# Dominance of the Forward Compression Wave in Determining Pulsatile Components of Blood Pressure

## Similarities Between Inotropic Stimulation and Essential Hypertension

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***Abstract***—Pulsatile components of blood pressure may arise from forward (ventricular generated) or backward wave travel in the arterial tree. The objective of this study was to determine the relative contributions of forward and backward waves to pulsatility. We used wave intensity and wave separation analysis to determine pulsatile components of blood pressure during inotropic and vasopressor stimulation by dobutamine and norepinephrine in normotensive subjects and compared pulse pressure components in hypertensive (mean±SD, 48.8±11.3 years; 165±26.6/99±14.2 mm Hg) and normotensive subjects (52.2±12.6 years; 120±14.2/71±8.2 mm Hg). Dobutamine (7.5 μg/kg per minute) increased the forward compression wave generated by the ventricle and increased pulse pressure from 36.8±3.7 to 59.0±3.4 mm Hg (mean±SE) but had no significant effect on mean arterial pressure or the midsystolic backward compression wave. By contrast, norepinephrine (50 ng/kg per minute) had no significant effect on the forward compression wave but increased the midsystolic backward compression wave. Despite this increase in the backward compression wave, and an increase in mean arterial pressure, norepinephrine increased central pulse pressure less than dobutamine (increases of 22.1±3.8 and 7.2±2.8 mm Hg for dobutamine and norepinephrine, respectively; $P<0.02$). An elevated forward wave component (mean±SE, 50.4±3.4 versus 35.2±1.8 mm Hg, in hypertensive and normotensive subjects, respectively; $P<0.001$) accounted for approximately two thirds of the total difference in central pulse pressures between hypertensive and normotensive subjects. Increased central pulse pressure during inotropic stimulation and in essential hypertension results primarily from the forward compression wave. (***Hypertension*****. 2014;64:1116-1123.)** ● **Online Data Supplement**

**Key Words:** hypertension ■ pulse pressure ■ pulse wave analysis



Pulsatile components of the aortic blood pressure waveform, such as the amplitudes at the first (P1) and second shoulders (P2) of the waveform (Figure 1), are important determinants of cardiovascular events.[1–3] The extent to which they are determined by ventricular contraction, Windkessel/reservoir properties, or other components of the impedance of the proximal arterial tree and reflections from the peripheral arterial tree is unclear.[4–6] Wave intensity and wave separation analysis allow pressure to be separated into a forward component traveling from the left ventricle toward the periphery of the arterial tree and a backward component traveling from the arterial tree toward the ventricle.[7] Pressure waves can be further categorized as compression or expansion (suction). A primary forward compression wave (FCW) arises from the push of the ventricle against the arterial tree and a systolic backward compression wave (BCW) from the push of the arterial tree against the ventricle. A midsystolic forward expansion wave (FEW) arises from the braking effect of the ventricle in late systole and other minor waves arise from other ventricular–vascular interactions (Figure 1).[8]

The objective of the present study was to determine the relative contributions of forward and backward waves attributable to pressures generated primarily from the ventricle and arterial tree, respectively, to (1) changes in pulse pressure during modulation of cardiac contractility and arterial tone by dobutamine and norepinephrine.[9] (2) elevated pulse pressure in subjects with essential hypertension.

## Methods

### Study 1: Effects of Dobutamine and Norepinephrine on Hemodynamics

Healthy volunteers (n=10; age, 35–63 years; 8 men) took part in this crossover study to investigate the change in pulsatile hemodynamics after inotropic/vasopressor stimulation. They received cumulative doses of dobutamine and norepinephrine on 2 separate visits ≥7 days apart. Measurements were performed in a quiet temperature controlled (24–26°C) vascular laboratory, and subjects were asked to avoid caffeine and alcohol on the day of the study. On arrival in the vascular laboratory, a peripheral venous catheter was inserted into the left antecubital fossa through which 0.9% saline (Baxter Healthcare)

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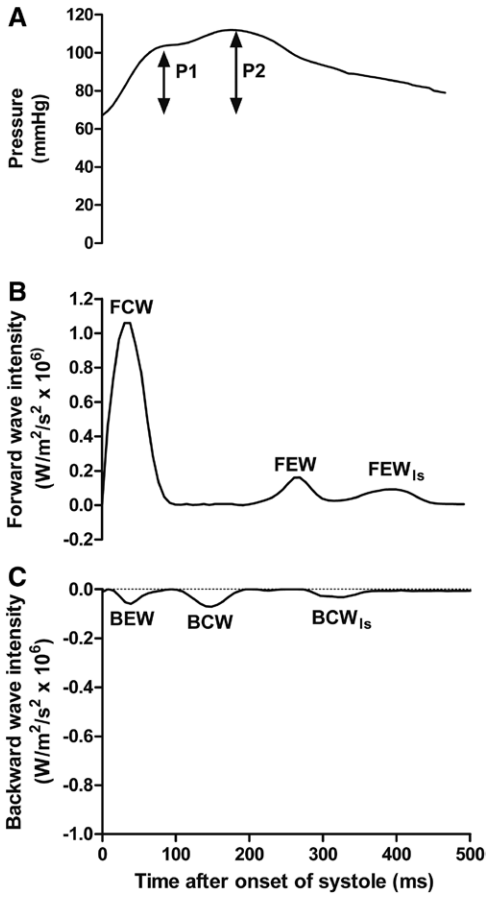


