Differences in the Magnitude of Wave Reflection Account for Differential Effects of Amlodipine- Versus Atenolol-Based Regimens on Central Blood Pressure: An Anglo-Scandinavian Cardiac Outcome Trial Substudy

Charlotte H. Manisty, Andrew Zambanini, Kim H. Parker, Justin E. Davies, Darrel P. Francis, Jamil Mayet, Simon A. McG Thom, Alun D. Hughes and on behalf of the Anglo-Scandinavian Cardiac Outcome Trial Investigators

Hypertension 2009;54;724-730; originally published online Aug 24, 2009;
DOI: 10.1161/HYPERTENSIONAHA.108.125740
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Differences in the Magnitude of Wave Reflection Account for Differential Effects of Amlodipine- Versus Atenolol-Based Regimens on Central Blood Pressure

An Anglo-Scandinavian Cardiac Outcome Trial Substudy

Charlotte H. Manisty, Andrew Zambanini, Kim H. Parker, Justin E. Davies, Darrel P. Francis, Jamil Mayet, Simon A. McG Thom, Alun D. Hughes, on behalf of the Anglo-Scandinavian Cardiac Outcome Trial Investigators

Abstract—Antihypertensive agents may differ in their effects on central systolic blood pressure, and this may contribute to treatment-related differences in cardiovascular outcomes. In a substudy of the Anglo-Scandinavian Cardiac Outcome Trial, we investigated whether directly measured carotid systolic blood pressure differed between people randomized to amlodipine- and atenolol-based therapies and whether this is accounted for by differences in wave reflection patterns. Additional analysis was undertaken to establish whether differences in carotid systolic blood pressure predicted left ventricular mass, accounting for between-treatment differences in left ventricular mass index. Blood pressure and flow velocity were measured in the right carotid artery of 259 patients. Wave intensity analysis was used to separate and quantify forward and backward waves. Brachial blood pressure did not differ significantly between groups, but carotid systolic blood pressure (127 [12] versus 133 [15] mm Hg; $P<0.001$), the ratio of backward:forward pressure (0.48 [0.17] versus 0.53 [0.19]; $P=0.01$), and wave reflection index (19.8% [10.9%] versus 23.3% [13.3%]; $P=0.02$) were significantly lower in patients randomized to amlodipine-based therapy. Left ventricular mass index was also lower in this group, and adjustment for carotid blood pressure attenuated treatment differences to a greater extent than brachial blood pressure. Carotid systolic blood pressure was also a significant independent predictor of left ventricular mass index in a multivariate model. Carotid systolic blood pressure is lower in people randomized to amlodipine-based compared with atenolol-based treatment despite there being no significant difference in brachial blood pressure. This difference is attributable to a lesser magnitude of wave reflection in patients randomized to the amlodipine-based regimen. **(*Hypertension*. 2009;54:724-730.)**

Key Words: blood pressure ■ hypertension ■ wave reflection ■ wave intensity ■ pressure ■ flow

Brachial blood pressure (BP) is an important predictor of cardiovascular events[1]; however, systolic BP (SBP) is influenced by wave reflection[2] and varies throughout the vascular tree, with aortic (central) SBP being consistently and variably lower than brachial SBP. The importance of wave reflection in hypertension is increasingly recognized, and, more recently, indices of wave reflection have been shown to independently predict cardiovascular events.[3–5]

Differential effects of antihypertensive agents on central SBP have been proposed to account for differential effects on cardiovascular and all-cause mortality,[6,7] possibly as a result of changes in the timing or magnitude of wave reflection. However, not all studies have observed differential effects of antihypertensive treatments on central SBP,[8] and the use of a generalized transfer function to estimate the central SBP from radial artery measurements has been criticized,[9–13] particularly when, as in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT), the comparator therapies have different effects on heart rate. In addition, there is considerable evidence that central augmentation index, a widely used index of wave reflection, is not measured accurately using a generalized transfer function applied to the radial waveform,[14–16] thereby compromising any interpretation of differences in central BP on the basis of radial measurements in terms of changes in wave reflection.

Received October 27, 2008; first decision November 17, 2008; revision accepted July 22, 2009.

From the International Centre for Circulatory Health (C.H.M., A.Z., K.H.P., J.E.D., D.P.F., J.M., S.A.M.T., A.D.H.), National Heart and Lung Institute Division, Faculty of Medicine, Imperial College London and Imperial College Healthcare National Health Service Trust, London, UK; Department of Bioengineering (K.H.P.), Faculty of Engineering, Imperial College London, London, UK.

Correspondence to Charlotte H. Manisty, International Centre for Circulatory Health, National Heart and Lung Institute Division, Faculty of Medicine, Imperial College London, 59-61 North Wharf Rd, London W2 1LA, UK. E-mail cmanisty@ic.ac.uk

Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.108.125740**

The purpose of this study, therefore, was to establish the effect of the therapeutic regimens used in ASCOT on central SBP and wave reflection using the direct measurement of carotid artery SBP (cSBP) combined with wave intensity analysis and wave separation to differentiate the direction, type, and amplitude of waves. Additional analysis was undertaken to establish whether differences in cSBP predicted left ventricular mass (LVMI) and could account for between-treatment differences in LVMI.

Methods

Subjects

A total of 259 participants (≈1 in every 3 patients) from a total of 879 participants in the Hypertension Associated Cardiovascular Disease ASCOT substudy at the St Mary's Hospital center participated in the carotid wave intensity substudy. All of the subjects fulfilled the criteria for inclusion in the main ASCOT study. All of the patients were randomized according to the ASCOT protocol[17] to a regimen of amlodipine with perindopril added as required or a regimen of atenolol with bendroflumethiazide-K added as required. Antihypertensive treatment was titrated to achieve target brachial BPs (<140/90 mm Hg for people without diabetes mellitus and <130/80 mm Hg for people with diabetes mellitus). If necessary, additional antihypertensive agents were administered according to a prespecified algorithm. Patients were also eligible for randomization to the factorial lipid-lowering arm of ASCOT if they had a total blood cholesterol concentration ≤6.5 mmol/L and were not taking a lipid-lowering agent at the time of randomization. Patients recruited into the lipid-lowering arm of ASCOT were randomized to receive 10 mg of atorvastatin daily or matching placebo.

