AJH 2006; 19:214–219

Atenolol and Eprosartan: Differential Effects on Central Blood Pressure and Aortic Pulse Wave Velocity

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Background: Recent data suggest that atenolol may be inferior to other antihypertensive drugs in reducing cardiovascular risk in older individuals with hypertension, despite lowering peripheral blood pressure (BP). We hypothesized that that atenolol fails to reduce central BP as much as other agents. The aim of the present study was to compare the hemodynamic effects of atenolol and eprosartan in a double-blind, randomized, cross-over study.

Methods: After a 2-week placebo run-in, 21 subjects with never-treated hypertension underwent 6 weeks of therapy with atenolol (50 mg) and eprosartan (600 mg). Central BP and augmentation index were assessed using pulse wave analysis, and aortic pulse wave velocity was measured, at baseline and at the end of each treatment.

Results: Both drugs reduced peripheral BP to the same degree. However, there was a significantly greater reduction in central systolic BP with eprosartan (means ± SEM: 16 ± 3 *v* 11 ± 2 mm Hg; $P = .03$). Despite identical reductions in mean pressure, atenolol reduced aortic pulse wave velocity more than eprosartan (0.8 ± 0.1 *v* 0.5 ± 0.1 m/sec; $P = .005$). Conversely, augmentation index and N-terminal pro–brain natiuretic peptide levels were reduced significantly after eprosartan (6% ± 2% and 11 ± 5 pg/mL, respectively) but were increased after atenolol (7% ± 2% and 67 ± 24 pg/mL, respectively).

Conclusions: These data indicate that despite similar effects on peripheral BP and a greater effect on aortic stiffness, atenolol had less impact on central systolic BP than eprosartan because it failed to reduce wave reflection. This provides one potential explanation for the failure of atenolol to improve outcome in older patients with essential hypertension. Am J Hypertens 2006;19:214–219

Key Words: Hypertension, β-blockers, angiotensin receptor antagonist, pulse wave velocity, augmentation index.

Hypertension is an important risk factor for cardiovascular disease, affecting ~25% of the adult population. Several randomized controlled trials clearly demonstrate that modest reductions in blood pressure (BP) can significantly reduce the excess morbidity and mortality associated with hypertension.[1] A meta-analysis[2] and the recent Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study[3] suggest that BP lowering per se is the major determinant of cardiovascular event reduction, although some controversy and debate still remain. However, a recent meta-analysis of the early BP trials involving atenolol, either placebo-controlled or using drug comparisons, has cast doubt on the suitability of atenolol as an antihypertensive agent.[4] In the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) Study, which compared atenolol and losartan in subjects with hypertension and cardiac hypertrophy, losartan appeared superior to atenolol despite similar reductions in peripheral BP, and the difference was most marked in older patients with ISH.[5,6] Interestingly, in the Medical Research Council trial of treatment of hypertension in older adults, published some years before, atenolol was no better than placebo for preventing cardiovascular events in older hypertensive subjects,[7] despite reducing BP to a similar degree. These observations have cast doubt on the efficacy of atenolol in older hypertensive individuals.

Blood pressure varies throughout the arterial tree because of the phenomenon of wave reflection and differences in arterial stiffness.[8] In all but the oldest individuals

Received March 7, 2005. First decision April 4, 2005. Accepted August 14, 2005.

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0895-7061/06/$30.00
doi:10.1016/j.amjhyper.2005.08.007

there is amplification of systolic BP moving away from the heart, such that brachial systolic BP may be 10 to 20 mm Hg higher than aortic pressure. This difference is likely to be important because the heart and brain "see" central rather than peripheral pressure. Indeed, central pulse pressure is a better predictor of left ventricular mass[9] and carotid–intima thickness[10] than peripheral pulse pressure. In patients with end-stage renal failure, central but not peripheral pulse pressure is a powerful independent predictor of cardiovascular and total mortality.[11] Importantly, the degree of pressure amplification depends on a number of factors including age,[8,12] mean arterial pressure (MAP),[13] and heart rate.[14]

We have previously demonstrated that bisoprolol reduces central BP less than other antihypertensive agents,[15] and that this is associated with an increase in plasma brain natiuretic peptide (BNP) levels,[16] a marker of left ventricular strain[17] and an independent predictor of outcome.[18] This led us to hypothesize that the results of the LIFE Study may reflect a difference in central BP, despite similar reductions in peripheral pressure between the two drugs.[16] The aim of this study was to compare directly the effects of atenolol and the angiotensin receptor antagonist eprosartan on central hemodynamic indices and measures of arterial stiffness in an older group of hypertensive individuals (>40 years of age).

