Differential Effects of Nebivolol and Metoprolol on Central Aortic Pressure and Left Ventricular Wall Thickness

Priit Kampus, Martin Serg, Jaak Kals, Maksim Zagura, Piibe Muda, Küllikki Karu, Mihkel Zilmer, Jaan Eha

See Editorial Commentary, pp 1047–1048

Abstract—The aim of this study was to investigate the effects of the vasodilating β-blocker nebivolol and the cardioselective β-blocker metoprolol succinate on aortic blood pressure and left ventricular wall thickness. We conducted a randomized, double-blind study on 80 hypertensive patients. The patients received either 5 mg of nebivolol or 50 to 100 mg of metoprolol succinate daily for 1 year. Their heart rate, central and brachial blood pressures, mean arterial pressure, augmentation index, carotid-femoral pulse wave velocity, and left ventricular wall thickness were measured at baseline and at the end of the study. Nebivolol and metoprolol significantly reduced heart rate, brachial blood pressure, and mean arterial pressure to the same degree. However, reductions in central systolic and diastolic blood pressures, central pulse pressure, and left ventricular wall thickness were significant only in the nebivolol group. The change in left ventricular septal wall thickness was significantly correlated with central systolic blood pressure change ($r=0.41; P=0.001$) and with central pulse pressure change ($r=0.32; P=0.01$). No significant changes in augmentation index or carotid-femoral pulse wave velocity were detected in either treatment group. This proof-of-principle study provides evidence to suggest that β-blockers with vasodilating properties may offer advantages over conventional β-blockers in antihypertensive therapy; however, this remains to be tested in a larger trial. (Hypertension. 2011;57:1122-1128.) ● Online Data Supplement

Key Words: antihypertensive therapy ■ central blood pressure ■ pulse wave velocity ■ β-blockers ■ left ventricular mass

Blood pressure (BP) varies throughout the arterial tree because of pulse wave amplification, a phenomenon of wave reflection and arterial stiffness.1 Because of pulse wave amplification, reduction in brachial BP does not reflect changes in central BP, which may become a more important target in the treatment of hypertension. Recent data from the Strong Heart Study2 confirm earlier results from smaller studies on high-risk patients3,4 that central pulse pressure is superior to brachial pulse pressure in the prediction of further cardiovascular events. Moreover, several studies have demonstrated that brachial BP is not a good surrogate for the hemodynamic effects of drug therapies on central circulation. The recently published EXPLOR Study5 and the Conduit Artery Function Evaluation Study6 clearly demonstrated that angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers have a more pronounced effect on reducing central BP compared with the cardioselective β-blocker (BB) atenolol. Different effects of BB on central BP can explain the findings of a recent meta-analysis published by Law et al.7 which demonstrates a slight inferiority of BB in preventing stroke. The detrimental effect of BB on central BP has generated criticism regarding its use as first line therapy for essential hypertension. Dhakam et al8 questioned the hypothesis that the inferiority of atenolol in reducing central BP is a class effect of BB. They demonstrated that the novel vasodilating BB nebivolol (NEB) reduces central BP significantly more than atenolol, despite their similar effects on brachial BP. However, in the above-mentioned and other studies, the BB as the investigated comparison drug was in most cases atenolol. No data are available about metoprolol (MET), which is a more widely used cardioselective BB in the Northern and Eastern European countries.

The main aim of the present study was to investigate the effect of the BB NEB and MET succinate on central hemodynamics, arterial stiffness, and left ventricular wall thickness in patients with essential hypertension during 1-year follow-up.

Methods

Study Design

The study participants, aged 30 to 65 years, with never-treated mild-to-moderate essential hypertension, were included in a random-
ized, double-blind, active controlled trial (NCT01248338). The trial was investigator initiated and was driven and supported by Berlin-Chemie AG (please see Figure S1 in the online Data Supplement at http://hyper.ahajournals.org).

