Myocardial Perfusion and the J Curve Association Between Diastolic Blood Pressure and Mortality

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BACKGROUND
The J-curve relationship between brachial diastolic blood pressure (DBP) and mortality is believed to be mediated through reduced myocardial perfusion. This study aimed to determine the relationship between DBP and subendocardial perfusion in patients with and without coronary artery disease (CAD) and to examine central hemodynamic variables that may explain the risk associated with low DBP (aortic stiffness, central pulse pressure, and augmentation index).

METHODS
Brachial DBP and radial tonometry were measured in 134 patients with CAD (aged 76 ± 7 years; 69% male), 134 individuals without a prior cardiovascular event (control subjects) (aged 77 ± 2 years; 69% male) and 47 patients (aged 63 ± 10 years) during dobutamine stress echocardiography. Central hemodynamics and subendocardial viability ratio (SEVR), a marker of subendocardial perfusion, were recorded by tonometry.

RESULTS
There was no difference in DBP or SEVR between control subjects and CAD patients (P > 0.05), nor was there a difference in SEVR across quartiles of DBP in CAD patients (P = 0.07) or control subjects (P = 0.14). After adjustment for age and height, associations between DBP and SEVR in control subjects (r = 0.185; P = 0.03) and CAD patients (r = 0.204; P = 0.02) were attenuated (P = 0.07 and P = 0.11, respectively). There were no significant relationships between DBP and central hemodynamics (P > 0.05 for all). At peak dobutamine stress, SEVR was significantly reduced in patients with inducible ischemia vs. those with nonischemic response (84 ± 17 vs. 101 ± 22%; P = 0.01). However, DBP was not significantly different (65 ± 14 vs. 67 ± 15 mm Hg; P = 0.32).

CONCLUSIONS
Brachial DBP is a poor marker of subendocardial perfusion. The J-curve relationship between DBP and mortality is unlikely attributable to reduced myocardial perfusion or adverse central hemodynamics.

Keywords. blood pressure; hypertension; ischemia; left ventricle; pressure waveform analysis; pulse pressure; subendocardial viability ratio.

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Multiple large studies have identified a J-curve relationship between brachial diastolic blood pressure (DBP) and cardiovascular mortality.1–4 The level of risk appears to increase with DBP ≤70 mm Hg, and this is particularly evident in the elderly and those with coronary artery disease (CAD).1–4 The mechanisms underlying this association are unknown, although many investigators have speculated that low brachial DBP may predispose to myocardial ischemia due to inadequate coronary filling pressures.1–3,5–7 This theory, based on the diastolic predominance of microvascular perfusion, has never been tested and assumes exhaustion of coronary vasodilator reserve at this level of driving pressure. In a normal heart, the coronary circulation autoregulates to maintain blood flow across a wide range of local mean perfusion pressures to as low as 60 mm Hg.5–10 Furthermore, brachial DBP is likely to only be a crude estimation of myocardial perfusion because it represents a single pressure point nadir in the cardiac cycle. Indeed, coronary blood flow begins much earlier in the cardiac cycle, immediately after closure of the aortic valve at end-systolic pressure, which is much higher than brachial DBP (e.g., >30 mm Hg).11,12 Thus, true myocardial perfusion is more a function of pressure and time during diastole.