**Figure 1. A**, The central arterial pressure pulse with pulsatile components P1 and P2 determined by the heights of first and second shoulders, respectively. **B**, Forward wave intensities showing the forward compression wave (FCW), midsystolic forward expansion wave (FEW), and late systolic forward expansion wave ($FEW_{ls}$). **C**, Backward wave intensities showing backward expansion wave (BEW), midsystolic backward compression wave (BCW), and late systolic backward compression wave ($BCW_{ls}$).

vehicle or drugs dissolved in saline were infused at 1 mL/min using a syringe driver (Injectomat; Agilia; Fresenius Kabi, Bad Homburg, Germany). After 30-minute resting supine during infusion of saline vehicle, baseline hemodynamic measurements were made as detailed below. Dobutamine (2.5, 5, and 7.5 μg/kg per minute; Hameln Pharmaceuticals, Gloucester, United Kingdom) or norepinephrine (12.5, 25, and 50 ng/kg per minute; Aguettant Ltd, Bristol, United Kingdom) dissolved in 0.9% saline vehicle were then infused at 1 mL/min and hemodynamic measurements repeated at each drug dose after 7 minutes of infusion when steady state was achieved.

## Study 2: Comparison of Hemodynamic Measures in Patients With Untreated Hypertension and Normotensive Controls

Patients with untreated essential hypertension or hypertension inadequately controlled on treatment were recruited from the hypertension clinics at Guy's and St Thomas' Hospital. Hypertension was diagnosed as an office blood pressure >140/90 mm Hg on ≥3 occasions and ambulatory blood pressure >130/85 mm Hg. Patients on treatment for hypertension were included if office blood pressure on treatment was >140/90 mm Hg. Exclusion criterion included intercurrent illness, pregnancy, significant systemic disease other than mild hypertensive nephropathy, history of ischemic heart disease, valvular heart disease, echocardiographic evidence of left ventricular ejection fraction <50%, regional wall motion abnormality, left ventricular outflow tract obstruction, pulmonary hypertension, and poor transthoracic acoustic window. Healthy volunteers on no regular medication of a similar age and sex distribution to hypertensive subjects were recruited by advertisement from the local community. Subject characteristics are shown in Table 1. Subjects were asked to avoid caffeine and alcohol on the day of the study. Hemodynamic measurements were performed as described below. Both studies 1 and 2 were approved by the London Westminster Research Ethics Committee, and written informed consents were obtained from all participants.

### Hemodynamic Measurements

Radial and carotid pressure waveforms were obtained by applanation tonometry performed by an experienced operator (H.F.) using the SphygmoCor system (AtCor, West Ryde, Australia). Approximately 10 cardiac cycles were obtained and ensemble averaged. Waveforms that did not meet the inbuilt quality control criteria in the SphygmoCor system were rejected. Brachial blood pressure was measured in triplicate by a validated oscillometric method (Omron 705CP; Omron Healthcare, Tokyo, Japan) and used to calibrate radial waveforms to obtain a mean arterial pressure (MAP). Carotid waveforms were calibrated from MAP and diastolic brachial blood pressure on the assumption of equality of these pressures at central and peripheral sites.[10] The primary analysis was performed on nontransformed carotid waveforms and a secondary analysis on waveforms transformed to aortic waveforms using the inbuilt transfer function in the SphygmoCor system.

Ultrasound imaging was performed by an experienced operator (B.J.) using the Vivid-7 ultrasound platform (General Electric Healthcare, Pollards Wood, United Kingdom). Velocity across the aortic valve was recorded using continuous wave Doppler obtained from an apical 5-chamber view. Stroke volume was calculated from the product of velocity time integral and cross-sectional area of the aortic valve (obtained in the parasternal long-axis view). All measurements were averaged over ≥3 cardiac cycles. Cardiac output (CO) was calculated from stroke volume and heart rate and total peripheral resistance from MAP divided by CO.

**Table 1. Characteristics of Patients With Hypertension and Normotensive Controls**

| Characteristic | Normotensive Controls (n=20) | Patients With Hypertension (n=20) |
|---|---|---|
| Age, y | 52.2±12.6 | 48.8±11.3 |
| Men, % | 85 | 75 |
| Systolic blood pressure, mm Hg | 120±14.2 | 165±26.6* |
| Diastolic blood pressure, mm Hg | 71.1±8.20 | 98.7±14.2* |
| Body mass index, kg/m² | 24.1±2.5 | 29.6±5.4† |
| Total cholesterol, mmol/L | 5.4±0.8 | 5.0±1.2 |
| High density lipoprotein, mmol/L | 1.7±0.6 | 1.5±0.5 |
| HbA1c, % | 5.5±0.2 | 5.8±0.5 |
| Drug therapy | | |
| ACEI, % | ... | 25 |
| ARB, % | ... | 25 |
| β-blocker, % | ... | 15 |
| Calcium channel blocker, % | ... | 65 |
| Diuretic, % | ... | 50 |
| α-blocker, % | ... | 30 |
| Statins, % | ... | 60 |
| Median no. of antihypertensive medications | ... | 2.5 |

Data are mean±SD or %. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and HbA1c, glycosylated haemoglobin.
*$P$<0.005, †$P$<0.01 compared with normotensive controls.