Methods

Study Population

Subjects with never-treated hypertension were recruited from the hypertension clinic at Addenbrooke's Hospital in Cambridge, England. Hypertension was defined as a seated BP ≥140 or 90 mm Hg on at least three occasions separated by 1 month. Subjects with secondary hypertension, diabetes mellitus, or renal impairment (creatinine >150 μmol/L) were excluded a priori. Local Research Ethics Committee approval was obtained for the study and written informed consent was given by all subjects.

Hemodynamics

Brachial (peripheral) BP was recorded in the dominant arm using a validated oscillometric method (HEM-705CP; Omron Corp., Kyoto, Japan) after 10-min seated rest. Radial artery waveforms were then recorded with a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX) from the wrist of the dominant arm. Pulse wave analysis (SphygmoCor; AtCor Medical, Sydney, Australia) was then used to generate a corresponding central (ascending aortic) waveform using a transfer function. This transfer function has been prospectively validated for the assessment of ascending aortic BP,[19] and the system shows good repeatability of measurements.[20] Aortic augmentation index (AIx), and heart rate were determined using the integral software. Augmentation index, a measure of systemic arterial stiffness,[21] was calculated as the difference between the second and first systolic peaks, expressed as a percentage of the pulse pressure. Aortic pulse wave velocity (PWV) was measured with the subject in the supine position, using the same device by sequentially recording electrocardiographically gated carotid and femoral artery waveforms, as previously described in detail.[20] Mean arterial pressure was calculated by integration of the pressure waveform. All measurements were made in duplicate unless they differed by >5%, in which case a third reading was taken and the mean values were used in the subsequent analysis.

Biochemical Analysis

Venous blood (10 mL) was drawn from the antecubital fossa into lithium–heparin tubes and centrifuged immediately at 4°C, and the plasma was separated and stored at −80°C for subsequent analysis. The N-terminal fragment of proBNP was assayed using a commercially available immunochemiluminescence technique (Roche Diagnostics, Welling Garden City, UK) with a lower limit of detection at 3 pg/mL and coefficient of variation <6%. All samples were analyzed as a single batch.

Study Protocol

All subjects received a 2-week placebo run-in after which eligibility criteria were reconfirmed. In a double-blind, cross-over manner subjects were then randomized to 6 weeks treatment with atenolol 50 mg and 6 weeks with eprosartan 600 mg, each given once daily in the morning. Hemodynamic and biochemical measurements were made after placebo (baseline) and again at the end of each treatment phase. All measurements were made at trough (ie, immediately before that morning's scheduled dosing).

Data Analysis

Data were analyzed using repeated-measures analysis of variance and post hoc testing to determine individual drug effects. There was no order effect. Plasma N-terminal proBNP levels were significantly skewed and were logarithmically transformed before analysis. Unless otherwise stated, data are presented as means ± SEM. A value of $P < .05$ was considered to be significant.

Table 1. Baseline characteristics of study subjects

Parameter	mean ± SD
Age (y)	51 ± 9
Sex (male/female)	13/8
Height (m)	1.73 ± 0.14
Weight (kg)	84 ± 13
Body mass index (kg/m^2)	28 ± 4
Smokers/nonsmokers (n)	5/16
Brachial systolic BP (mm Hg)	160 ± 17
Brachial diastolic BP (mm Hg)	102 ± 12

BP = blood pressure.