The dependence of myocardial perfusion on diastolic pressure and time underpins the quantification of the area under the aortic diastolic (DPTI) and systolic (TTI) pressure–time curves as reliable estimates of myocardial perfusion and oxygen consumption, respectively.13,14 The ratio of DPTI/TTI (termed the subendocardial viability ratio (SEVR)) is related to subendocardial/subepicardial blood flow ratio and thus analogous to subendocardial perfusion.14 SEVR can be measured noninvasively by radial applanation tonometry11 and may provide a useful technique to explore the relationship between DBP and subendocardial perfusion (and ischemia) in large populations. The first aim of this study was to test the hypothesis that low DBP is a marker of poor myocardial perfusion (through correlation of DBP with SEVR) in a group of individuals without a prior cardiovascular event compared with those with established CAD. In these participants, our second aim was to examine the relation between DBP and...
central hemodynamic parameters that may help to explain the increased mortality risk associated with low DBP (i.e., aortic stiffness, central pulse pressure (PP), and augmentation index). In our third aim, we sought to determine the brachial DBP and SEVR response to myocardial ischemia induced during dobutamine stress echocardiography (DSE). Although ischemia during DSE is related to myocardial demand, according to J-curve theory, the presence of low DBP should be a contributor because of insufficient myocardial supply. However, we hypothesized that this would not be the case and that DBP would not be associated with SEVR at rest or during conditions of induced ischemia.

METHODS

Study participants and protocol

Participants for the first and second aims of this study were drawn from a large Australian population-based cohort who were randomly identified from the electoral roll. Of the participants of this study, all 134 subjects with known CAD (confirmed by a functional or anatomical coronary artery assessment and/or a coronary event) were included in this analysis. From the same cohort, 134 individuals without a prior cardiovascular event (control subjects) were stratified by sex and then matched by the closest age to each of the 134 CAD patients to minimize the potential for selection bias. All subjects underwent assessment including measurement of brachial BP and radial applanation tonometry for assessment of aortic waveform characteristics, including SEVR (see Figure 1 for example).

For the third aim, 50 consecutive patients with suspected CAD undergoing standard, clinically indicated diagnostic dobutamine stress echocardiography at the Princess Alexandra Hospital, Brisbane, Australia, were studied. These patients were enrolled for evaluation of inducible myocardial ischemia but were considered unable to exercise sufficiently using exercise treadmill protocols. Each of these participants underwent measurement of brachial BP and radial applanation tonometry (using the same technique to derive SEVR as per aim 1) at the time of assessment of inducible myocardial ischemia by DSE. Measures were recorded under baseline conditions and at peak pharmacological stress (30–40 µg/kg/min dobutamine ± atropine). Three patients were excluded from analysis because of baseline wall motion abnormalities. At the time of recording the BP and tonometry measures, the status of each participant with respect to CAD or ischemic response to dobutamine was unknown to the person recording the data. Ethics approval was obtained from local institutions, and research procedures were carried out in accordance of the Declaration of Helsinki (2000).

Blood pressure, radial applanation tonometry, and aortic stiffness

For the first and second aims, brachial systolic blood pressure (SBP) and DBP were obtained in the seated position by a trained technician after a period of 10 minutes rest. The average of 2 measures was recorded as the BP value. For the third aim, BP was recorded as the average of 2 measurements in the supine position, made using an automated device (GE Healthcare, DinamapPlus; Critikon, Sydney) under baseline conditions and at peak dobutamine stress. In all participants for each study aim, central BP parameters were estimated using hand-held radial applanation

![Figure 1. Example of central (aortic) pressure waveform. P1 and P2 represent the first and second systolic peaks respectively, TTI is the tension–time index (area under the systolic pressure–time integral), and DPTI is the diastolic pressure–time integral (area under the diastolic pressure–time integral) both measured from 0 mm Hg pressure.](https://academic.oup.com/ajh/article-abstract/26/4/557/190387)
tonometer linked to software with a generalized transfer function (SphygmoCor 8.1; AtCor Medical, Sydney, Australia) that has been shown to be valid and reproducible under modified hemodynamic conditions. All measures were performed in the supine position in duplicate immediately following brachial BP recordings. The average of the brachial BP measures (SBP and DBP) was used to calibrate the radial pressure waveform. Figure 1 depicts a central pressure waveform. Augmentation pressure was calculated from the central pressure waveform as \( P_2 - P_1 \) (mm Hg) and then expressed as a percentage of the central PP (SBP – DBP) to define augmentation index. TTI was calculated as the area under the systolic portion of the central pressure curve from the foot of the waveform to the incisura at end systole and closure of the aortic valve. DPTI was calculated as the area under the diastolic portion of the central pressure curve from the incisura to end diastole. SEVR was calculated as the ratio of DPTI/TTI \( \times 100 \) (%) as an analogue of subendocardial perfusion. SEVR values below 60%–80% have been shown to be representative of impaired subendocardial perfusion and may be indicative of ischemia. Pulse wave timing (Tr) was calculated as the time (in milliseconds) from the beginning of the systolic upstroke to the first inflection point. Aortic stiffness was measured through carotid–femoral pulse wave velocity (PWV) and applanation tonometry (SphygmoCor 8.1; AtCor Medical). Sequential electrocardiogram-gated waveforms were acquired in the supine position at the carotid and femoral artery sites as per guidelines.

