Changes in Left Ventricular Structure and Function Predict the Onset of Hypertension in Adults

Rajender R. Gheysen, Peter J. Geleijnse, Roberta C. van Dop, et al.

Background: Alterations in left ventricular (LV) structure and function have been previously described in normotensive offspring of hypertensive (HT) families but their significance is still unclear.

Methods: To verify if these alterations have predictive value for the onset of HT disease, 205 normotensive adults (mean age 43±10 yrs) with family history of HT, were examined echocardiographically (2D, M mode, Doppler) at baseline and then repeatedly at 12 months intervals, during a follow-up period of 7.1 yrs (range 4.7-7.5 yrs).

Results: During this period, 57 subjects (28%) became hypertensive (H group). These subjects had higher values for the baseline LV mass index (LVMi) (97±25 g/m² vs 81±21 g/m²; p<0.01), and lower LV ejection fraction (EF) (60±5% vs 65±5%; p<0.01) and lower LV fractional shortening (0.16±0.03 vs 0.19±0.03; p=0.03), compared to those who did not develop HT (N group). The subjects in the H group had also higher initial systolic blood pressure (SBP) (134±12 mmHg vs 117±11 mmHg; p<0.01) and a higher number of 1st degree relatives with HT (2.9±0.3 vs 1.5±0.4; p<0.04).

There was no significant difference in baseline LVEF. LV circumferential fractional shortening, LV end diastolic diameter and left atrial size between H and N subjects at baseline.

SBP at the end of the follow-up was predicted independently by the initial SBP (beta=0.359; p<0.01), age (beta=0.01, p=0.042) and LVMi (beta=0.185; p<0.01).

During the follow-up period, the subjects who subsequently developed HT, experienced a significant increase in LVMi (from 97±25 g/m² to 104±26 g/m²; p<0.03), and increase in aortic diameter (from 32±4 mm to 36±6 mm; p<0.01). The paired differences for all these parameters were significantly higher in the H group compared to the N group. H subjects also had higher variations in LV-E/A between the echo exams in the follow-up period when compared to the N group (mean 9% vs 12%; p<0.01).

Conclusions: Increased LV mass and alterations in LV diastolic and systolic longitudinal function predict the onset of HT in normotensive subjects with family history of HT. Increased variability in LV diastolic function seem to appear during the period of developing HT.

N-Terminal Pro-Brain Natriuretic Peptide Predicts Cardiovascular Events In Hypertension: A LIFE Substudy

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Background: N-Terminal pro-brain natriuretic peptide (NT-proBNP) is a strong vascular risk factor in patients with chronic heart failure as well as in the general population. We wanted to investigate whether high NT-proBNP could predict the composite endpoint (CEP) of cardiovascular death, non-fatal stroke or non-fatal myocardial infarction in patients with hypertension and left ventricular hypertrophy as well.

Methods: After two weeks of placebo treatment and yearly for 4.5 years clinical laboratory, and echocardiographic variables were assessed in 184 hypertensive patients from the LIFE Echo substudy aged 55-66 (mean 66±7 years), with echocardiographic LV hypertrophy. NT-proBNP was measured by immunoassay (Eliksys proBNP) at baseline and after one year of treatment.

Results: CEP occurred in 20 patients, baseline nT-proBNP above the mean value of 113 pg/ml was associated with higher incidence of CEP (18.7% vs 9.7%, P=0.05).

Known cardiovascular disease (n=60) defined as diabetes (n=20), or history of either ischemic heart disease (n=26), cerebrovascular disease (n=10), peripheral vascular disease (n=8) or chronic heart failure (n=2), was also associated with higher incidence of CEP (24.6% vs 8.9%, P=0.01). NT-proBNP above the median value was not associated with higher incidence of CEP in this high-risk group (24.3% vs 21.7%, NS), but was in the remaining 124 "low-risk" hypertensive patients (14.8% vs 4.3%, P=0.01). In Cox regression analyses controlling for treatment assignment NT-proBNP (P=0.05) predicted CEP slightly more strongly than prior cardiovascular disease (P=0.054) and current smoking (P=0.06). Systolic blood pressure, gender and body mass index did not enter the model. NT-proBNP levels after one year of treatment also tended to predict the CEPS that occurred subsequently (18.6% vs 9.2%, P=0.07).