Table 2. Hemodynamic and biochemical parameters of study subjects

Parameter	Baseline	Atenolol	Eprosartan	*P* value
Brachial systolic BP (mm Hg)	152 ± 2	135 ± 2*	136 ± 2*	.7
Brachial diastolic BP (mm Hg)	98 ± 2	90 ± 2*	92 ± 2*	.5
Brachial PP (mm Hg)	54 ± 1	45 ± 2*	44 ± 2*	.7
MAP (mm Hg)	117 ± 2	106 ± 1*	106 ± 2*	.9
Aortic systolic BP (mm Hg)	139 ± 3	128 ± 2*	123 ± 3*	.03
Aortic diastolic BP (mm Hg)	100 ± 2	91 ± 2*	92 ± 2*	.4
Aortic PP (mm Hg)	39 ± 1	37 ± 2	31 ± 2*	.005
PP amplification	1.38 ± 0.04	1.21 ± 0.04*	1.42 ± 0.04*	<.001
Heart rate (beats/min)	76 ± 3	57 ± 2*	76 ± 3	<.001
AIx (%)	22 ± 3	28 ± 2*	16 ± 3*	<.001
Aortic PWV (m/sec)	7.5 ± 0.3	6.8 ± 0.2*	7.1 ± 0.3*	.005
N-terminal proBNP (pg/mL)	31 (51)	71 (113)	14 (74)	.003

AIx = augmentation index; BP = blood pressure; MAP = mean arterial pressure; PP = pulse pressure; proBNP = pro–brain natriuretic peptide; PWV = pulse wave velocity.

Data represent means ± SEM, or medians (interquartile range). Significance was determined using repeated measures ANOVA, and values in the final column represent differences between drugs.

* significant change from baseline value (post placebo phase) based on post hoc testing.

Results

A total of 21 subjects were entered into the study, and all subjects completed it. Baseline data for the study subjects are presented in Table 1.

There was a significant reduction in brachial systolic BP, diastolic BP, and MAP with both atenolol and eprosartan but no difference in the response to the drugs (Table 2). Similarly, aortic pressure was reduced significantly by both drugs, but there was a greater reduction in aortic systolic BP with eprosartan than with atenolol. Although brachial pulse pressure fell similarly in response to both therapies, aortic pulse pressure was only reduced significantly by eprosartan. The overall effect was a significant reduction in pulse pressure amplification with atenolol but an increase with eprosartan. As expected, there was a significant reduction in heart rate with atenolol but no change with eprosartan.

Both drugs significantly reduced aortic PWV, but atenolol produced a greater effect than eprosartan. Treatment with atenolol led to a significant increase in AIx compared with the placebo phase, whereas there was a significant reduction after eprosartan. Likewise, plasma N-terminal proBNP levels rose significantly after atenolol but fell after eprosartan therapy. There was a significant correlation between N-terminal proBNP levels and the change in augmentation index on therapy ($r = 0.56$; $P < .001$) (Fig. 1). Stepwise multiple linear regression analysis was used to identify predictors of N-terminal proBNP levels on therapy. Parameters entered into the model were drugs used and changes in the following: MAP, central systolic BP, peripheral systolic and diastolic BP, heart rate, AIx, and PWV. Only the change in AIx was significantly associated with N-terminal proBNP levels ($P < .001$; for model, $R^2 = 0.52$, $P < .001$).

Discussion

Several studies have suggested that β-blockers—atenolol in particular—may not reduce mortality in hypertensive subjects despite lowering peripheral BP.[4,6,7] We have previously demonstrated that bisoprolol reduces central systolic BP less than other antihypertensive drugs, despite similar effects on peripheral BP.[15] This led us to hypothesize that the results of the LIFE study may be caused by differences in central BP between the two treatment arms.[16] The aim of the present study was to compare the central hemodynamic effects of atenolol and the angiotensin receptor antagonist eprosartan in older individuals with hypertension. The main findings were that despite similar reductions in peripheral BP, eprosartan had a significantly