Dobutamine stress echocardiography

DSE was performed by standard clinical technique using the dobutamine–atropine protocol. All echocardiography images were obtained using the parasternal long and short axis and apical two- and four-chamber views. All patients were under continuous echocardiography and ECG monitoring before and during infusion of dobutamine at doses of 5, 10, 20, 30, and 40 ml/kg/min. The test was terminated at the onset of severe side effects, severe chest pain or ischemia, or at the completion of the protocol. If patients did not reach a heart rate of 85% of their age-predicted maximum at maximal dose, atropine (0.25 mg/min) was administered to a total of 1 mg. Results were interpreted offline by 2 trained cardiologists blinded to the DBP and aortic waveform data. Ischemia was defined by identification of wall motion abnormalities on DSE. The wall motion score index was determined by the sum of the score divided by the number of segments using the 16-segment model, as per American Society of Echocardiography recommendations. Results were reported as normal if no wall motion abnormalities were identified at >85% of age-predicted maximum heart rate. End-diastolic and end-systolic volumes, stroke volume, and ejection fraction were measured at baseline and peak stress.

Statistical analysis

All data were analyzed using SPSS for windows software version 17.0 (SPSS, Chicago, IL). Data are expressed as mean ± SD unless otherwise stated. Differences in patient characteristics for continuous variables were analyzed using independent t tests, whereas hemodynamic variables were assessed by multiple linear regression correcting for diabetes, hyperlipidemia, and use of antihypertensive medications. Analysis of SEVR, aortic PWV, central PP, and augmentation index between quartiles of DBP were analyzed by 1-way analysis of variance. In Table 2 and Table 3, multiple linear regression analysis using the enter method correcting for age and smoking history was undertaken. All categorical variables were compared by the \( \chi^2 \) test for independence. Pearson product moment correlations were performed to assess relationships between variables and adjusted for possible confounding variables (age, height, diabetes, hyperlipidemia, and use of antihypertensive medications) using partial correlation analysis. A logistic regression model using the forced entry method was undertaken to determine univariable predictors of myocardial ischemia. A multivariable model was then constructed to assess the independent utility of univariable predictors. Overall predictive value of the multivariable model was assessed using the Hosmer–Lemeshow \( \chi^2 \) statistic and the positive and negative predictive values. Statistical significance was defined as \( P < 0.05 \).

RESULTS

Relationship between DBP and SEVR: Control subjects vs. CAD patients

The clinical and hemodynamic characteristics of participants with respect to the first and second aims of the study are outlined in Table 1. Patients with CAD were closely matched with control subjects for age, sex, body mass index, and height. There were also no significant differences in percentage of current smokers between control subjects and CAD patients. There was, however, a greater percentage of CAD patients with diabetes, hyperlipidemia, and using antihypertensive medication (DBP < 0.05 for all), DBP was not significantly different between the control and CAD patients (DBP > 0.05), and there were no significant between-group differences in any of the pressure waveform variables, including central DBP, TTI, DPTI, and SEVR (DBP > 0.05 for all). These comparisons remained nonsignificant after adjustment for diabetes, hyperlipidemia, and antihypertensive medication (DBP > 0.05 for all). There was a weak but significant correlation between brachial DBP and SEVR in both the control subjects (r = 0.185; \( P = 0.03 \)) and those with CAD (r = 0.204; \( P = 0.02 \)) as illustrated in Figure 2 (panel A). However, after adjustment for age and height, this relationship was no longer significant in control subjects or patients with CAD (DBP > 0.05 for both).