A total of 80 patients were randomly assigned into 2 treatment groups receiving either NEB (Nebilet, dL-nyvobol hydrochloride, Berlin-Chemie AG) or MET (Betacal zoc, MET succinate, Astra Zeneca). The NEB-treated patients received 5 mg of the drug daily, and the MET-treated patients started with 50 mg of the drug daily with possible up-titration to 15 mg daily 2 weeks after randomization. If the target BP of <140/90 mm Hg was not achieved, the investigator was free to add 12.5 to 25 mg of hydrochlorothiazide (Hypothiazid, Chinon Pharmaceuticals and Chemical Works Private Co Ltd) daily 4 weeks after randomization. The duration of the study was 52 weeks plus the screening period of 2 weeks. The patients attended follow-up visits at weeks 2, 4, 12, 24, 40, and 52. After 15 minutes of rest, BP was measured at each visit; pulse wave analysis and carotid-femoral pulse wave velocity (PWV) registration were performed at baseline and at weeks 24 and 52. Echocardiography was performed at baseline and at the end of the study (please see Figure S2). Mild or moderate hypertension was defined as systolic BP 140 to 179 mm Hg and/or diastolic BP 90 to 109 mm Hg on ≥2 occasions separated by 1 month. Patients were excluded during the screening period in case they had diabetes mellitus; adiposity; ischemic heart disease; clinically relevant heart failure; chronic pulmonary disease; valve disease; arrhythmias; secondary hypertension; clinically relevant atherosclerotic disease of the lower extremities; acute or chronic inflammatory disease; hypercholesterolemia; known hypersensitivity or allergic reaction to BB; pregnancy or breastfeeding; history of hepatic, renal, metabolic, or endocrine diseases; heavy smoking; and excessive alcohol consumption (please see the online Data Supplement at http://hyper.ahajournals.org).

The subjects were studied and the plasma samples were collected between 8:00 and 10:00 AM after an overnight fast and abstention from tobacco, alcohol, tea, or coffee. The study was approved by the local research ethics committee, and written informed consent was given by all of the subjects before the study.

**Measurements of Hemodynamics**

**Brachial BP**

Brachial BP was measured in a sitting position from the nondominant arm as a mean of 3 consecutive measurements at 5-minute intervals using a validated oscillometric technique (OMRON M4-I; Omron Healthcare Europe BV). The mean of the 2 closest BP readings was used in further analysis. Brachial pulse pressure was calculated as the difference between brachial systolic BP and diastolic BP.

**Central Pressure and Amplification Index**

Radial artery waveforms were recorded with a high-fidelity micro-manometer (applanation tonometry) from the wrist of the dominant arm, and pulse wave analysis was performed of the systolic portion (Sphygmocor, version 7.1, AtCor Medical). The timing of these waveforms was compared with that of the R wave on a simultaneously recorded ECG. The PWV was determined by calculation of the difference between the carotid and the femoral path lengths divided by the difference in the R wave to waveform foot times. The difference between the carotid and the femoral path lengths was estimated from the distance of the sternal notch to the femoral pulse measured in a direct line.4 The pulse wave analysis and PWV measurements were made in duplicate, and their mean values were used in subsequent analysis.

**Echocardiography**

Echocardiographic examination was performed by 2 experienced sonographers, who were blinded to patient characteristics, using a commercially available device (Sonos5700, Philips Medical Systems, Inc) with a 3.5-MHz transducer and digital recording capabilities. The images were stored digitally, coded with a random number, and read by 2 blinded observers. Using the 2D and the M-mode, long-axis measurements were obtained at the level distal to the mitral valve leaflets. Left ventricular internal dimension and septal and posterior wall thicknesses were measured at the end of the diastole (subscript “d”) according to the recommendations of the American Society of Echocardiography.11 Left ventricular mass was calculated using the following formula: 0.81(1.04 [LVIDd + PWTd + SWTd]3/2 - LVIDd3)] + 0.6 g, where LVIDd indicates left ventricular internal dimension, PWTd indicates posterior wall thickness, and SWTd indicates septal wall thickness. Left ventricular mass was indexed for the power of its allometric or growth relation to height (height in meters1.72)3; this method was used to adjust for differences in body size. Relative wall thickness was calculated using the formula (2 × PWTd/LVIDd)1.1

**Biochemical Analysis**

White blood cell and red blood cell counts, hematocrit, hemoglobin, and platelets were estimated with a Sysmex XE 2100 autoanalyzer (Sysmex Corporation). Plasma glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, creatinine, and high-sensitivity C-reactive protein were determined by standard laboratory methods, using certified assays, in a local clinical laboratory.

