Influence of drugs and gender on the arterial pulse wave and natriuretic peptide secretion in untreated patients with essential hypertension

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ABSTRACT

Recent studies have suggested a differential influence of mean pressure and pulse pressure on myocardial infarction and stroke, and differences among the major drugs in their efficacy at preventing these individual endpoints. We hypothesized that antihypertensive drugs have differing influences upon the pulse wave even when their effects on blood pressure are the same. We studied 30 untreated hypertensive patients, aged 28–55 years, who were rotated through six 6-week periods of daily treatment with amlodipine 5 mg, doxazosin 4 mg, lisinopril 10 mg, bisoprolol 5 mg, bendrofluazide 2.5 mg or placebo. The best drug was repeated at the end of the rotation. Blood pressure readings and radial pulse tonometry (by Sphygmocor™) were performed at each visit, and blood was taken for measurement of levels of atrial natriuretic peptide and brain natriuretic peptide (BNP). The Sphygmocor derivation of the central aortic pulse wave was used to measure time for transmission of the reflected wave ($T_R$) and the augmentation index (AI), which is the proportional increase in systolic pressure due to the reflected wave. There was a dissociation between the effects of the drugs on blood pressure and pulse wave analysis. Bisoprolol caused the greatest falls in blood pressure and $T_R$, but was the only drug to increase AI. This paradoxical response to bisoprolol was associated with a 3-fold increase in plasma BNP levels. There was a smaller elevation of BNP in women compared with men, as described previously, and this elevation also was associated with significantly higher values of AI. Other drugs reduced AI, and this was associated with a significant decrease in BNP by amlodipine. In conclusion, antihypertensive drugs differ in their short-term effects on augmentation of the systolic pulse wave and secretion of BNP from the heart, regarded as a sensitive measure of strain on cardiomyocytes. These differences may help to explain cause-specific differences in outcome in recent trials.

INTRODUCTION

The publication of trials comparing older and newer drugs in the treatment of hypertension has created some consensus that it is the blood pressure achieved, rather than choice of drug, that determines most of the primary outcomes in the trials [1,2]. When heart failure is included, however, some substantial differences do emerge between drugs [3–5]. Moreover, meta-analysis of the trials suggests small but distinct differences among drug classes in their ability to prevent specific outcomes, with calcium blockers being most effective in preventing strokes, but angiotensin-converting enzyme (ACE) inhibitors and diuretics having the edge in preventing coronary disease [1,2]. Most recently, the Losartan Intervention For Endpoint Reduction in Hypertension
A. J. Deary and others (LIFE) study reported a 25% higher incidence of stroke in patients randomized to atenolol compared with losartan therapy [6].

These specific differences in outcome for different drugs raise the question of whether the drugs have different effects on the pulse wave. This possibility was suggested to us by the epidemiological observations that pulse pressure is better than mean blood pressure for predicting coronary disease, whereas the reverse is true for strokes [7,8]. In the present crossover study, we have investigated whether the main classes of antihypertensive drugs differ in their effects on the pulse wave.

METHODS

The Amlodipine, Doxazosin, Lisinopril, Bisoprolol, Bendrofluazide (ADLIB) study was a double-blind, placebo-controlled crossover rotation designed to determine the proportion of patients for whom each of these agents is the most effective at lowering blood pressure and improving quality of life [9]. During the study we acquired the facility for performing pulse wave analysis, and present here a substudy from the final 30 ADLIB patients.

The subjects were previously untreated hypertensive patients, with diastolic blood pressure \( \geq 95 \) mmHg. After a 2-week placebo run-in, patients rotated, in random order, through six 6-week periods of double-blind treatment with placebo, amlodipine 5 mg, doxazosin 4 mg, lisinopril 10 mg, bisoprolol 5 mg and bendrofluazide 2.5 mg. Each subject’s most effective and tolerated treatment was repeated at the end of the rotation. Pulse wave analysis was undertaken at each visit by pressure tonometry (Sphygmocor; PWV Medical Pty. Ltd, Sydney, Australia) at the radial pulse. The Sphygmocor algorithm recreates the pulse wave at the aortic root, and has been used to calculate the central aortic pressure, together with two indices of arterial stiffness (Figure 1) [10,11]. In a comparison of direct and derived estimations of central aortic pressure in 62 anaesthetized patients, the Sphygmocor apparatus fulfilled the Association for the Advancement of Medical Instrumentation criteria for validation of blood pressure measurements, with a correspondence of 0 \( \pm 4.4 \) mmHg between readings [12]. The augmentation index (AI) measures the height of the second peak of the systolic pulse wave, which is produced by reflection of the pulse wave from branch points in the muscular arteries; this reflection increases with arterial stiffness, but is also influenced by other parameters, including height and heart rate [13,14]. The velocity of the pulse wave, which also increases with stiffness, is inversely proportional to the time for transmission of the reflected wave (\( T_R \)), measured as the time between the first and reflected peaks of the pulse wave [15]. \( T_R \) increases with the height of the patient (Figure 2), but in a crossover study the differences in \( T_R \) between treatments are due mainly to differences in pulse wave velocity. Plasma levels of natriuretic peptides [atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)] were measured at each visit.

