) or obese (≥ 30 kg/m²). Stroke volume (SV) and derived haemodynamic parameters such as stroke index (SI, mL/beat/m²), cardiac index (CI, L/min/m²), and systemic vascular resistance index (SVRI, dyn/sec/cm⁵/m²) were continuously recorded by impedance cardiography (EBI100C module, BIOPAC Systems, Inc.) R-R interval (RRI) was recorded by ECG, and BP levels were repeatedly measured over 5 minutes. The main findings of our study are also shown in the figure.



Results and Conclusions: Multivariate analysis adjusting for age, sex, smoking, and BMI (ANCOVA), showed significant differences for most haemodynamic parameters between IS and IR subgroups in the whole population: IR individuals were characterized by higher BP levels and SVRI, and a reduced RRI, SI and CI. These differences were significant also when analyses were performed within each BMI category.

9.19 Insulin Resistance and Beat-to-Beat Cardiovascular Dynamics: A Continuous Relationship Across Different Blood Pressure Categories

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Introduction: Haemodynamic effects of insulin resistance (IR) are thought to be largely dependent on its frequent association with elevated BP levels.

Aim: To test whether IR is independently associated with haemodynamic indices of cardiovascular (CV) function across different categories of BP.

Methods: For the present analysis a total of 731 non-diabetic subjects from the general population of Medellin (Colombia) were included. A value of HOMA-IR index of 2.09 (75th percentile of distribution curve) was considered as the threshold to classify subjects as insulin-sensitive (IS, HOMA <2.09) or insulin-resistant (HOMA ≥2.09). Subjects were further classified according to their BP levels into three categories: normal BP (<130/85 mmHg), high-normal BP (130–139/85–89 mmHg), and hypertension (≥140 and/or 90 mmHg). Stroke volume (SV) and derived haemodynamic parameters such as stroke index (SI, mL/beat/m²), cardiac index (CI, L/min/m²), and systemic vascular resistance index (SVRI, dyn/sec/cm⁵/m²) were continuously

recorded by impedance cardiography (EBI100C module, BIOPAC Systems, Inc.). R-R interval (RRI) was recorded by ECG, and BP levels were repeatedly measured over 5 minutes.

Results: Multivariate analysis adjusting for age, sex, MAP and BMI (ANCOVA), showed significant differences for most haemodynamic parameters between IS and IR subgroups in the whole population. The main findings of our study are also shown in the figure.

Conclusions: When analyses were performed within each BP category IR individuals were characterized by higher SVRI, and a reduced RRI, SI and CI, in absence of significant differences for BP levels.

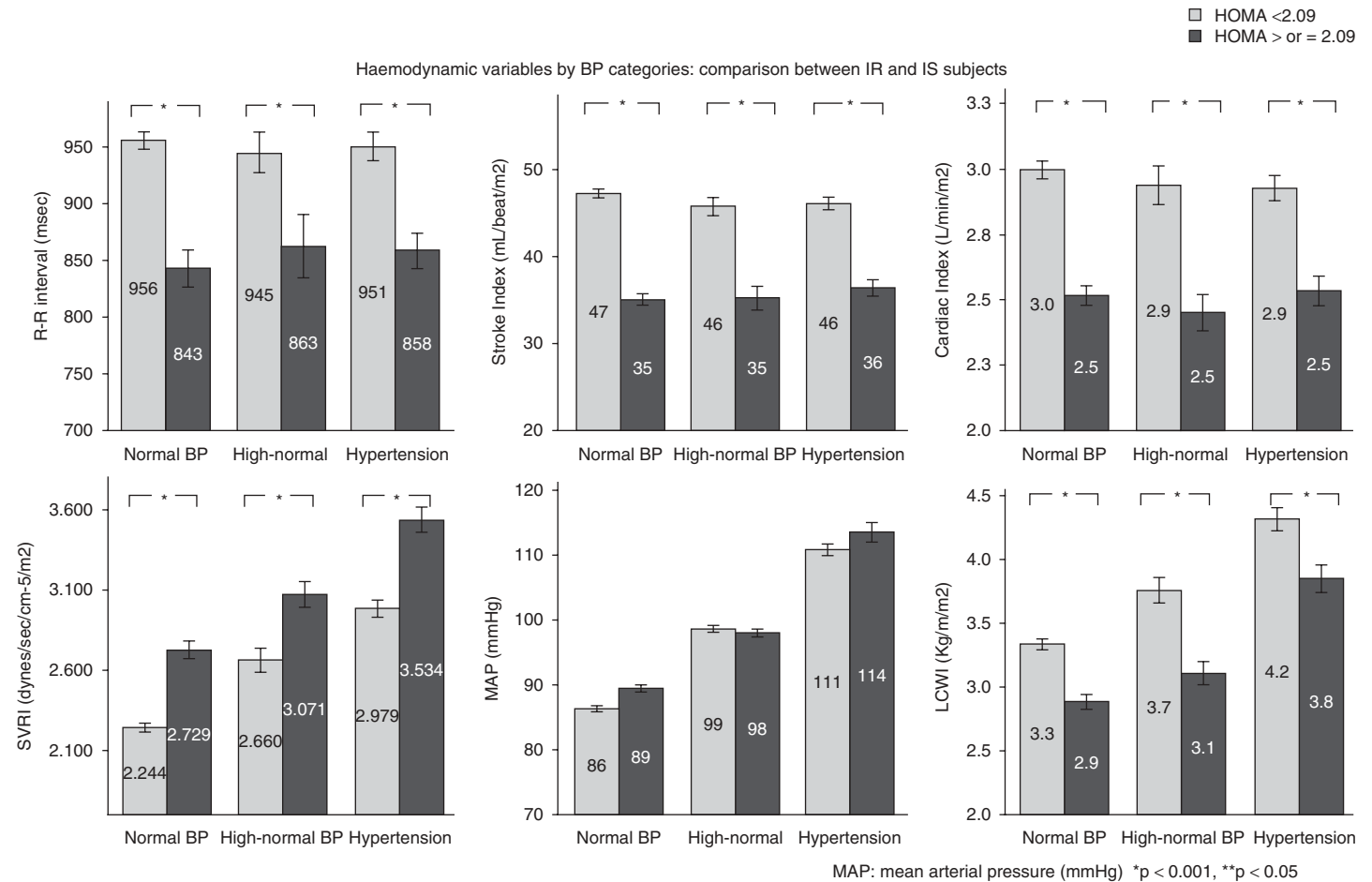
9.20 Higher Night-Time Blood Pressure and Cardiac Damage in 1827 Patients: Effects of BMI and Drug Therapy

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Introduction: In order to understand the relationship between different degrees of obesity (classified by the body mass index, BMI), 24 h blood pressure, day-time and night-time BP and cardiac organ damage, a cross-sectional study has been conducted on patients with clinical indication to undergo ambulatory blood pressure monitoring (ABPM) and echocardiography.

Methods: ABPM was performed using Spacelabs 90207. Exclusion criteria were: age <18 years, atrial fibrillation, low recorder quality and lack of information about anti-hypertensive therapy. Treatment Intensity Score (TIS), calculated on the basis of drug number and dosages, has been used to quantify different anti-hypertensive therapies.

Results: According to BMI, there were no significant differences in mean 24-hour and daytime SBP and DBP between normal weight (n=592), overweight (n=786) and obese patients (n=449), also after adjustment for sex, age and TIS. On the other hand, mean night-time SBP increased significantly from normal weight (122.6 ± 15.0 mmHg) to overweight (123.9 ± 15.4 mmHg) and to



obese patients (125.0 ± 15.7 mmHg; $p = 0.044$ among groups) with a parallel increase in night-time pulse pressure (from 50.7 ± 11.1 mmHg to 51.3 ± 11.2 mmHg to 52.7 ± 10.9 mmHg respectively; $p = 0.018$). A higher prevalence ($p < 0.001$) of non-dipper patients and reverse-dippers was associated to an increase in BMI even if TIS was significantly higher in obese and over weight (TIS 1.35) compared with normal weight (TIS = 1.1; $p < 0.001$). The left atrial diameter, left ventricular mass index ($LVM/h^{2.7}$), LVEF and the E/A ratio were significantly worse from normal weight patients to obese patients. Dividing the population by the presence/absence of the anti-hypertensive therapy and based on the pressure control obtained, we found significant differences in the night-time SBP and in the echocardiographic parameters of cardiac organ damage only in hypertensive patients that did not undergo any therapy or in patients who did not get controlled BP values in therapy.

Conclusions: Increasing adiposity is associated with a worsening of night-time blood pressure and higher prevalence of non dipper and reverse dipper patterns. Obesity is also associated with a worsening in cardiac function indexes and cardiac organ damage. This is especially evident in untreated and uncontrolled hypertensive patients. Appropriate pressure control is not associated with increased night-time BP and cardiac damage despite increasing BMI. The evidence of a higher night-time SBP in obese patients, despite higher TIS indicate also that obesity is associated to a relative resistance to antihypertensive treatment but appropriate treatment can reverse at risk conditions.

9.21 Improvement of Cardiovascular Risk Profile and Reduction of Biomarkers of Oxidative Stress and Proatherogenic Inflammation after Cocoa Flavanol Consumption in Subjects with Mild Cognitive Impairment: Cocoa, Cognition and Aging (Cocoa) Study

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Introduction: In recent years numerous studies have led to the hypothesis of a pathophysiological role of cardiovascular risk factors in the onset and progression of both vascular dementia and Alzheimer's disease. On the other hand, the improvement of the cardiovascular risk profile seems to exert a relevant protective effect against development of dementia. Starting from the scientific evidence showing that cocoa flavanols are able to play an important protective effects on vascular system, either directly or through an improved cardiovascular risk profile, we investigated the effects of cocoa flavanols on cardiovascular risk factors in patients with mild cognitive impairment, a clinical condition characterized by early impairment of cognitive functions and the particular susceptibility to develop into full-blown dementia.

Methods: We conducted a double-blind, parallel arm study in 90 elderly individuals with MCI randomized to consume once daily for 8 weeks a drink containing high (HF: ≈ 990 mg flavanols/day), intermediate (IF: ≈ 520 mg flavanols/day) or low levels (LF: ≈ 45 mg flavanols/day) of cocoa flavanols. Seventy-three percent of the enrolled patients were hypertensive, 58% of cases in drug treatment with a good control of blood pressure, 20% were diabetic, 72% of cases treated with oral hypoglycaemic agents, 3% were hypercholesterolaemic.

Results: At the end of follow-up was a significant decrease of blood pressure in groups. At the end of follow-up a significant decrease of blood pressure was observed in HF groups (SBP: -10.0 ± 3.1 mmHg, $p < 0.000$, DBP: -4.8 ± 1.8 mmHg, $p < 0.0001$) and IF (SBP: -8.2 ± 3.5 mmHg, $p < 0.0001$, DBP: -3.4 ± 2.0 mmHg, $p < 0.0001$) but not in the LF group (SBP: -1.4 ± 5.4 mmHg, $p = 0.16$, DBP: -0.9 ± 3.4 mmHg, $p = 0.14$). In parallel, there was a significant improvement in insulin resistance index HOMA-IR in the HF group (-1.7 ± 1.0 , $p < 0.0001$) and IF (-0.9 ± 0.2 , $p < 0.0001$) but not in the LF group (-0.1 ± 0.5 , $p = 0.29$). HOMA-IR at the end of the study was significantly better in the HF group compared with IF ($p < 0.05$). Similar findings were observed with regard to circulating levels of isoprostanes, lipid peroxidation products and recognized biomarkers of oxidative stress, and soluble CD40 ligand, a mediator of vascular inflammation atherogenic. At the end of follow-up circulating levels of 8-iso-PGF₂ were significantly reduced in the HF group (-99.8 ± 60.3 pg/L, $p < 0.0001$) and IF (-65.2 ± 87.2 pg/L, $p = 0.0003$) but not in IF (-3.6 ± 51.4 pg/L, $p = 0.71$). Similarly, circulating levels of soluble CD40 ligand were significantly reduced in the HF group (-1.0 ± 1.2 ng/L, $p < 0.0001$) and IF (-1.0 ± 1.6 ng/L, $p < 0.001$) but not in the IF (-0.4 ± 1.5 pg/L, $p = 0.10$).

Conclusions: Our results indicate that intake of cocoa flavanols may induce a significant improvement of blood pressure and metabolic biomarkers of oxidative stress and inflammation in patients with early cognitive impairment. It remains to be seen whether this will result in a reduction of the evolution toward full-blown dementia, particularly frequent in these patients.

9.22 Gamma Glutamyl Transferase and Cardiovascular Risk in Hypertensive Patients: A New Vision for an Old Enzyme

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Introduction: The purpose of our study is to identify the role played by gamma-glutamyl-transpeptidase (GGT) in the stratification of cardiovascular risk in hypertensive subjects. In particular, our attention was focused on its relationship with classical risk factors and indicators of preclinical organ damage, and ultimately on the cost/benefit analysis related to its possible clinical use.

Methods: 339 newly diagnosed hypertensive patients never treated (aged 29–69 years) free of cardiovascular disease have undergone medical history, recognition of the principal anthropometric indices, measurement of blood pressure (BP), both clinical and monitored, blood assay of metabolic parameters, Echo colour-Doppler cardiac, dose of microalbuminuria. It was calculated for each subject the Framingham cardiovascular risk score. The comparison between groups was performed using the Student t-test for unpaired data in case of continuous variables; were considered significant p values < 0.05 . The linear correlation between the parameters was made using the Pearson method.

Results: 39% of the subjects examined meet the criteria for diagnosis of metabolic syndrome (MS) according to ATP III. The subjects with MS have plasma levels of GGT significantly higher ($p < 0.001$) than those without MS. There is a positive correlation of plasma levels of GGT, even when included in the normal range, with values of waist circumference ($r = 0.21$), alcohol consumption ($r = 0.20$), fasting plasma glucose ($r = 0.20$), triglycerides ($r = 0.24$), total cholesterol and LDL ($r = 0.26$) and serum uric acid ($r = 0.20$), as well as with the values of indexed left ventricular mass ($r = 0.11$) and with the Framingham score ($r = 0.14$). These correlations persist even after adjustment for alcohol consumption. Therefore, there is no correlation at all with age, with cigarette smoking, blood pressure levels both clinical and monitored.

Conclusions: GGT, despite not having the dignity of a cardiovascular risk factor, can be a useful indicator of cardiometabolic risk showing the advantage, compared with more sophisticated biomarkers, to be applicable to a population as large as that of hypertensive subjects without colliding with the economic needs realities of public health care.

9.23 Metabolic Syndrome and Cardiovascular Risk in Hypertensive Subjects: Differences between Males and Females

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Introduction: Within a population of newly diagnosed hypertensive subjects without comorbidities, with no clinically obvious organ damage, not previously treated, we evaluated the differences between females and males with regard to the level of global cardiovascular risk and the presence of metabolic syndrome (MS) defined according to ATP III criteria, in order to highlight the key risk parameters distinguishing the sexes.