There was no significant correlation between central DBP and SEVR in control subjects (r = 0.150; \( P = 0.08 \)), and this relationship was of borderline significance in those with CAD (r = 0.169; \( P = 0.05 \)). The relationship between central DBP and SEVR in both populations was not significant after adjustment for age and height (DBP > 0.05 for both) (Figure 2, panel B). Participants were divided into quartiles of brachial DBP (quartile 1 (Q1), ≤73 mm Hg; quartile 2 (Q2), 74–81 mm Hg; quartile 3 (Q3), 82–88 mm Hg; quartile 4 (Q4), ≥89 mm Hg). SEVR was not significantly different across quartiles in
control subjects (P = 0.14) or in those with CAD (P = 0.07) (Figure 3).

Relation between brachial DBP and aortic PWV, central PP, and augmentation index

Aortic PWV was not significantly associated with brachial DBP in control subjects or CAD patients (r = 0.14, P = 0.11; and r = 0.02, P = 0.86, respectively) nor were there any significant differences for aortic PWV across quartiles of brachial DBP in control subjects (Q1 = 10.3 ± 1.9 m/s; Q2 = 10.7 ± 2.3 m/s; Q3 = 10.2 ± 2.6 m/s; Q4 = 11.3 ± 2.3 m/s; P = 0.20) or CAD patients (Q1 = 11.2 ± 2.6 m/s; Q2 = 11.0 ± 2.6 m/s; Q3 = 10.8 ± 2.9 m/s; Q4 = 11.4 ± 2.6 m/s; P = 0.87). Central PP was not significantly associated with brachial DBP in control subjects or CAD patients (r = −0.03, P = 0.71; and r = 0.02, P = 0.86, respectively) nor were there any significant differences for central PP across quartiles of brachial DBP in control subjects (Q1 = 61 ± 18 mm Hg; Q2 = 56 ± 17 mm Hg; Q3 = 56 ± 14 mm Hg; Q4 = 59 ± 16 mm Hg; P = 0.59) or CAD patients (Q1 = 63 ± 22 mm Hg; Q2 = 60 ± 17 mm Hg; Q3 = 62 ± 14 mm Hg; Q4 = 60 ± 18 mm Hg; P = 0.82). Augmentation index was not significantly associated with brachial DBP in control subjects or CAD patients (r = 0.17, P = 0.06; and r = 0.16, P = 0.06, respectively) nor were there any significant differences for augmentation index across quartiles of brachial DBP in control subjects (Q1 = 31% ± 9%; Q2 = 31% ± 10%; Q3 = 34% ± 10%; Q4 = 35% ± 8%; P = 0.20) or CAD patients (Q1 = 31% ± 11%; Q2 = 32% ± 6%; Q3 = 35% ± 8%; Q4 = 33% ± 7%; P = 0.21).