Because the majority of patients received a variety of treatment before commencement of ASCOT, all of the measurements for this substudy were performed between 12 and 18 months after randomization, when study drugs had been fully up-titrated and the BP had achieved target and was stable. The study was approved by the St Mary's Hospital Local Research Ethics Committee, and all of the subjects gave written informed consent.

Investigations

All of the studies were conducted in a temperature-controlled darkened room, with subjects having rested supine for ≥10 minutes. Brachial BP was measured after ≥5 minutes of rest using a validated, semiautomated device (Omron 705CP, Omron).[18] Pressure was measured in the right common carotid artery by applanation tonometry using a Millar tonometer (SPT-301, Millar Instruments Inc) and calibrated to brachial artery pressure, as described previously.[19,20] Carotid waveforms were carefully monitored during acquisition to ensure high quality and stability of recordings, over ≈1 minute of measurement. Flow velocity measurements were made in the right common carotid artery by pulsed wave Doppler with an HDI 5000 ultrasound machine (Philips Medical Systems) equipped with a 7.5- to 10.0-MHz linear array transducer at a Doppler angle of 60° in a 1-mm sample volume placed in the center of the vessel ≈2 cm from the carotid bulb. All of the measurements were made by a single observer, who remained masked to individual patient treatment. Details of validation of both pressure and flow measurements have been described by us previously.[21] In all of the patients, the pressure data were collected first, followed by the velocity. The time taken to acquire both pressure and velocity data was ≈5 minutes.

Carotid pressure and flow velocity data were sampled at a frequency of 200 Hz. After acquisition, waveforms were ensemble averaged offline, as described previously,[21] using custom-written software in Matlab 5.3 (Mathworks). Care was taken to ensure that only good quality beats (generally, 6 beats) were included in the ensemble. The members of the ensemble were identified by using the peak of the R wave as the fiducial point. After constructing the ensemble, the members were checked for good temporal alignment. Occasionally, because of variability in the duration of the isovolumic contraction period, there was a small degree of misalignment (<5 ms) between the systolic rise phase of the beats, and, if this was the case, this was corrected. The cross-correlation coefficient between the initial 600 ms of each beat was also used as a quantitative measure of agreement between waveforms, with a value $r>0.95$ being regarded as acceptable. Local carotid artery wave velocity was calculated using the pressure-velocity loop method.[21,22] Reproducibility of these methods has been published previously,[21,23] and the validity of the approach has been confirmed in vitro and in vivo.[22,24] The within-observer coefficient of variation was <10% for the major waves in this study and between 15% and 20% for minor waves.

In addition to measurement of carotid artery pressure and flow, all of the subjects had fasting blood samples taken and underwent echocardiography. Details of echocardiography and related measurements have been described recently elsewhere.[25]

Wave Intensity Analysis and Wave Separation

Changes in pressure and flow in the circulation result from waves of varying magnitude, character, and direction. The timing, magnitude character, and direction of such waves can only be definitively established from combined pressure and flow data. Waves can originate either from the proximal (forward-traveling) or distal (backward-traveling) end of the circulation and can be either a compression ("pushing") or decompression ("sucking") wave. A compression wave will accelerate or decelerate blood flow depending on its origin: if it arises proximal to the site of measurement, it will increase pressure and accelerate flow, but compression waves of distal origin will increase pressure and decelerate blood flow. Additional information regarding the type and origin of waves in the carotid artery is provided in the online Data Supplement (please see http://hyper.ahajournals.org).

Wave intensity is a measure of the power density of a wave and is given by the product of the simultaneous incremental changes in local pressure (dP) and velocity (dU) in a given time interval.[26] Pressure changes attributed to forward-traveling (dP_+) and backward-traveling (dP_-) waves can be separated using equations 1 and 2.

$$dP_+ = 1/2(dP + \rho\, c\, dU) \quad (1)$$

$$dP_- = 1/2(dP - \rho\, c\, dU) \quad (2)$$

where ρ is the density of blood (1050 kg^{-3}) and "c" is the local wave speed. This time-domain approach to wave separation gives results that are essentially identical to impedance-based approaches (data not shown).

Waves were quantified by measuring both the peak of the individual wave intensity and cumulative intensity of each wave (ie, the integral under the wave); this is an index of energy per unit area carried by the wave. Other authors[27,28] have used different units to express wave intensity to allow for differences in sampling rates. To convert between units based on a sampling rate of 200 Hz, values in watts per meter squared (Wm^{-2}) should be multiplied by 40 000 to convert to watts per meter squared per second squared ($Wm^{-2}\ s^{-2}$) and by 300 to convert to millimeters of mercury meter per cubic second (mm Hg m s^{-3}).

Reflection was assessed by 2 measures. First, the wave reflection index was calculated as the sum of the cumulative wave intensity of the reflected compression waves from the head and body (c^-1 and c^+1, respectively) expressed as a percentage of the cumulative intensity of the initial systolic (S) wave generated by the left ventricle (please see the online Data Supplement for details regarding these waves). The ratio of peak backward:peak forward pressure (P_b/P_f) after wave separation and subtraction of diastolic pressure was also measured as an index of reflection,[29] although this ratio may be influenced by decompression waves arising from rereflection of backward compression waves.[21] The time of arrival (ΔT) of a specific wave with respect to the S wave was calculated from the intervals between the timing of the peak intensities of the waves generated by the left ventricle, because this is more readily identified than the foot of the wave intensity. The distance (L) to an apparent reflection site in the head was calculated as follows: $L=(1/2)c.\Delta T$,