**Statistical Analysis**

The statistics were performed using the Software SAS, version 9.1 (SAS Institute Inc), and R (www.r-project.org). All of the analyses were performed on an intention-to-treat basis. All of the data were tested for normality. Normally distributed data are presented as mean ± SD; nonnormally distributed data are presented as the median with the interquartile range. For categorical variables, contingency tables were composed and the χ2 or Fisher exact test, was used to compare the distributions for the 2 randomized groups. For continuous variables, which were not normally distributed for ≥1 group, the Wilcoxon rank-sum test was used to test the difference between the groups. In other cases, the t test was used to test for difference. Changes from the baseline to the end point were also tested for the difference from 0 using the t test or the signed-rank test. The 2-way ANOVA with repeated measures was used to test the interaction between time and drug, as well as error (drug × time). Correlations between the variables were examined using univariate linear regression analysis. Multivariated regression analysis was performed using enter method to determine whether the change in baseline factors influenced the change in hemodynamic parameters. Significance was defined as P < 0.05.

**Results**

The baseline characteristics of the untreated hypertensive subjects are presented in Table 1. Before randomization there were no statistically significant differences in the demographic and clinical characteristics between the treatment groups. A total of 40 patients (50%) were enrolled in the NEB arm, and 40 (50%) were enrolled in the MET arm. Of the 80
patients enrolled, 63 (79%) completed the study. Seventeen patients were withdrawn from the study for various reasons (please see the online Data Supplement).

Up-titration of MET to 100 mg was performed for 13 patients (32%). During the treatment period, 30.0% of the patients (12 subjects) in the NEB group and 22.5% of the patients (9 subjects) in the MET group (P=0.5) received an additional 12.5 to 25 mg of hydrochlorothiazide.

The hemodynamic indices for each treatment group before and after 1 year of therapy are presented in Table 2. Brachial and central systolic or diastolic BP were not different for the groups at baseline. The AIx, AIxHR75, and central pulse pressure were significantly higher in the NEB group at baseline.

Both drugs significantly reduced HR, brachial systolic and diastolic BP, and mean arterial pressure (Table 2), without differences between the groups (Figure 1). However, only the patients of the NEB treatment group showed significantly decreased brachial pulse pressure (P=0.02). The reduction in central systolic BP, central diastolic BP (Figure 2), and central pulse pressure was significant only in the NEB group. At the same time, these parameters did not display significant changes in the MET group (Table 2). Mean reduction in central pulse pressure was 6.2 mm Hg in the NEB group and 0.3 mm Hg in the MET group (P=0.01). Pulse pressure amplification did not change during the treatment period in either treatment arm.

The AIxHR75 (22.88±11.89% to 18.60±11.25%; P=0.02) and PWV (7.5±1.51 to 6.80±1.17 m/s; P=0.03) were significantly decreased after 6 months of treatment only in the NEB group. However, no significant change was detected in AIx, AIxHR75, or PWV after 1-year treatment period for either treatment group (Table 2). There was a trend for correlation (not significant) between the HR change and the AIx change for the whole study group (r=−0.24; P=0.06). However, the

Table 2. Hemodynamic Indices and Left Ventricular Wall Thickness Before and After the 1-Year Treatment Period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nebulol (n=30)</th>
<th>Metoprolol (n=33)</th>
<th>From Baseline</th>
<th>2-Way ANOVA, Drug × Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial systolic BP, mm Hg</td>
<td>146.3±12.49</td>
<td>129.3±8.33</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Brachial diastolic BP, mm Hg</td>
<td>90.0±8.15</td>
<td>78.2±7.58</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Brachial pulse pressure, mm Hg</td>
<td>56.3±11.10</td>
<td>51.1±7.24</td>
<td>0.02</td>
<td>0.7</td>
</tr>
<tr>
<td>Central systolic BP, mm Hg</td>
<td>134.8±19.06</td>
<td>122.4±12.47</td>
<td>&lt;0.001</td>
<td>0.3</td>
</tr>
<tr>
<td>Central diastolic BP, mm Hg</td>
<td>85.6±9.51</td>
<td>79.6±9.13</td>
<td>0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>Central pulse pressure, mm Hg</td>
<td>49.2±12.86</td>
<td>42.9±7.22</td>
<td>0.002</td>
<td>0.7</td>
</tr>
<tr>
<td>Pulse pressure amplification, %</td>
<td>1.18±0.17</td>
<td>1.31±0.28</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>7.5±1.51</td>
<td>7.1±1.18</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Augmentation index, %</td>
<td>27.2±11.37</td>
<td>28.9±11.3</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>AbxHR75, %</td>
<td>22.88±11.89</td>
<td>20.75±10.82</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Transit time, ms</td>
<td>146.2±14.43</td>
<td>148.9±15.92</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67.9±9.05</td>
<td>60.1±7.47</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVED diameter, mm</td>
<td>44.3±5.52</td>
<td>45.5±0.54</td>
<td>0.1</td>
<td>0.9</td>
</tr>
<tr>
<td>IVS thickness, mm</td>
<td>10.3±1.6</td>
<td>9.7±1.5</td>
<td>0.06</td>
<td>0.4</td>
</tr>
<tr>
<td>LV thickness, mm</td>
<td>10.3±1.5</td>
<td>9.3±1.3</td>
<td>&lt;0.001</td>
<td>0.4</td>
</tr>
<tr>
<td>LV relative wall thickness, mm</td>
<td>0.47±0.07</td>
<td>0.41±0.08</td>
<td>&lt;0.001</td>
<td>0.4</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>159.80±49.70</td>
<td>149.23±42.29</td>
<td>0.089</td>
<td>0.3</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>37.3±9.9</td>
<td>34.9±8.3</td>
<td>0.09</td>
<td>0.2</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; PWV, carotid-femoral pulse wave velocity; AbxHR75, augmentation index corrected for a heart rate of 75 bpm; LVED, left ventricular end diastolic; IVS, interventricular septal wall; LV, left ventricular; NEB, nebivolol; MET, metoprolol. Values are the mean±SD.
correlation was significant only for the NEB treatment arm ($r = -0.40$; $P = 0.03$).