Methods: The 523 subjects, 165 females and 358 males, were subjected to: medical history, recognition of the principal anthropometric indices, blood pressure (PA), both clinical and monitored, serological assay of the main metabolic parameters, dose of microalbuminuria, the calculation of the score of cardiovascular risk using the Framingham score and that of the Italian risk chart. Descriptive statistics were obtained for all variables. Mean values and standard deviation were used for quantitative variables, while qualitative variables are counts and percentages were used. Gender differences were analysed using both uni- and multivariate models of conditional logistic regression.

Results: The percentage of patients with MS is similar in the two sexes (M 25% F 24%), whereas the distribution of diagnostic parameters for MS among males and females is different. In fact, males have higher BMI, triglycerides and glucose, while more women, and that is really significant from a statistical point of view, have an increased (> 88 cm) abdominal circumference (AC). By analysing the correlation between the risk score and some of the metabolic parameters examined, but not included in the calculation of the score, there was a difference between males and females with regard to triglycerides, the CA and the BMI. For these variables, the correlation coefficient with the Framingham score is statistically significant in females but not in males ($r = 0.524$ Tg, respectively, BMI $r = 0.276$, AC $r = 0.274$ in females).

Conclusions: Women, although with a lower overall level of CV risk than men peers, seem more sensitive to the risks deriving from visceral obesity and hypertriglyceridaemia. In hypertensive women, some parameters that characterize MS such as visceral obesity and hypertriglyceridaemia may play a crucial role in determining cardiovascular risk and therefore require special attention on weight control and physical activity level.

Nervous System

10.1 Obstructive Sleep Apnoea Syndrome and Sympathetic Nerve Traffic: Regional Behaviour

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Introduction: Obstructive sleep apnoea, both when detected in obese and in lean subjects, is characterized by a marked sympathetic activation. No information exists, however, as to whether the OSA-dependent adrenergic overdrive is confined to selected vascular districts or it is rather generalized to the whole cardiovascular system.

Methods: In 46 middle-age normotensive subjects classified according to body mass index, waist-to-hip ratio and apnoea/hypopnoea index (overnight polysomnographic evaluation) as lean subjects without (n=14) or with (n=8) OSA and as obese subjects without (n=10) or with (n=15) OSA we measured arterial blood pressure (Finapres), heart rate (ECG), venous plasma norepinephrine (high-performance liquid chromatography) and postganglionic sympathetic nerve traffic in the skeletal muscle and skin areas (MSNA and SSNA respectively, microneurography). MSNA and SSNA measurements were made in a randomized sequence over two periods of 30 min each, spaced by a 20- to 30-min interval. Measurements also included evaluation of skin sympathetic responses to emotional stimuli (acoustic stimulus).

Results: The 4 groups were matched for age, gender and BP values, the 2 obese groups without and with OSA showing a similar significant (p<0.05) increase in body mass index (33.1 vs 32.3 kg/m², respectively) and waist-to-hip ratio (0.97 vs 0.96, respectively) compared with the 2 lean groups with or without obstructive sleep apnoea (body mass index 24.0 vs 23.5 kg/m² and waist-to-hip ratio 0.76 vs 0.76, respectively). While MSNA was greater in OSA lean subjects as compared with the non-OSA lean individuals (61.8±2.9 vs 42.4±3.8 bs/100 hb, p<0.04) SSNA was superimposable in the two groups (12.4±1.6 vs 12.3±0.9 bursts/minute, p=NS), paralleling the behaviour of plasma norepinephrine values which failed to show significant differences in the OSA and non-OSA lean subjects (268±39 vs 220±28 pg/mL). Similarly, while MSNA was greater in OSA obese subjects as compared with the non-OSA individuals (72.8±4.2 vs 59.4±3.1 bs/100 hb), p<0.04, SSNA was superimposable in the two groups (13.5±1.4 vs 12.6±1.1 bursts/minute, p=NS). Also in this instance venous plasma norepinephrine values were not significantly different in the two groups (404±41 vs 385±37 pg/mL). SSNA responses to emotional arousal were similar for magnitude in the 4 groups.

Conclusions: These data provide evidence that the sympathetic activation characterizing OSA is not generalized to the entire cardiovascular system. This phenomenon, which takes places both in lean and obese subjects with OSA, may depend on the fact that skin and muscle sympathetic neural districts are governed by mechanisms that are differently affected by the OSA syndrome.

10.2 Changes in Cognitive Function During Acute Exposure to Hypobaric Hypoxia at High Altitude

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Introduction: Exposure to high altitude (HA) reduces the amount of oxygen available to the CNS and can lead to a wide range of cognitive impairment. Studies at HA, indeed, can be considered as an ecological model for analysis of the cognitive functioning of patients with clinical conditions associated with hypoxemia, which are often associated with clinical hypertension. Data previously obtained from the HIGHCARE have shown cognitive changes at HA mostly involving frontal efficiency, together with a greater sensitivity of computerized assessment with respect to traditional neuropsychological measures in these settings.

Aim: To obtain a deeper insight into the cognitive effects of acute exposure to HA hypobaric hypoxia, by means of computerized measures focused on executive-attentional efficiency.

Methods: 39 healthy subjects (18 females, 21 males, mean age: 37.15±8.87 years; mean education: 18.71±3.68 years) were enrolled and underwent to a short neuropsychological assessment at sea level (SL) and during acute exposure to hypobaric hypoxia at 4559 m. Attentional skills and frontal functioning were investigated with a computerized neuropsychological battery named TEA (Test for the Examination of Attention), from Zimmerman and Fimm (1994). A clinical tool

for assessing anxiety was also administered. The data so obtained were correlated with parameters of respiratory and cardiovascular functioning.

Results: Our data show quantitative differences in cognitive performances between SL and HA conditions, mainly in some attentional and frontal abilities assessed by TEA. In particular, with respect to SL, a significant increase in reaction times was found at HA in the Alert subcomponent, both without warning (SL 246.71±56.65 vs HA 274.30±56.07; p<0.0001) and with warning (SL 254.63±66.70 vs HA 271.59±60.62; p<0.02); in Divided Attention subcomponent, with reference to the Auditory task (SL 520.07±77.77 vs HA 545.87±81.11; p<0.01); in Sustained Attention subcomponent, in the 5–10 minutes condition (SL 643.00±128.85; HA 614.86±128.01; p<0.05) and in the left Incompatibility subcomponent (SL 490.05±104.98; HA 464.23±89.53; p<0.05).

Conclusions: By means of a computerized neuropsychological assessment even small frontal cognitive changes could be outlined in the hypoxic condition at HA. In particular, reaction times, more than error assessment, seem more useful to detect the influence of hypoxia over cognitive performance. These results may have implications also for the cognitive assessment of chronic patients with diseases associated with hypoxemia.

10.3 Insufficient Blood Pressure Control Impairs the Executive Functions in Hypertensive Patients

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Introduction: High blood pressure (BP) represents a major risk factor, besides age, for cerebrovascular diseases and cognitive decline.

Aim: To evaluate the association between BP control and cognitive profile, regardless of anti-hypertensive treatment.

Methods: As assessed by medical visit (off) and ABPM (day-night), 283 grade-1 hypertensive patients, 156 with higher (HC-HTN) and 127 with lower (LC-HTN) BP control, with similar age, sex and metabolic assessment, underwent a neuropsychological evaluation by tests for global cognitive and frontal functions (MMSE, FAB), verbal long and short memory (Prose Memory, Digit Span Forwards and Backwards), attention and executive functions (Selective Attention, Stroop, FAS and Clock Drawing), adjusted for age and education. The SBPoff-day% served as measure of 'white-coat effect' (WCEff) and carotid intima-media thickness (IMT) was used as index of vascular damage.

Results: The findings of our study are reported in the table (data are shown as mean±STD; in the table: * p<0.05; ** p<0.01; *** p<0.001). Pearson analysis in LC-HTN, adjusted for IMT and metabolic assessment, showed associations between SBPoff and MMSE (−0.366; p<0.01), FAB (−0.266; p<0.05), CLOCK (−0.350; p<0.001) and STROOP-Errors (0.427; p<0.001). Association between WCEff and FAB (−0.414; p<0.05), CLOCK (−0.323; p<0.01) and STROOP-Errors (0.284; p<0.05) also occurred. Linear regression highlights significant associations between SBPoff and MMSE (−0.336; p<0.001), FAB (−0.238; p<0.05), STROOP-Errors (0.385; p<0.001) and CLOCK (−0.311; p<0.01).

pt/var	SBP/DBPoff	SBP/DBPday	SBP/DBPnight	IMT	WCEff
HC-HTN	122.9±8.6/80±4.6	128.9±10.4/80.3±7	107.6±12/65.4±8.3	0.83±0.2	−6.4±1
LC-HTN	146.4±12.7/90±8***	138.1±14.3/84±8.1***	119.3±16.6/70±9***	0.93±0.2***	7.7±14.5***
pt/var	FAB	ATTENTION	STROOP-Time	FAS	
HC-HTN	16.2±1.8	48.8±5.3	19.2±9.	31.8±9.1	
LC-HTN	15.4±2.3**	46.8±6.8*	22±11.6*	28.6±10.2**	

Conclusions: The insufficient BP control, associated with WCEff, impairs the executive functions as potential causal factor for reducing of inhibitory automatic responses and mental planning.

10.4 Relationship between Coping Styles and Blood Pressure

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Introduction: It is well known that a prolonged physiological activation condition represents a risk factor for hypertension. Therefore, stress perception and the typology of Coping Style adopted play a central role in the development of essential hypertension and cardiovascular diseases. Coping strategies that prompt to face stressful situations are characterized by an increased sympathetic activity, while passive coping strategies are associated with a decreased sympathetic activity.

Aim: To evaluate the relationship between different coping styles and both systolic (SBP) and diastolic (DBP) blood pressure values.

Methods: Fifty-one hypertensive therapy naïve patients from Policlinico "Umberto I" in Rome were included in the study (M/F = 22/29; mean age = 54.2 ± 12.4 years). All participants completed the questionnaire Coping Inventory for Stressful Situations (CISS) for the assessment of coping strategies and their blood pressure was measured three times consecutively. Univariate analysis of variance (ANOVA) was performed considering, as independent factors, Gender and coping styles and as dependent factors SBP and DBP averaged from the three measures taken.

Results: For SBP, the ANOVA Gender x Task Coping showed a main effect of coping ($p < 0.02$): patients who use more often a task coping style have higher blood pressure values compared to those who use it less. For DBP, the ANOVA gender x avoidant coping showed a main effect of Coping ($p < 0.03$): patients who use more often an avoidant coping style have higher blood pressure values compared to those who use it less.

Conclusions: These results, although are to be considered with caution because of the limited number of participants, point out that coping styles affect SBP and DBP in different ways. This suggests that assessing coping styles in hypertensive patients might become useful.

10.5 Promoting Emotional Regulation Skills, Version 2.0 (PERS 2.0): Efficacy in Hypertensive Patients

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Introduction: Hypertensive patients show a deficit in emotional regulation (Alexithymia). A 12 sessions group in Promoting Emotional Regulation Skills (PERS) allows to decrease blood pressure (BP) at 3 months follow-up.

Aim: To verify the efficacy of a new version of PERS (PERS 2.0) in reducing BP in hypertensive patients in the short term and at 1 year after treatment.

Methods: PERS 2.0 is characterized by a larger number of sessions than the previous version (14 instead of 12) and by more flexibility in the experience of "emotional play" proposed by the psychologists to the group on the basis of participants' psychological features. 43 hypertensive patients were recruited at the Centre for the treatment of hypertension of the I Clinica Medica of Policlinico Umberto I in Rome. PERS 2.0 comprehended two groups of 12 subjects; waiting list, including 19 participants, was considered as control group. The use of antihypertensive drug was homogeneous in PERS and WL, gender and levels of alexithymia were balanced among participants. Before and after treatment, at 3 months follow-up and 1 year after the beginning of the treatment, clinical recordings of BP were collected. A medical-psychological anamnesis was also performed. PERS 2.0 groups completed 14 weekly sessions of 2 hours. In each session, the psychologist alternatively proposed an experience of "psychological play", focused on some particular aspects of emotions and followed by a cognitive-emotional elaboration on the topics treated in the PERS and reflection on what happened in the group. Participants were invited to extend their elaboration on daily emotional experiences. After the 14 sessions, there was a further individual clinical interview in order to plan how to use in daily life the emotional skills developed during the treatment.

Results: Main results showed lower levels of systolic and diastolic BP both in PERS and in WL ($p = 0.001$) group, but the decrease was greater in PERS than in WL, in particular at the 3 months follow-up ($p = 0.0004$). In the PERS group, we found the BP decrease also 1 year after the beginning of the treatment ($p = 0.002$).

Conclusions: Even if the blood pressure decreasing is present in both the groups, only in the PERS one this improvement in BP has persisted over time. Comparing the two versions of PERS treatment we could evaluate if PERS 2.0 is more effective than the previous version, as to support the enlargement of the number of the sessions.

10.6 Effects of Insulin Resistance on Resting Heart Rate, Baroreflex Sensitivity and Indices of Autonomic Cardiovascular Modulation in Individuals with High Blood Pressure Levels

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Introduction: Clinical and experimental data indicate that insulin resistance (IR) and the associated hyperinsulinaemia contribute to the pathogenesis of hypertension and cardiovascular (CV) disorders through their effects on the autonomic nervous system.

Aim: To assess the effects of IR on resting heart rate, baroreflex sensitivity (BRS) and indices of CV autonomic modulation in individuals with high BP levels.

Methods: We previously reported on the association between IR, resting HR and BP levels in a random sample ($n = 800$) from the general population of Medellín (Columbia). For the present analysis a total of 85 non-diabetic individuals with a diastolic BP >70th percentile of distribution curve (≥ 85 mmHg, non-treated) were included. Subjects were classified into IR tertiles, based on the distribution of HOMA-index values. CV autonomic modulation was assessed by computer analysis of 10 min beat-to-beat BP and ECG recordings obtained while resting supine (Task Force Monitor, Graz, Austria). RR interval and its standard deviation (SDRR) were averaged. BRS was estimated both with the sequence method (up- and down- slopes) and with the alpha-coefficient. Low-frequency (LF) and high-frequency (HF) spectral components of heart rate variability (HRV) were assessed by auto regressive analysis.

Results: The main findings of our study are reported in the table. After multiple regression adjusting for age, sex, BMI, smoking and SBP, there was a significant overall effect of IR on most parameters. IR was associated with an increased resting heart rate, a reduced BRS (slopes and alpha-coefficient), and lower parasympathetic indices (SDRR, HF-power) of autonomic CV modulation.

Autonomic parameters by HOMA-IR tertiles*

Variable*	T1 (<1.03) [n=28]	T2 (1.03-1.78) [n=27]	T3 (>1.78) [n=30]	Adjusted p (ANCOVA)
RR (ms)	963 ± 21	850 ± 20	848 ± 21	<0.001
SD-RR (ms)	46 ± 3.0	39 ± 2.9	33 ± 2.9	0.02
HF-power (ms ²)	1100 ± 396	300 ± 308	201 ± 300	0.002
LF-power (ms ²)	471 ± 64	287 ± 62	202 ± 63	0.002
Total power (ms ²)	2106 ± 428	850 ± 414	506 ± 419	0.03
Down-slope (ms/mmHg)	15.2 ± 1.2	12.1 ± 1.1	10.5 ± 1.2	0.03
Up-slope (ms ² /mmHg ²)	14.6 ± 1.2	11.5 ± 1.1	10.6 ± 1.2	0.05
Alpha-HF (ms ² /mmHg ²)	16.0 ± 1.7	11.7 ± 1.6	8.5 ± 1.6	0.01
Alpha-LF (ms ² /mmHg ²)	9.1 ± 1.0	7.0 ± 0.9	5.8 ± 1.0	0.03

*Values are expressed as least square means ± standard error.