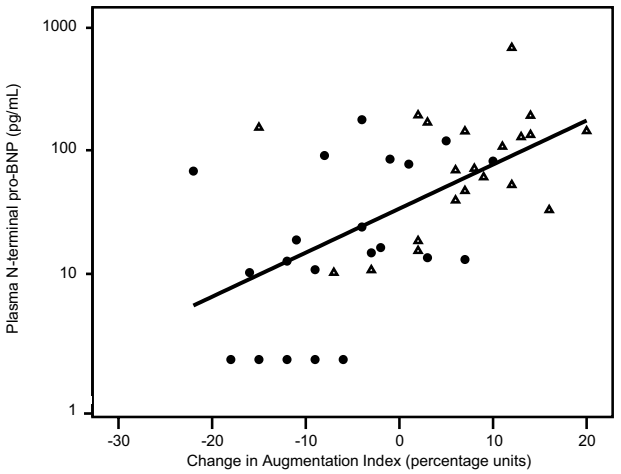

FIG. 1 Plasma brain natiuretic peptide (BNP) and augmentation index. Relationship between N-terminal pro-BNP levels at the end of each treatment phase and the change in augmentation index for all subjects after therapy with eprosartan (●) or atenolol (△). The regression line is for the whole data set $r = 0.56$; $P < .001$. The individual correlation coefficients were 0.26 for eprosartan and 0.19 for atenolol (both P = NS).

greater effect on central systolic BP and pulse pressure than atenolol. Moreover, aortic PWV fell significantly more after atenolol than eprosartan, despite identical changes in MAP. In contrast, AIx and plasma N-terminal proBNP increased significantly after atenolol treatment, whereas both fell after eprosartan. Interestingly, the N-terminal proBNP levels were independently related to the change in AIx but not pressure, heart rate, or PWV.

Arterial stiffness can be assessed with a variety of indices and devices.[22] However, the aortic PWV is often considered as the gold-standard measure of stiffness and independently predicts outcome in a variety of populations, including individuals with essential hypertension.[23] In the present study, although both drugs significantly reduced aortic PWV, atenolol had a greater effect than eprosartan. This was despite identical reductions in MAP, an important determinant of PWV, which suggests a greater reduction in regional aortic stiffness by atenolol. Several studies have previously demonstrated that β-blockers[24–26] and angiotensin receptor antagonists[27,28] reduce aortic PWV. Interestingly, Pannier et al. reported a greater reduction in aortic PWV with atenolol than with perindopril in subjects with essential hypertension.[25] However, interpretations of these data and our own are complicated by concomitant changes in MAP. Using local intra-arterial drug infusions and thereby avoiding changes in MAP, we have previously reported that atenolol has no direct effect on conduit artery distensibility in an ovine hind-limb model.[29] Although this may not be the situation in humans, one alternative explanation for the greater impact of atenolol on aortic stiffness is a systemic or central effect, such as a reduction in sympathetic tone, which is known to influence conduit artery function.[30] An alternative but controversial possibility[31–33] is that the reduction in heart rate with atenolol may, in part be responsible for the greater effect of atenolol on PWV.

The AIx represents the degree to which the central systolic BP is influenced by wave reflection; and it depends on the amplitude and site of wave reflection and the speed with which pressure waves travel in the arterial tree. Thus, the AIx provides a composite measure of wave reflection and systemic arterial stiffness[21] and can change independently of aortic PWV.[34] In the present study, the AIx fell after treatment with eprosartan but increased after atenolol, which is in agreement with previous, separate observations concerning angiotensin receptor antagonists and β blockers.[24,27] One obvious explanation for this difference is the differential effect of the two drugs on heart rate, as we have previously demonstrated that the AIx is confounded by changes in heart rate because of alterations in the absolute duration of systole.[35] The observed 19–beats/min differences in heart rate between atenolol and eprostaran would be expected to lead to a difference of ~8% in AIx, assuming that our previous data concerning heart rate and AIx are correct. However, there was a measured difference of 12%, despite a greater reduction in PWV with atenolol, and identical changes in MAP, suggesting that there was less wave reflection after eprosartan than after atenolol therapy. Without resolving forward- and backward-moving waves, by simultaneously recording flow and pressure it is impossible to know whether atenolol reduced wave reflection, but to a smaller degree than eprosartan, whether it had no effect, or whether it increased reflection. Nonetheless, the measured AIx was actually higher after treatment with atenolol, as we and others have previously reported.[15,24,25,36]

We also assessed the impact of therapy on plasma N-terminal pro-BNP levels, an index of left ventricular stretch and cardiac afterload.[17] Treatment with atenolol was associated with a significant increase in pro-BNP levels, whereas levels fell after treatment with eprosartan. Interestingly, there was a significant correlation between pro-BNP levels and AIx but not with peripheral or central BP. This suggests that the rise in AIx is sensed by the myocardium and may therefore have adverse long-term consequences. Indeed, among hypertensive subjects, BNP levels correlate with left ventricular mass,[37] and BNP levels predict outcome in subjects with cardiovascular disease.[18] However, data concerning outcome in hypertensive subjects are lacking as yet.