Conclusion: NT-proBNP is a strong cardiovascular risk factor in patients with hypertension and LV hypertrophy, especially in the group without diabetes or clinically overt cardiovascular disease. Furthermore, our data suggest the possible use of NT-proBNP - even measured during treatment - as a practical tool for risk stratification in hypertension.

Cardiovascular Morbidity and Mortality in Hypertensive Patients With Atrial Fibrillation: The LIFE Study

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Background: Optimal treatment of hypertensive patients with atrial fibrillation (AF) to reduce the risk of cardiovascular morbidity and mortality remains unclear.

Methods: As part of the LIFE study, 324 patients (42% women) with AF and hypertension (mean age 70±6, pressure 176±14/96 ±10 mmHg) and electrocardiographic left ventricular (LV) hypertrophy, were assigned to losartan- or atenolol-based therapy for 1,385 patient-years of follow up.

Results: The primary composite endpoint occurred in 36 patients in the losartan-group (n=150) vs 64 in the atenolol-group (n=174); relative risk (RR) 0.60 [95% CI 0.40–0.92], P=0.018. Cardiovascular deaths occurred in 20 vs. 37 patients in the losartan- and atenolol-group, respectively: RR 0.59 [CI 0.34–0.91], P=0.053. Stroke occurred in 18 vs. 35 patients (RR 0.56 [CI 0.31–0.97], P=0.040), and myocardial infarction in 11 vs. 7 patients (P=NS). There was a trend towards lower all-cause mortality: 30 vs. 48 RR 0.67 [CI 0.43–1.07], P=0.092, and hospitalization for heart failure took place in 15 vs. 23 patients (P=NS). Adjustment for blood pressure levels during follow-up has little impact on cardiovascular benefit of losartan.

Conclusions: Losartan was more effective than atenolol-based therapy in reducing the risk of the primary composite endpoint of cardiovascular morbidity and mortality, as well as the secondary endpoints of stroke and cardiovascular death, in hypertensive patients with electrocardiographic LV hypertrophy and AF and these was a trend towards lower all-cause mortality. Hypertensive patients with electrocardiographic LV hypertrophy and AF seem to benefit more, for the same blood pressure lowering, from losartan than from conventional antihypertensive and antithrombotic therapy by atenolol.

Cardiovascular Safety of Vardenafil in Patients Receiving Antihypertensive Medications: A Post-Hoc Analysis of Five Placebo-Controlled Clinical Trials

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Background: Hypertension is associated with erectile dysfunction (ED). Phosphodiesterase-5 (PDE-5) inhibitors may potentiates blood pressures (BP) reduction of antihypertensive agents (HTM). This study evaluated the cardiovascular safety of vardenafil, a potent, selective PDE-5 inhibitor when used with HTM.

Methods: Data were extracted from 5 double-blind Phase III trials in which 2,718 men with ED received vardenafil 5, 10, or 20 mg or placebo as needed for up to 26 weeks. Adverse events and vital signs were tabulated at all visits; in a patient subgroup (n=703), vital signs were recorded 11 min to 5 h post-dose. Vardenafil doses were pooled and analyzed by HTM use.

