A randomized, double-blind study of valsartan versus metoprolol on arterial distensibility and endothelial function in essential hypertension

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Abstract

Background. Antihypertensive drugs may have differential, pressure-independent effects on hypertension-associated alterations of arterial function. We compared the effects of a 12-week therapy with the AT1-receptor antagonist valsartan (Val) versus the beta-blocker metoprolol (Met) on arterial stiffness and endothelial function in mildly hypertensive patients at rest and during generalized sympathetic stimulation.

Methods. Sixty-eight patients (37 male, 31 female, 46 ± 6 years) were randomized to Val (80–160 mg/d) or Met (50–100 mg/d). Effects of therapy on endothelial function, brachial and carotid artery distensibility coefficients, pulse wave velocity, carotid intima-media thickness and elastic modulus were assessed at rest and during the cold pressor test.

Results. Fifty-two patients were available for per protocol analysis. Blood pressure was comparably reduced in both treatment groups. Effects on endothelial function and large artery elastic wall properties did not differ significantly between the two antihypertensive treatment regimens. Trends did not differ significantly between groups for any parameter including carotid intima-media thickness and elastic modulus.

Conclusion. Short-term treatment with Val and Met had similar effects on large artery functional vessel wall properties in a population of mildly hypertensive patients.

Keywords: arterial distensibility and compliance; AT1-receptor blocker; endothelial function; essential hypertension; intima-media thickness

Introduction

Essential hypertension is associated with impaired endothelial function determined as a reduced endothelium-dependent vasodilation in most studies in humans [1–3]. Moreover, viscoelastic properties of arteries are impaired by hypertension resulting in a decreased arterial compliance that contributes to increased cardiovascular morbidity and mortality in these patients [4,5]. Antihypertensive drugs interfering with the renin–angiotensin system have been shown to improve endothelial function by pressure-dependent and -independent effects in humans [6,7]. Angiotensin-converting enzyme (ACE) inhibitors have been found to improve endothelium-dependent vasodilation in the coronary and the renal vasculature; however, in the forearm vasculature evidence is less convincing [8–10]. Moreover, findings on the role of AT1 blockade and its effect on arterial function are equivocal.

Long-term treatment with an AT1-receptor antagonist may have favourable effects on arterial compliance and distensibility although convincing studies addressing this issue are still lacking [7,11]. Sympathetic nerve activity influences arterial elasticity [12] and angiotensin II increases sympathetic outflow. Moreover, endothelial function is related to arterial compliance and nitric oxide improves regional arterial distensibility [13].

The aim of our study was therefore to simultaneously assess the effects of antihypertensive drugs on large artery mechanical vessel wall properties and endothelial function at rest and during sympathetic activation in a population of mildly hypertensive patients. We tested whether the AT1-receptor antagonist valsartan (Val) improves endothelium-dependent vasodilation in the brachial artery and/or has beneficial effects on arterial pulse wave velocity or regional arterial distensibility of large arteries in a randomized and double-blinded study design with a control group treated with the beta-blocker metoprolol (Met).

Methods

Study design

All patients gave their written informed consent to the parallel group, randomized (1:1 randomization), double-blind and prospective trial design.
Antihypertensive drugs in pretreated patients were withdrawn in a wash-out period up to 2 weeks and a single-blind 2-week placebo run-in phase was performed before patients underwent baseline vessel wall measurements. Patients were randomized to 12-week treatment with either Val 80 mg o.d. (or 160 mg o.d. if the target diastolic blood pressure of <140/90 mmHg was not achieved after 4 weeks) or with Met 50 mg o.d. (dosage could be increased to 100 mg o.d. according to blood pressure levels after 4 weeks). Hydrochlorothiazide (12.5 mg/day) was added if the target blood pressure of <140/90 mmHg was not achieved after 8 weeks. After 12 weeks of active treatment, vessel wall measurements were repeated (see the flow chart in Figure 1). Patient compliance was assessed by pill count.