Table 1. Baseline Characteristics of the 2 Treatment Groups

Baseline Characteristic	Amlodipine-Based Regimen (N=122)	Atenolol-Based Regimen (N=138)	*P*
Women, n (%)	23 (19)	19 (14)	0.3
Age, y	64.3 (7.1)	63.3 (7.6)	0.3
Brachial SBP, mm Hg	162.5 (20.3)	160.7 (18.2)	0.5
Brachial diastolic BP, mm Hg	94.8 (10.9)	93.5 (10.1)	0.4
Heart rate, bpm	69.1 (13.7)	68.2 (12.3)	0.6
BMI, kg/m^2	28.1 (3.8)	28.6 (4.4)	0.3
Weight, kg	82.8 (13.5)	83.1 (15.8)	0.8
Height, cm	172 (8.6)	170 (9.1)	0.2
Total cholesterol, mmol/L	6.0 (1.1)	5.9 (1.3)	0.8
HDL cholesterol, mmol/L	1.4 (0.4)	1.3 (0.4)	0.6
Triglycerides, mmol/L	2.2 (1.4)	2.4 (1.3)	0.1
Glucose, mmol/L	6.3 (2.7)	6.4 (3.0)	0.7
Creatinine, mmol/L	99.0 (14.4)	98.7 (19.2)	0.9
Diabetes mellitus, n (%)	24 (20)	32 (23)	0.5
LVH, n (%)	23 (19)	25 (18)	0.9
Current smoker, n (%)	28 (23)	23 (17)	0.2
Lipid-lowering therapy, n (%)	40 (33)	37 (27)	0.3

Data are mean (SD) for continuous data or frequency (%) for categorical data. HDL indicates high-density lipoprotein; BMI, body mass index; LVH, left ventricular hypertrophy.

where "c" is the local wave velocity in the carotid artery. However, because tapering can give the appearance of a single apparent reflection site,[30] this distance should not be interpreted as necessarily corresponding with a unique physical site of impedance mismatching. Carotid artery augmentation index (AI_c), the pressure difference between the first shoulder of the pressure waveform and the systolic peak expressed as a percentage of the pulse pressure, was calculated from the carotid waveform. The beginning of the pressure wave upstroke was taken to correspond with the first zero crossing of the fourth derivative, and the shoulder was taken to correspond with the second zero crossing in same direction, as described by Kelly et al.[20]

Statistics

Statistical analysis was performed using StatView (version 5.0, SAS Institute, Inc) and Stata (version 10.0, Stata Corp). Continuous variables are reported as mean (SD) or median (interquartile range) for skewed data. Statistical comparisons between treatment groups were made using an unpaired Student *t* test or an unpaired nonparametric Wilcoxon rank-sum test for skewed data. The level of statistical significance for between-treatment group comparisons was taken to be $P<0.05$. Multivariate regression modeling was also performed, and stepwise backward-selection estimation was undertaken using a significance level for removal of $P<0.05$ on the basis of the Wald test.

Results

The 2 treatment groups were well matched (Table 1), and their characteristics were very similar to the main ASCOT cohort and the Conduit Artery Function Evaluation substudy cohort.[7,17] Comparison of the 2 treatment groups showed that heart rate was significantly lower with the atenolol-based regimen. There were no statistically significant differences in brachial BP, although pressures tended to be higher in subjects treated with the atenolol-based regimen (Table 2), in keeping with the findings of the main ASCOT study.[17]

Table 2. Comparison of BP and Other Measures Between Treatment Groups

Variable	Amlodipine-Based Regimen (N=121)	Atenolol-Based Regimen (N=138)	*P*
Brachial SBP, mm Hg	140.4 (12.8)	143.3 (14.8)	0.1
Brachial diastolic BP, mm Hg	79.5 (7.5)	81.6 (8.9)	0.05
Brachial pulse pressure, mm Hg	60.7 (12.3)	61.7 (12.8)	0.5
Heart rate, bpm	71.0 (11.4)	56.0 (9.5)	<0.001
No. of antihypertensive agents	1.93 (0.96)	2.42 (0.93)	<0.001
Cardiac output, L/min	4.24 (1.64)	3.81 (1.29)	0.03
Stroke volume, mL	59.6 (21.6)	64.7 (20.6)	0.07
Total peripheral resistance, PRU	22.8 (18.1 to 32.7)	25.4 (20.0 to 33.6)	0.05
LVMI, g^{-2}	111.6 (25.5)	117.6 (27.1)	0.08
cSBP, mm Hg	127.0 (11.9)	132.9 (14.7)	<0.001
Carotid pulse pressure, mm Hg	47.0 (11.0)	51.6 (12.7)	0.003
Peripheral pulse pressure amplification	1.33 (0.29)	1.22 (0.17)	<0.001
Brachial−carotid amplification, mm Hg	14.2 (10.7)	11.8 (9.5)	0.02
AI_c, %	22 (11)	25 (12)	0.02
Time of foot (T_f), ms	50 (24)	57 (23)	0.02
Time of inflection point (T_i), ms	181 (31)	185 (34)	0.5
T_i-T_f, ms	130 (24)	129 (24)	0.6
Pressure at inflection point, mm Hg	116 (12)	118 (14)	0.4
Carotid wave velocity, ms^{-1}	8.5 (3.1)	9.0 (5.4)	0.4
Cumulative S wave, mJ/m^{-2}	701 (291)	694 (295)	0.9
S wave intensity, Wm^{-2}	19.6 (9.0)	18.7 (8.3)	0.4
Cumulative D wave, mJ/m^{-2}	167 (83)	162 (79)	0.6
D wave intensity, Wm^{-2}	4.3 (2.1)	4.0 (1.9)	0.2
Cumulative c^-_1 wave, mJ/m^{-2}	114 (76)	126 (65)	0.04
c^-_1 wave intensity, Wm^{-2}	1.8 (1.1 to 2.7)	1.9 (1.1 to 2.8)	0.5
ΔT c^-_1 wave, ms	60 (50 to 70)	60 (49 to 74)	>0.9
Cumulative c^+_1 wave, mJ/m^{-2}	7 (3 to 18)	12 (4 to 28)	0.007
c^+_1 wave intensity, Wm^{-2}	0.2 (0.1 to 0.4)	0.3 (0.1 to 0.6)	0.04
ΔT c^+_1 wave, ms	145 (115 to 170)	153 (124 to 171)	0.4
Reflection distance (head), m	0.24 (0.18 to 0.32)	0.23 (0.16 to 0.32)	0.7
WRI, %	19.6 (10.3)	23.3 (13.3)	0.01
WRI (head), %	16.3 (7.1)	19.3 (9.3)	0.004
WRI (body), %	3.9 (5.5)	4.8 (6.3)	0.04
P_f, mm Hg	33.7 (9.2)	34.7 (10.6)	0.4
P_b, mm Hg	15.2 (4.4)	17.3 (5.4)	<0.001
P_b/P_f	0.48 (0.17)	0.53 (0.19)	0.01

