Paradoxical Pressor Effects of β-Blockers in Standing Elderly Patients With Mild Hypertension

A Beneficial Side Effect

T.J. Cleophas, MD, PhD; I. Grabowsky, MD; M.G. Niemeyer, MD, PhD; W.M. Mäkel, MD; E.E. van der Wall, MD, PhD; on Behalf of the Nebivolol Follow-Up Study Group

Background—Baroreflex sensitivity declines with age, creating a fall in systolic blood pressure and pulse pressure when standing. If, in addition, blood pressure is reduced as a result of antihypertensive medication, compensatory mechanisms may be inadequate and orthostatic problems may occur. This may be less true in patients on β-blockers. β-blockers cause pressor effects in standing patients with autonomic neuropathy, but their effects on standing pulse pressures in elderly subjects with mild hypertension have not been systematically studied.

Methods and Results—We studied 3741 patients with mild hypertension for 6 months who were being treated with the β-blocker nebivolol 5 mg daily. Blood pressures were measured after 10 minutes in the supine position and after 1 minute in the standing position. Overall, systolic and diastolic blood pressures rose slightly while standing, whereas pulse pressures remained unchanged. When previously untreated patients (n=2085) >60 and ≤60 years of age were assessed separately, supine pulse pressures were consistently higher in the elderly group compared with those of the younger subjects by 6 to 11 mm Hg (P<0.001 to 0.0001). However, while standing, pulse pressures rose in the younger subjects, whereas they tended to fall in the elderly group. After 6 months of β-blockade, this pattern was unchanged in the younger subjects but reversed into significant rise of pulse pressures in the elderly group by 4 (SD 1) mm Hg (P<0.001). In the patients previously treated with other classes of antihypertensive drugs (n=712), the effects were essentially the same.

Conclusions—In elderly patients with mild hypertension, a depressor trend of pulse pressure while standing can be turned into a significant pressor response by treatment with a β-blocker. (Circulation. 2002;105:1669-1671.)

Key Words: hypertension ■ risk factors ■ atherosclerosis

Baroreflex sensitivity declines with age, creating a fall in pulse pressure while standing.1 If, in addition, blood pressure is reduced as a result of antihypertensive medication, compensatory mechanisms may be inadequate and orthostatic problems may occur. This may be less true in patients on β-blockers. Unlike other classes of drugs, β-blockers cause paradoxical pressor effects while standing.2-5 This phenomenon has been ascribed to alpha-receptor-mediated vasoconstriction unopposed by β-receptor-mediated vasodilatation and was held responsible for the beneficial effect of β-blockers in various studies of patients with orthostatic hypotension.6 The pressor effect has not been demonstrated in elderly patients with mild hypertension, and it may be clinically relevant because dizziness and orthostatic complaints are common in elderly with antihypertensive drugs and are the main reason for antihypertensive drug withdrawal.7

Thus, we assumed that β-blockers would change the depressor effect on standing pulse pressures into a pressor effect. For that purpose we tested pulse pressures in mildly hypertensive patients >60 years of age after 5 minutes in the supine position and after 1 minute of standing. Patients were measured before and after 6 months of monotherapy with nebivolol, a third generation vasodilator β-blocker,8 given 5 mg once daily. Patients with mild hypertension younger than 60 years of age and treated similarly were used as controls.

Methods

This was a multicenter study of 6 months of monotherapy with nebivolol 5 mg daily in patients with mild hypertension. Patients were sampled at the outpatient clinics of 110 clinical facilities throughout the Netherlands between January 1997 and February 2000. Inclusion criteria included a diastolic blood pressure between 96 and 116 mm Hg measured at least twice at different occasions or treatment for hypertension with monotherapy. Exclusion criteria included atrioventricular conduction abnormality, heart failure, laboratory evidence of hepatic or renal failure, chronic obstructive pulmonary disease, and inadequate knowledge of language for self-administration of a questionnaire. Patients were not allowed to use additional antihypertensive compounds. The study started after oral informed consent had been obtained according the Safety

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From the Albert Schweitzer Hospital, Dordrecht (T.J.C., I.G., W.M.M.), and the Academic Hospital, Leiden (M.G.N., E.E.v.d.W.), the Netherlands. Correspondence to Ton J. Cleophas, MD, PhD, Associate-Professor, Albert Schweitzer Hospital, Box 306 3300 AH Dordrecht, The Netherlands. E-mail ajm.cleophas@wxs.nl
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Assessment of Marketed Medicines (SAMM) Guidelines. The primary endpoints were a safety assessment and review of the effect of prolonged β-blocker treatment on standing pulse pressures. Patients were evaluated every 4 weeks during a period of 6 months at the outpatient clinic. Safety data have been reported separately.

For the assessment of effects on standing pulse pressures, the patients were evaluated at baseline and after 6 months of treatment at trough, after 5 minutes in the supine position, and after 1 minute in the standing position. We used sphygmomanometers, Korotkoff phases I and V, to identify systolic and diastolic blood pressures.