**Patients**

Essential hypertension was defined as an average diastolic blood pressure from three measurements ≥90 mmHg, but ≤110 mmHg at week 0; 68 hypertension patients (37 male, 31 female, 46 ± 6 years) were included and randomized to Val or Met (Table 1).

Exclusion criteria were hypercholesterolaemia (LDL-cholesterol >175 mg/dl), triglycerides (TG) >300 mg/dl, current smokers, ultrasound evidence of atherosclerotic plaques, hyperkalaemia (>5 mmol/l), angina with ECG changes or heart failure NYHA classifications III and IV, history of myocardial infarction, diabetes, bradycardia, liver, cardiac or kidney diseases and serum creatinine concentrations >150% of the upper normal range. No concomitant antihypertensive medication was allowed.

Left brachial artery blood pressure was measured using an automatic sphygmomanometer (Critikon Dinamap model 1846 SX, Tampa, FL, USA).

**Vessel wall measurements.** All measurements were performed between 8 and 12 a.m. by the same investigator who was blinded to the patient’s treatment status. Twelve to fourteen hours had elapsed between the measurements and previous intake of antihypertensive drugs. Aortic femoral pulse wave velocity, distensibility of the brachial and carotid arteries as well as endothelium-dependent flow-mediated and endothelium-independent nitroglycerine-mediated vasodilation of the brachial artery were studied, as described earlier, using a 7.5 MHz linear array transducer and a multigate pulsed Doppler system (Pie Medical Equipment B.V., Maastricht, The Netherlands) [12,14,15].

The relative systolic increase of the vessel diameter \([\Delta d \times d^{-1} \%]\) and the arterial wall distensibility coefficient \([DC = 2\Delta d \times d^{-1}/(SBP-DBP) (10^{-3}kPa)]\) were calculated. Additionally, isobaric distensibility of the carotid artery was calculated at 100 mmHg taking a pressure window of 10 mmHg using IGOR PRO software (Wave Metrics Inc., Lake Oswego, OR, USA) with a procedure designed by Wisstech GmbH (Sprechbach, Germany). Carotid artery blood pressure was calibrated against brachial artery blood pressure.

**Table 1. Demographic and clinical data**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Body mass index (kg/m²)</th>
<th>Duration of hypertension (months)</th>
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<td>Val (n = 35)</td>
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<td>45.4 ± 5</td>
<td>29.0 ± 5</td>
<td>31 ± 32</td>
<td>ACE inhibitors</td>
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<td>Met (n = 33)</td>
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<td>Calcium-channel blockers</td>
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<td>46.2 ± 6</td>
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<td>Heart rate (min⁻¹)</td>
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Displayed are baseline data for age, body mass index, gender, duration of hypertension, antihypertensive pre-medication (withdrawn 4 weeks before randomization), systolic and diastolic blood pressure, serum creatinine and heart rate of patients at randomization assigned to either valsartan (Val) or metoprolol (Met) treatment. Data are means ± SD.
The coefficient of variation was 3.4% for the end-diastolic diameter, 7.4% for the relative systolic increase of vessel diameter and 10.8% for the distensibility coefficient (n = 25).

The intima-media thickness of the carotid artery was measured using image analysis by the echo tracking system wall track system 2 (Pie Medical, Maastricht). The incremental elastic modulus ($E_{inc}$) was calculated taking into account the thickness of the arterial wall using the formula $E_{inc} = [3 (1+4/WCSA)]/DC$ (WCSA = wall cross-sectional area of the artery, $A$ = vessel cross-sectional area).

**Sympathetic stress test.** The right hand was submerged into ice water for 2 min (cold pressor test). Immediately after removal of the hand from the ice water, another measurement of carotid artery distensibility was taken.

**Statistics**

**Power calculation.** For this trial, the two-sided type-I-error was set to 5% and the type-II-error to 10%. Carotid and brachial distension and aortic pulse wave velocity were primary endpoints. Assuming from previous studies of our group that a change in the studied primary endpoints of 20% could be expected and was clinically relevant and on the basis of a normal distribution using the a.m. treatment difference and a conservative estimate of the standard deviation, a total sample size of 25 patients per treatment group was necessary [12,14–17]. Considering an expected dropout rate of 20% we aimed for randomization of at least 65 patients.