Data are mean (SD) or median (interquartile range) for continuous data or frequency (%) for categorical data. Reported timings are with respect to the peak of the ECG R wave. WRI indicates wave reflection index; PRU, peripheral resistance unit.

cSBP and Wave Reflection

cSBP, carotid pulse pressure, and AI_c were significantly lower in the amlodipine group than in the atenolol group (Table 2). Pulse pressure amplification ratio (calculated as peripheral pulse pressure:central pulse pressure), brachial-carotid amplification pressure, and local wave velocity were higher in the amlodipine±perindopril arm than in the atenolol±bendroflumethiazide arm (Table 2). Differences in cSBP between treatment arms remained significant after statistical adjustment for age, sex, heart rate, or all of these variables combined in a multivariate model (Table 3).

Table 3. Multivariate Regression Models Relating cSBP to Treatment Regimen Adjusted for Other Potential Confounders

Model	β (SE)	P
Model 1		
Treatment (unadjusted)	5.49 (1.90)	0.004
Model 2		
Treatment	5.81 (1.89)	0.002
Age	0.31 (0.13)	0.017
Model 3		
Treatment	5.60 (1.91)	0.004
Sex	2.17 (2.7)	0.4
Model 3		
Treatment	5.53 (1.91)	0.004
Height	−2.99 (10.74)	0.8
Model 4		
Treatment	6.78 (2.20)	0.002
Heart rate	0.10 (0.09)	0.2
Model 5		
Treatment	7.68 (2.22)	0.001
Age	0.35 (0.13)	0.009
Sex	1.71 (3.45)	0.6
Height	4.46 (13.47)	0.7
Heart rate	0.15 (0.09)	0.11

Wave intensity analysis indicated that there was no significant difference in the magnitude of the peak or cumulative intensity of the S wave or D wave (Figure 1 and Table 2), but the peak and cumulative intensities of reflected waves from the head ($c^{-}1$ wave) and the body ($c^{+}1$ wave), measures of wave reflection (wave reflection index and P_b/P_f), and AI_c were significantly higher in the atenolol group (Table 2 and Figure 2). Reflected waves from the head were undetectable in 21% and 17% of individuals in the amlodipine and atenolol groups, respectively, and reflected waves from the body were undetectable in 67% and 54% of individuals in the amlodipine and atenolol groups, respectively. The timing of reflected waves and the distance to the apparent reflection sites in the head or in the body did not differ significantly between treatment groups despite the difference in heart rate (Table 2).

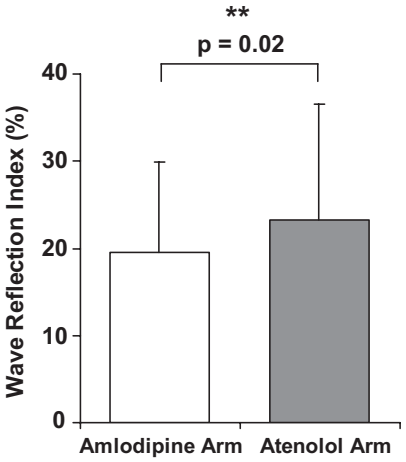

Figure 2. The wave reflection index was significantly lower in patients randomized to amlodipine-based therapy than atenolol-based therapy (19.8% [10.9%] vs 23.3% [13.3%]; $P=0.02$).