## Waveform Postprocessing

Ensemble averaged carotid pressure was used as surrogate for ascending aortic pressure.[11] This together with aortic flow velocity was processed offline using custom software in MATLAB (MathWorks, Natick, MA) for wave intensity, wave decomposition analysis, and pulse wave analysis. P1 and P2 were calculated as the pressures above diastolic pressure at the first and second shoulders of the carotid pressure pulse, respectively. These shoulders were automatically identified from the derivatives of the pressure signal and their position verified visually by an experienced operator. Augmentation pressure (AP) was taken as the difference between P2 and P1. Wave intensity was calculated as the product of the first derivative of pressure and the first derivative of flow velocity, as described by Parker et al[7]:

$$\text{Wave intensity} = \frac{dP}{dt} \times \frac{dU}{dt},$$

where $P$ and $U$ are the pressure and the flow velocity, respectively. Pressure waves were decomposed into forward pressure waves (FPW) and backward pressure waves (BPW) using the equations established by Euler in 1775 that derive from the physical principles of conservation of mass and momentum. The aorta is assumed to act as a thin-walled elastic tube, blood as an incompressible fluid, and flow assumed to be 1-dimensional. The following formulas were thus used for FPW and BPW:

$$\text{FPW} = \frac{1}{2}\int_0^T \left(\frac{dp}{dt} + \rho c.\frac{dU}{dt}\right)dt$$

$$\text{BPW} = \frac{1}{2}\int_0^T \left(\frac{dP}{dt} - \rho c.\frac{dU}{dt}\right)dt$$

where $T$ is the foot-to-foot duration of a pulse, ρ is the density of blood, and $c$ is the speed of travel of waves equal to the local pulse wave velocity. This produces the same waveform separation as an analysis in the frequency domain.[12] The wave speed $c$ was calculated using the single-point method described by Davies et al.[13]

## Statistical Analysis

Subject characteristics are summarized as mean±SD and results as mean±SEM. Differences between hemodynamic measures in hypertensive and normotensive subjects were examined using Student's unpaired $t$-test. Responses to the vasoactive drugs relative to baseline were sought by repeated measures ANOVA. $P<0.05$ was considered significant, and all tests were 2 tailed. Analysis was performed using SPPSS version 19.

# Results

## Effects of Dobutamine and Norepinephrine on Pressure Wave Components and Wave Intensities

The major effect of dobutamine was to increase CO and pulsatility (particularly P1), this being associated with a trend to an increase in MAP and decrease in total peripheral resistance (Table 2). Norepinephrine increased total peripheral resistance and MAP and also P2 and AP but not P1 (Table 3). There was a small but significant fall in CO after norepinephrine (Table 3). Dobutamine increased pulsatility, increasing both P1 and P2 by increasing the FPW, with no significant contribution of the BPW to the increase in P2 (Figures 2 and 3). Dobutamine increased the FCW and also the late systolic FEW, BEW, and late systolic BCW. However, there was no significant change in the ratios of the secondary waves to the FCW. Norepinephrine tended to increase the BPW component of P2, particularly in subjects with a positive AP (Figures 2 and 3) and, by contrast to dobutamine, increased the midsystolic BCW both in absolute terms and as a proportion of the FCW (Table 3). However, the forward wave remained the major component of both P1 and P2 during stimulation with norepinephrine. When using transformed carotid waveforms, there were modest but significant differences in absolute pressures from those obtained from the nontransformed waveform (Table S1 in the online-only Data Supplement). However, the main findings that majority of the pulse pressure components during stimulation with both dobutamine and norepinephrine derive from the FPW remained unchanged.

## Comparison of Hemodynamic Measures in Normotensive and Hypertensive Subjects

Compared with normotensive subjects, hypertensive subjects were characterized by increased MAP and increased central aortic pulsatility with P1, P2, and AP and increased by 11.8±2.8, 24.3±4.8, and 12.5±3.8 mm Hg, respectively, compared with normotensive subjects. P1 and P2 were of approximately equal magnitude in normotensive subjects so that AP was close to zero. However, in hypertensive subjects, P2 exceeded P1 giving an AP of 12.6±3.5 mm Hg. Total peripheral resistance was greater in hypertensive when compared with that in normotensive subjects but CO was similar in the 2 groups (Table 4).

## Relative Contribution of Forward and Backward Waves to Pulsatile Components of Blood Pressure in Normotensive and Hypertensive Subjects

Wave separation analysis demonstrated that, in normotensive subjects, both P1 and P2 were determined almost exclusively by forward components of the pressure wave, although in subjects with a positive AP, the BPW did contribute to P2. In hypertensive subjects (in whom AP was positive), P1 was also determined by the forward wave, and the forward wave provided the major contribution to P2. However, the BPW provided a greater contribution to P2 than in normotensive subjects (7.3±1.9 mm Hg compared with 1.0±0.7 mm Hg in normotensive subjects; $P<0.01$; Figure 4) and contributed 7.1±2.1 mm Hg to the total AP of 12.6±3.5 mm Hg in hypertensive subjects.

## Wave Intensities in Normotensive and Hypertensive Subjects

The FCW was greater in hypertensive when compared with that in normotensive subjects (Table 4). The midsystolic BCW was also greater in hypertensive when compared with that in normotensive subjects, both in absolute terms and as a proportion of the FCW and tended to arrive earlier in systole in hypertensive when compared with that in normotensive subjects although the difference in timing was not statistically significant (Table 4). The FEW were also greater in hypertensive when compared with that in normotensive subjects, but the FEW/FCW ratios were not significantly different in the 2 groups (Figure 5).