Changes in flow-mediated vasodilatation (FMD), nitroglycerine-induced vasodilatation, blood pressure, brachial and carotid DC, intima-media thickness, elastic modulus and changes in parameters during sympathetic stress tests were secondary endpoints.

Differences in biochemical, clinical and haemodynamic parameters between groups were tested for by Student’s $t$-test. Inter-group trend differences were tested for in a per-protocol analysis by ANCOVA by treatment with baseline variables as covariate. Multivariate analysis was performed in order to assess a potential influence of differences in baseline values on the between-group changes in arterial function parameters.

**Results**

Demographic data, clinical and biochemical parameters of both patient groups are shown in Table 1 and were not different between groups. Ten patients of the Val group and six patients of the Met group had to be excluded before the per-protocol analysis because of protocol violations, e.g. incomplete patient follow up, or withdraw of consent. Overall, ten patients of the Val group and seven patients of the Met group were available for per protocol analysis; Table 2 shows haemodynamic data and values of the vascular function tests. Blood pressure reduction was marked and comparable between both treatment groups. There was a mild positive effect on endothelial function measured as FMD in both groups, which reached statistical significance only in the Met group; however, there was no significant inter-group trend difference (Figure 2). Nitroglycerine-induced vasodilation as a marker of endothelium-independent dilatory capacity of the vessel was comparable between groups and stable over the study period.
Depicted is flow-mediated vasodilatation (FMD) of the brachial artery at study entry and after 3 months of treatment with either valsartan or metoprolol, expressed as percent change from the baseline brachial artery diameter. In the valsartan group, an apparent increase in FMD did not reach statistical significance, whereas in the metoprolol group, there was a significant increase in FMD. However, there was no significant inter-group trend difference (\( P > 0.05 \)).

Neither treatment had a significant effect on parameters of arterial stiffness (brachial or carotid isobaric distensibility coefficients), pulse wave velocity, intima-media thickness or incremental elastic modulus. Response to cold pressure tests (blood pressure increase and arterial compliance changes) was comparable between both groups and was not influenced by treatment (Figure 3).

Arterial diameters of the brachial and carotid arteries were very stable over the study period in both groups, showing a high reproducibility and accuracy of the method used for vascular function assessment.

To test for a possible dependence of changes in vessel wall parameters from differences in baseline values of groups and other determinants, a multivariate regression analysis was performed. Pulse wave velocity was dependent on baseline TG (\( P = 0.004 \)) and cholesterol (\( P = 0.04 \)) and on baseline SBP and DBP (\( P = 0.02 \) and 0.03) and BMI (\( P = 0.02 \)). NMD was dependent on BMI (\( P = 0.03 \)); carotid DC was found to be dependent on SBP (\( P = 0.02 \)) and strongly dependent on age (\( P \leq 0.0001 \)). However, changes in functional vessel parameters were independent from treatment.

Discussion

In the presented double-blind, randomized and active-treatment-controlled study, 12-week treatment with the AT1-receptor antagonist Val did not have significant effects on large artery vessel wall function compared to therapy with Met despite marked blood pressure reduction. To our knowledge this is the first study that assesses the effects of antihypertensive treatment on both endothelial function and large artery elastic wall properties at rest and during sympathetic activation in patients with essential hypertension.

There were mild positive effects on endothelial function assessed as FMD of the brachial artery that can be attributed to the significant blood pressure reduction in both treatment
groups. However, these effects did not differ significantly between the two antihypertensive treatment regimens and neither drug did significantly influence large artery elastic wall properties or blood pressure response to sympathetic stimulation. Multivariate regression analysis also showed independence of changes in vessel wall parameters from treatment arms.