Conclusions: Our results show a significant effect of IR on resting HR, cardiac baroreflex modulation and HRV in subjects with elevated BP levels, supporting a pathogenic role of IR through its effects on autonomic CV modulation.

Nutraceuticals

11.1 Effects of a Combined Nutraceutical Agent on Metabolic Parameters and Biomarkers of Vascular Remodelling in Post-Menopausal Women

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Introduction: Menopause is associated with a broad, even if usually not massive, changes in a large number of metabolic parameters.

Aim: To evaluate the efficacy and tolerability of a combined nutraceutical approach on a large number of cardiometabolic risk markers and menopause symptoms in otherwise healthy mildly dyslipidaemic post-menopausal women.

Methods: 40 women were enrolled in the context of a controlled, randomized, prospective study with parallel groups. They were randomized to treatment with a nutraceuticals containing soy isoflavones 60 mg and berberine 500 mg or calcium 240 mg + vitamin D3.5 µg at a dosage of 1 tablet daily between meals for 12 weeks.

Results: All patients completed the study without significant side effects. Anthropometric measures, blood pressure, HOMA index, and basal homocysteinaemia significantly improved in isoflavone-berberine treated group when compared with the baseline, but not when compared with the calcium-vitamin D3 treated patients. Compared with calcium-vitamin D3 treated patients, the isoflavone-berberine treated ones experienced a significant improvement in plasma lipid and metalloproteinases serum levels, but also in the main menopausal symptoms.

Conclusions: The short-term assumption of a nutraceutical containing isoflavones and berberine was well tolerated and improved menopausal symptoms, the plasma lipid level, and the level of MMPs in a cohort of mildly dyslipidaemic post-menopausal women, when compared with a neutral control.

11.2 A New Approach for Treatment of Patients with High-Normal Blood Pressure

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Introduction: High-normal blood pressure (BP) is associated with increased risk of cardiovascular (CV) disease. Since BP is a major determinant of global CV risk, BP normalization is expected to reduce the risk of CV events. According to hypertension management guidelines, the balance between potential side effects and benefit of the currently available antihypertensive medications do not support their use in patients with high-normal BP.

Methods: We designed a controlled, randomized, parallel-group clinical trial aimed to compare the magnitude of the antihypertensive effect of two different patented combinations of nutraceuticals (NUT) containing berberine, red yeast rice extract, policosanol, folic acid and coenzyme Q10 respectively with (group A, Armolipid Prev[®], n=20) or without (group B, Armolipid Plus[®], n=10) the addition of Orthosiphon stamineus, a NUT with a documented anti-hypertensive activity. Assessment of effect was performed using 24-hour ambulatory blood pressure monitoring (ABPM).

Results: Group A exhibited significant reduction in mean 24-hour systolic and diastolic BP levels compared with baseline (130.9±7.2 vs 135.9±8.2 mmHg; 83.7±3.8 vs 87.3±4.4 mmHg; both p<0.0001) and these results were confirmed in both daytime (137.2±8.2 vs 141.8±8.1 mmHg; 89.3±4.5 vs 92.8±4.4 mmHg) and in night-time period (115.3±8.5 vs 121.5±10.8 mmHg; 70.3±5.6 vs 74.0±7.5 mmHg; all p<0.001). In contrast, Group B did not exhibit any significant reduction in mean 24h systolic and diastolic BP levels compared with baseline (131.4±8.7 vs 130.1±7.7 mmHg; 87.1±9.8 vs 86.3±6.9 mmHg; both p=NS) and these results were confirmed in both daytime (138.2±8.3 vs 136.2±7.4 mmHg; 92.9±8.8 vs 91.8±5.8 mmHg) and night time period (116.0±10.9 vs 115.3±10.3 mmHg; 73.1±10.4 vs 73.1±12.2 mmHg; all p=NS). The smoothness Index calculated for systolic (0.76 in group A vs 0.32 in group B) and diastolic BP (0.62 in group A vs 0.03 in Group B; both p<0.0001) confirmed the greater efficacy of Armolipid Prev[®] in terms of BP reduction, and shows more homogeneous effect over 24 h.

Conclusions: NUT with a demonstrated antihypertensive effect may represent a promising approach for BP control in subjects not deserving a pharmacological treatment for BP control.

11.3 Improvement of Cognitive Function after Short-Term Flavanol-Rich Cocoa Consumption in Subjects with Mild Cognitive Impairment: Cocoa, Cognition and Aging (Cocoa) Study

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Introduction: Findings from human cognition studies are suggestive of a positive association between flavanol consumption and cognitive function.

Aim: To verify the hypothesis that cocoa flavanols might improve cognitive function in subjects with mild cognitive impairment (MCI) we conducted a double-blind, parallel arm study in 90 elderly individuals with MCI randomized to consume once daily for 8 weeks a drink containing high (HF:990 mg flavanols/day), intermediate (IF:520 mg flavanols/day) or low levels (LF:45 mg flavanols/day) of cocoa flavanols.

Methods: Changes in cognitive function as assessed by a combination of four standardized tests: Mini Mental State Examination (MMSE), Trail Making Test (TMT) A, TMT B and verbal fluency test (VFT). Baseline performance on the cognitive function tests was similar for the three treatment groups indicating an adequate randomization procedure.

Results: At the end of the follow-up period, MMSE was similar in the three treatment groups (p=0.13). The time required to complete TMT A and TMT B was significantly (p<0.05) lower in subjects assigned to HF (38.10±10.94 sec and 104.10±28.73 sec, respectively) and IF (40.20±11.35 sec and 115.97±28.35 sec, respectively) in comparison to those assigned to LF (52.60±17.97 sec and 139.23±43.02 sec, respectively). Similarly, VFT score was significantly (p<0.05) better in subjects assigned to HF (27.50±6.75 words/60 sec) in comparison to those assigned to LF (22.30±8.09 words/60 sec). Consistent with these findings, composite cognitive z-score, calculated as the mean of the psychometric tests score after z transformation, at the end of follow-up was significantly better (p<0.05) in subjects assigned to HF (0.687±0.482) in comparison to those assigned to LF (0.000±0.803). Changes of composite cognitive z score through the study period were strongly correlated with reductions in insulin resistance (delta HOMA-IR/ delta z score: beta: -0.20596, p<0.0001, partial r²=0.4013).

Conclusions: The current study provides encouraging evidence that the regular consumption of cocoa flavanols may be effective in improving cognitive function in adults with MCI. Findings suggest that this effect may be mediated in part by improvements in insulin sensitivity.

12.1 Blood Pressure-Lowering Effect of Aliskiren and its Role on Cardiac and Renal Damage in High-Risk Hypertensive Subjects: A 12-Month Study

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Introduction: The blood pressure (BP) lowering effect of ACE inhibitors, angiotensin-II receptor blockers agents on hypertension and organ damage, alone or in combination therapy, is limited by the compensatory increase of renin because it activates renin/prorenin receptors and escape mechanisms of angiotensin activation.

Aim: To evaluate the antihypertensive efficacy, cardiac and renal damage effect and safety of aliskiren, a renin direct inhibitor, that it was added in a group of hypertensive high-risk subjects with uncontrolled BP (i.e. >130/80 mmHg) despite a 2-fold antihypertensive treatment.

Methods: 47 subjects (27 men and 20 women) aged 59.7 ± 11.1 years, were assigned to receive once-daily aliskiren 150–300 mg for 12 months. Office BP measurements were taken at every follow-up visit (after 1, 6 and 12 months), while 24-hour ambulatory BP measurements (ABPM), echocardiography, TC^{99m}-DTPA renal scintigraphy and 24-hour albuminuria assessment were evaluated at the enrolment and at the end of follow-up. Analysis of variance compared BP, left ventricular mass index (LVMI), glomerular filtration rate (GFR) and albuminuria values changes from baseline to the follow-up.

Results: A significant reduction of systolic (–32 mmHg, $p < 0.0001$) and diastolic (–13.5 mmHg, $p < 0.0001$) office BP values, of mean systolic (–9.2 mmHg, $p < 0.0001$) and diastolic (–5.1 mmHg, $p < 0.003$) 24-hour ABPM values were found. LVMI was reduced from 128.7 g/m² to 113.8 g/m² ($p < 0.005$); GFR was steady (from 61.3 to 61.5 mL/min/1.73 m², NS), while albuminuria values significantly decreased from 57.4 ± 116.2 to 21.3 ± 41 mg/24-hour ($F = 5.67$, $p > 0.02$). Adverse events caused withdrawal of 4 subjects (3 cases of gastrointestinal disease, 1 case of alopecia).

Conclusions: Aliskiren was effective in lowering both office and 24-hour ABPM values; it was also effective on LVMI improvement in men and women; there was no significant influence on GFR which maintained stable, while albuminuria significantly decreased. Safety was good, even in combination with ACE inhibitors and angiotensin II receptor blockers.

12.2 Antihypertensive Effect of Lactotripeptides in a Large Cohort of Normotensive and Mild-to-Moderate Hypertensive Subjects: A Double-Blind, Randomized, Clinical Trial

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Introduction: A large number of randomized clinical trials show conflicting results regarding the antihypertensive effects of VPP-IPP lactotripeptides in different ethnicities.

Aim: To evaluate their effect on a large cohort of Mediterranean subjects.

Methods: This is a large, double-blind, randomized, clinical trial involving normotensive subjects ($n = 100$) or patients affected by mild-to-moderate hypertension ($n = 61$). Thus, we enrolled 161 subjects in primary prevention for cardiovascular disease (mean age: 44 ± 11 years; body mass index: 25 ± 4 kg/m²; SBP: 132 ± 12 mmHg; DBP: 83 ± 8 mmHg; PP: 50 ± 9 mmHg), and, after a 1-month period of stabilization diet, we randomized them to placebo or to VPP-IPP lactotripeptides (kindly offered by Barilla SpA, Parma, I). The efficacy and tolerability of the tested treatment was evaluated after 1 month.

Results: The tested treatment has been well tolerated. When compared with the baseline, office SBP significantly improved in the VPP-IPP treated patients (–3.4 ± 6.5 mmHg, $p < 0.001$), while office DBP significantly improved in both treatment groups. However, when comparing the blood pressure changes during the study, either SBP ($p < 0.001$) or DBP ($p = 0.002$) (but not PP) significantly improved in the VPP-IPP treated subjects when compared with the placebo group. Either SBP ($p = 0.005$) or DBP ($p = 0.014$) significantly improved versus placebo in men, while only SBP ($p = 0.001$) in women. The change in SBP was significantly related to the baseline SBP, while the one in DBP to the baseline DBP, heart rate and body mass index. ABPM evaluation did not confirm the previously listed results.

Conclusions: A short-term supplementation with VPP-IPP lactotripeptides is associated with a significant improvement of office SBP and DBP when compared with placebo in a large sample of Mediterranean subjects, especially in male subjects.

12.3 Persistence and Compliance to Treatment with Diuretics as First Choice in Antihypertensive Therapy

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Aim: To evaluate efficacy and tolerability of antihypertensive treatment started with thiazide diuretics (T), compared with initiation with different antihypertensive therapies (A).

Methods: 80 general practitioners (GPs) selected 2302 hypertensive patients (57.5% men, age 54 ± 11 years), either recently diagnosed or with uncontrolled blood pressure (BP), who were referred to the Hypertension Center of Federico II University Hospital. Patients were randomly assigned to therapy with either T or A. During follow up, GPs collected information about tolerability and side effects of the therapy and, if appropriate, they could make changes by adding any different class of drugs in order to try to achieve optimal BP control. The on-line medical chart was updated and shared with the Hypertension Center. Routine blood tests were performed at baseline, after 1 year and at the end of the study period. They included: blood tests, ECG, echocardiogram and carotid ultrasound.

Results: During follow-up (2 years), 61.5% of patients had to change their initial therapy (79% in group T and 44% in group A; $p < 0.0001$). Reasons for change in therapy were: insufficient BP control (61% in group T, 39% in group A), adverse side effects (10% in group T, 3% in group A), drug intolerance (7% in group T, 1% in group A; all $p < 0.0001$). At the end of follow up, hypertensive therapy was as follow: β -blockers (21% in T, 24% in A; NS), ATI-receptor antagonists (35% in T, 39% in A; NS) ACE inhibitors (30% in T, 29% in A; NS), calcium-channel blockers (17% in T, 19% in A; NS), diuretics (52% in T, 30% in A, $p < 0.0001$). Patients in group T took an average of 1.55 pills a day, versus an average of 1.44 pills a day of patients in group A ($p < 0.0001$). Optimal BP control was obtained in 55% of patients in group T and in 54% of patients in group A (NS). No difference was observed in variation of blood tests parameters and markers of target organ damage when compared to baseline values, no significant difference was found in incidence of fatal and non-fatal CV events.

Conclusions: The initiation of antihypertensive therapy by thiazide diuretics, compared with any other class of drugs, does not significantly affect the final result in terms of blood pressure control, but it implies a more frequent modification in therapy and the use of a slightly larger number of medications. This study also showed that a more integrated cooperation between the 1st and 2nd level of medical assistance improves BP control in a high proportion of the studied population.

12.4 Effects of Addition of Aliskiren Compared with Ramipril or Losartan in Diabetic Patients with Uncontrolled Hypertension and Microalbuminuria

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Introduction: Drugs inhibiting the rennin-angiotensin-aldosterone system (RAAS) such as ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), have been shown to be effective for controlling blood pressure (BP) and organ damage. Recently, direct renin inhibitor aliskiren provide a new approach to inhibiting the RAS at the most proximal, specific, and rate-limiting step.

Aim: To evaluate the effect of an additional treatment with aliskiren versus ramipril or losartan, in hypertensive patients with additional risk factors including diabetes and nephropathy already treated with a conventional first-line therapy.

Methods: We included 126 hypertensive patients (65 M and 61 F, mean age 66.8 ± 8.9 years) already treated with conventional therapy that add-in an ARBs or ACEIs from at least 6 months. Patients were eligible for enrolment if they maintained systolic blood pressure (SBP) >130 and diastolic blood pressure (DBP) >80 mmHg, also suffering from type 2 diabetes mellitus and microalbuminuria. After the enrolment, hypertensive patients were randomly assigned to receive for 6 months an additional dose of aliskiren (group A) or losartan/ramipril (group B). Thus, two groups of patients were followed-up, the group A (hypertensive patients treated with a combination of aliskiren and a RAS blocker) and the group B (hypertensive patients treated with losartan if already treated with ACEI, and with ramipril if already treated with ARB).