Central systolic and pulse pressure fell less after treatment with atenolol than with eprosartan, despite similar reductions in peripheral pressures and identical reductions in MAP. The net effect was a fall in pulse pressure amplification with atenolol but an increase with eprosartan. Again, we have previously demonstrated that pulse pressure amplification is dependent on heart rate,[14] and the difference in heart rate between the two drugs is one obvious explanation for these observations. As heart rate falls, amplification is reduced because of a rise in AIx, and a relatively greater impact of the reflected pressure wave on the central systolic BP. In contrast, the brachial artery systolic BP is unaffected by wave reflection from the rest of the body, because the composite reflected wave reaches the brachial artery mainly in diastole in all but the oldest individuals and thus does not augment or enhance peripheral systolic BP.

The importance of central systolic and pulse pressure has previously been highlighted,[11] and the present study re-emphasizes that brachial pressure is not always a reliable predictor of central values, especially during pharmacologic intervention. Whether such differences translate into outcome remains to be proved. However, epidemiologic data indicate that a 20–mm Hg higher peripheral systolic BP doubles the risk for stroke,[1] suggesting that the 5– mm Hg difference in central systolic BP in the present study may be clinically important.

In summary, despite similar reductions in peripheral BP, atenolol reduced central systolic BP less than eprosartan. Both drugs reduced aortic stiffness, but only eprosartan reduced wave reflection. These observations offer one potential explanation for the failure of atenolol to improve outcome in older patients with essential hypertension—namely, that atenolol fails to reduce central BP as much as other antihypertensive drugs because of increased

wave reflection. This may also help to explain the results of the LIFE Study, in which atenolol was found to be inferior to losartan. However, further studies are clearly required to relate changes in central hemodynamic parameters and aortic stiffness to outcome in hypertensive patients. Interestingly, the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) Study included such measurements in a subset of patients and may help to address this issue.

Acknowledgment

The authors thank Solvay Healthcare Ltd. for providing the drugs used in this study.