Some possible explanations may have contributed to the failure of our study to demonstrate an effect of AT1-receptor blockade on functional vessel properties. First, the treatment period of 12 weeks may have been too short to result in a marked increase in endothelial function or elastic vessel wall properties. Ghidoni et al. reported an increase in acetylcholine-induced vasodilation after 12 months of candesartan treatment but not after 2 months [18]. The same may be true for changes in structural vessel wall properties that possibly require a longer period of treatment for normalization [5].

Second, the average dose of Val of <100 mg/day may have been too low to observe improvements of large artery functional vessel wall properties after the treatment period of 3 months. In recent trials Val is generally administered in doses between 160 and 320 mg/day.

Third, patients recruited in our study were relatively young and healthy, although endothelial function and arterial compliance at baseline were moderately impaired. A putative positive effect of the intervention on these surrogate parameters of vascular function may be more marked in patients with severely impaired vascular function. There are several studies showing a positive effect of ACE inhibition and AT1 blockade on arterial function in more advanced hypertension and arterial impairment [6,7,11,19].

Finally, our study may be underpowered. However, the a priori power of our study was adequately calculated from the results of previous studies and we chose a sample large enough to exclude significant treatment effects on arterial function parameters >20%. A posteriori power calculations are often considered problematic as they are biased by the results of previous studies. Nonetheless we also performed a posteriori power calculations which take into account our actual results in the primary end points, brachial and carotid arterial distension and pulse wave velocity, that showed that, given our sample size, we may have missed a treatment-induced effect of 11–17% of the mean values. We considered a change of at least 20% to be clinically relevant.

In this study, we had somewhat higher standard deviations in FMD than expected; therefore, the power of our study may have been inadequate to detect a change in the range of 20%. However, FMD was a secondary endpoint in our study.

Our results contrast with results of long-term AT1-receptor blockade and ACE inhibition showing an improvement of endothelium-dependent vasodilation along with structural alterations of the arteries. Thus, in contrast to patients with atherosclerosis and hypercholesterolemia an improvement in endothelial function in patients with essential hypertension seems to require longer periods of treatment and to be linked to changes in arterial wall structure [11,20]. However, there are also some studies showing effects of a relatively short period of treatment with AT1-receptor blockers on functional vessel wall properties in small arteries and the microvasculature [19]. The stiffness of wall components of small arteries was decreased by losartan but not by atenolol in hypertensive patients [21] and short-term irbesartan treatment improved endothelium-dependent vasodilation in patients with mild-to-moderate hypertension [22].

The discrepancy between these studies and our data may in part be explained by differential effects of drugs interfering with the renin–angiotensin system in different vascular regions. Whereas ACE inhibitors have been convincingly demonstrated to improve endothelium-dependent vasodilation in the coronary and the renal vasculature, findings in the forearm vasculature of hypertensive individuals are equivocal [8,10,23]. The same appears to be true for angiotensin II type 1 receptor antagonists. In essential hypertension, only one trial has been published reporting that an AT1-receptor antagonist, as compared to a beta-blocker, normalizes endothelium-dependent vasodilation of resistance arteries; however, this was an in vitro study [11].

Anderson and co-workers could—in accordance with our data—not confirm an improvement of FMD in the brachial artery in response to losartan [24]. Nevertheless, on the basis of the data of our study we cannot exclude a beneficial effect of AT1-receptor blockade on endothelial function and arterial compliance in different vascular territories.

Our results are in accordance with data of Klingbeil and co-workers who also studied the brachial artery in a comparable patient cohort and who did not find an effect of 6-week treatment with Val compared to placebo or hydrochlorothiazide on endothelial function determined by the increase in forearm blood flow after intra-arterial administration of acetylcholine [25].

In conclusion, short-term treatment with the AT1-receptor antagonist Val and the beta-blocker Met had similar effects on blood pressure and large artery functional vessel wall properties in a population of young, mildly hypertensive patients.

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Conflict of interest statement. The manuscript has been seen and approved by all authors, there is no potential conflict of interest of any author and the content of the paper—or part of it—has not been published and is not being submitted elsewhere.

References


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