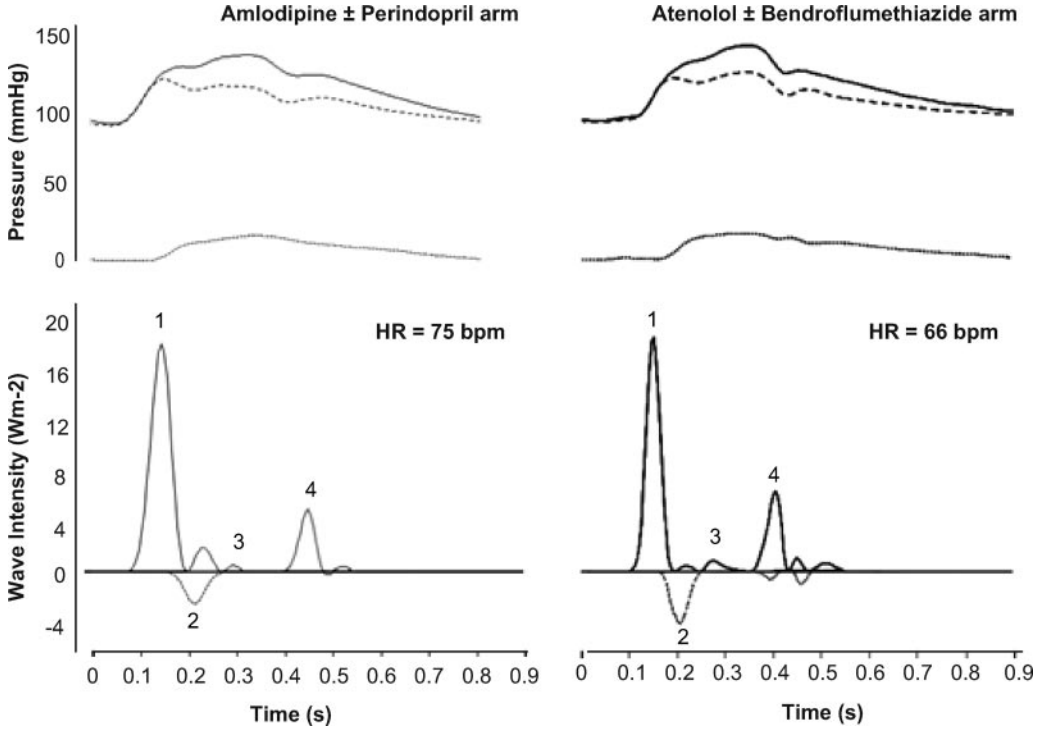

Figure 1. Example traces comparing measured pressure waveforms P_{total}, P_f, and P_b separated pressure waveforms and wave intensity between treatment regimens (amlodipine±perindopril vs atenolol±bendroflumethiazide). The shoulder or inflection point in the pressure waveform (P_i) is indicated. The S wave (1), the $c^{-}1$ wave (2), the $c^{+}1$ wave (3), and the D wave (4) are shown on the wave-intensity profiles.

Table 4. Stepwise Multivariate Model of Predictors of LVMI

Predictors of LVMI	β	SE	P
Sex	−9.81	4.64	0.04
Risk factors	4.57	1.86	0.02
BMI	0.87	0.41	0.03
cSBP	0.23	0.10	0.02
Heart rate	−0.47	0.12	<0.001
HDL cholesterol	8.75	4.14	0.04
Stroke volume	0.36	0.07	<0.001
Constant	51.09	20.4	0.01

$r^2=0.27$; adjusted $r^2=0.25$; $P<0.001$. HDL indicates high-density lipoprotein; BMI, body mass index.

There was a significant correlation between the timing of the start of the reflected wave $c^{-}1$ and the time of the shoulder on the pressure waveform (Spearman rank correlation, $\rho=0.51$; $P<0.001$).

Age, sex, and height have been reported to influence wave reflection, and because heart rate differed between treatments, we constructed multivariate regression models to adjust for these possible confounders in the between-treatment effect on cSBP. Inclusion of age, sex, height, or heart or all of these variables combined did not substantially affect between-treatment differences in cSBP (Table 3).

Relationship of Carotid and Brachial BPs to LVMI

Increased carotid BP was significantly correlated with increased LVMI (Spearman $r=0.2$; $P=0.011$), and this relationship was stronger than the relationship between brachial systolic BP and LVMI ($r=0.1$; $P=0.048$). In multivariate analysis adjusting for age, sex, and number of risk factors at baseline, LVMI was significantly lower in patients receiving the amlodipine-based regimen. This difference was slightly attenuated when brachial SBP was included in the model and further attenuated in a model where cSBP replaced brachial SBP; when cSBP was included in the model, the effect of treatment regimen was no longer statistically significant. A full backward stepwise multivariate regression, including age, sex, risk factors at randomization, treatment regimen, number of antihypertensive drugs, SBP, diastolic BP, cSBP heart rate, stroke volume, total peripheral resistance, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, creatinine, presence of microalbuminuria, and body mass index, indicated that cSBP was an independent predictor of LVMI; sex, risk factors at randomization, body mass index, heart rate, high-density lipoprotein cholesterol, and stroke volume were also significant predictors of LVMI in the final model (Table 4).

Discussion

cSBP, a direct measure of central systolic pressure, is reduced to a greater extent in subjects treated with an amlodipine-based regimen than an atenolol-based regimen. cSBP also correlates with LVMI, an established independent predictor of cardiovascular events,[31] and adjustment for differences in cSBP attenuated between-treatment differences in LVMI. Wave-intensity analysis and wave separation show that the lower cSBP is attributable to a lower magnitude of wave reflection and not to changes in the timing of reflected waves, differences in heart rate, or changes in the forward wave resulting from ventricular ejection.

These observations extend the findings of another ASCOT substudy (Conduit Artery Function Evaluation),[7] which reported higher central SBP in patients randomized to atenolol and increased central aortic augmentation index estimated from radial tonometry. However, central augmentation index is not simply a measure of wave reflection,[32] and the poor accuracy of radial-derived estimates of central augmentation index[14–16] make it difficult to draw firm conclusions from this study with regard to wave reflection. Our study observed a significantly higher SBP and AI_c in the carotid artery and wave intensity analysis, and separation clearly demonstrated that this was because of increased wave reflection in individuals randomized to an atenolol-based regimen. These findings may also offer an explanation for other studies that have used pulse wave analysis to show that β-blockers reduce central SBP less than other antihypertensive medications.[33,34] Recently, Dart et al[8] also used carotid tonometry to measure central SBP in a substudy of the Second Australian National Blood Pressure Trial but failed to find differences in central BP between patients receiving an angiotensin-converting enzyme inhibitor–based regimen and those receiving a diuretic-based regimen. Our data indicate that the differences between the findings in the Second Australian National Blood Pressure Trial and ASCOT (Conduit Artery Function Evaluation) are unlikely to be related to the method used to measure central pressure (carotid versus radial tonometry) and are more likely to be explained by the different therapeutic regimens used, such as the use of a β-blocker as first-line therapy in 1 treatment arm in ASCOT or some other factor, such as age or cardiovascular risk factor profiles of the participants.

The mechanism by which amlodipine-based therapy alters the magnitude of wave reflection remains to be established, but waves are reflected when they meet sites of impedance mismatching, for example, at bifurcations. Vasoconstriction is associated with increased wave reflection,[35] and previous studies have also suggested that calcium channel blockers can normalize the impedance pattern of hypertensive subjects as a result of vasodilation.[36,37] We suggest that the greater vasodilator action of amlodipine-based therapy compared with atenolol-based therapy may account for reduced wave reflection as a result of improved impedance matching. This suggestion is consistent with our observation of a higher total peripheral resistance in people randomized to atenolol-based therapy and the findings of Bleasdale et al,[27] who reported that hypercapnia, a cerebral vasodilator, reduced the magnitude of the reflected $c^{-}1$ wave in the carotid artery in normal subjects.