The research was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association, and the study was approved by the research ethics committee of Addenbrookes Hospital. Patients gave informed consent to inclusion in the study.

Data were analysed by repeated-measures ANOVA, with gender as an independent variable, for both trends across all treatments and between each individual drug and placebo, applying a Bonferroni correction. The distribution of plasma BNP was log normal, and these data were therefore log-normalized before analysis.

RESULTS

A total of 22 men and eight women (median age 47 years) participated in the study. There were significant differences among drugs with regard to their effects on most of the parameters listed in Table 1, which were mostly
Table 1  Crossover comparison of haemodynamic variables following treatment with each of the five antihypertensive drugs
Mean (S.D.) results are shown separately for men (upper row) and women (lower row) for each parameter. Values significantly different ($P < 0.01$) from placebo are indicated by *. The listed $P$ values (right-hand column) were calculated by repeated-measures ANOVA for the trend across the five active drugs only, for both genders together. BP, blood pressure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Amlodipine</th>
<th>Droxazosin</th>
<th>Lisinopril</th>
<th>Bisoprolol</th>
<th>Bendrofluazide</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mmHg)</td>
<td>157 (9.9)/99 (8.2)</td>
<td>148 (10.0)/91 (6.6)*</td>
<td>148 (10.0)/91 (5.7)*</td>
<td>142 (11.4)/88 (9.1)*</td>
<td>138 (15.0)/88 (8.8)*</td>
<td>151 (11.7)/96 (7.9)*</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Central systolic BP (mmHg)</td>
<td>143 (10)</td>
<td>133 (11)*</td>
<td>131 (9)*</td>
<td>128 (13)*</td>
<td>129 (14)*</td>
<td>138 (12)</td>
<td>0.16</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 (9)</td>
<td>76 (12)</td>
<td>75 (12)</td>
<td>74 (10)</td>
<td>65 (11)*</td>
<td>74 (12)</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>85.3 (8.9)</td>
<td>84.5 (9.1)</td>
<td>86.6 (9.1)</td>
<td>84.5 (8.8)</td>
<td>85.1 (9.3)</td>
<td>84.4 (9.3)</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Plasma ANP (pg/ml)</td>
<td>62 (24)</td>
<td>49 (14)</td>
<td>75 (88)</td>
<td>46 (20)</td>
<td>73 (38)</td>
<td>54 (22)</td>
<td>0.07</td>
</tr>
<tr>
<td>log [Plasma BNP (pg/ml)]</td>
<td>0.76 (0.30)</td>
<td>0.64 (0.20)*</td>
<td>0.78 (0.29)</td>
<td>0.71 (0.27)</td>
<td>1.07 (0.44)*</td>
<td>0.65 (0.24)*</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>AI (%)</td>
<td>24 (7)</td>
<td>19 (14)</td>
<td>18 (14)*</td>
<td>19 (11)</td>
<td>27 (7)*</td>
<td>20 (13)</td>
<td>0.0039</td>
</tr>
<tr>
<td>$T_a$ (ms)</td>
<td>136 (10)</td>
<td>142 (9)</td>
<td>138 (10)</td>
<td>142 (9)</td>
<td>144 (10)*</td>
<td>137 (7)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