Results: After 6 months, in both groups of treatment, there was a reduction of the pressure values. Aliskiren treatment reduced significantly the levels of SBP in group A in respect to group B ($p < 0.001$), while no difference was found in DBP lowering between two groups. There was a significant reduction of microalbuminuria in both two treatment groups ($p < 0.0001$ in group A and $p < 0.001$ in group B compared to baseline), with a greater reduction in group A (–17% vs group B, $p < 0.001$). No difference was noticed relatively to the fasting glucose levels. The side-effects incidence was similar between the two groups; no patient dropped out the follow-up.

Conclusions: Our experience shows that the addition of the direct renin inhibitor aliskiren to a standard first-line therapy with a RAS blocker (ACEI or ARB) provides additional therapeutic effects in terms of achievement of blood pressure target and reduction of urinary albumin excretion in respect not only to the standard therapy, but also to the combination therapy with losartan and ramipril. Moreover, the combination therapies used showed substantial efficacy and safety.

12.5 Use of Aliskiren in a Population of Patients Affected by Resistant Hypertension

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Introduction: Aliskiren is a non peptidic drug with good oral bioavailability that acts through direct renin inhibition.

Aim: To evaluate effects of aliskiren in a population of patients (pts) with resistant hypertension.

Methods: Data were collected on a population of 43 out-clinic patients (age 71 ± 1), 41–85 years, 26 women, 26 patients with metabolic syndrome) affected by resistant hypertension. Aliskiren was prescribed at time 0, patients were assessed at time 0 and after 6 months of therapy.

Results: The main findings of our study are reported in the table. Blood pressure (systolic – SBP – and diastolic – DBP) at baseline was (mean ± SD) 159 ± 14/87 ± 10 mmHg and heart rate (HR) 67 ± 10 bpm. After 6 months of therapy the values were modified as follows: PA 138 ± 13/80 ± 6 (p < 0.001 for both SBP and DBP) and HR 65 ± 8 bpm (p = NS). Of our patients, 28 were treated with aspirin (ASA) and 27 were on statin therapy. Subgroups ASA yes/ASA no and statin yes/statin no showed no significant differences at baseline, but differences were present after treatment (as shown in the table below).

	ASA yes			ASA no			Statin yes			Statin no		
	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR
Baseline	161 ± 15	88 ± 10	66 ± 9	155 ± 11	86 ± 11	68 ± 12	160 ± 15	86 ± 11	66 ± 9	158 ± 14	88 ± 9	69 ± 11
After 6 mo	135 ± 9	79 ± 6	63 ± 7	143 ± 17	81 ± 5	69 ± 9	137 ± 11	80 ± 5	63 ± 7	139 ± 16	80 ± 7	69 ± 10
p-Value	<0.001	<0.001	NS	0.03	NS	NS	<0.001	0.004	NS	0.001	0.009	NS

In particular, after 6 months of therapy, patients of ASA yes and statin yes groups showed significantly lower heart rate compared with patients in ASA no and statin no groups.

Conclusions: When aliskiren is used in patients with uncontrolled hypertension, it can significantly lower blood pressure and have important synergies with other drugs often taken by this population.

12.6 Effect of Antihypertensive Treatment on Morning Blood Pressure Surge: Detailed Assessment by Combination of 24-Hour Ambulatory Blood Pressure Monitoring and Polysomnography

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Introduction: 24-hour, daytime or night-time blood pressure (BP) average values correlate with hypertension-related organ damage and predict cardiovascular risk more closely than office BP. In particular, the rate of morning BP rise, at the time of awakening, appears to significantly contribute to the higher morning incidence of cardiovascular events. Little information is available on the ability of antihypertensive drugs with different duration of action to specifically buffer morning BP rise.

Aim: To compare the effects on 24h- and on morning BP of once a day (od) administration of telmisartan (T) and valsartan (V) in patients with mild to moderate hypertension, according to a randomized, double blind design. Sleep was objectively quantified by polysomnography.

Methods: Consecutive patients (age range 18–65 years) with essential hypertension (clinic systolic (S) BP ≥ 140 and/or diastolic (D) BP ≥ 90 mmHg; 24-hour SBP ≥ 125 and/or DBP ≥ 80 mmHg) and untreated since at least 10 days were enrolled. Patients underwent 24 h ambulatory (A) BP monitoring (both with Spacelabs 90217 arm cuff device and with beat by beat Portapres device combined with full polysomnography, Siesta device) three times, under placebo (P), T 40–80 mg or V 80–160 mg, each administered in the morning for 8 weeks according to a randomized sequential order.

Results: 31 subjects (24 males, mean age 54 years, mean BMI 26.6 kg/m², (range, 19.7–30.0) were included. Complete data were available from 21 subjects (16 males). At the end of each 2-month treatment period the rate of patients with controlled ASBP and ADBP was 95% versus 50% for early morning hours (6:00 or awakening time to 09:59 a.m., <135/85 mmHg); 62% versus 37% for 24-hour ABP (<125/80 mmHg); 69% versus 31% for daytime ABP (<135/85 mmHg) and 69% versus 50% for night-time ABP (<120/70 mmHg), with T and V, respectively (all T-to-V differences, p < 0.05). The corresponding rates of ABP normalization with P were 50% for early morning hours, 0% for 24h, 12% for daytime, 14% for night-time ABP. The rate of clinic BP normalization (<140/90 mmHg) was 81% versus 62% with T and V, respectively (p < 0.05). The proportion of dippers (night-time SBP or DBP fall > 10% of daytime value) was 69% with P, 75% with T and 56% with V (T vs P and T vs V p < 0.05).

Conclusions: T administration od offered a significantly better clinic and 24-hour ABP control than either P or V, also when focusing on early morning hours at the time of awakening (defined by polysomnography), when the highest rate of cardiovascular events occur. T on morning administration was also associated with greater ABP dipping rate than P or V.

12.7 Use of Aliskiren in Clinical Practice: Data from a Large Italian Cohort of Hypertensive Patients Included in the National AIFA Web-Based Drug Monitoring System

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Introduction: In Italy, prescriptions of the direct renin inhibitor aliskiren (aliskiren) to high-risk hypertensive patients must be electronically filled by specialized physicians only when a therapeutic plan, including at least two antihypertensive drugs (independently of the class or the dosage), fails to normalize BP levels.

Aim: To retrospectively analyse the effects of the addition of aliskiren 150–300 mg daily to antihypertensive therapy in a setting of clinical practice in a non-controlled population of high CV risk hypertensive patients.

Methods: Clinical data were derived from patients included in the national web-based drug monitoring system. Follow-up visits were required for measuring BP levels, and collecting data on drug safety and tolerability. At 1-month or 6-month follow-up visits, aliskiren could be up-titrated from 150 mg to 300 mg daily in uncontrolled hypertensive patients, if needed.

Results: Between March 2009 and February 2010, aliskiren was prescribed to 11 511 treated, uncontrolled hypertensive patients (47.6% female, aged 68.0 ± 11.1 years, BMI 28.4 ± 4.9 kg/m²). In those patients who have 1-month follow-up visit (n = 8197; 70.6%), systolic and diastolic BP was reduced from 158.9 ± 16.8 to 142.1 ± 15.2 mmHg (p < 0.0001) and from 90.8 ± 9.6 to 83.1 ± 8.5 mmHg (p < 0.0001), respectively. In those patients who have 6-month follow-up visit (n = 4907; 42.3%), BP was reduced from 158.7 ± 17.0 to 141.9 ± 15.0 mmHg at 1 month and to 137.9 ± 13.9 mmHg at 6 months for the systolic and from 90.5 ± 9.7 mmHg to 83.0 ± 8.4 mmHg at 1 month and to 81.3 ± 8.0 mmHg at 6 months for the diastolic BP levels. Only a few drug-related side effects was reported (n = 33).

Conclusions: Although data derived from registries need to be interpreted with caution, the Italian web-based drug monitoring system provided information on 'real-life' use of aliskiren in hypertension. Systolic and diastolic BP levels were markedly and consistently reduced after addition of aliskiren to antihypertensive therapy (including ACE inhibitors or ARBs). This effect was associated with very low rates of reported side effects.

12.8 Blood Pressure Control in Italy: Analysis of Clinical Data from 2005–10 Surveys on Hypertension

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Introduction: Worldwide blood pressure (BP) control is reported to be poor in hypertensive populations. In 2007, we reported a poor rate of BP control in hypertension surveys performed between 1995–2005 in Italy.

Aim: To evaluate clinic BP levels, rate of BP control and prevalence of cardiovascular (CV) risk factors and organ damage in recent hypertension surveys performed in our Country.

Methods: We reviewed the medical literature for all hypertension surveys, performed between 2005–10, which clearly reported information on clinic BP levels, rates of BP control, proportions of treated and untreated patients and prevalence of CV risk factors, signs of organ damage and associated clinical conditions in different clinical settings (general population, general clinical practice, outpatient clinics and hypertension centres).

Results: The overall sample included 162,633 hypertensive patients (96,394 women, mean age 56.6 ± 10.2 years, BMI 27.1 ± 4.2 kg/m², duration of hypertension 90.2 ± 12.4 months). In this population, average systolic and diastolic BP levels were 144.5 ± 16.1 and 86.8 ± 9.8 mmHg, respectively; these values were higher in patients followed by hypertension centres (146.5 ± 17.3/88.5 ± 10.3 mmHg) than by general practitioners (143.5 ± 14.1/85.08.9 mmHg; p < 0.01). More than half of the patients was on stable antihypertensive treatment (n = 93,871, 57.7%), among which 36,453 (44.1%) were controlled. In treated hypertensive patients, ACE inhibitors were the most frequently prescribed drugs (31.5%), followed by calcium antagonists (26.5%), diuretics (22.1%), β-blockers (21.9%), and ARBs (16.8%).

Conclusions: Our analysis of a large sample derived from recent observational studies on hypertensive patients in Italy demonstrates the persistence of poor BP control and relatively high prevalence of risk factors and organ damage, supporting the need for a more effective and comprehensive approach to improve clinical management of hypertension at all level of care in Italy.

12.9 Different Effect of Aliskiren and Ramipril on Arterial Stiffness and Wave Reflection in Previously Untreated Essential Hypertension Patients

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Introduction: Essential hypertensive patients (EH) are characterized by increased arterial stiffness. The renin-angiotensin system (RAS) activation is an important pathophysiological mechanism for arterial stiffening. Aliskiren is a novel direct renin inhibitor, whose effects on arterial elastic properties in EH are unknown.

Aim: To evaluate whether aliskiren, compared with the ACE inhibitor ramipril, can improve arterial stiffness and peripheral wave reflection in untreated mild-moderate EH, according to a double-blind, parallel-group study.

Methods: 40 EH were randomized to a 12-week treatment with aliskiren (300 mg/daily) or ramipril (10 mg/daily) [n=20 each group]. At baseline and after treatment arterial stiffness

was assessed as carotid-to-femoral pulse wave velocity (PWV) by arterial tonometry (Sphygmocor). Central blood pressure and augmentation index (AIx) was also assessed by pulse wave analysis.

Results: Blood pressure values were similarly normalized by aliskiren (from $147 \pm 8/95 \pm 2$ to $131 \pm 9/85 \pm 4$ mmHg) and ramipril (from $149 \pm 6/96 \pm 6$ to $133 \pm 8/86 \pm 3$ mmHg). Central pulse pressure was also similarly decreased (aliskiren from 39.5 ± 7.7 to 35.5 ± 6.9 mmHg, $p < 0.01$; ramipril from 38.4 ± 8.9 to 34.8 ± 5.7 mmHg, $p < 0.01$). Aortic PWV was similarly decreased by aliskiren (from 7.7 ± 1.2 to 7.1 ± 1.3 m/s, $p < 0.05$) and ramipril (from 7.5 ± 1.1 to 6.9 ± 1.1 m/s, $p < 0.05$). AIx was reduced after aliskiren (from 18.0 ± 8.1 to $13.6 \pm 17.4\%$, $p < 0.05$) and after ramipril treatment (from 19.1 ± 8.3 to $17.1 \pm 8.1\%$, $p < 0.05$), but aliskiren induced a significantly greater reduction ($p < 0.05$).

Conclusions: These results indicate that RAS blockade by aliskiren and ramipril can improve aortic stiffness in EH. The direct renin inhibitor seems to have an additional positive effect on wave reflection, possibly linked to an effect on the peripheral microcirculation.

Vessels and Endothelium

13.1 Central Blood Pressure is an Independent Predictor of Worse Outcome in Young to Middle-Aged Subjects Screened for Stage I Hypertension

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Introduction: Central blood pressure (BP) has been found to be associated with target organ damage in adult and elderly hypertensive patients. The clinical significance of central BP in young to middle-aged hypertensive subjects is less known.

Aim: To evaluate the association of central BP with target organ damage and the risk of future hypertension in a cohort of subjects from the HARVEST study.

Methods: We studied 305 subjects screened for stage I hypertension (mean age, 38 ± 10 years), to determine which subjects developed hypertension needing therapy according to current guidelines. Central BP was obtained from radial artery tonometry using the Specaway DAT System. Target organ damage was defined as the presence of left ventricular hypertrophy and/or microalbuminuria. Central mean BP and central pulse pressure were tested in the multiple regression models.

Results: Baseline peripheral BP was $138 \pm 12/86 \pm 7$ mmHg, 24-hour BP was $130 \pm 11/80 \pm 8$ mmHg and central BP was $125 \pm 13/86 \pm 8$ mmHg. In a multiple logistic regression including ambulatory BP, central mean BP was associated with degree of target organ involvement ($p = 0.01$). During 9 years of follow-up, 156 subjects developed hypertension needing treatment. In logistic regression analyses including sex, age, smoking, alcohol and coffee use, physical activity, parental hypertension, body mass index, and heart rate, central mean BP was an independent predictor of future hypertension ($p = 0.004$), whereas central pulse pressure was not associated with outcome. Also ambulatory systolic ($p = 0.002$) and diastolic ($p = 0.02$) BPs were independent predictors of future hypertension. When all pressures were included in the same logistic model, central mean BP remained a predictor of new onset hypertension ($p = 0.004$) on top of ambulatory BP. In the subjects divided according to whether their central mean BP was above or below the median (98.7 mmHg), sustained hypertension was developed by 38.8% of the subjects with low central mean BP and by 64.5% of the subjects with high central mean BP ($p < 0.001$). Subjects with high central BP had a 2.5 (95% CI 1.4, 4.2) increased adjusted risk of hypertension compared with those with low central BP.

Conclusion: These data show that in young to middle-aged subjects in the early stage of hypertension, high central BP is a significant predictor of adverse outcome on top of 24-hour BP.

13.2 Hypertension and Antiangiogenetics: An Emerging and Intriguing Issue

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Introduction: In the last decade a new class of anticancer drugs targeting the angiogenesis was developed. These compounds, antagonizing the vascular endothelial growth factor activity (anti-VEGF), are 'tyrosine kinase inhibitors' (i.e. sunitinib: Sutent[®], and sorafenib: Nexavar[®]) and 'anti-VEGF-receptor' (i.e. bevacizumab: Avastin[®]); other new drugs are under investigation. Their employment is currently approved for colorectal, lung, breast, kidney and liver cancer, but they are being evaluating in almost all neoplasms. Since the beginning of their use a significant increase in blood pressure was noticed in a number of patients but, up to date, no definitive data about the management of this 'class' of side effect do exist.