# Discussion

Temporal variation of blood pressure during systole not only offers an insight into ventricular–vascular interaction but also contributes to the risk of future cardiovascular events. At any age, pulse pressure provides additional prognostic information to MAP, and in older subjects, is the single most important component of blood pressure in determining outcome.[3] Central (aortic or carotid) pressures generated at the interface between the ventricle and the arterial tree propagate along

**Table 2. Hemodynamic Changes During Infusion of Dobutamine**

| | | Dobutamine, μg/kg Per Minute | | |
|---|---|---|---|---|
| Measure | Baseline | 2.5 | 5 | 7.5 |
| pSBP, mm Hg | 117±5.25 | 125±3.94 | 138±4.29 | 145±4.15* |
| pDBP, mm Hg | 65.9±2.88 | 65.5±2.57 | 66.2±2.28 | 67.2±1.98 |
| MAP, mm Hg | 80.3±3.48 | 82.0±3.25 | 85.1±2.57 | 87.9±2.04 |
| HR, bpm | 64.7±3.51 | 66.7±4.51 | 69.0±4.74 | 73.0±5.24† |
| cSBP, mm Hg | 103±5.13 | 110±4.86 | 119±3.56 | 127±2.44* |
| P1, mm Hg | 36.8±3.74 | 43.7±3.23 | 51.3±3.76 | 59.0±3.41* |
| P2, mm Hg | 32.5±3.02 | 38.0±2.35 | 41.4±2.47 | 47.2±3.17† |
| AP, mm Hg | −4.29±2.46 | −5.73±2.84 | −9.91±3.82 | −11.8±4.48 |
| CO, L/min | 6.92±0.341 | 7.45±0.482 | 8.21±0.576 | 9.11±0.741* |
| TPR, mm Hg min/L | 12.0±0.925 | 11.4±0.928 | 10.7±0.694 | 10.2±0.999 |
| PWV, m/s | 4.07±0.402 | 4.52±0.371 | 5.10±0.391 | 5.58±0.31† |
| Wave intensity ($W/m^2/s^2 \times 10^6$) | | | | |
| FCW | 1.42±0.226 | 2.17±0.267 | 3.05±0.348 | 3.65±0.434* |
| FEW | 0.137±0.0452 | 0.140±0.0452 | 0.193±0.0399 | 0.243±0.0614 |
| $FEW_{ls}$ | 0.128±0.0235 | 0.181±0.0357 | 0.168±0.0273 | 0.339±0.0955‡ |
| BEW | −0.0285±0.0745 | −0.0499±0.0198 | −0.0715±0.0146 | −0.0921±0.0227† |
| BCW | −0.0200±0.00505 | −0.0409±0.00835 | −0.0468±0.00833 | −0.0399±0.0136 |
| $BCW_{ls}$ | −0.0472±0.0120 | −0.0471±0.0133 | −0.0982±0.0267 | −0.164±0.0390† |
| BCW:FCW | 0.0188±0.00632 | 0.0201±0.00380 | 0.0171±0.00402 | 0.0161±0.00468 |
| Wave timing, ms | | | | |
| FCW | 34.4±1.28 | 33.6±1.67 | 30.5±0.781 | 30.5±0.781† |
| FEW | 199±30.5 | 195±28.4 | 190±23.4 | 152±28.4 |
| $FEW_{ls}$ | 332±21.3 | 326±24.8 | 298±17.2 | 281±20.4 |
| BEW | 71.1±13.0 | 91.4±7.09 | 82.8±11.3 | 67.2±12.0 |
| BCW | 206±19.7 | 224±21.9 | 195±10.8 | 118±29.8* |
| $BCW_{ls}$ | 334±22.7 | 340±17.6 | 297±16.6 | 257±32.9 |

Data are expressed as mean±SEM. AP indicates augmentation pressure; BCW, mid systolic backward compression wave; $BCW_{ls}$, late systolic backward compression wave; BEW, backward expansion wave; CO, cardiac output; cSBP, central systolic blood pressure; FCW, forward compression wave; FEW, mid systolic forward expansion wave; $FEW_{ls}$, late systolic forward expansion wave; HR, heart rate; MAP, mean arterial pressure; P1, pressure at first systolic shoulder; P2, pressure at second systolic peak; pDBP, peripheral diastolic blood pressure; pSBP, peripheral systolic blood pressure; PWV, pulse wave velocity; and TPR, total peripheral resistance.

*$P<0.005$, †$P<0.01$, and ‡$P<0.05$ repeated measures ANOVA for dose–response curve.



the arterial tree to determine peripheral blood pressure and seem to be at least as important a determinant of outcome as peripheral pressures.[14] In addition to central pulse pressure, the difference between P1 and P2 as expressed by AP or augmentation index may be an independent determinant of outcome.[14] Despite the importance of P1 and P2, the properties of the ventricle and arterial tree that generate increased pulsatility are still poorly understood. Previous studies have focused on central pulse pressure (equal to P2 in older subjects and P1 in younger subjects) and the established view is that an elevated pulse pressure in hypertension results from increased augmentation of the FPW by the backward wave, this in turn arising from increased amplitude and earlier return of the backward wave.[4,15] An alternative view is that increased pulse pressure results from increased aortic characteristic impedance (which has greater dependence than pulse wave velocity on aortic cross-sectional area) and relates, in part, to an effective decrease in aortic diameter.[16]

To our knowledge, this is the first study to use wave separation analysis to make direct estimates of the contributions of the forward and backward waves to pulsatile components of central blood pressure at rest and during modulation of pulsatility using dobutamine and norepinephrine, drugs that both have inotropic properties but which have divergent actions on the peripheral arterial tree and produce markedly different effects on pulse pressure and peripheral resistance. At rest, in normotensive individuals, both P1 and P2 pulsatile components were determined almost exclusively by the FPW. Dobutamine produced a marked increase in both P1 and P2 that was again almost exclusively because of effects on the forward wave, as would be expected from an inotrope increasing contractility of the ventricle from which the forward wave derives. In comparison with dobutamine, norepinephrine produced a greater increase in MAP but only a modest increase in pulse pressure (determined by an increase in P2) for which forward and backward components were approximately equal. These results suggest,