There occurred significant reduction in left ventricular posterior wall thickness and left ventricular relative wall thickness, as well as a trend for reduction in left ventricular septal wall thickness and indexed left ventricular mass compared with the baseline values only for the NEB group (Table 2). Moreover, changes in septal wall thickness were more significantly correlated with changes in central systolic BP ($r = 0.41$; $P = 0.001$) and with changes in central pulse pressure ($r = 0.32$; $P = 0.01$; Figure 3) compared with changes in brachial BP values ($r = 0.32$, $P = 0.01$ and $r = 0.26$, $P = 0.04$, respectively). Multiple regression analysis showed that only changes in central systolic BP ($P = 0.009$) were independently correlated with changes in septal wall thickness as the dependent variable but not with medication used, body mass index, changes in mean arterial pressure, or changes in heart rate ($R^2$ for model $= 0.2$; $P = 0.01$). Finally, no correlation was revealed between changes in brachial systolic BP and changes in septal wall thickness after adjustment for changes in mean arterial pressure in multiple regression analysis.

**Discussion**

The aim of the present study was to investigate the effects of NEB and MET on central hemodynamics in patients with essential hypertension during a 1-year treatment period. The main findings were that both drugs reduced similarly brachial systolic and diastolic BP; however, only the patients receiving NEB showed a significant reduction in central BP. The decrease in central BP was correlated with degree of reduction in left ventricular wall thickness. At the same time, neither drug had an effect on AIx, AIxHR75, or PWV after the 1-year treatment period.

**BB and Reduction in Central Aortic Pressure**

The results of the present study generally indicate that the novel third generation BB NEB significantly reduces central BP. However, it is the first attempt to explore the effects of the cardioselective BB MET on central BP. The results of the study confirm that BB without vasodilating properties have less impact on central BP. Two short-term studies (4 to 5 weeks) reported that NEB had a significantly greater effect on central pulse pressure compared with the cardioselective BB atenolol.$^{8,13}$ Dhakam et al$^{8}$ in their study demonstrated that
Overall aortic pulse pressure was 4 mm Hg lower after NEB therapy than after atenolol therapy. Moreover, the results from the Conduit Artery Function Evaluation Study indicate that even a 3-mm Hg reduction in central pulse pressure was associated with better cardiovascular outcome. In the present study, the effect of BB was tested during a 1-year period. Overall central pulse pressure reduction was 6.2 mm Hg in the NEB group and only 0.3 mm Hg in the MET group. The recently published EXPLOR Study demonstrated that treatment with the calcium channel blocker amlopidine combined with the cardioselective BB atenolol during 24 weeks had less impact on central BP than amlopidine combined with valsartan (the difference in reducing central systolic BP was also 4 mm Hg). The authors concluded that the addition of amlopidine to atenolol did not abolish the adverse effect of cardioselective BB on central BP through bradycardia and changes at reflection sites. In the present study both treatment arms similarly reduced HR and mean arterial pressure. It could be suggested that the main mechanism for the reduction in central BP in the nebivolol arm acted through vasodilation and structural remodeling of the small arteries, leading to the reduction in reflection site intensity. It has been demonstrated that nebivolol vasodilates the human forearm vasculature through the L-arginine pathway, improves small artery distensibility index, and increases endothelium-dependent cutaneous vasodilation. At the same time, cardioselective BB do not reduce total peripheral resistance or sympathetic activity, which may lead to small artery vasoconstriction and increased media/lumen ratio.