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Figure 3 Comparison of drug effects on plasma BNP levels (upper panel) and AI (lower panel)
AI and plasma BNP levels were measured after 6 weeks of each active drug and placebo, administered double-blind in random order. The “best” drug (most effective at lowering systolic BP and well tolerated) was repeated for 6 weeks at the end of the rotation. In 11 patients the best drug was bisoprolol. An extra sample for plasma BNP was also taken at the end of the 2-week single-blind placebo run-in period (left-hand bar). Values are means \( \pm S.E.M. \) consistent in males and females. As expected for this age group, the average falls in blood pressure were greatest with the ACE inhibitor and the \( \beta \) blocker. Of these two, the \( \beta \) blocker was better at reducing brachial systolic pressure; the best value during rotation was achieved by bisoprolol in 14 patients, compared with three for lisinopril. Not all patients tolerated the drugs equally well; the numbers who repeated each drug at the end of the rotation, chosen by efficacy and tolerability, were respectively 4, 4, 8, 11 and 2 for amlodipine, doxazosin, lisinopril, bisoprolol and bendrofluazide.

In contrast with its efficacy in reducing brachial blood pressure, bisoprolol was the only drug to have an adverse effect on AI and plasma BNP levels (Figure 3). AI was substantially lowered by all other drugs, especially amlodipine, whereas bisoprolol caused a significant increase. As a consequence of this increase in wave reflection, bisoprolol was overtaken by lisinopril as the most effective drug in reducing central aortic pressure (Table 1 and Figure 4).

A similar pattern as for AI was seen for BNP, which also increased on bisoprolol treatment, by more than 3-fold compared with placebo; amlodipine caused a significant decrease, and the other drugs were similar to placebo. These effects of bisoprolol were not only consistent between the genders, but were additive to the higher values of AI and BNP in women than in men.

Figure 4 Comparison of brachial and central systolic blood pressure
Each patient’s lowest reading during the rotation is shown, with the symbol coding for the drug being taken at the time. The numbers in parentheses on the left and right of each drug name are the totals that may be read from the Figure for the numbers of patients for whom each drug was most effective in reducing, respectively, brachial and central systolic pressure. Bendro, bendrofluazide.

Figure 5 Comparison of drug effects on pulse wave velocity, measured as \( T_R \)
\( T_R \) was calculated from the same tonometric recordings as were used for the AI measurements in Figure 3. Values are means \( \pm S.E.M. \).
The increase in AI on bisoprolol was in contrast with the beneficial effect of this drug on T\(_R\). This parameter varies inversely with pulse wave velocity. T\(_R\) increased (i.e. improved) more on bisoprolol than on any other drug (Figure 5). Changes in plasma ANP were smaller than those in BNP, and for some drugs appeared to reflect changes in body weight.

**DISCUSSION**

The present study has demonstrated differences among the main classes of antihypertensive drugs in their short-term effects on the arterial pulse wave. The precision of the measurements was enhanced by using a single, tonometric recording of the pulse wave from the most superficial, and therefore easiest, site for doing this, namely the radial artery. Normally the pulse wave has to be recorded at two sites in order to calculate pulse wave velocity, with certain assumptions about the length of artery between them. In a crossover study, however, each patient is their own control, and differences in pulse wave velocity between treatments can be assessed by measuring T\(_R\), i.e. the time between the start of the systolic ejection period and the reappearance at the aortic root of the systolic pulse wave from its main reflection points. T\(_R\) cannot be used reliably in comparisons between patients, because a major determinant of T\(_R\) is height. As illustrated in Figure 3, T\(_R\) is greater in men than in women, although pulse wave velocity does not differ between genders [16]. On the other hand, the shorter time for wave reflection in women results in their having a much higher AI than men, because the pulse wave returns during the ejection period [14,16]. This gender difference means that augmentation data should probably be presented and analysed separately for men and women, but has otherwise been regarded as an artifact of the measurement. As will be discussed, our data suggest otherwise.