**Table 3. Hemodynamic Changes During Infusion of Norepinephrine**

| | | Norepinephrine, ng/kg Per Minute | | |
|---|---|---|---|---|
| Measure | Baseline | 12.5 | 25 | 50 |
| pSBP, mm Hg | 114±4.43 | 117±4.56 | 120±3.97 | 126±4.01* |
| pDBP, mm Hg | 67.1±2.31 | 69.1±2.62 | 73.4±2.82 | 78.4±2.84† |
| MAP, mm Hg | 80.3±3.48 | 82.0±3.25 | 85.1±2.57 | 94.3±3.22† |
| HR, bpm | 61.5±2.89 | 57.7±2.91 | 55.2±2.81 | 52.7±2.63* |
| cSBP, mm Hg | 103±4.90 | 109±5.01 | 111±5.05 | 123±6.29† |
| P1, mm Hg | 35.5±1.67 | 36.5±2.05 | 33.1±2.72 | 36.8±2.84 |
| P2, mm Hg | 33.0±2.66 | 35.8±3.18 | 37.3±2.72 | 43.7±4.31† |
| AP, mm Hg | −2.45±2.39 | −0.664±2.43 | 4.26±2.19 | 6.92±3.29† |
| CO, L/min | 6.36±0.328 | 5.99±0.327 | 5.64±0.152 | 5.13±0.240† |
| TPR, mm Hg min/L | 13.2±0.908 | 14.6±1.13 | 16.0±0.606 | 19.2±1.38† |
| PWV, m/s | 4.35±0.286 | 4.71±0.464 | 4.68±0.163 | 5.55±0.598 |
| Wave intensity ($W/m^2/s^2 \times 10^6$) | | | | |
| FCW | 1.03±0.104 | 1.01±0.0729 | 0.803±0.104 | 0.867±0.114 |
| FEW | 0.0990±0.0327 | 0.149±0.0315 | 0.105±0.0216 | 0.162±0.0396 |
| $FEW_{ls}$ | 0.115±0.0404 | 0.115±0.0282 | 0.123±0.0343 | 0.0971±0.0182 |
| BEW | −0.0215±0.00550 | −0.0410±0.0107 | −0.0357±0.0104 | −0.0363±0.00642 |
| BCW | −0.0187±0.00417 | −0.0310±0.00633 | −0.0308±0.00661 | −0.0357±0.00827‡ |
| $BCW_{ls}$ | −0.0547±0.0171 | −0.0540±0.0103 | −0.0543±0.0133 | −0.0465±0.00956 |
| BCW:FCW | 0.0191±0.00272 | 0.0317±0.00662 | 0.0383±0.00901 | 0.0428±0.00887‡ |
| Wave timing, ms | | | | |
| FCW | 37.5±1.04 | 35.9±1.28 | 37.5±1.04 | 38.3±0.781 |
| FEW | 202±32.6 | 256±25.5 | 243±35.5 | 304±19.7 |
| $FEW_{ls}$ | 333±24.9 | 381±18.9 | 381±17.9 | 427±21.2* |
| BEW | 93.0±12.4 | 105±8.25 | 96.9±8.09 | 93.0±7.22 |
| BCW | 192±30.6 | 224±18.0 | 234±18.8 | 234±21.7 |
| $BCW_{ls}$ | 307±38.6 | 334±23.1 | 387±13.0 | 402±29.1 |

Data are expressed as mean±SEM. AP indicates augmentation pressure; BCW, mid systolic backward compression wave; $BCW_{ls}$, late systolic backward compression wave; BEW, backward expansion wave; CO, cardiac output; cSBP, central systolic blood pressure; FCW, forward compression wave; FEW, mid systolic forward expansion wave; $FEW_{ls}$, late systolic forward expansion wave; HR, heart rate; MAP, mean arterial pressure; P1, pressure at first systolic shoulder; P2, pressure at second systolic peak; pDBP, peripheral diastolic blood pressure; pSBP, peripheral systolic blood pressure; PWV, pulse wave velocity; and TPR, total peripheral resistance.

*$P<0.01$, †$P<0.005$, and ‡$P<0.05$ repeated measures ANOVA for dose–response curve.



therefore, that the contribution of the backward wave to pulsatile components of blood pressure in normotensive subjects at rest and during inotropic and vasopressor stimulation is minor in comparison with that of the forward wave. Wave intensity analysis provides further insight into the hemodynamic origin of forward and backward waves. This analysis confirms that the increased FPW components of P1 and P2 generated by dobutamine acting to increase myocardial contractility result from an increased FCW, which also occurs earlier in systole. Interestingly Schultz et al[17] have reached a similar conclusion on dominance of the FPW as responsible for change in the central pulse during exercise, a physiological stimulus to increased myocardial contractility. Changes in other waves (backward expansion, late systolic FEW, and late systolic BCW) could be secondary to the greater intensity and earlier timing of the FCW.