The AIx and pulse pressure amplification are related to wave reflection depending on the amplitude and site of wave reflection and on the speed at which pressure waves travel along the arterial tree. In the present study, AIx and pulse pressure amplification did not change during the 1-year treatment period in either treatment arm. Previous data about the effect of NEB on AIx and pulse pressure amplification have been conflicting. In patients with isolated systolic hypertension, Dhakam et al. showed a slight increase of AIx and no effect on pulse pressure amplification after 5 weeks of treatment with NEB. On the contrary, Mahmud and Feely demonstrated, after treatment with NEB, a significant reduction in AIx and an increase in pulse pressure amplification in patients with essential hypertension. In the above studies, pulse pressure amplification and AIx were found to be very strongly correlated with HR change, which could explain the described controversial results. The present study also revealed a trend for correlation, although not significant, between HR change and AIx change for the whole study group. Moreover, the correlation was significant only for the NEB treatment arm. No correlation was detected between central pulse pressure change and HR change, which may suggest that more intensive central BP reduction in the NEB-treated patients appeared to be a concomitant effect of HR and AIx change and reduction in peripheral vascular resistance rather than PWV change. It should be noted that there was already a difference in baseline AIx and that the reduction in HR was not sufficient to produce significant AIx change after 1-year therapy.

The PWV is considered a gold standard measure of arterial stiffness, which independently predicts outcome in hypertensive patients. In the present study, there occurred a significant reduction in PWV after 6 months of treatment in the NEB group. However, after the 1-year treatment period there was no significant difference in the change in PWV, radial-carotid PWV (data not shown), or pulse wave transit time between the 2 treatment arms. Previous studies have demonstrated a significant reduction in PWV after treatment with NEB. It has been suggested that the effect of BB on PWV may be related to the concomitant effect of reduction in mean arterial pressure, sympathetic tone, and HR. Consequently, one possible explanation for the nonsignificant change in PWV in the present study is also the significantly smaller reduction in HR during the 1-year treatment period (~6 bpm). It should be noted that previous studies were of short duration, and long-term use of BB may not have such a significant effect on HR and sympathetic activity, which are considered important determinants of PWV. The time-dependent effect of BB on vascular stiffness was also suggested in a recent review by Protogerou et al. Another possibility is that, in the present study, baseline mean PWV was in the normal range. Also, because of the very strict inclusion criteria of the present study, the patients were at low total cardiovascular risk, which may also explain the weak effect of treatment on PWV.

**BB and Left Ventricular Mass Reduction**

The present study provides the first long-term evidence that the reduction in central systolic BP in the NEB group was directly related to the reduction in left ventricular septal and posterior wall thicknesses. It has been demonstrated previously that, compared with brachial BP, central BP is a stronger determinant for left ventricular hypertrophy. Recent data from the Strong Heart Study also indicate that, in terms of reduction in left ventricular hypertrophy, it is more important to target central systolic than brachial BP. Moreover, a recent study has shown that the BB atenolol was less effective than losartan to reduce left ventricular hypertrophy, despite the fact that both drugs reduced brachial BP to a similar degree. In a small open study, NEB monotherapy 12 months resulted in a reduction in left ventricular wall thickness, and NEB was as effective as telmisartan in reducing left ventricular mass after 3 months of treatment. However, a recent meta-analysis provides evidence that BBS show less regression of left ventricular mass compared with other antihypertensive drugs. Regrettably, the results of 20 of the reviewed 31 studies were obtained with atenolol, the results of 3 studies with MET, and the results of only 1 study with NEB. One plausible explanation for the lesser regression of left ventricular hypertrophy by BB in the above meta-analysis is that central BP may not be reduced as effectively as brachial BP, which ensures less afterload reduction with a cardioselective BB without vasodilating properties. Moreover, the failure to reduce central BP with conventional BB was probably also the main reason for the inferiority of BB in preventing stroke in a recent meta-analysis by Law et al. Regarding the diabetogenic role of BB and diuretics, there was no change in fasting plasma glucose after the 1-year
treatment period in either group, because we excluded patients predisposed to diabetes mellitus (eg, those with metabolic syndrome or with increased fasting glucose level).