Both the T\(_R\) and AI measurements showed differences among the drugs that did not entirely correspond with their expected differences in efficacy in lowering blood pressure in this age group of patients. In particular, the \(\beta\) blocker bisoprolol had opposite effects on T\(_R\) and AI, suggesting that, as with the gender difference in AI, there may be critical artifacts in interpreting drug effects on AI. T\(_R\) could be misleading if a drug changed the reflection points responsible for the second peak of the pulse wave; however, this would not explain the opposing effects of \(\beta\) blockade on AI and T\(_R\). The likely explanation is the fall in heart rate on \(\beta\) blockade, which prolongs both parts of the cardiac cycle and, like short height, permits the peak of the reflection wave to occur before the end of systole. Two studies of pacing have indeed shown an inverse correlation between heart rate and AI [17,18]. A study of \(\beta\) blockade in paced subjects may be necessary to demonstrate whether heart rate changes alone are responsible for the effect on AI. In previous studies of pulse wave contour, an adverse effect of \(\beta\) blockade was noted in patients receiving atenolol, but not the vasodilating isomer of labetalol, dilevalol, and further comparisons of \(\beta\) blockers may be helpful [19,20].

In order to estimate whether short-term differences in large artery function might influence cardiac function, we measured levels of natriuretic peptides at each visit. A possible effect of \(\beta\) blockade on BNP secretion has been noted previously in cross-sectional studies of patients on different drugs [21,22]. However, this is the first prospective study of the BNP response to different antihypertensive drugs. The co-incidence of increases in both AI and the plasma BNP level on bisoprolol, in both genders, suggests a possible mechanism for the increase. Despite the beneficial effect of bisoprolol on other parameters of stiffness in both the present and other studies, and the lack of a gender difference except when the stiffness measure is influenced by height, the higher BNP values on bisoprolol raise the question of what the net effect of \(\beta\) blockade is for the heart [14,16,23–25]. Our study was not designed to compare BNP values between genders, but our findings are consistent with a report that these are higher in women [21]. The left ventricle pressure curve, being the same as that of the aorta during systole, will show enhanced augmentation in women and during \(\beta\) blockade. The secretion of BNP from isolated cardiomyocytes is stimulated by physical strain [26], and in vivo rises with systolic blood pressure, left ventricular hypertrophy and heart failure [21,27]. The reflected wave effectively prolongs the duration of peak systolic pressure [28]; since the central aortic pressure is reduced by bisoprolol, it may be that area under the curve, rather than absolute height of the pulse wave, mediates the unexpected effects of gender and \(\beta\) blockade on BNP secretion.

Other mechanisms may also contribute, since previous studies have demonstrated significantly higher plasma ANP levels in patients with \(\beta\) blockade [29], and we saw some changes of marginal significance with the other drugs which did not correlate with changes in AI (Table 1). Elevations of both ANP and BNP are more often associated with tachycardia, whether caused by arrhythmias, catecholamine infusion or endogenous catecholamines in heart failure. Indeed, their measurement may be a useful test to exclude heart failure [30,31]. *In vitro*, \(\beta\)-adrenergic stimulation of cAMP production is associated with increased BNP secretion [32]. It is unlikely, therefore, that the effect of \(\beta\) blockade is mediated through reduced cAMP generation in the cardiomyocyte, and for BNP, at least, cell signalling systems other than cAMP are more important in regulating transcription [33]. There is no evidence that bisoprolol lowers natriuretic peptide clearance, which could in theory elevate BNP more than ANP, and another \(\beta\) blocker, carvedilol, has been shown to increase BNP mRNA levels in rat heart [34,35].

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Our study did not find any evidence that the drugs associated with a marginally lower risk of coronary events in the meta-analyses, i.e. diuretics and ACE inhibitors, have a more beneficial effect on the pulse wave. However, we did find a decrease in AI when patients received the drug class – calcium blockade – associated with a slightly reduced stroke risk, and a striking increase in AI caused by the drug class – β-blockade – now associated with a marked increase in stroke risk [6].

On the other hand, the increase in BNP secretion seen with bisoprolol is sufficient to contribute beneficially to the haemodynamic consequences of β-blockade, particularly the vasodilatation and natriuresis required to compensate for a fall in cardiac output and renal perfusion pressure [35–37]. In the International Nifedipine Study, we noticed, post hoc, that when atenolol was used as add-on treatment, it prevented the excess in heart failure associated with the calcium blocker; indeed, none of the patients developed heart failure [4]. Although BNP secretion may help to protect the heart from hypertension, much higher levels of circulating BNP are required in established heart failure in order to overcome up-regulation of renal phosphodiesterases to their actions [37–39]. As a practical point, if BNP is to be introduced as a diagnostic test for heart failure, the normal values will need to take into account the effects of drugs and gender that we have illustrated here.

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Effects of β-blockade on arterial pulse wave and plasma natriuretic peptides


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