By contrast to dobutamine, norepinephrine did not increase the FCW. Although the intrinsic action of norepinephrine on the myocardium is to increase contractility, its action on the peripheral vascular tree to increase peripheral resistance will depend on basal sympathetic tone and can result in a reflex decrease in sympathetic output, decrease in myocardial contractility, and a decrease in CO (as seen in the present study).[18] Thus, the lack of effect of norepinephrine on the FCW is expected. Norepinephrine did increase the midsystolic BCW both in absolute terms and as a proportion of the FCW, an action consistent with increased reflection that would be expected to increase the backward pressure wave. However, quantitative analysis of the relative contributions of forward and backward waves shows that the contribution of the latter to increased pulsatility is minor.

In hypertensive subjects, both P1 and P2 components were greater than in normotensive subjects. As in normotensive subjects, P1 was determined exclusively by the forward wave component. P2 was determined by both the forward and the backward waves. However, the forward wave accounted for the majority of P2 and approximately two thirds of the total difference in P2 between hypertensive and normotensive

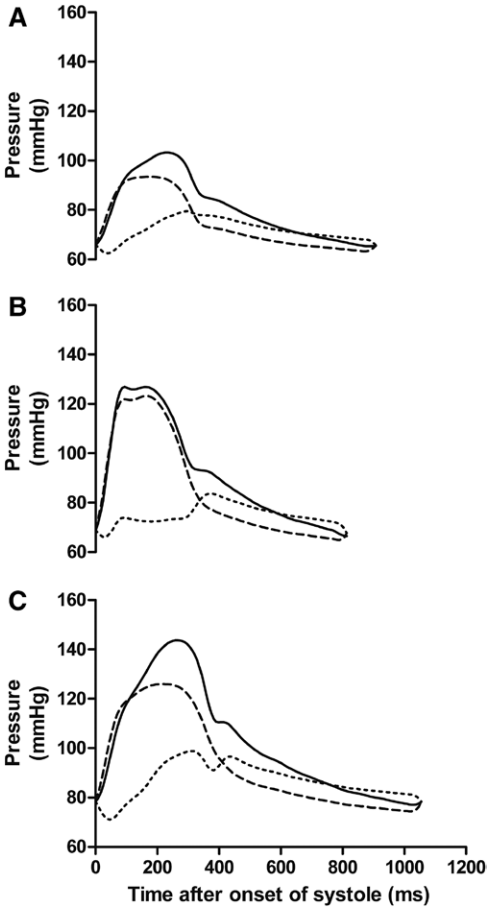


**Figure 2.** Typical pressure pulses decomposed into forward (dashed) and backward (dotted) components: (**A**) baseline, (**B**) after dobutamine, and (**C**) after norepinephrine.

subjects. The backward wave was a significant component of AP in hypertensive subjects, but even for AP, the backward wave only accounted for ≈50% of AP. Wave intensity

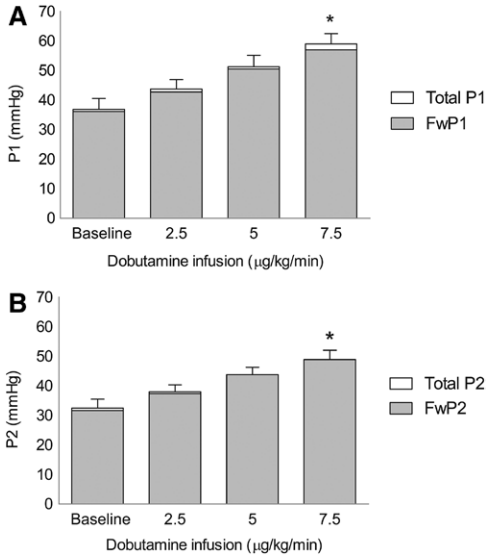


**Figure 3.** Pressure pulse components showing total pressure pulse and forward (Fw) component of pressure pulse for (**A**) P1 and (**B**) P2 during dobutamine infusion in normotensive subjects. Error bars are SEM of total pressure.

**Table 4. Hemodynamics in Patients With Hypertension and Normotensive Controls**

| Measure | Normotensive Controls | Patients With Hypertension |
|---|---|---|
| pSBP, mm Hg | 120±14.2 | 165±26.6* |
| pDBP, mm Hg | 71.1±8.20 | 98.7±14.2* |
| MAP, mm Hg | 87.3±1.97 | 122±3.38* |
| HR, bpm | 63.0±1.66 | 66.2±2.14 |
| cSBP, mm Hg | 109±2.67 | 159±5.06* |
| P1, mm Hg | 33.9±1.67 | 45.7±2.26* |
| P2, mm Hg | 34.1±2.13 | 58.4±4.35* |
| T1, ms | 106±2.97 | 99.6±3.34 |
| T2, ms | 221±4.02 | 211±5.79 |
| AP, mm Hg | 0.133±1.58 | 12.6±3.49* |
| CO, L/min | 5.30±0.306 | 5.98±0.404 |
| TPR, mm Hg·min/L | 17.9±1.41 | 22.7±1.95† |
| PWV, m/s | 4.49±0.294 | 5.74±0.345* |
| Wave intensity ($W/m^2/s^2\times10^6$) | | |
| FCW | 0.92±0.0779 | 1.50±0.118† |
| FEW | 0.143±0.0171 | 0.267±0.0343* |
| $FEW_{ls}$ | 0.0860±0.0151 | 0.163±0.0192‡ |
| BEW | −0.0403±0.00666 | −0.0562±0.00938 |
| BCW | −0.0242±0.00478 | −0.0904±0.0226† |
| $BCW_{ls}$ | −0.0460±0.00942 | −0.0575±0.0112 |
| BCW:FCW | 0.0296±0.00659 | 0.0573±0.00765* |
| Wave timing, ms | | |
| FCW | 36.3±1.03 | 39.5±1.20 |
| FEW | 255±18.4 | 257±13.5 |
| $FEW_{ls}$ | 389.5±13.9 | 374±16.0 |
| BEW | 96.5±4.98 | 81.6±5.8 |
| BCW | 209±16.7 | 175±9.68 |
| $BCW_{ls}$ | 353±22.3 | 346±12.2 |