Results: In 2,605 patients valid for safety (vardenafil-1,812, placebo-793), 21 HTM was
used by 40% to 42% of placebo-venlafaxine-treated patients. The mean change from pre-
treatment standing SBP/DBP (mmHg), and HR (bpm) in the subgroup having post-dose data is summarized below.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo mean (SD)</th>
<th>Venlafaxin mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>DBP</td>
</tr>
<tr>
<td>All Patients</td>
<td>-0.1</td>
<td>-0.02 (10.1)</td>
</tr>
<tr>
<td></td>
<td>(16.7)</td>
<td>(19.6)</td>
</tr>
<tr>
<td>No HTN</td>
<td>-1.6</td>
<td>-0.4 (8.4)</td>
</tr>
<tr>
<td></td>
<td>(15.6)</td>
<td>(10.0)</td>
</tr>
<tr>
<td>≥1 HTN</td>
<td>1.5</td>
<td>0.4 (10.9)</td>
</tr>
<tr>
<td></td>
<td>(13.7)</td>
<td>(10.0)</td>
</tr>
</tbody>
</table>

In patients on placebo ≥1 HTN, no significant changes in SBP and HR were seen. Venlafaxin was associated with mild reduction in BP and small increase in HR. Concomitant HTN minimally incrementally reduced SBP/DBP which were generally similar across HTN (ACE-I, Ca2+ antagonist, alpha or beta-blockers, diuretic, or ARB). Incidence of angina, arrhythmia, MI or syncope was low and similar irrespective of treatment. Conclusion: In this study, concomitant HTN and venlafaxine use did not result in vital sign changes of clinical concern compared to those observed by venlafaxine alone.

1133-146


**Hyperhomocysteinemia Alters Collagen Metabolism in the Hypertensive Heart**

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We have recently reported the novel association of hyperhomocysteinemia (HHC) with adverse cardiac remodeling in hypertension (Joseph et al, American Journal of Physiology-In Press). Specifically, we demonstrated that HHC increased myocardial collagen levels and worsened diastolic function in spontaneously hypertensive rats (SHR). The present study was undertaken to further characterize the mechanisms by which an elevated homocysteine levels in the SHR model.

**Methods:** Left ventricular myocardial tissue homogenates from SHRs given one of three diets: control, intermediate HHC-inducing (IH) or severe HHC-inducing (SH) were used in this study. Western blot analysis was done to analyze collagen I and III protein levels. Gelatinolysis was used to assess total gelatinolytic activity, of the left ventricular myocardium.

**Results:** Homocysteine levels (micromolar) after 10 weeks of treatment were control - 4.7±1.1; IH - 6.7±1.1 and SH - 20.7±1.5. We observed an increase in collagen I protein level in the HHC groups as compared to control. The level of collagen III decreased in all HHC groups, increasing the type III collagen ratio as compared to control. Total gelatinolytic activity was also increased in both HHC groups.

**Conclusions:** The fibrillar collagens type I and III are major determinants of myocardial stiffness and diastolic dysfunction. Collagen type I has high tensile strength, while type III collagen is much more compliant. The increase in the ratio of type I/III collagen with HHC offers a potential explanation for the increased myocardial stiffness and diastolic dysfunction seen in this model. An increase in total gelatinolysis activity accompanied the increase in collagen synthesis, similar to other conditions of fibrosis. In conclusion, altered collagen metabolism seems to be an important determinant of HHC-induced adverse cardiac remodeling.

1133-150

**Trends in Hypertension-Related Mortality in the United States, 1980-1998**

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**Background:** Deaths from heart disease and stroke have declined in past decades; however, national trends in hypertension (HTN)-related mortality have not been assessed. National vital statistics multiple cause mortality files from 1960-1996 were analyzed by the Hypertensive Heart Disease code (401-405) listed as one of up to 20 conditions causing death. Racial/ethnic comparisons of HTN-related death were assessed using age-standardized and age-specific rates (per 100,000).

**Methods:** National vital statistics multiple cause mortality files from 1960-1996 were analyzed by the Hypertensive Heart Disease code (401-405) listed as one of up to 20 conditions causing death. Racial/ethnic comparisons of HTN-related death were assessed using age-standardized and age-specific rates (per 100,000).