**Limitations**

The current study has several limitations. The number of patients recruited in the study was small. When this study was designed in 2005, there were no studies of appropriate size providing the data about the effect of antihypertensive drugs on aortic pressure derived from applanation tonometry to undertake formal power calculation; larger studies are therefore needed to confirm our results. Also, 17 of the 80 study patients were withdrawn, which is quite a high proportion. The main reason for poor treatment compliance was that the study patients were relatively young, with newly diagnosed mild-to-moderate hypertension, who did not have any symptoms or complaints attributed to high BP. In the case of mild adverse events after the initiation of treatment, they tended to withdraw their consent.

Also, the inclusion criteria of the study were very strict, and the patients were at low cardiovascular risk, which may explain the relatively normal mean values of central hemodynamics and account for the disparity between several studied parameters and those used in other studies. Although both study groups were comparable with regard to brachial pressure, there occurred a shift in central hemodynamics (AIx and central PP) at baseline.

We cannot exclude an additional effect of the thiazide diuretic on the results. It has been proposed that diuretics have a neutral or minimal beneficial effect on central BP, aortic stiffness, and pressure wave reflection.10,27

**Perspectives**

Our study expands earlier observations of BB and shows that, despite the similar effect of both drugs on brachial BP and arterial stiffness, NEB has a more significant impact on central BP and left ventricular wall thickness than MET. This proof-of-principle study provides evidence to suggest that BB with vasodilating properties may offer advantages over conventional BB in reduction of target organ damage in antihypertensive therapy; however, this remains to be tested in a larger trial. Moreover, noninvasive assessment of central BP change might become a good surrogate for estimating reduction in left ventricular wall thickness in the future.

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**Disclosures**

None.

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ONLINE SUPPLEMENT

DIFFERENTIAL EFFECTS OF NEBIVOLOL AND METOPROLOL ON CENTRAL AORTIC PRESSURE AND LEFT VENTRICULAR WALL THICKNESS

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Running head: Beta-blockers and central aortic blood pressure

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Diabetes was defined as fasting venous plasma glucose >6.4 mmol/L or use of antidiabetic medication. Adiposity was defined as body mass index >30kg/m². Clinically relevant heart failure was defined as NYHA class II – IV. Chronic pulmonary disease was defined as bronchial asthma or chronic obstructive airway disease. Valve disease was defined as abnormality at physical examination and echocardiography. Arrhythmias and conduction disturbances were defined as sinus bradycardia <50 bpm, sick sinus syndrome, AV II-III degree block. Secondary hypertension was defined as urea >8.3 mmol/L, creatinine >120 μmol/L (males), >103 μmol/L (females), TSH >4.0 and <0.4 mIU/L, free T4 >27 pmol/L. Hypercholesterolemia was defined as total cholesterol >6.5 mmol/L. Heavy smoking was defined as cigarette consumption >10 cigarettes per day. Excessive alcohol consumption was defined as consumption of >7 drinks per week (1 drink = 330 mL beer, 120 mL wine or 30 mL strong alcoholic drinks).

2. Online supplement. Results. Drug tolerance.

Of 80 studied patients, 37 (46%) reported at least one adverse event during the trial. Most of the adverse events were of mild to moderate intensity. The proportion of patients who had experienced an adverse event was not different for either treatment group (P=0.5). The reasons for withdrawal were the following: seven patients (four from the nebivolol group and three from the metoprolol group) because of consent withdrawal, two (both from the metoprolol group) because they were non-responders; and eight patients (four patients from either group) because of adverse events. The adverse events resulting in the withdrawal from the study were: dizziness (two patients from either group), bradycardia (one patient from either group), hyperglycemia (one patient from the metoprolol group) and anxiety (one patient from the nebivolol group). None of the patients experienced any serious adverse events or cardiovascular complications.
3. Online supplement. Figure S1. Study design.

Excluded patients n=42
- Not fulfilling inclusion criteria: n=38
- Withdrawal of consent: n=6

Screened patients n=122

Randomized patients n=80

Nebivolol n=40
- Early termination n=10
  - Adverse event/side effect: n=4
  - Treatment failure: n=2
  - Consent withdrawal: n=4

Metoprolol n=40
- Early termination n=7
  - Adverse event/side effect: n=4
  - Consent withdrawal: n=3
4. Online supplement. Figure S2. Study protocol.

BP – blood pressure; PWV – carotid-femoral pulse wave velocity; ECHO – echocardiography; HTZ – hydrochlorothiazide; MET – metoprolol; NEB – nebivolol.

* Was added if target brachial blood pressure was not achieved (<140/90 mmHg) with previous dosage.