Aim: To perform a literature review in order to better focus on anti-VEGF-related hypertension (HT).
Methods: A PubMed search was performed ('hypertension and bevacizumab', 'hypertension and sorafenib', 'hypertension and sunitinib'). Twenty out of about 500 papers were selected and reviewed. EMEA summaries of products' characteristics were also consulted (www.EMA.europa.eu).

Results: The prevalence of HT, was 22–36%, 17–24% and 15–47%, for the three drugs, respectively (with grade 3–4 HT: 6%, 7% and 7%). The prevalence of HT appeared to be dose-related. The possible underlying (but not completely clarified) mechanisms explaining HT development are: (i) decrease in nitric oxide synthesis; (ii) neurohormonal factors (i.e. renin, aldosterone, catecholamines, endothelin I); and (iii) vascular rarefaction. The management of anti-VEGF-related HT was not different from that of general population (the more commonly used drugs being ACE inhibitors, β -blockers, calcium channel blockers, and diuretics); a dose reduction of anti-VEGF was successfully applied in more severe HT cases. Unfortunately, only few clinical trials have been performed in this view, and data about the better approach and the outcome of these patients were not available. Moreover, two intriguing issues are the probable correlation with a better cancer prognosis in patients developing HT, and the possible cytostatic effect of ACE inhibitors. Both these aspects have been documented in some papers, but not extensively investigated yet.

Conclusions: Anti-VEGF induced HT represents a quite common side effect. To date, no clear data about management of these patients exist and they are usually treated as per the general population. In addition, the interesting suggestions of a better cancer prognosis in HT patients and the possible cytostatic role of ACE inhibitors deserve to be better explained and evaluated. According to these evidences, more data, possibly in clinical trials context, are advocated in order to better define an optimal and tailored approach to these patients.

13.3 Overweight or the Obese State does not Influence the Retinal Microvascular Patterns

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Introduction: Previous studies by our group and others have provided evidence that blood pressure (particularly systolic) is an important determinant of the retinal vascular network characteristics and that the microvascular alterations seen in hypertension are directly related to the severity of the hypertensive state. Whether bodyweight and body fat depot are also major determinants of the patterns of the retinal microcirculation is debated. It is also debated the impact of the overweight or the obese state on the retinal microvascular network.

Methods: In 278 healthy subjects of both genders (age 53.4 ± 0.6 years, mean \pm SEM), displaying a wide range of bodyweight values, we measured anthropometric parameters, clinic and ambulatory blood pressure and metabolic variables (insulin, HOMA index, leptin). Measurements also included arterial-venular ratio (AVR), central retinal artery and vein equivalent (CRAE and CRVE, respectively), assessed via non-mydratric retinography (TopCon TRC-NW200).

Results: In the population as a whole clinic blood pressure values amounted to $134.2/84.6$ mmHg, 24-hour blood pressure to $120.9/79.6$ mmHg, body mass index (BMI) and abdominal circumference (AC) to 26.1 kg/m² and $89.4/97.9$ (female/male) cm respectively. BMI was <25 kg/m² in 115 individuals (classified as lean), while it was between 25 and 30 kg/m² in 111 (overweight) and >30 kg/m² in 52 (obese). The 3 groups were age-matched and displayed systolic and diastolic BP values in the normal range with a tendency to greater values in the obese group. In the population as a whole AVR did not show any significant relationship with BMI ($r=0.027$, $p=NS$) and AC ($r=0.2$, $p=NS$), this being the case also for CRAE and CRVE. Furthermore AVR ratio was similar in lean, overweight and obese subjects (0.85 ± 0.01 , 0.84 ± 0.005 and 0.87 ± 0.009 a.u., respectively, $p=NS$). No significant difference in AVR was also found by subdividing the obese group according to the central or peripheral distribution of the excessive fat depot (0.89 vs 0.84) both in male and female subjects. A similar behaviour was seen for CRAE and CRVE. No relationship was finally found between insulin, HOMA and leptin with the three markers of the retinal microvasculature.

Conclusions: Our data show that in contrast to blood pressure bodyweight is not a major determinant of the patterns of the retinal microcirculatory network. They also show that the obese state does not affect the main features of the retinal microcirculation and that this is the case independently on the central or peripheral nature of the obese state.

13.4 Effects of Physical Training on Platelets Activation in Patients with Claudicatio Intermittens at Rest and After Ischaemia

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Introduction: training is a documented effective treatment in patients affected from peripheral arterial disease. Platelet activation plays a pivotal role in atherosclerosis progression and cardiovascular events. In ischaemic heart disease, platelet activation is reduced by aerobic training, while strenuous exercise is associated with enhanced activation. Few data can be found for patients with peripheral arterial disease on training.

Aim: to evaluate the effects of aerobic training on platelet activation and oxidative stress at rest and after maximal walking exercise.

Methods: 18 patients with claudication were enrolled and underwent a 15 days aerobic training period (cycling and treadmill exercise under maximal walking capacity). At the beginning and at the end of the treatment we analysed: platelet aggregation (PFA-100), P-selectin, malondialdehyde. We also performed: ankle-brachial index, absolute walking distance. After treadmill test we repeated: PFA-100, P-selectin and malondialdehyde.

Results: Absolute walking distance increased after training. At the end of training absolute walking distance increased (450 ± 180 vs 250 ± 108 m; $p > 0.05$), malondialdehyde decreased (124 ± 20 vs 147 ± 25 μ g/l; $p < 0.05$), P-selectin decreased (0.81 ± 0.31 vs 1.40 ± 0.62 $p < 0.005$) and epinephrine platelet activation decreased ($p < 0.05$). Maximal treadmill test increased ADP platelet activation, while it decreased at the end of training ($p < 0.05$).

Conclusions: Aerobic supervised training in patients with peripheral arterial disease improves platelets aggregation, oxidative stress and platelets aggregation during ischaemia. These data support and help explaining the benefit of training in atherosclerosis.

13.5 Aortic Size Index Enlargement is Associated to Central Haemodynamics in Essential Hypertension

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Introduction: Arterial hypertension is a recognized leading cause of aortic root dilatation (ARD). Mechanical stress in the aortic wall is proportional to blood pressure (BP) and vessel diameter, thus hypertension and aortic dilation represent important risk factors for aortic dissection.

Aim: To evaluate the association between brachial and central blood pressure (bBP and cBP) levels and aortic root dilatation (ARD) in essential hypertensive patients.

Methods: 190 essential hypertensive patients (mean \pm SD) 55 ± 11 years; SBP/DBP $137.5 \pm 13.9/82.6 \pm 9.5$, mean \pm STD deviation) underwent echocardiographic and a tonometric evaluation for aortic root dimensions and central blood pressure levels.

Results: 91 of the 190 studied patients had an ARD (defined as Aortic Size Index [ASI] >2 cm/m²). Central haemodynamic variables were significantly associated to ASI. Patients with increased ASI, were significantly older (60 ± 10 vs 50 ± 11 years; $p < 0.0001$), had higher levels of augmentation index (Aix; 28 ± 10 vs 21 ± 10 , $p < 0.0001$), augmentation pressure (AP; 13 ± 6 vs 8 ± 5 mmHg, $p < 0.0001$), and central pulse pressure (cPP; 44 ± 10 vs 39 ± 8 mmHg $p < 0.0001$) compared with patients with normal ASI. In a logistic regression analysis Aix resulted the only significant predictor of ASI.

Conclusions: In hypertensive patients, augmentation index and central blood pressure were associated with aortic root dilatation, whereas brachial pulse pressure was not. Patients with increased aortic size index may lose part of the elastic properties of the aorta, demonstrating a more strict correlation between ASI and central haemodynamic indexes, in particular central pulse pressure and augmentation.

13.6 Antiretroviral Therapy and Endothelial Function in HIV Patients

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Introduction: The introduction of antiretroviral drug therapy (ART) led to a significant reduction of morbidity and mortality in HIV patients. In ART-treated patients it has been noticed an increased number of fatal and non-fatal cardiovascular events, even in absence of a blood pressure elevation. Recent studies have suggested that the increased cardiovascular risk may depend on the fact that ART and the viral infection may adversely affect endothelial function.

Methods: We studied 43 normotensive, euglycaemic HIV positive patients. 20 were treated with ART (age 44 ± 7 years; blood pressure: $123/73 \pm 13/9$ mmHg, mean \pm SD), and 23 were untreated (i.e. naive, age 40 ± 8 years; BP $131/78 \pm 12/9$ mmHg). Endothelial function was studied as brachial artery flow-mediated dilation (5 min hand exclusion), while non-endothelial (non-specific) vasodilation was evaluated as the increase in arterial diameter obtained after sublingual administration of 0.3 mg of nitroglycerin (TNG). Brachial artery diameter and blood flow were measured by an Echotracking system with a 7.5 MHz probe (ARTLAB).

Results: Blood pressure values were similar in the two groups. A significantly greater basal diameter of the brachial artery was found in ART treated patients (4261 ± 895.5 vs 3673 ± 890.5 μ , $p = 0.02$). No significant difference in flow-mediated dilation ($9.5 \pm 5.8\%$ vs $9.6 \pm 6\%$, $p = 0.99$) or in nitroglycerin-induced dilation (26.3 ± 8.7 vs $30.3 \pm 14.5\%$, $p = 0.6$) was found between ART-treated and naive HIV-patients. Also, no difference was found in the increase in blood flow triggered by FMD and TNG, and no difference in the mean carotid IMT (597 ± 152 vs 542 ± 120 μ ; $p = 0.39$) between the two groups.

Conclusions: The large arteries endothelial function and the media layer response to exogenous nitric oxide are not affected by antiretroviral therapy. It can be thus concluded that in HIV patients the endothelial dysfunction does not depend on ART and/or that the unfavourable effects of ART on the cardiovascular system act selectively on the smaller arteries and microcirculation.

13.7 Arterial Stiffness and Collagen Type 1 Turnover in Treated Hypertensive Patients

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Introduction: Recent studies have demonstrated that a decrease in extracellular matrix degradation is associated with hypertension and with left ventricular hypertrophy. However, there is no agreement on what are the modifications of collagen turnover associated to arterial stiffness, a well known cardiovascular risk factor.

Aim: To evaluate aortic stiffness and plasma levels of metalloproteinases 1 (MMP1, responsible of collagen type 1 degradation) and tissue inhibitor (TIMP1) in hypertensive patients with blood pressure values well controlled by antihypertensive treatment.

Methods: We enrolled 42 hypertensive outpatients (HT, age 57 ± 10 mean \pm SD) under treatment for at least 4 years with a combination of different drugs (ACE inhibitors, angiotensin II blockers, calcium channel blockers, diuretics and β -blockers) and with BP values $<140/90$ mmHg. We assessed along with sphygmomanometric BP, aortic stiffness by carotid-femoral PWV (cf-PWV, Complior) values. Furthermore, we measured serum levels of MMP-1 and TIMP-1 (ELISA). A group of 40 healthy normotensive individuals (NT) were used as controls. The means of the two group variables were compared by t-test.

Results: Treated HT patients showed BP values similar to NT controls ($118 \pm 10/73 \pm 9$ mmHg for HT vs $117 \pm 9/74 \pm 8$ mmHg for NT, $p = NS$). In HT subjects cf-PWV was higher than in NT (10.2 ± 2.1 vs 9 ± 1.3 m/sec, $p < 0.01$) and the same was for TIMP-1 (153.4 ± 41.3 vs 128.5 ± 21.1 ng/mL, $p < 0.001$). In contrast, MMP-1 had a lower trend in HT (54.2 ± 32.4 vs 67.8 ± 41.5 ng/mL, $p = NS$). Finally, MMP1/TIMP1 was significantly higher in NT showing a higher availability of MMP1 (0.37 ± 0.2 NT vs 0.54 ± 0.4 HT $p = 0.02$).

Conclusions: In our study, HT patients, despite well controlled BP values, showed cf-PWV values still higher than NT controls. Therefore, the antihypertensive drug treatment did not allow a complete normalization of arterial stiffness. Similarly, blood levels of TIMP1 and MMP1 showed an imbalance of collagen turnover to its synthesis in HT, suggesting a possible relationship between these two phenomena.

13.8 Inappropriate Left Ventricular Mass is Related to Vascular Organ Damage Independently of Left Ventricular Hypertrophy in Hypertension

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Introduction: Evidence exists showing that left ventricular hypertrophy is associated with both functional and structural alterations of the large arteries. It is undefined whether this is also the case for inappropriate left ventricular mass (ILVM, i.e. a LVM $>128\%$ of the value predicted by an equation including age, sex and stroke work), known to carry an increased cardiovascular risk independently on the presence of left ventricular hypertrophy.

Methods: In 739 treated hypertensive patients aged 53.8 ± 13.7 years (mean \pm SD, 57% males) we measured, along with clinic blood pressure (BP), left ventricular mass by standard echocardiography and carotid intima media thickness (IMT) via vascular ultrasonography. Arterial stiffness was measured with carotid-femoral pulse wave velocity (PWV, Complior). We then calculated ILVM as the ratio between LV observed mass and LV predicted mass (derived from the formula: $55.37 + 6.64 \times h^{2.7} + 0.64 \times SW - 18.07 \times \text{gender}$, where SW (stroke work) is = systolic blood pressure \times stroke volume $\times 0.0144$ and gender = 1 (male) or 2 (female); $h = m$). ILVM was considered abnormal when the ratio is higher than 1.28.

Results: Mean systolic and diastolic BP were $142 \pm 18.2/86.7 \pm 10.4$ mmHg. In 264 patients (36%), according to reference values of European Guidelines, LV hypertrophy was found, while ILVM was detected in 67%. Patients with ILVM showed values of PWV and IMT significantly greater than patients without ILVM (11 ± 0.13 vs 10 ± 0.15 m/sec for PWV, and 0.68 ± 0.009 vs 0.59 ± 0.009 mm for IMT, $p < 0.001$ for both). Both the vascular functional (PWV) and structural (IMT) parameters correlated with ILVM ($r = 0.16$, $p < 0.001$ for PWV, and $r = 0.27$, $p < 0.001$ for IMT). The subgroup of patients with ILVM but without LVH (n: 236; 32% of the population, 49% of patients without LVH) showed PWV and IMT values significantly greater than patients without ILVM (10.68 ± 0.18 vs 10.19 ± 0.16 m/sec for PWV; and 0.64 ± 0.012 vs 0.59 ± 0.009 mm for IMT; $p < 0.001$ for both). In this group without LVH but with ILVM, 48 patients (20.3%) had values of PWV >12 m/sec and 32 patients (13.6%) had values of IMT >0.9 mm and thus displayed vascular target organ damage.

Conclusions: According to our data, ILVM is (i) of frequent detection in treated hypertensive patients, even when LVH is not present; and (ii) associated with profound alterations of the functional and structural characteristics of the large arteries. This association may participate at the increased cardiovascular risk seen in this condition. Thus ILVM may help to stratify hypertensive patients, identifying vascular organ damage, in the absence of subclinical cardiac organ damage.