Data are expressed as mean±SEM. AP indicates augmentation pressure; BCW, mid systolic backward compression wave; $BCW_{ls}$, late systolic backward compression wave; BEW, backward expansion wave; CO, cardiac output; cSBP, central systolic blood pressure; FCW, forward compression wave; FEW, mid systolic forward expansion wave; $FEW_{ls}$, late systolic forward expansion wave; HR, heart rate; MAP, mean arterial pressure; P1, pressure at first systolic shoulder; P2, pressure at second systolic peak; pDBP, peripheral diastolic blood pressure; pSBP, peripheral systolic blood pressure; PWV, pulse wave velocity; T1, time of P1 after onset of systole; T2, time of P2 after onset of systole; and TPR, total peripheral resistance.

*$P<0.005$, †$P<0.05$, and ‡$P<0.01$, compared with normotensive controls.

analysis confirmed a greater FCW and midsystolic BCW in hypertensive when compared with that in normotensive subjects consistent with the relative contribution of forward and backward waves to pulsatility. Comparison of the difference between hypertensive and normotensive subjects with the results of inotropic and vasopressor stimulation in normotensive subjects shows that increased pulsatility in hypertension most closely resembles that simulated with dobutamine in normotensives. These results, therefore, challenge the view that increased pulsatility in essential hypertension results from increased wave reflection. Instead they underline the dominance of the forward wave generated by ventricular contraction. Increased sympathetic activation is invariably present in

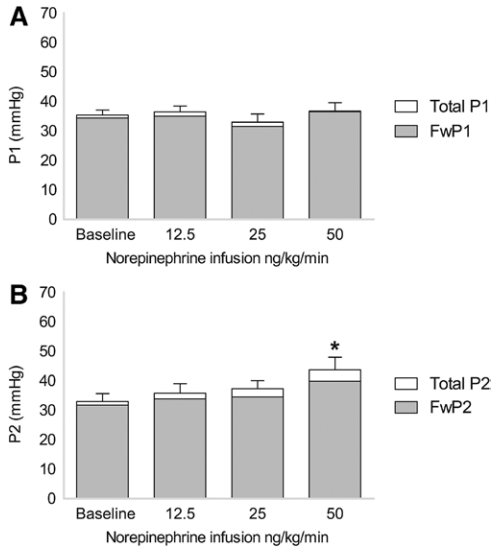


**Figure 4.** Pressure pulse components showing total pressure pulse and forward (Fw) component of pressure pulse for (**A**) P1 and (**B**) P2 during norepinephrine infusion in normotensive subjects. Error bars are SEM of total pressure.

essential hypertension and either alone or in combination with increased preload may explain increased ventricular ejection early in systole and hence increased forward wave components of pulsatility in hypertension.[19]

This study is subject to several limitations. The majority of the hypertensive subjects we studied were on treatment with diuretics and vasodilator drugs that would tend to increase sympathetic activity. Thus, although sympathetic activation is thought to be an early event in the pathogenesis of hypertension,[19] we cannot be certain that our results apply to untreated hypertension. It is likely that the relative contribution of FCW and BCW components to increased pulsatility differs across the spectrum of essential hypertension, and additional studies will be required to determine the relative importance of these components according to age, neuroendocrine profile, and blood pressure treatment. Errors in our analysis could relate to noninvasive derivation of pressure and flow and the use of carotid pressure as a surrogate for aortic pressure. However, scaling errors relating to the exact point at which flow velocity is measured do not influence wave intensity values or wave separation analysis. We also obtained similar findings relating to the dominance of the FPW irrespective of whether we used a carotid-to-aortic transfer function. Furthermore, the use of the inotropic and vasopressor drugs to verify that the FCW arises primarily from myocardial contractility and the BCW from vasoconstriction of the arterial tree strongly supports the conclusions from these analyses.

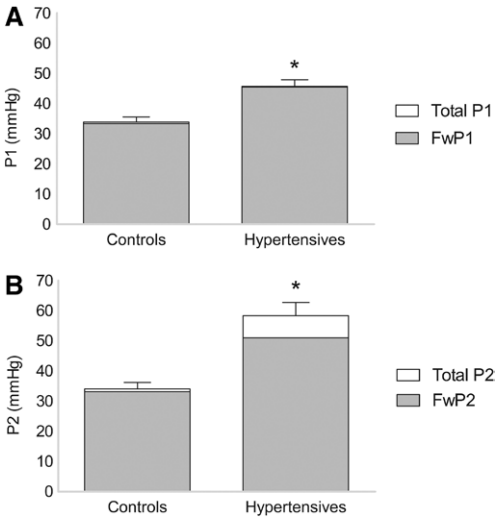


**Figure 5.** Pressure pulse components showing total pressure pulse and forward (Fw) component of pressure pulse for (**A**) P1 and (**B**) P2 in normotensive controls and hypertensive subjects. Error bars are SEM of total pressure.