References

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–1913.
2. Turnbull F: Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527–1535.
3. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering: Treatment to Prevent Heart Attack Trial (ALLHAT). J Am Med Assoc 2002;288: 2981–2997.
4. Carlberg B, Samuelsson O, Lindholm LH: Atenolol in hypertension: is it a wise choice? Lancet 2004;364:1684–1689.
5. Kizer JR, Dahlof B, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristianson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H, Wachtell K, Edelman JM, Snapinn SM, Harris KE, Devereux RB: Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: the Losartan Intervention For Endpoint reduction in hypertension study. Hypertension 2005;45: 46–52.
6. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995–1003.
7. MRC Working Party: Medical Research Council trial of treatment of hypertension in older adults: principal results. Br Med J 1992; 304:405–412.
8. Kroeker EJ, Wood EH: Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man. Circ Res 1955;3:623–632.
9. Saba PS, Roman MJ, Pini R, Spitzer M, Ganau A, Devereux RB: Relation of arterial pressure waveform to left ventricular and carotid anatomy in normotensive subjects. J Am Coll Cardiol 1993;22: 1873–1880.
10. Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, Laurent S: Association between local pulse pressure, mean blood pressure, and large-artery remodeling. Circulation 1999;100:1387–1393.
11. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, London GM: Central pulse pressure and mortality in end-stage renal disease. Hypertension 2002;39:735–738.
12. Remington JW, Wood EH: Formation of the peripheral pulse contour in man. J Appl Physiol 1956;9:433–442.
13. Wilkinson IB, Franklin SS, Hall IR, Tyrrell S, Cockcroft JR: Pressure amplification explains why pulse pressure is unrelated to risk in young subjects. Hypertension 2001;38:1461–1466.
14. Wilkinson IB, Mohammad NJ, Tyrrell S, Hall IR, Webb DJ, Levy T, Paul VE, Cockcroft JR: Heart rate dependence of pulse pressure amplification and arterial stiffness. Am J Hypertens 2002;15:24–34.
15. Deary AJ, Schumann AL, Murfet H, Haydock S, Foo RS, Brown MJ: Influence of drugs and gender on the arterial pulse wave and natriuretic peptide secretion in untreated patients with essential hypertension. Clin Sci 2002;103:493–499.
16. Cockcroft JR, Brown MJ: Losartan for cardiovascular disease in patients with and without diabetes in the LIFE study. Lancet 2002; 359:2202–2204.
17. Marttila M, Hautala N, Paradis P, Toth M, Vuolteenaho O, Nemer M, Ruskoaho H: GATA4 mediates activation of the B-type natriuretic peptide gene expression in response to hemodynamic stress. Endocrinology 2001;142:4693–4700.
18. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, Hall C, Cannon CP, Braunwald E: The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001;345:1014–1021.
19. Pauca AL, O'Rourke MF, Kon ND: Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 2001;38:932–937.
20. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ: The reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998;16:2079–2084.
21. Safar ME, London GM: Therapeutic studies and arterial stiffness in hypertension: recommendations of the European Society of Hypertension. The Clinical Committee of Arterial Structure and Function. Working Group on Vascular Structure and Function of the European Society of Hypertension. J Hypertens 2000;18:1527–1535.
22. Mackenzie IS, Wilkinson IB, Cockcroft JR: Assessment of arterial stiffness in clinical practice [review]. Q J Med 2002;95:67–74.
23. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S: Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 2002;39:10–15.
24. Kelly R, Daley J, Avolio A, O'Rourke M: Arterial dilation and reduced wave reflection. Benefit of dilevalol in hypertension. Hypertension 1989;14:14–21.
25. Pannier BM, Guerin AP, Marchais SJ, London GM: Different aortic reflection wave responses following long-term angiotensin-converting enzyme inhibition and beta-blocker in essential hypertension. Clin Exp Pharmacol Physiol 2001;28:1074–1077.
26. Kahonen M, Ylitalo R, Koobi T, Turjanmaa V, Ylitalo P: Influences of nonselective, beta(1)-selective and vasodilatory beta(1)-selective beta-blockers on arterial pulse wave velocity in normotensive subjects. Gen Pharmacol 2000;35:219–224.
27. Mahmud A, Feely J: Reduction in arterial stiffness with angiotensin II antagonist is comparable with and additive to ACE inhibition. Am J Hypertens 2002;15:321–325.
28. Takami T, Shigemasa M: Efficacy of various antihypertensive agents as evaluated by indices of vascular stiffness in elderly hypertensive patients. Hypertens Res 2003;26:609–614.
29. McEniery CM, Schmitt M, Qasem A, Webb DJ, Avolio AP, Wilkinson IB, Cockcroft JR: Nebivolol increases arterial distensibility in vivo. Hypertension 2004;44:305–310.
30. Boutouyrie P, Lacolley P, Girerd X, Beck L, Safar M, Laurent S: Sympathetic activation decreases medium-sized arterial compliance in humans. Am J Physiol 1994;267:H1368–H1376.
31. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H: Heart rate: an important confounder of pulse wave velocity assessment. Hypertension 2002;39:1083–1087.
32. Noble MIM, Gabe IT, Trenchard D, Guz A: Blood pressure and flow in the ascending aorta of conscious dogs. Cardiovasc Res 1967;1:9–20.
33. Eliakim M, Sapoznikov D, Weinman J: Pulse wave velocity in healthy subjects and in patients with various disease states. Am Heart J 1971;82:448–457.

34. Kelly RP, Millasseau SC, Ritter JM, Chowienczyk PJ: Vasoactive drugs influence aortic augmentation index independently of pulse-wave velocity in healthy men. Hypertension 2001;37: 1429–1433.
35. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ: The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol 2000;525:263–270.
36. Morgan T, Lauri J, Bertram D, Anderson A: Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens 2004;17:118–123.
37. Nishikimi T, Yoshihara F, Morimoto A, Ishikawa K, Ishimitsu T, Saito Y, Kangawa K, Matsuo H, Omae T, Matsuoka H: Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. Hypertension 1996;28:22–30.