13.9 Heart Failure with Preserved Ejection Fraction (HFPEF): Aortic Stiffness, Biohumoral Markers and Echocardiographic Evaluation

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Introduction: Heart failure with preserved ejection fraction (HFPEF) is characterized by a fibrotic process involving myocardial tissue and possibly arterial walls. Evidence exists showing that serological markers of collagen turnover could predict HFPEF.

Aim: To evaluate plasma levels of a serological marker of collagen degradation (MMP2), along with aortic stiffness (PWV, PP, Aix), carotid intima-media thickness (IMT) and echocardiographic parameters (conventional and TDI).

Methods: In 21 treated hypertensive HFPEF patients (at least 1 acute heart failure episode in their clinical history, age 65.8 ± 11.3 years, mean \pm SD) we evaluated echocardiographically (GE, Vivid 7) the diastolic function both by classical mitral inflow (E/A, Dec Time) and TDI (E', E'/A, E'/E') approach. PWV (Complior System) and radial tonometry (PP, Aix, Sphygmocor SPT-301) was performed to evaluate arterial stiffness. Carotid IMT was assessed by echotracking (Esaote MyLab 60). Finally we measured plasma level of MMP2 (immunoassay). 19 age- and sex-matched hypertensive patients served as controls (C, age 66.1 ± 11.8 years).

Results: Compared with C, HFPEF showed slightly greater blood pressure ($138 \pm 21/78 \pm 9$ vs $135 \pm 16/77 \pm 6$ mmHg), HR (71 ± 8 vs 68 ± 14 bpm), IMT (676.0 ± 15 microm vs 599.3 ± 13 microm, and similar values of PWV (11.29 ± 2.9 vs 11.38 ± 2.6 m/s). HFPEF patients showed a significantly lower E/A (0.7 ± 0.2 vs 1.02 ± 0.3 , $p < 0.001$) and a prolonged Dec Time (258.8 ± 54.6 ms vs 205.7 ± 29.7 ms, $p < 0.001$) in association with a left atrial (LA) size significantly greater than C (42.5 ± 4.9 mm vs 38 ± 9.8 mm, $p < 0.03$). MMP2 serum levels showed no significance difference in the two groups (1912.8 ± 551.1 vs 1663.6 ± 533 ng/mL, $p = NS$), this was the case also for diastolic function (TDI approach). In the population, as a whole, we found a significant correlation between MMP2 levels and age ($r = 0.54$, $p < 0.001$), PP ($r = 0.32$, $p < 0.02$), IMT ($r = 0.36$, $p < 0.02$), PWV ($r = 0.35$, $p < 0.02$) and indexes of cardiac stiffness in terms of Dec T ($r = 0.34$, $p < 0.03$), E'/E' ($r = 0.37$, $p < 0.02$) and LA volume ($r = 0.33$, $p < 0.04$).

Conclusions: HFPEF is characterized not only by a marked impairment of left ventricular diastolic function but also by an alteration of left atrial geometry, suggesting a chronic increase in LV filling pressure. Our data show that MMP2 is related to these cardiac alterations and to direct markers of vascular function confirming the importance of this biohumoral marker related to cardiovascular stiffness.

13.10 Impact of T2238C ANP Gene Molecular Variant on Endothelial Function

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Introduction: The T2238C molecular variant of human ANP gene has been previously related to an increased cardiovascular risk in genetic-epidemiological studies. *In vitro* studies have shown that the mutant ANP peptide exerts deleterious effects on endothelial cells by promoting the increase of reactive oxygen species.

Aim: On the basis of these observations and of the well known contributory role of ANP to endothelial function, we hypothesized that T2238C molecular variant could alter endothelial function *in vivo*.

Methods: In a first set of experiments we investigated the acetylcholine-induced vasodilation in the presence of either mutant or wild type ANP by using rings of rat mesenteric and aortic arteries ($n = 6$ for both). In a second set of experiments, 10 healthy subjects carrying the ANP variant (mean age 35 ± 7) and 10 healthy subjects carrying the wild type peptide (mean age 35 ± 8) underwent flow mediated dilation (FMD) in order to study endothelial-mediated vasodilation in response to ischaemia-induced cuff inflation. Endothelium-independent vasodilation was also investigated through sublingual administration of nitrates. All subjects also underwent echocolor Doppler carotid ultrasonography; a venous blood sample was drawn for measurement of plasma atrial natriuretic peptide level.

Results: Experiments performed on rat vascular rings showed a significant decrease of acetylcholine-induced vasodilation in the presence of CC2238/ANP compared with the wild type peptide ($p < 0.05$). In humans, we observed that, in the absence of significant differences in cardiovascular risk factors distribution and in circulating levels of ANP, carriers of mutant CC2238/ANP had a significant reduction of endothelial-dependent vasodilation compared with wild type subjects (6.97 ± 2.4 vs 9.31 ± 1.6 , $p = 0.02$). In contrast, no differences were observed with regard to endothelium-independent vasodilation (13.4 ± 3.4 vs 14.5 ± 5.6 , ns). No structural abnormalities of carotid arteries were revealed by echocolor Doppler ultrasonography.

Conclusions: Our results show that the T2238C molecular variant of human ANP gene, significantly associated in previous studies to an increased cardiovascular risk and to deleterious effects on endothelial cells *in vitro*, exerts a significant impairment of endothelial function *in vivo*. In particular, the early impairment of endothelial function observed in human subjects may contribute to the increased predisposition to cardiovascular events observed in CC2238/ANP carriers.

13.11 Pulse Wave Velocity after Mental Stress in Obese and in Type 1 Diabetic Adolescents

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Introduction: Obesity and diabetes are characterized, since childhood, by an increased arterial stiffness. The mental stress test is largely used to assess the integrity of the cardiovascular system.

Aim: To assess changes of the mechanics of large vessels after acute mental stress in obese adolescents and in their peers with type 1 diabetes.

Methods: 28 obese children (14 males), aged between 9 and 15 years (mean age: 11.9 ± 1.7 years), 17 children with type 1 diabetes (10 males), aged between 8 and 17 years (mean age: 13.0 ± 2.4 years) and 22 normal-weight volunteers (8 males), aged between 10 and 15 years (average age: 12.6 ± 1.6 years), were recruited. Carotid-femoral pulse wave velocity (c-fPWV), which is an arterial stiffness index, was measured by applanation tonometry (PulsePen, Dia Tecne SRL, Milano) and brachial blood pressure (Bp) was registered by validated oscillometer (Omron M6). Subsequently, it was given a mental stress (arithmetic calculation), lasting 10 minutes. During and after testing blood pressure and heart rate (HR) were monitored. At the end of the test c-fPWV was measured again.

Results: The main findings are reported in the table.

		Basal	p-Value	After stress
Controls	c-fPWV (m/s)	4.174 ± 0.866	<0.01	4.576 ± 0.909
	HR (beats/min)	70 ± 10	0.74	71 ± 12
	SBP (mmHg)	107 ± 9	0.94	107 ± 10
	DBP (mmHg)	63 ± 8	0.24	65 ± 7
Obese	c-fPWV (m/sec)	4.212 ± 0.701	0.66	4.255 ± 0.750
	HR (b/min)	71 ± 7	0.03	69 ± 9
	SBP (mmHg)	111 ± 10	0.23	113 ± 11
	DBP (mmHg)	65 ± 7	0.06	68 ± 9
Diabetic	c-fPWV (m/sec)	4.295 ± 0.772	0.35	4.511 ± 0.736
	HR (beats/min)	69 ± 11	0.54	68 ± 10
	SBP (mmHg)	107 ± 5	0.69	107 ± 5
	DBP (mmHg)	62 ± 6	0.55	63 ± 5

Conclusions: The different adaptation of arterial stiffness to mental stress, in obese and diabetic compared with controls, for the same changes in blood pressure and heart rate, demonstrates, in obese and diabetic subjects, an altered response to physiological stress.

13.12 Aliskiren Restores Nitric Oxide Availability in the Forearm Microcirculation of Essential Hypertensive Patients

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Introduction: Essential hypertensive patients (EH) are characterized by endothelial dysfunction caused by a reduced nitric oxide (NO) availability due to reactive oxygen species (ROS) excess.

Despite the common knowledge, literature failed to demonstrate that the renin-angiotensin system (RAS) blockers ACE inhibitors and AT-1 receptor antagonists can ameliorate NO availability in the forearm microcirculation of EH. Aliskiren is a novel direct renin inhibitor, whose effects on endothelial dysfunction in EH are unknown.

Aim: In this study we evaluated whether aliskiren, compared with the ACE inhibitor ramipril, can improve END dysfunction in the forearm microcirculation of untreated mild-moderate EH, according to a double-blind, parallel-group study.

Methods: In EH, randomized to a 12-week treatment with aliskiren (300 mg/daily) or ramipril (10 mg/daily) ($n = 14$ each group), we studied the forearm blood flow (strain-gauge plethysmography) response to intrabrachial acetylcholine (ACH, $0.15\text{--}15 \mu\text{g}/100 \text{ mL}/\text{min}$) with and without NO synthase blockade by L-NMMA ($100 \mu\text{g}/100 \text{ mL}/\text{min}$), or the antioxidant vitamin (Vit) C ($8 \text{ mg}/100 \text{ mL}/\text{min}$).

Results: Blood pressure values were similarly normalized by aliskiren (from $148.8 \pm 9.9/93.5 \pm 8.4$ to $135.9 \pm 8.9/85.7 \pm 7.1 \text{ mmHg}$) and ramipril (from $147.9 \pm 7.5/92.1 \pm 5.7$ to $135.2 \pm 7.1/84.9 \pm 5.6 \text{ mmHg}$). Aliskiren increased ($p < 0.001$) the maximal vasodilation (VD, %) to ACH (from 409 ± 17 to 541 ± 18) and restored the inhibitory effect of L-NMMA on ACH (from 394 ± 19 , $-1.5 \pm 1\%$ to 267 ± 23 , $-50 \pm 7\%$; $p < 0.001$). Vit C, which at baseline potentiated the VD to ACH (540 ± 29 , $+36 \pm 6\%$), no longer improved response to ACH after aliskiren treatment (518 ± 31 , $-3 \pm 2\%$). In contrast, ramipril administration failed to affect the VD to ACH (from 390 ± 18 to 375 ± 31 ; NS), the lacking inhibitory effect of L-NMMA (from 382 , $-2 \pm 4\%$ to 361 , $-4 \pm 5\%$; NS) or the potentiating effect of Vit C (from 548 , $+40 \pm 3\%$ to 538 ± 41 , $+43 \pm 6\%$). Response to sodium nitroprusside was not affected by treatments.

Conclusions: Aliskiren is able to increase END-dependent VD by restoring NO availability in the forearm microcirculation of EH, an effect probably determined by antioxidant activity. These results indicate that a more complete RAS blockade by aliskiren may provide an endothelial protective effect in peripheral microcirculation of EH.

13.13 Endothelium and Aortic Vasomotility in an Experimental Model of Menopause in Rats Fed with Omega-3 Diet Supplementation

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Introduction: Menopause is associated with endothelial dysfunction. In diabetic rats, it has been described a protective effect of omega-3 on endothelial function.

Aim: To investigate the effects of omega-3 diet supplementation in aortic vasomotility (*in vivo* and *in vitro*) in an experimental model of surgical menopause.

Methods: Thirty, 6-month-old, Wistar-Kyoto rats were equally divided into 3 groups: (i) control: sham surgery, normal diet (CTRL); (ii) ovariectomy, normal diet (OVX); and (iii) ovariectomy, + omega-3 ($0.8 \text{ g}/\text{kg}/\text{day}$ daily gavages administration) supplementation diet (OVX + omega-3). Two months after surgery, carotid-femoral pulse wave velocity (c-f PWV) and arterial pressure were directly measured, by aortic and femoral catheters; superoxide anion generation (SOD-inhibitable cytochrome C reduction assay), vasodilation acetylcholine (Ach)-mediated (endothelial dependent vasodilatation) and vasodilatation diethylamine NONOate (DEA)-mediated (endothelial independent vasodilatation) were measured, in aorta rings. Erythrocyte membranes omega-3 were measured by gas-chromatography.

Results: The main findings are reported in the table.

VARIABLES	CTRL	p-Value	OVX	p-Value	OVX +omega-3
c-fPWV (cm/sec)	378.49 ± 3.7 ; $n = 10$	<0.0001	562.5 ± 7.5 ; $n = 10$	<0.0001	366.17 ± 1.9 ; $n = 10$
Superoxide (nmol/min/mm ²)	97.39 ± 8.3 ; $n = 9$	0.01	142.4 ± 14.6 ; $n = 7$	0.04	105.03 ± 9.8 ; $n = 9$
Vasodilatation Ach-mediated (%)	26.09 ± 5.9 ; $n = 10$	0.04	44.11 ± 6.3 ; $n = 10$	0.05	31.59 ± 3.53 ; $n = 10$
Vasodilatation DEA-mediated (%)	7.21 ± 1 ; $n = 10$		6.77 ± 0.32 ; $n = 10$		4.47 ± 0.09 ; $n = 10$
Membrane omega-3 index	3.19 ± 0.14 ; $n = 10$	0.01	2.54 ± 0.076 ; $n = 10$	<0.0001 vs OVX, CTRL	5.18 ± 0.24 ; $n = 10$

Conclusions: Treatment with omega-3 improves endothelium-dependent but not endothelium-independent vasodilatation. This effect could explain the reduction of arterial stiffness we observed in this and a previous study, in the same experimental model of surgical menopause.

13.14 Subcutaneous Small Resistance Artery Morphology and Circulating Indices of Inflammation/Oxidative Stress in Obese Patients Before and After Bariatric Surgery and Consistent Weight Loss

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Introduction: Structural alterations of subcutaneous small resistance arteries of hypertensive patients, as indicated by an increased media to lumen (M/L) ratio, are frequently present in hypertensive and/or diabetic patients, and may represent the earliest alteration observed. In addition, M/L of small arteries have a strong prognostic significance. Also, obesity is associated with an increased M/L. However, no data are presently available about the structure of small resistance arteries of obese patients after weight loss.

Methods: We investigated eight patients with severe obesity. All patients underwent a biopsy of subcutaneous fat during bariatric surgery. In all patients a second biopsy was obtained after consistent weight loss (about 1 year after), during a surgical intervention for abdominoplasty. Subcutaneous small resistance arteries were dissected and mounted on a wire myograph, and M/L and media cross-sectional area were measured. In addition, circulating levels of C-reactive protein (CRP), proinflammatory cytokines interleukin-6 (IL-6) and interleukin-18 (IL-18), macrophage chemotactic factor-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), soluble vascular cell adhesion molecule 1 (VCAM-1) and soluble inter-cellular adhesion molecule 1 (sICAM-1) have been measured in plasma by ELISA. Total antioxidant power, malonyldialdehyde (MDA) and lipid peroxidation (LPO) were also measured in plasma using spectrophotometric assay.