Statistical Analysis
The data are presented as numbers (n), and as means ± standard errors (SEMs). A P value <0.05 was considered statistically significant. We used paired Student’s t tests or repeated measures ANOVA with Student’s t test as contrast test. Intention to treat analysis was performed.

Results
We included 3741 patients between 41 and 80 years of age, with mean age 60 years. Of those, 46% were men, 52.7% of whom were >60 years of age. In the 1656 patients who changed regimens, previous therapies consisted of β-blockers (n=944), angiotensin converting enzyme (ACE) inhibitors (n=250), calcium channel blockers (n=234), diuretics (n=92), and angiotensin II receptor blockers (n=85). In total, 461 patients (12.3%) did not complete the study; 278 were lost for follow-up, 86 needed more intensive therapy, and 97 were withdrawn because of adverse effects.

Overall, β-blockade reduced systolic/diastolic blood pressures by 24/14 (±1/1) mm Hg in previously untreated patients and by 14/8 (±1/1) mm Hg in previously treated patients after 6-month treatment (both results significantly different from baseline at P<0.0001). Pulse pressures were, thus, reduced by 10 (±1) mm Hg and 6 (±1) mm Hg, respectively (both P<0.0001).

Figure 1 gives the overall mean values of supine and standing blood pressures as obtained from the accumulated data from the current study. Because both systolic and diastolic blood pressures rose similarly while standing, the pulse pressures remained unchanged.

Figure 2 shows the effects of prolonged β-blockade on pulse pressures in previously untreated patients (n=2085). Patients older and younger than 60 years of age were assessed separately. As expected from the overall data, β-blockade reduced pulse pressures by 6 to 10 mm Hg, and did so irrespective of age or position of the body (all of the comparisons at P<0.001 to <0.0001, during β-blockade versus prior). Figure 2 also shows that pulse pressures were consistently 6 to 11 mm Hg higher in the elderly group than in the younger subjects (all of the comparisons at P<0.001 to P<0.0001). Finally, Figure 2 shows that, while standing, pulse pressure rose in the younger subjects, whereas it tended to fall in the elderly group. After 6 months of β-blockade, this pattern was unchanged in the younger subjects, but it reversed into a significant rise of pulse pressure of 4 (±1) mm Hg in the elderly group.

We also analyzed the patients previously treated with other antihypertensive drugs after exclusion of the patients previously treated with β-blockers (n=1656–944=712). Essentially, the same effects were observed (Figure 3).

Discussion
In the present study we observed that, while standing, pulse pressure rose in the younger subjects, whereas it tended to fall in the elderly group. This effect is compatible with a supposed decrease in baroreflex sensitivity in elderly. After 6 months of β-blockade, this pattern was unchanged in the younger subjects, but it reversed into a steep and significant rise of pulse pressure in the elderly group. The data were confirmed when patients previously treated were similarly assessed. These findings suggest that β-blockers can indeed restore a lacking pressor effect.
effect on pulse pressure in elderly mildly hypertensive patients while standing.

Baroreceptor sensitivity is reduced with age. The cause of this is unknown, but increased rigidity of the arterial wall may be involved. Despite this reduced baroreceptor sensitivity, the elderly do not necessarily suffer from orthostatic complaints because pulse pressures increase with age, as demonstrated in the recent study of Khattar et al and, also, as observed in our data (Figures 2 and 3). The outcome may be different if blood pressure in the elderly subjects is excessively reduced as a result of medication. Compensatory mechanisms are inhibited then, and hypertensive responses are particularly at risk. This problem has been recognized and is considered to not be uncommon. It is the main reason for antihypertensive drug withdrawal in this category of patients.

Currently, baroreflex sensitivity and pulse pressure are given little emphasis in the scientific assessment of hypertension because they are considered to be mainly involved in the pathophysiology of hypertension. This, however, may not be entirely justified. Recent data suggest that an increase in pulse pressure, rather than systolic or diastolic blood pressures, is the most important predictor of cardiovascular events in elderly. Also, this study suggests that pulse pressures should receive more attention in future hypertension research.

Limitations of the present study include the facts that the data, though prospective, are observational in nature, and that they do not directly assess clinical symptoms of orthostatic hypotension, nor do they assess the potential disadvantage of an increased pulse pressure in patients without orthostatic hypotension. On the other hand, the data are from a large database, and they confirm our prior hypothesis that β-blockers produce pressor effects in elderly patients while standing. These data also confirm the results of previous research on the beneficial effects of β-blockers in patients with orthostatic complaints and show that the pressor effect can be observed not only with non-vasodilatory but also with vasodilatory β-blockers.

Conclusions

In elderly patients, unlike in their younger counterparts, subjects with mild hypertension experience a decrease pulse pressure while standing. This effect is offset and turned into a pressor effect by long-term β-blocker treatment. β-blockers may, better than other antihypertensive classes, protect the elderly from orthostatic complaints.

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