## Perspectives

An increase in pulse pressure is the major hemodynamic change contributing to hypertension in an aging population. It could result from either an increase in a FCW generated by the ventricle or BCW generated from the arterial tree. The present results suggest that the former dominates both during inotropic stimulation with dobutamine and in subjects with treated essential hypertension. Even when arterial tone is increased with norepinephrine, the contribution of the backward wave to increased pulsatility is relatively modest. The results highlight the potential importance of ventricular dynamics and arterial stiffness in the genesis of systolic hypertension and suggest that interventions that might modify this may be particularly effective in reducing pulse pressure and systolic hypertension.

In conclusion, wave separation and intensity analysis suggest that increased pulsatile components of blood pressure in essential hypertension derive predominantly from a FPW generated by increased myocardial contractility. An increased backward wave does contribute to increased central pulse pressure in hypertension, but its contribution is less than predicted from AP, which is influenced by both forward and backward waves.

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## Disclosures

King's College London has formed a spin-out company to develop technology in central blood pressure measurement (not used in the present study). Dr Guilcher, Dr Brett, Dr Clapp, and Prof Chowienczyk have an interest in this company. The other authors report no conflicts.

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## Novelty and Significance

### What Is New?

- Increased pulse pressure generated by inotropic stimulation and in essential hypertension results primarily from the forward (ventricular) generated pressure wave.
- An increase in the backward wave can be generated by increasing arterial tone with norepinephrine and does contribute to pulse pressure in essential hypertension, but its contribution to this is less than that of the forward wave.

### What Is Relevant?

- These results highlight the potential importance of ventricular dynamics, as well as arterial stiffness in the genesis of systolic hypertension.
- Interventions that modify ventricular dynamics may be particularly effective in reducing pulse pressure and in treating systolic hypertension.

### Summary

Wave separation and intensity analysis suggest that increased pulsatile components of blood pressure in essential hypertension derive predominantly from a forward pressure wave generated by increased myocardial contractility that can be simulated by inotropic stimulation in normotensive subjects. An increased backward wave that can be simulated by increased arterial tone in normotensive subjects does contribute to increased central pulse pressure in hypertension, but its contribution is less than predicted from augmentation pressure, which is influenced by both forward and backward waves.

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# Dominance of the Forward Compression Wave in Determining Pulsatile Components of Blood Pressure: Similarities Between Inotropic Stimulation and Essential Hypertension

Henry Fok, Antoine Guilcher, Sally Brett, Benyu Jiang, Ye Li, Sally Epstein, Jordi Alastruey, Brian Clapp and Phil Chowienczyk

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Running title: forward compression waves in hypertension


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**S1**

**Forward and backward pulse pressure components determined using non-transformed and transformed carotid waveforms**

| Measure | Baseline | Db 7.5μg/kg/min | Baseline | NE 50ng/kg/min |
|---|---|---|---|---|
| **Non-transformed** | | | | |
| P1(mmHg) | 36.8±3.74 | 59.0±3.41 | 35.5±1.67 | 36.8±2.84 |
| P1f (mmHg) | 36.1±3.81 | 56.9±3.14 | 34.5±1.61 | 36.5±3.05 |
| P1b (mmHg) | 0.670±0.233 | 2.08±0.50 | 0.989±0.509 | 0.237±0.982 |
| P1f (%) | 98.0±0.709 | 96.6±0.797 | 97.3±1.31 | 99.4±2.40 |
| P1b (%) | 2.00±0.709 | 3.36±0.797 | 2.69±1.31 | 0.588±2.40 |
| P2 (mmHg) | 32.5±3.02 | 47.2±3.17 | 33.0±2.66 | 43.7±4.31 |
| P2f (mmHg) | 31.6±3.35 | 48.9±3.24 | 31.7±2.75 | 39.9±3.41 |
| P2b (mmHg) | 0.88±1.52 | -1.66±2.08 | 1.27±1.54 | 3.82±2.10 |
| P2f (%) | 97.3±3.65 | 105±5.55 | 96.1±4.18 | 92.4±4.22 |
| P2b (%) | 2.74±3.65 | -4.62±5.55 | 3.93±4.18 | 7.63±4.22 |
| **Transformed** | | | | |
| P1(mmHg) | 29.9±3.05† | 48.3±2.95† | 29.0±1.37† | 30.1±2.35† |
| P1f (mmHg) | 29.7±3.09† | 46.2±2.94† | 28.5±1.33† | 30.8±2.53† |
| P1b (mmHg) | 0.219±0.182† | 2.11±0.895 | 0.498±0.498 | -0.757±0.865 |
| P1f (%) | 99.2±0.662† | 95.7±2.20† | 98.4±1.60 | 103±2.68 |
| P1b (%) | 0.789±0.662† | 4.33±2.70† | 1.56±1.60 | -2.89±2.68 |
| P2 (mmHg) | 33.0±2.89 | 45.7±2.52 | 33.3±2.41 | 43.0±4.04 |
| P2f (mmHg) | 29.6±2.94† | 43.8±2.82† | 29.9±2.13 | 36.5±3.11 |
| P2b (mmHg) | 3.40±1.25† | 1.91±1.74† | 3.33±1.20 | 6.53±1.74 |
| P2f (%) | 89.7±3.13† | 96.1±4.38† | 90.2±2.79 | 85.4±3.08† |
| P2b (%) | 10.3±3.13† | 3.90±4.38† | 9.78±2.79 | 14.6±3.08† |

Data are means ±SEM; P1, pressure at first systolic shoulder; P1f forward pressure wave at P1; P1b backward pressure wave at P1; P2, pressure at second systolic peak; P2f forward pressure wave at P2; P2b backward pressure wave at P2; *P<0.05, †P<0.01 for comparison between wave separation analysis indices using carotid pressure pulse versus synthesized aortic pressure pulse.