Results: After surgical correction of obesity and consistent weight loss, a significant improvement of microvascular structure was observed, characterized by a correction of hypertrophic remodelling (reduction in growth index and media cross-sectional area), together with an improvement of endothelial function and a decrease of some indices of inflammation/oxidative stress. The main findings of our study are reported in the table (data are expressed as mean ± SEM; in the table: * p < 0.05, ** p < 0.01, *** p < 0.001 vs before weight loss).

	Obese patients before weight loss (n=8)	Obese patients after weight loss (n=8)
Body mass index (kg/m ²)	45.8 ± 2.16	27.4 ± 1.42***
Media cross-sectional area (µm ²)	28027 ± 5765	16322 ± 2267*
Media to lumen ratio	0.0916 ± 0.003	0.0841 ± 0.002*
Remodelling index (%)	33	140
Growth index (%)	110	22
LPO (µmol/L)	1.59 ± 0.18	0.97 ± 0.10*
MDA (µmol/L)	0.63 ± 0.10	0.34 ± 0.04*
IL-6 (pg/mL)	4.29 ± 1.16	2.18 ± 0.76*
sICAM-1 (ng/mL)	633 ± 56.6	473 ± 41.4*
CRP (ng/mL)	1465 ± 334	726 ± 300*

Conclusion: Our data suggest that weight loss obtained with bariatric surgery may improve microvascular structure and may decrease indices of inflammation/oxidative stress.

13.15 Close Relationship between Media to Lumen Ratio of Subcutaneous Small Arteries and Wall to Lumen Ratio of Retinal Arterioles Evaluated Non-Invasively by Scanning Laser Doppler Flowmetry

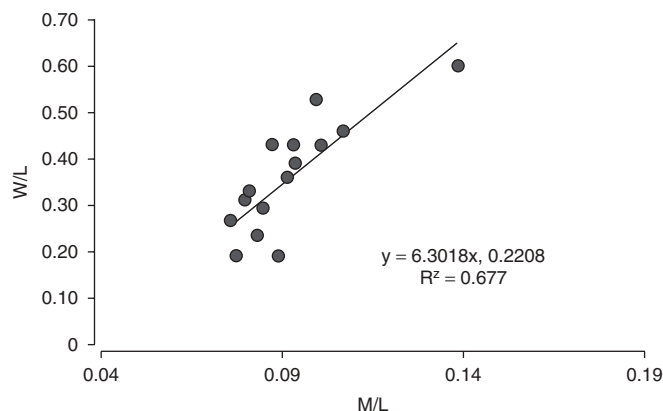
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Introduction: Structural alterations of subcutaneous small resistance arteries, as indicated by an increased media to lumen (M/L) ratio, are frequently present in hypertensive and/or diabetic patients, and may represent the earliest alteration observed. In addition, M/L of small arteries evaluated by micromyography has a strong prognostic significance; however, its extensive evaluation is limited by the invasivity of the assessment, since a biopsy of subcutaneous fat is needed.

Non-invasive measurement of wall to lumen (W/L) of retinal arterioles using scanning laser doppler flowmetry (SLDF) has been recently introduced. However, this new technique was never compared with micromyographic measurement, considered the gold standard approach.

Methods and Results: We investigated 18 subjects and patients. Twelve of them were hypertensive patients and six normotensive subjects. Blood pressure values were 131/72 ± 9/8 mmHg (on treatment values in 7 of 12 patients) and 113/63 ± 6/6 mmHg, respectively (p < 0.05). All patients underwent a biopsy of subcutaneous fat during an elective surgical intervention. Subcutaneous small resistance arteries were dissected and mounted on a wire myograph, and M/L was measured. In addition, an evaluation of W/L of retinal arterioles by SDLF was performed (Heidelberg Retina Flow-meter, Heidelberg Engineering). A close correlation was observed between M/L of subcutaneous small arteries and W/L of retinal arterioles (figure): r = 0.82, r = 0.677, p < 0.001, y = 6.3018x, 0.2208.



Conclusions: A non-invasive and easily repeatable procedure (intraobserver and interobserver variation coefficient <10%) such as an evaluation of the arterioles in the fundus oculi by SDLF may provide similar information regarding microvascular morphology compared with an invasive, accurate and prognostically relevant micromyographic measurement of M/L.

13.16 Reduced Nitric Oxide Availability in Small Arteries from Patients with Pheochromocytoma: Role of COX-2-Derived Contracting Prostanoids

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Introduction: Previous reports documented an impaired endothelial function in small vessels from patients with pheochromocytoma (pheo). However, the mechanisms accounting for this alteration are not known.

Aim: Therefore, in this study we assessed endothelial function in isolated small resistance arteries taken from the periadrenal visceral fat from pheo patients (Pheo, n = 7, age 47.0 ± 17 years). A group of small vessels from normotensive subjects (NT, n = 7, age 49.0 ± 14 years) was used as controls.

Methods: Each subject underwent a biopsy of the visceral fat during a surgical laparoscopic procedure. Small arteries were dissected and investigated on a pressurized micromyograph. Endothelium-dependent vasodilation (VD) was assessed by acetylcholine (ACh, 0.001-100 µM)-induced relaxation. NO availability and ROS production were evaluated by repeating ACh under the NO synthase inhibitor L-NAME (100 µM) and the superoxide scavenger ascorbic acid (Vit C, 10 mM), respectively. ACh was also tested under SC-560 (1 µM, COX-1 inhibitor), DuP 697 (1 µM, COX-2 inhibitor) and SQ 29548 (1 µM, thromboxane receptor-TP antagonist).

Results: Pheo patients showed: BP 150 ± 96 mmHg; urinary normetanephrine (uNM): 3826 ± 2405, urinary metanephrine (uM): 1353 ± 970 µg/24h. NT showed: BP 120 ± 81 mmHg, uNM: 42 ± 11, uM: 34 ± 18 µg/24h. In NT, maximal VD to ACh (95.1 ± 1.8%) was blunted by L-NAME (61.2 ± 3.4%; inhibitory effect: 33.9 ± 2.1%; p < 0.001), and unmodified by SC-560 (94.0 ± 1.1%), DuP (94.9 ± 0.8%), SQ 29548 (94.1 ± 2.6%) or Vit C (95.6 ± 1.5%). In pheo, VD to ACh was blunted vs controls (53.8 ± 1.1%; p < 0.001), less sensitive to L-NAME (45.6 ± 0.6%; 8.9 ± 0.3% inhibition; p < 0.001 vs controls), not affected by SC-560 (53.9 ± 0.9%), enhanced (p < 0.01) by DuP (73.6 ± 2.1%), SQ 29548 (75.2 ± 1.6%) or their combination (75.0 ± 1.9%), and normalized by Vit C (92.6 ± 3.5%). Response to sodium nitroprusside was similar between the two groups.

Conclusions: Small resistance vessels from the visceral fat of patients with pheochromocytoma are characterized by a markedly blunted endothelium-dependent relaxation, an alteration caused by mechanisms involving a reduced NO availability, an oxidant excess generation. COX-2 participates on this alteration by producing prostanoids acting on TP receptors.

13.17 The Relationship between Vascular Endothelial Growth Factor and Microalbuminuria in Patients with Essential Hypertension

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Introduction: The existence of microalbuminuria (MAU) in patients with essential hypertension is a strong indicator of microvascular damage. Although endothelial dysfunction and increased vascular permeability both have a role in the development of MAU, its etiopathogenesis in hypertensive patients is not clearly understood. Vascular endothelial growth factor (VEGF) is the most important regulator of pathological or physiological angiogenesis and it additionally leads to increased vascular permeability.

Aim: To assess the relationship of serum VEGF levels to MAU in non-complicated, newly diagnosed, never-treated, essential hypertensive patients (EHs).

Methods: This study included 50 EHs with MAU, 50 EHs without MAU and 50 healthy controls. Serum VEGF levels were measured using the ELISA method.

Results: Serum levels of VEGF were significantly higher in EHs with MAU when compared with patients without MAU ($p=0.04$) or controls ($p=0.007$). On the other hand, no significant difference was observed between the non-MAU and controls groups. In the univariate analysis, serum levels of VEGF, were positively correlated with systolic blood pressure ($R=0.261$, $p=0.001$), diastolic blood pressure ($R=0.173$, $p=0.04$), mean arterial pressure ($R=0.247$, $p=0.002$), creatinine clearance ($R=0.182$, $p=0.004$) and MAU ($R=0.346$, $p=0.002$). In the multiple linear regression analysis, VEGF levels were independently related to MAU ($R=0.254$, $p=0.02$).

Conclusions: In this study, VEGF levels are higher in EHs in the presence of MAU; these data suggest that VEGF may increase glomerular permeability and lead to MAU in EHs. Serum VEGF levels may be important in the early diagnosis of vascular damage in EHs.

13.18 Arterial Stiffness and Central Blood Pressure: Relationship with Microcirculation Structure in Hypertensive Patients

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Introduction: The possible relationships between indicators of small resistance artery structure and of large artery distensibility have not yet been evaluated.

Aim: To assess the relationship between carotid-femoral pulse wave velocity (CF-PWV), central blood pressure (cBP) and vascular alterations in small resistance arteries (media to lumen ratio, M:L) in patients with primary and secondary hypertension

Methods: In 65 patients (mean age 53 ± 14 years, 31 F, 21 with diabetes mellitus type 2, 14 never treated) with essential ($n=32$) and secondary ($n=33$) hypertension, pulse wave velocity was measured (Complior) and PW analysis was performed (Sphygmocor). In all patients small-resistance arteries were dissected from subcutaneous fat biopsies and mounted on an isometric myograph, for the measurement of the M:L.

Results: Mean values of PWV and of M:L ratio were 11.4 ± 2.6 m/s and 0.09 ± 0.019 , respectively. M:L ratio was significantly related to brachial systolic blood pressure (SBP) and pulse pressure (PP) [$r=0.40$ and 0.39 , $p<0.001$, respectively] and to central SBP and PP ($r=0.44$ and 0.46 , $p<0.001$, respectively). A positive correlation was observed between M:L and PWV ($r=0.43$, $p<0.001$); this correlation remained statistically significant after adjustment for age and SBP ($\beta=0.29$, $p=0.03$). M:L ratio was also associated to augmentation pressure ($r=0.42$, $p<0.001$); again this correlations remained statistically significant after adjustment for age, gender, mean BP and also for CF PWV.

Conclusions: In hypertensive patients the presence of structural alterations of small resistance arteries may be associated with the increase in large arteries stiffness and, possibly contribute to an increase in central pressure by earlier wave reflections.

13.19 Effects of Acetazolamide on Blood Pressure and Pulse Waveform Changes Induced by High Altitude Exposure

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Introduction: Exposure to high altitude (HA) may induce mountain sickness and increase blood pressure (BP) but little is known on the effects of this condition on arterial properties. Acetazolamide (AC), antagonizing chemoreflex activation effects, has been proposed to prevent and treat mountain sickness, but no information is available on its effects on cardiovascular parameters at HA.

Aim: To assess these issues in a group of healthy volunteers acutely exposed to very HA.

Methods: 42 healthy normotensive volunteers (mean age 36.8 ± 8.9 , 21 male) were randomized to receive AC 250 mg bid or placebo (PL) both at sea level (SL) and HA. A tonometric evaluation of

arterial properties (PulsePen, DiaTecne, Milan) by assessing carotid-femoral and carotid-radial PWV (CF-PWV, CR-PWV) and pulse wave analysis (augmentation index, AIx and sub-endocardial viability ratio, SEVR) was performed in the following conditions: at baseline (BAS), after 2 days of randomized treatment at SL; within 6 hours from arrival at Capanna Margherita (Mount Rosa, Italian-Swiss Alps, 4559 m, HA1); and on 3rd full day of exposure to HA (HA2). Systolic (S) and diastolic (D)BP were measured by a validated oscillometric device (AND UA 767-PC). Heart rate (HR) was derived from an ECG signal. Mean arterial pressure (MAP) was calculated by PulsePen software. Data are shown as means \pm SD.

Results: In all subjects, during acute exposure to HA, CF-PWV and CR-PWV did not change, while AIx (adjusted for HR) increased compared with SLpost both at HA1 (from $-7.3 \pm 11.3\%$ to 1.5 ± 12.6 in PL group, $p=0.038$; and from $-15.5 \pm 10\%$ to -7.5 ± 12.6 in AC group, $p=0.004$) and HA2 ($p<0.001$ in PL group and $p=0.0011$ in AC group) but its values were significantly lower in AC group ($p=0.037$ at HA1 and $p=0.010$ at HA2). SEVR significantly decreased from SL to HA1 in both groups ($p<0.01$), with a smaller reduction in the AC group: from 0.89 ± 0.19 to 0.58 ± 0.14 for PL and from 0.86 ± 0.2 to 0.67 ± 0.13 for AC ($p=0.055$ PL vs AC at HA1). At HA2 SEVR was significantly lower in PL compared with AC (0.74 ± 0.17 vs 0.87 ± 0.15 $p=0.02$). Acute exposure to HA significantly ($p<0.01$) increased SBP, DBP, MAP and HR. Subjects in AC group, compared with PL group, showed, however, significantly lower values of SBP (115.6 ± 9.8 vs 108.3 ± 9.6 mmHg, $p=0.027$), DBP (77.4 ± 6.8 vs 70.0 ± 5.3 mmHg, $p<0.001$), MAP (92.7 ± 6.8 vs 85.3 ± 5.9 mmHg, $p=0.001$) and HR (83.5 ± 10.4 vs 76.4 ± 8.8 bpm, $p=0.031$) at HA1. DBP and MAP were significantly lower with AC also at HA2 ($p<0.01$).

Conclusions: Our study shows that acute exposure to HA induces both a BP rise and changes in vascular function, whose magnitude is partly counteracted by treatment with AC. The effects of AC on the haemodynamic changes induced by HA may contribute to the beneficial role of this drug in subjects prone to mountain sickness. Based on these findings, also the possible clinical usefulness of AC in patients with diseases associated to hypoxemia might deserve to be re-assessed.

13.20 The Progress of the Metabolic Syndrome Impairs both Microcirculation and Cerebral Arterial Dilating Reserve in Mild Hypertensive Patients

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Introduction: Ischaemic stroke represents the most invalidating damage in hypertension (HTN) and metabolic disorders, clustered in the metabolic syndrome (MS).

Aim: To evaluate if mild HTN, characterized by capillary rarefaction, may be affected by microcirculatory rarefaction and impaired cerebral blood flow with a progressive clustering of components of MS.

Methods: 22 normotensive subjects (NTN-0), 29 hypertensive patients (HTN-0) with 0, 30 with 1 (HTN-1), 29 with 2 (HTN-2), 27 with 3 (HTN-3) and 25 with 4 (HTN-4) further components of MS, with similar age, underwent capillaroscopy to determine basal (CAP) and structural (CVC), during venous congestion, capillarity as indices of micro-vascular damage. Cerebral vasodilating reserve, during breath hold index (BHI), by trans-cranial Doppler, was measured in HTN-1 and HTN-2.