**Results:** Age-standardized death rates for HTN-related mortality increased 175% (95% Cl 20%-246%) for ages 65-74 years, and 6% (65% CI 2-21%) for ages 75-84 years, and 8% (65% CI 2-15%) for ages 85+ years. Among older persons, HTN-related mortality for adults under age 65 years may have been influenced by national improvements in detection and use of management strategies during the past two decades.

1133-151

**Left Ventricular Mechanics and Tissue Characterization in Hypertensive Children: What Are the Earlier Markers of Heart Damage?**

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**Background:** Early LV functional abnormalities of hypertension in paediatric age has not been extensively investigated. Thus, we newly in-silico assessed LV mechanics and tissue characterization in hypertensive children.

**Methods:** 21 untreated pts (aged 12.16 ± 4.7 years) with renal disease and a recent diagnosis (≤6 months) of hypertension at ambulatory blood pressure monitoring underwent an echocardiographic evaluation. Sex- and age-specific cutoff levels for LV mass/height2.7 and relative wall thickness were defined to assess LV geometry, as normal, concentric remodeling (CR), concentric hypertrophy (CH), eccentric hypertrophy (EH). As load-independent index of myocardial contractility, the relation between the midwall rate-corrected velocity of circumferential fiber shortening and minimal end-systolic stress (mWVCFCS) was defined. LV diastolic function was evaluated by the mitral flow indexes (peak E, peak A, E/A ratio, deceleration time) and isovolumic relaxation time. Finally, univariate tissue characterization of the LV myocardium was performed by integrated backscatter. In addition, 35 age- and BSA-matched normal subjects were used as control group.

**Results:** LV geometry was abnormal in 6/21 pts (2 CR, 1 CH, 2 EH) (23%). LVMI height2.7, which significantly correlated with mean 24-hours systolic pressure (r = 0.60, p < 0.05) was > 51 g/m2.7 in 22/1 (9.5%) pts. The mWVCFCS relation was normal (MaxSDZ) in all pts. Isovolumic relaxation time was prolonged in 12/21 (57%) pts and deceleration time in 11/21 (52%) pts; peak A was increased in 14/21 (66%) and E/A ratio was decreased in 12/21 (57%) pts. Finally, compared to control group, integrated backscatter analysis did not show significant differences in hypertensive children.

**Conclusions:** Majority of hypertensive children show early abnormal LV filling, suggestive of impaired diastolic relaxation. Significantly, abnormal LV geometry was detected in 23% and LVMI height2.7 was > 51 g/m2.7 in 9.5% of pts. Thus, an early echocardiographic evaluation of LV diastolic function and geometry allows us to identify a subset of hypertensive children with heart damage and increased risk of cardiovascular mortality.

1133-152

**Diastolic Function in Obese Children Assessed by Tissue Doppler Imaging**

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**Background:** Our previous studies show that obese children have enhanced LV systolic performance and LV hypertrophy. Using traditional mitral inflow indices, diastolic function has not been apparent. Tissue Doppler imaging (TDI) indices may be more sensitive for detecting diastolic dysfunction. Our aim was to compare TDI indices in obese versus normal children, and to determine correlates of these indices.

**Methods:** 145 obese children (males and females) were evaluated by transthoracic echocardiography. Sex- and age-specific cutoff levels for LV mass/height2.7 were defined. LV diastolic function was assessed by the mitral flow Indexes (peak E, peak A, E/A ratio, deceleration time) and isovolumic relaxation time. Finally, univariate tissue characterization of the LV myocardium was performed by integrated backscatter. In addition, 35 age- and BSA-matched normal subjects were used as control group.

**Results:** The TDI indices for E waves (E-sep, E-lat) were lower than controls, and the E-wave correlated with A-sep (r = 0.19, p = 0.02). There was no correlation with body mass index (BMI).

**Conclusions:** TDI indices were significantly different in obese children. These newer indices of diastolic function, may provide a method for serial monitoring for cardiovascular disease. Identification of these children could allow for earlier initiation of interventional strategies aimed at reducing cardiovascular risk.