It is notable that S-wave intensity was only slightly lower in people receiving atenolol than in those randomized to amlodipine-based therapy and that the difference was not statistically significant. A previous study in dogs[38] reported that intravenous administration of propranolol to dogs resulted in a significant reduction in S-wave intensity. How-

ever, the dose of atenolol used for treatment of hypertension in ASCOT was less (in terms of dose in milligrams per kilogram) than that used experimentally in dogs, and 50 mg of atenolol is insufficient to achieve full β-blockade.[39] In addition, acute and chronic effects of β-blockade on cardiac function may differ. For example, in chronic heart failure, β-blockers increase cardiac index and stroke work index after chronic administration, although they cause a reduction when administered acutely.[40] Additional studies examining the acute effect of β-blockers on wave intensity in humans would be of interest.

This study has a number of limitations. The majority of participants were men, and in view of the limited number of women, it should not be assumed that our observations apply equally to both sexes. The lack of pretreatment baseline data means that we cannot comment on how treatment changed wave reflection from the pretreatment state; however, it should be recalled that hardly any individuals were treatment naive, so baseline data would be difficult to interpret. Moreover, with regard to the comparison of treatment regimens, the lack of baseline data is not a major problem, because this was a randomized study, and potential confounders at baseline should be balanced by randomization. Another limitation relates to the treatment regimens themselves: a minority of individuals (≈26%) were receiving monotherapy (amlodipine or atenolol) at the time of the study, and individuals randomized to atenolol received more add-on therapy than those randomized to amlodipine. The observed differences, therefore, relate only to treatment combinations, and no conclusion should be drawn regarding the effects of the individual agents used as initial monotherapy.

This study also has a number of strengths. It is a large, prospectively randomized clinical trial where carotid BP was measured directly. Unlike previous studies, it measured both BP and flow and was, therefore, able to undertake wave separation and to establish with confidence that the differences in central SBP were attributable to a difference in the magnitude of wave reflection, rather than effects on timing of waves, alterations in heart rate,[12] changes in stroke volume,[41] or modification of the pattern of systolic ejection.

Perspectives

The importance of central BP as a target for antihypertensive medication is increasingly accepted. This study has shown that directly measured cSBP is lower with an amlodipine-based regimen than with atenolol-based treatment. This difference is because of a lesser magnitude of wave reflection in patients randomized to an amlodipine-based regimen.

Acknowledgments

We are grateful to Sheila Raynor for her expert technical skills and also acknowledge the invaluable support of clinicians, nurses, and support staff involved in ASCOT. We also thank all of the patients who participated in the study.

Sources of Funding

We are grateful for an unrestricted educational grant from Pfizer International and the support of the National Institute for Health Research Biomedical Research Centre funding scheme. C.H.M. was supported by a Research Training Fellowship from the Wellcome Trust (077049/Z/05/Z) and the Coronary Flow Trust.

Disclosures

None.

References

1. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Int Med*. 1993;153:598–615.
2. Nichols WW, O'Rourke MF. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. V ed. London, United Kingdom: Hodder Arnold; 2005:166–267.
3. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. *Hypertension*. 2001;38:434–438.
4. Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, Eber B. Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation*. 2004;109:184–189.
5. Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Lamm G, Stark N, Rammer M, Eber B. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *Eur Heart J*. 2005;26:2657–2663.
6. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, Umans JG, Howard BV. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension*. 2007;50:197–203.
7. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) Study. *Circulation*. 2006;113:1213–1225.
8. Dart AM, Cameron JD, Gatzka CD, Willson K, Liang YL, Berry KL, Wing LMH, Reid CM, Ryan P, Beilin LJ, Jennings GLR, Johnston CI, McNeil JJ, MacDonald GJ, Morgan TO, West MJ, Kingwell BA. Similar effects of treatment on central and brachial blood pressures in older hypertensive subjects in the Second Australian National Blood Pressure Trial. *Hypertension*. 2007;49:1242–1247.
9. Lehman ED. Where is the evidence that radial artery tonometry can be used to accurately and noninvasively predict central aortic blood pressure in patients with diabetes? *Diabetes Care*. 2000;23:869–871.
10. Williams B. Pulse wave analysis and hypertension: evangelism versus scepticism. *J Hypertens*. 2004;22:447–449.
11. Dart AM, Gatzka CD, Kingwell B. Letter by Dart et al regarding article, "Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) Study." *Circulation*. 2006;114:e537.
12. Cameron JD, Meredith IT, Hope SA. Letter by Cameron et al regarding article, "Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) Study." *Circulation*. 2006;114:e538.
13. Hope SA, Meredith IT, Tay D, Cameron JD. 'Generalizability' of a radial-aortic transfer function for the derivation of central aortic waveform parameters. *J Hypertens*. 2007;25:1812–1820.
14. Chen CH, Ting CT, Nussbacher A, Nevo E, Kass DA, Pak P, Wang SP, Chang MS, Yin FC. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. *Hypertension*. 1996;27:168–175.
15. Cameron JD, McGrath BP, Dart AM. Use of radial artery applanation tonometry and a generalized transfer function to determine aortic pressure augmentation in subjects with treated hypertension. *J Am Coll Cardiol*. 1998;32:1214–1220.
16. Segers P, Rietzschel E, Heireman S, De BM, Gillebert T, Verdonck P, Van BL. Carotid tonometry versus synthesized aorta pressure waves for the estimation of central systolic blood pressure and augmentation index. *Am J Hypertens*. 2005;18:1168–1173.
17. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.

18. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Phillips HP5332, and Nissei DS. *Blood Press Monit*. 1996;1:55–61.
19. London GE, Guerin AP, Marchais SJ, Pannier B, Safar ME, Day M, Metivier F. Cardiac and arterial interactions in end-stage renal disease. *Kidney Int*. 1996;50:600–608.
20. Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation*. 1989;80: 1652–1659.
21. Zambanini A, Cunningham SL, Parker KH, Khir AW, McG Thom SA, Hughes AD. Wave-energy patterns in carotid, brachial, and radial arteries: a noninvasive approach using wave-intensity analysis. *Am J Physiol Heart Circ Physiol*. 2005;289:H270–H276.
22. Khir AW, O'Brien A, Gibbs JS, Parker KH. Determination of wave speed and wave separation in the arteries. *J Biomech*. 2001;34:1145–1155.
23. Zambanini A, Khir AW, Byrd SM, Parker KH, Thom SAM, Hughes AD. Wave intensity analysis: a novel non-invasive method for determining arterial wave transmission. *Comput Cardiol*. 2002;29:717–720.
24. Davies JE, Whinnett ZI, Francis DP, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Use of simultaneous pressure and velocity measurements to estimate arterial wave speed at a single site in humans. *Am J Physiol Heart Circ Physiol*. 2006;290:H878–H885.
25. Sharp A, Tapp R, Francis DP, McG Thom SA, Hughes AD, Stanton AV, Zambanini A, Chaturvedi N, Byrd S, Poulter NR, Sever PS, Mayet J. Ethnicity and left ventricular diastolic function in hypertension an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) substudy. *J Am Coll Cardiol*. 2008;52:1015–1021.
26. Parker KH, Jones CJ. Forward and backward running waves in the arteries: analysis using the method of characteristics. *J Biomech Eng*. 1990;112:322–326.
27. Bleasdale RA, Mumford CE, Campbell RI, Fraser AG, Jones CJ, Frenneaux MP. Wave intensity analysis from the common carotid artery: a new noninvasive index of cerebral vasomotor tone. *Heart Vessels*. 2003;18:202–206.
28. Davies JE, Whinnett ZI, Francis DP, Manisty CH, guado-Sierra J, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, Mayet J. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation*. 2006;113:1768–1778.
29. Ting CT, Brin KP, Lin SJ, Wang SP, Chang MS, Chiang BN, Yin FC. Arterial hemodynamics in human hypertension. *J Clin Invest*. 1986;78: 1462–1471.
30. Segers P, Verdonck P. Role of tapering in aortic wave reflection: hydraulic and mathematical model study. *J Biomech*. 2000;33:299–306.
31. Levy D, Garrsion RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Study. *N Engl J Med*. 1990;322:1561–1566.
32. Nichols WW, Singh BM. Augmentation index as a measure of peripheral vascular disease state. *Curr Opin Cardiol*. 2002;17:543–551.
33. Dhakam Z, McEniery CM, Yasmin, Cockcroft JR, Brown MJ, Wilkinson IB. Atenolol and eprosartan: differential effects on central blood pressure and aortic pulse wave velocity. *Am J Hypertens*. 2006;19:214–219.
34. London GM, Asmar RG, O'Rourke MF, Safar ME. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. *J Am Coll Cardiol*. 2004;43:92–99.
35. Nichols WW, Avolio AP, Kelly R. Effects of age and hypertension on wave travel and reflections. In: O'Rourke MF, Safar M, Dzau V, eds. *Arterial Vasodilatation: Mechanisms and Therapy*. London, United Kingdom: Edward Arnold; 1993:23–40.
36. Chen CH, Ting CT, Lin SJ, Hsu TL, Yin FC, Siu CO, Chou P, Wang SP, Chang MS. Different effects of fosinopril and atenolol on wave reflections in hypertensive patients. *Hypertension*. 1995;25:1034–1041.
37. Ting CT, Chen JW, Chang MS, Yin FC. Arterial hemodynamics in human hypertension: effects of the calcium channel antagonist nifedipine. *Hypertension*. 1995;25:1326–1332.
38. Jones CJ, Sugawara M, Kondoh Y, Uchida K, Parker KH. Compression and expansion wavefront travel in canine ascending aortic flow: wave intensity analysis. *Heart Vessels*. 2002;16:91–98.
39. Conway FJ, Fitzgerald JD, McAinsh J, Rowlands DJ, Simpson WT. Human pharmacokinetic and pharmacodynamic studies on atenolol (ICI 66,082), a new cardioselective β-adrenoceptor blocking drug. *Br J Clin Pharmacol*. 1976;3:267–272.
40. Kukin ML, Mannino MM, Freudenberger RS, Kalman J, Buchholz-Varley C, Ocampo O. Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure. *J Am Coll Cardiol*. 2000;35:45–50.
41. Nieminen T, Kahonen M, Koobi T. Letter by Nieminen et al regarding article, "Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) Study." *Circulation*. 2006 10;114:e536.

ONLINE SUPPLEMENT

DIFFERENCES IN THE MAGNITUDE OF WAVE REFLECTION ACCOUNT FOR DIFFERENTIAL EFFECTS OF AMLODIPINE- VS ATENOLOL-BASED REGIMEN ON CENTRAL BLOOD PRESSURE: AN ASCOT SUBSTUDY.

Charlotte H Manisty[1], Kim H. Parker[1, 2], Justin E. Davies[1], Darrel P. Francis[1], Jamil Mayet[1], Simon A McG Thom[1], Alun D. Hughes[1] on behalf of the ASCOT investigators

[1] International Centre for Circulatory Health, NHLI Division, Faculty of Medicine Imperial College London & Imperial College Healthcare NHS Trust, London, United Kingdom.
[2] Department of Bioengineering, Faculty of Engineering, Imperial College London

Short Title – Carotid pressure and wave reflection in ASCOT

Appendix 1: The carotid artery wave intensity profile

A wave is a transmitted disturbance that propagates in time and space and the propagation of a wave invariably involves some exchange of energy. In our use, the term wave should be distinguished from the term waveform by which we mean a measured pressure or velocity waveform. Waves in arteries can be classified by their direction of travel (forward or backward) and their relationship to pressure changes (waves occurring during positive changes in pressure are termed compression waves, and waves occurring during negative pressure changes are termed decompression wave).