Results: ABPM confirmed the hypertensive state. The main findings of our study are reported in the table (in table: * $p<0.001$ vs NTN-0; ° $p<0.05$, °° $p<0.001$ vs HTN-0; ^ $p<0.05$, ^^ $p<0.001$ vs HTN-1. Pearson test, adjusted for age, smoke and history of hypertension, showed that BHI was associated with CVC in HTN-2 (0.502; $p<0.001$) but not in HTN-1 (0.194; $p=NS$). Multiple regression analysis with BHI, as dependent variable, showed that only CVC entered in the equation (0.404; $p<0.001$).

var/paz	NTN-0	HTN-0	HTN-1	HTN-2	HTN-3	HTN-4
SBP	119 \pm 9	141 \pm 11*	145 \pm 12*	147 \pm 12*	149 \pm 11*	147 \pm 9*
DBP	74 \pm 7	87 \pm 7*	89 \pm 11*	88 \pm 12*	89 \pm 9*	87 \pm 7*
CAP	37.2 \pm 4.1	32.1 \pm 3.8*	31.6 \pm 4*	30.6 \pm 4.4*	31.1 \pm 3.3*	
30.6 \pm 4.6*	CVC	55.1 \pm 1.6	48.8 \pm 7.8*	48.2 \pm 9.8*	46.1 \pm 5.4**	
		43.1 \pm 4.6**	41.9 \pm 4.7***			
BHI			1.45 \pm 0.24	1.01 \pm 0.25**		

Conclusions: The findings show that mild hypertensive patients are affected by capillary rarefaction, but when the MS is superimposed, a part of the nature of the components, a progressive greater microcirculatory rarefaction and impaired cerebral arterial dilating reserve occur.

13.21 Endothelial Function and Renal Vasodilation, but not Arterial Stiffness, are Impaired in Lean, Normotensive Patients with Sleep Apnoea Syndrome

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Introduction: Patients with obstructive sleep apnoea syndrome (OSAS), a condition with a strong co-morbidity with hypertension and obesity, exhibit an accelerated vascular aging and renal damage.

Aim: To evaluate endothelial function, arterial stiffness and renal vasodilating response to glyceryl trinitrate (GTN) (25 µg), evaluating renal vasodilation as percent RI change. Endothelium-dependent (flow-mediated-dilation, FMD) and -independent (response to GTN) vasodilation in the brachial artery was assessed by computerized edge detection system. Arterial stiffness was assessed as carotid-femoral pulse wave velocity (PWV).

Methods: 17 patients with moderate-severe OSAS (AHI 31 ± 19) and 21 matched healthy controls were recruited. Renal resistive index (RI) was obtained by Duplex ultrasound at baseline and after sublingual GTN (25 µg), evaluating renal vasodilation as percent RI change. Endothelium-dependent (flow-mediated-dilation, FMD) and -independent (response to GTN) vasodilation in the brachial artery was assessed by computerized edge detection system. Arterial stiffness was assessed as carotid-femoral pulse wave velocity (PWV).

Results: OSAS patients and controls presented similar RI (0.61 vs 0.59, *p*=ns), but impaired renal vasodilation to GTN (−5.7 ± 6.2% vs −10.3 ± 4.6%, *p*<0.05). FMD was reduced (4.1 ± 2.5% vs 6.2 ± 3.1%, *p*<0.05), while endothelial-independent brachial artery vasodilation was preserved. PWV was not different between OSAS and controls (7.9 ± 1.5 vs 7.7 ± 1.4 m/s, *p*=ns).

Conclusions: Even in the absence of hypertension and obesity, OSAS is characterized by endothelial dysfunction and impaired renal vasodilating capacity. Thus, OSAS could predispose *per se* to vascular and renal damage.

13.22 Arterial Stiffness is Associated with Carotid Atheromatosis in Hypertensive Patients (Campania Salute Network)

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Introduction: Pulse pressure/stroke volume indexed to height^{2.04} (PP/SVi) is a validated measure of arterial stiffness, but its relation to carotid atheromatosis is unknown.

Methods: Data from 6209 hypertensive patients without known cardiovascular disease in the Campania Salute Network were used. The population was grouped into tertiles of PP/SVi. From carotid ultrasound peak and presence of carotid plaques in the common and internal carotid arteries were reported.

Results: Increasing PP/SVi tertile was associated with older age, higher systolic and diastolic blood pressure (BP), and higher total cholesterol and number of antihypertensive drugs, as reported in the table (in the table data are expressed as percentage or as mean ± SD; * *p*<0.01 vs other groups; ** *p*<0.05 vs other groups). Higher PP/SVi tertile was also associated with larger peak and mean carotid intima-media thickness and higher prevalence of carotid plaques (table). In multivariate logistic regression analysis, compared to the lowest tertile, the prevalence of carotid plaque increased by 16% (95% confidence interval [CI] 1, 34; *p*<0.05) in PPSVi tertile 2 and by 33% (95% CI 15, 55; *p*<0.01) in PPSVi tertile 3 independent of significant associations with diabetes mellitus, age, gender and total cholesterol.

Variable	Tertile 1 PP/SVi (range 0.77–2.08)	Tertile 2 PP/SVi (range 2.09–2.65)	Tertile 3 PP/SVi (range 2.66–6.15)
Women (%)	39.7	40.1	49.0
Age (y)	52 ± 10	53 ± 11	55 ± 12*
Diabetes mellitus (%)	8.0	8.2	12.3*
Clinic systolic BP (mmHg)	138 ± 15	144 ± 16	153 ± 19*
Clinic diastolic BP (mmHg)	89 ± 11*	90 ± 11	90 ± 12
Carotid plaque (%)	52.8	57.8	64.8*
Combination therapy (n)	1.8 ± 1.1	1.9 ± 1.1	2.0 ± 1.1*
Total cholesterol (mg/dL)	206 ± 37	206 ± 39	210 ± 40**
Max carotid IMT (mm)	1.50 ± 0.64	1.58 ± 0.70	1.74 ± 0.81*
Mean carotid IMT (mm)	1.11 ± 0.32	1.15 ± 0.34	1.26 ± 0.45*

Conclusions: In treated hypertensive patients participating in the Campania Salute Network, higher PP/SVi is associated with carotid atheromatosis independently of other confounders.

13.23 The Pressure Dependence of Arterial Stiffness as a Novel Marker of Vascular Function Obtained from Pulse Wave Velocity and Brachial Blood Pressure Taken at Different Arm Heights

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Introduction: The increase of arterial stiffness with blood pressure (BP) reflects the nonlinear increase of BP with volume. Stiffness can be represented by the square of the pulse wave velocity (PWV), and is currently measured for the diastolic BP (DBP).

Aim: By analysing the changes in DBP and diastolic PWV (PWVd) induced by changing arm position, we evaluated a linear relation between stiffness and DBP in individual subjects, and used it for calculating systolic stiffness.

Methods: In 27 healthy subjects (66% men, age 51 ± 17 years, BP 134/78 ± 17/12 mmHg), we measured brachial BP and carotid-radial PWVd in supine position with arm supported at three postures: below, at, and above the heart level. The linearity of PWVd2 versus DBP was evaluated by the correlation coefficient. PWVd2 was expressed by the model 0.127β (DBP − α), where the parameters β and α were best fitted for each subject, and then used for determining the systolic stiffness PWVs2 from the SBP, according to the model 0.127β (SBP − α). β ('stiffness constant', or the change in PWVd2 for a given change in DBP) expresses the steepness of the pressure-volume exponential curve.

Results: PWVd2 highly correlated with DBP for individual subjects (*r*=0.95 ± 0.03). β increased significantly at older age (*r*=0.49, *p*<0.001). While diastolic PWV increased linearly with age (*r*=0.64), calculated systolic PWV increased with age exponentially (*r*=0.65, *p*<0.001) and became steep over age 50 years.

Conclusions: The gravity effect on brachial DBP generated by arm height variation induces linear changes in diastolic PWV, which increase steeply with age. The dynamic changes of PWV and DBP with the cuff height provide a novel and simple measure of systolic PWV in an individual subject, which shows greater age sensitivity than diastolic PWV.

13.24 Additive Effect of Cardiovascular Risk Factors on Carotid and Aortic Stiffness in Essential Hypertensive Patients

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Introduction: Arterial tree ageing, expressed as arterial stiffening, is accelerated by the presence of cardiovascular risk factors, especially by arterial hypertension. The role of other cardiovascular risk factors on top of hypertension in worsening arterial elastic properties is still unknown.

Aim: To evaluate whether classical cardiovascular risk factors can influence aortic and carotid stiffness in essential hypertensive patients.

Methods: 314 hypertensive patients and 110 age- and sex-matched healthy subjects were recruited. Carotid-to-femoral pulse wave velocity (PWV) and carotid pulse pressure were obtained by applanation tonometry. An automated system for ultrasound sequence images 'Carotid Studio', allowed to obtain common carotid diameter, intima-media thickness, and carotid stiffness (CS). PWV and CS were classified as 'increased' when greater than the 90th percentile, calculated on the healthy subjects sample. Medical history, physical examination, and blood exams were used to identify the following risk factors: family history of early cardiovascular disease, smoking, previous cardiovascular events, diabetes mellitus, obesity, hypercholesterolaemia, hypertriglyceridaemia, low HDL, metabolic syndrome and chronic renal failure.

Results: Hypertensive patients had higher PWV and CS compared with healthy subjects (9.4 vs 7.4 m/s and 6.9 vs 6.2 m/s, *p*<0.0001 for both). Hypertensive patients with previous cardiovascular events, diabetes mellitus, obesity, hypercholesterolaemia, metabolic syndrome and chronic renal failure had higher PWV compared with patients who did not had these risk factors. Age- and sex-adjusted multiple logistic regression, including all the above-mentioned factors, demonstrated that only diabetes mellitus (OR 5.4, CI 95% 2.6, 11.2) and chronic renal failure (OR 7.7, CI 95% 2.2, 25.6) are independently associated to an increased PWV. Hypertensive patients with diabetes mellitus, hypertriglyceridaemia, metabolic syndrome and chronic renal failure had higher CS compared with patients who did not have these risk factors. Age- and sex-adjusted multiple logistic regression, including all the above-mentioned factors, demonstrated that only diabetes mellitus is independently associated to an increased CS (OR 3.2, CI 95% 1.4, 7.1).

Conclusions: In a hypertensive population, the additive presence of diabetes mellitus is associated with a further carotid and aortic stiffening, while the presence of chronic renal failure is associated to a further increased PWV. The other cardiovascular risk factors seem to exert a marginal role when added to arterial hypertension.

13.25 The Direct Renin Inhibitor Aliskiren Improves Vascular Remodelling in Transgenic Rats Harbouring Human Renin and Angiotensinogen Genes

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Introduction: The selective human renin inhibitor aliskiren (ALK) reduces blood pressure and ameliorates cardio-renal organ damage in hypertensive double transgenic rats (dTGRs), which express both human renin and angiotensinogen. Little is known about the effect of ALK on hypertension-related functional and structural alterations of resistance arteries.

Aim: We tested the hypothesis that chronic treatment with ALK in dTGRs improves resistance arteries' vascular remodelling which represents the earliest manifestation of target organ damage in hypertensive subjects and has prognostic significance.

Methods: dTGRs (5 weeks old) were treated with ALK (3 mg/kg/day, n=5) or ramipril (RAM, 1 mg/kg/day, n=5) for 14 days and compared with age-matched untreated dTGRs. Blood pressure (BP) was measured by tail-cuff method. Resistance arteries media-to-lumen ratio (M/L) was evaluated on mesenteric arteries as pressurized preparations. Endothelium-dependent and -independent relaxations were assessed by dose-responses curves to acetylcholine (Ach, 10⁻⁹ to 10⁻⁴ mol/L) and sodium nitroprusside (SNP, 10⁻⁸ to 10⁻⁴ mol/L), respectively, in vessels precontracted with norepinephrine (10⁻⁶ mol/L). The expression of AT1 receptor, AT2 receptor, eNOS and the NADPH subunit gp91phox in aorta was evaluated by immunoblotting. The reactive oxygen species (ROS) production was evaluated in aorta by dihydroethidium (DHE) staining.

Results: BP was similarly reduced in both ALK-treated and RAM-treated rats compared with untreated dTGRs (167 ± 1.18 mmHg and 169.4 ± 1.5 mmHg vs 196.8 ± 3.9 mmHg, respectively p < 0.05; reduction of -15% and -14%; p < 0.05). M/L was equally reduced in ALK-treated and RAM-treated rats compared to untreated rats (6.3 ± 0.5% and 6.4 ± 0.2% vs 9.8 ± .04%, respectively; p < 0.05). Endothelium-dependent and -independent relaxations were not different between ALK-treated and RAM-treated dTGRs. AT1 and AT2 receptor expression was similar in all the groups. eNOS expression was increased only in ALK-treated rats (+41.3 ± 6.3% vs untreated dTGRs, p < 0.05). gp91phox was slightly reduced in both ALK- and RAM-treated dTGRs. Both ALK and RAM similarly reduced ROS production in dTGRs compared with untreated rats (14.7 ± 0.2 AU and 13.9 ± 0.3 AU vs 18.1 ± 0.9 AU, respectively; p < 0.05).

Conclusions: Equieffective antihypertensive dose of ALK or RAM improved oxidative stress and reduced M/L of mesenteric arteries. Only ALK increased the eNOS bioavailability. Hence, in dTGRs renin inhibition compares favourably to ACE inhibition in improving vascular remodelling.

13.26 Assessment of Carotid Elasticity in Exercise: A Reproducibility Study

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Introduction: Arterial stiffness may vary with physiological stimulus and, therefore, its quantification in dynamic conditions could enhance the characterization of vascular elastic properties.

Aim: To evaluate the feasibility and reproducibility of the assessment of carotid artery elasticity during exercise.

Methods: Eighteen healthy volunteers (9 men, 34 ± 3 years) underwent a maximal exercise testing on a graded semi-supine cycle ergometer. Ultrasound B-mode image sequences (DICOM format, high frame-rate) of right common carotid arteries were acquired at pre-defined steps (60%, 70%, 80% and 85% of maximal heart rate), and analysed by an automatic system (Carotid Studio, IFC-CNR) for the measurement of arterial diastolic diameter (D) and distension (ΔD). In addition, central pulse pressure (PPa) was estimated by tonometry (radial-aortic transfer function, Sphygmocor, AtcorMedical). Cross-sectional compliance (CC) and distensibility (DC) coefficients were then obtained at each step. Subjects were analysed in two different sessions 3 days apart, in order to evaluate intersession reproducibility of the measurements; variability was expressed as coefficient of variation (CV) for each step of the examination and by Cohen's Kappa statistics for the entire examination.

Results: At rest, CV were: 3 ± 3% for D, 8 ± 6% for ΔD and PPa, 8 ± 10% for CC and 8 ± 8% for DC. At exercise peak, CV were: 7 ± 5% for D, 12 ± 8% for ΔD, 10 ± 7% for PPa, 19 ± 6% for CC and 24 ± 15% for DC. The reproducibility of the evaluation during the entire examination resulted in kappa value = 0.48 for CC and kappa value = 0.40 for DC.

Conclusions: The reproducibility of carotid parameters, which is excellent at rest, remains more than satisfactory during exercise. Hence, the proposed approach is appealing for the dynamic behaviour of arterial elasticity.