Wave intensity analysis at the carotid artery reveals a characteristic pattern of waves that are similar to those seen elsewhere in the systemic circulation including the aorta (reviewed in [1]). By convention forward travelling waves are assigned positive wave intensity. Details of the type and presumed origins of the waves are described in Figure S1 and accompanying legend.

References

1. Hughes AD, Parker KH, Davies JE. Waves in arteries: A review of wave intensity analysis in the systemic and coronary circulations. *Artery Research*. 2008; 2:51-59.

2. Zambanini A, Cunningham SL, Parker KH, Khir AW, McG Thom SA, Hughes AD. Wave-energy patterns in carotid, brachial, and radial arteries: a noninvasive approach using wave-intensity analysis. *Am J Physiol Heart Circ Physiol*. 2005; 289:H270-H276.

3. Khir AW, Henein MY, Koh T, Das SK, Parker KH, Gibson DG. Arterial waves in humans during peripheral vascular surgery. *Clin Sci (Lond)*. 2001; 101:749-757.

4. Parker KH, Jones CJ, Dawson JR, Gibson DG. What stops the flow of blood from the heart? *Heart Vessels*. 1988; 4:241-245.

5. MacRae JM, Sun YH, Isaac DL, Dobson GM, Cheng CP, Little WC, Parker KH, Tyberg JV. Wave-intensity analysis: a new approach to left ventricular filling dynamics. *Heart Vessels*. 1997; 12:53-59.

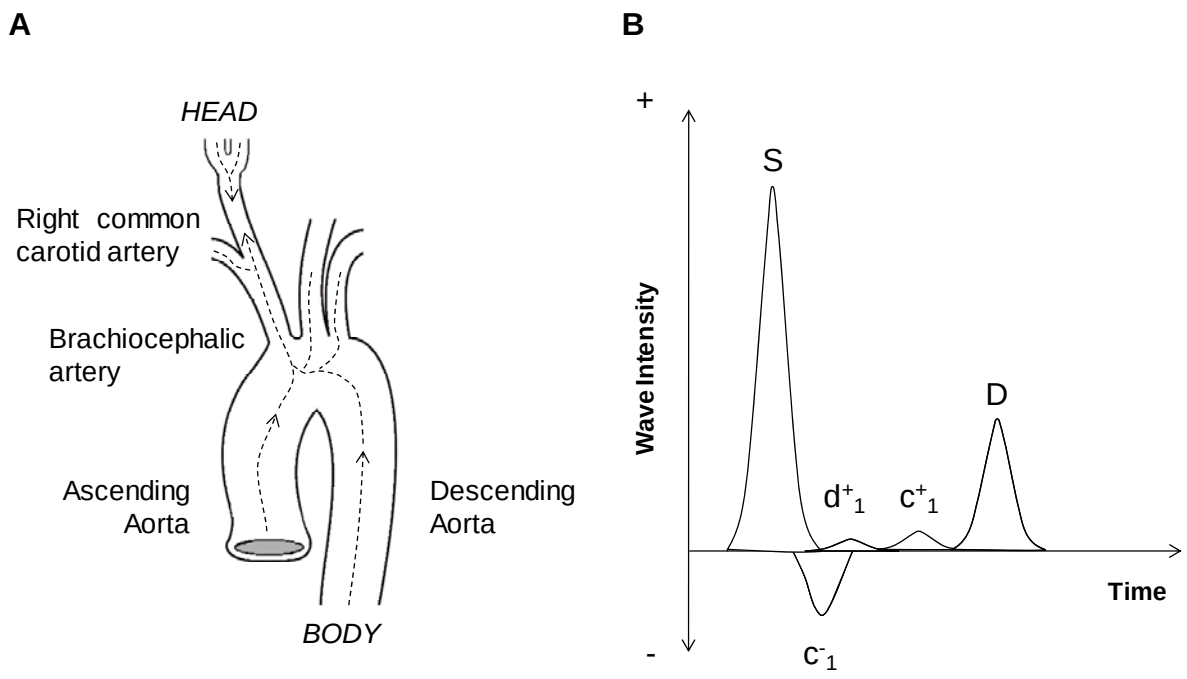

Figure S1.

A) Right common carotid artery and its relation to other arteries, indicating routes followed by waves arising from the head and body and their direction in the common carotid artery.

B) Schematic representation of a typical wave intensity profile in the right common carotid artery. Left ventricular contraction results in a forward travelling compression wave (S wave) that propagates into the carotid artery in early systole causing an acceleration of flow velocity. Subsequently there is a backward-travelling compression wave (c^-_1) which is due to reflection of the systolic wave from presumed sites of admittance mismatching in territory supplied by the carotid artery (the head). This wave decelerates blood flow velocity in the carotid artery. Subsequently there is a small forward travelling decompression wave (d^+_1) that causes a deceleration of flow. The d^+_1 wave is thought to result from re-reflection of c^-_1reflected wave at the junction between the carotid and brachiocephalic artery (or the carotid artery and aorta in the left carotid) which generates a decompression or 'open end' type of reflection[2]. The magnitude of this re-reflected wave is variable and can be absent in some individuals. The d^+_1 wave is followed by another forward compression wave (c^+_1) that is attributed to reflection of the initial systolic S wave from sites of admittance mismatching in the rest of the body [3]. Although c^+_1 is a reflected wave (i.e. it travels retrogradely in the aorta (see Figure S1A), it appears as a forward travelling wave in the carotid artery as a result of the anatomical relationship of the carotid artery to the aorta. A forward travelling decompression wave (D wave) appears at the end of systole (protodiastole) and results from a decline the rate of myocardial contraction and this wave contributes to aortic valve closure[4,5].