Brachial DBP and SEVR response to myocardial ischemia induced during DSE

The clinical and echocardiography characteristics of patients who underwent DSE are outlined in Table 2. Patients with inducible ischemia were older and more likely to have a smoking history than those without inducible ischemia (P < 0.05). There were no differences in use of antihypertensive medications or presence of diabetes (P > 0.05). All echocardiography variables were similar between patients with and without inducible ischemia after correction for age and smoking history (P > 0.05), except for ejection fraction at peak stress, which was significantly greater in individuals without inducible ischemia (P < 0.05), and end systolic volume, which was greater in individuals with inducible ischemia (P < 0.05). Hemodynamic responses to dobutamine stress are outlined in Table 3. Under baseline conditions,
Figure 2. Pearson correlations. (a) the relationship between the subendocardial viability ratio and brachial diastolic blood pressure and (b) the relationship between the subendocardial viability ratio and central diastolic blood pressure in both coronary artery disease patients (n = 134; open circles, solid line) and control subjects (n=134; closed circles, broken line). *Correlation coefficients and P values are adjusted for age and height.
conditions, there were no significant differences in DBP or any other hemodynamic variable between patients with and without inducible ischemia before or after adjustment for age and smoking history ($P > 0.05$ for all). At peak stress, there was no significant difference in DBP between patients with and without inducible ischemia ($P > 0.05$). However, the SEVR was significantly lower at peak stress in patients with inducible ischemia before and after adjustment for age and smoking history ($P < 0.05$). There were no other significant differences between hemodynamic variables at peak stress or in the change values from baseline in both ischemic and nonischemic individuals ($P > 0.05$ for all). Table 4 presents the results of the logistic regression modeling. Significant predictors of inducible ischemia were age and SEVR at peak stress ($P < 0.05$ for both). Both univariable predictors remained significant in the multivariable analysis ($P < 0.05$), and the overall model was an excellent predictor of inducible ischemia (Hosmer–Lemeshow $\chi^2 = 6.26$; $P = 0.51$; positive predictive value = 82%; negative predictive value = 72%).

**DISCUSSION**

The novel findings of this study were, first, that brachial DBP was a poor correlate of the pressure waveform marker of subendocardial perfusion and ischemia, SEVR. This finding was evident in a large cohort of individuals without a prior cardiovascular event as well as in CAD patients closely matched for age and sex. Second, we found no significant relationships between brachial DBP and central hemodynamic variables, including aortic stiffness, central PP, and augmentation index. Finally, we have demonstrated that brachial DBP was not significantly altered under conditions of myocardial ischemia when SEVR was significantly reduced in a group of patients undergoing DSE. Taken together, these findings indicate that brachial DBP is a poor marker of myocardial perfusion and low brachial DBP is not associated with adverse central hemodynamics.

Importantly, our results suggest that the J-curve relationship between brachial DBP and mortality is unlikely to be related to poor myocardial perfusion per se.
The J-curve relationship between brachial DBP and cardiovascular mortality is particularly evident in the elderly and in those with CAD. There is also evidence that in hypertensive individuals, aggressive lowering of BP through antihypertensive therapy may predispose to increased cardiovascular risk due to low DBP. Although it is important to note that the cardiovascular risk associated with a low diastolic BP may be confounded in the presence of left ventricular (LV) dysfunction, there is relative acceptance of the existence of J-curve. Despite this, there is no consensus on the pathophysiological mechanisms involved. One frequently purported mechanism is that a low brachial DBP may lead to reduced perfusion pressure of the epicardial arteries, thus predisposing to myocardial ischemia. However, to our knowledge, there is no evidence that brachial DBP is a surrogate of myocardial perfusion. Although

### Table 2. Clinical and echocardiography characteristics of patients undergoing dobutamine stress echocardiography with and without inducible myocardial ischemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonischemic (n = 22)</th>
<th>Ischemic (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59 ± 10</td>
<td>65 ± 9</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>16 (73)</td>
<td>22 (88)</td>
<td>0.18</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29 ± 5</td>
<td>28 ± 6</td>
<td>0.49</td>
</tr>
<tr>
<td>Baseline end diastolic volume, ml</td>
<td>81 ± 27</td>
<td>89 ± 41</td>
<td>0.31¹</td>
</tr>
<tr>
<td>Peak stress end diastolic volume, ml</td>
<td>55 ± 18</td>
<td>69 ± 37</td>
<td>0.12¹</td>
</tr>
<tr>
<td>Baseline end systolic volume, ml</td>
<td>33 ± 17</td>
<td>38 ± 26</td>
<td>0.22¹</td>
</tr>
<tr>
<td>Peak stress end systolic volume, ml</td>
<td>17 ± 9</td>
<td>29 ± 27</td>
<td>0.04¹</td>
</tr>
<tr>
<td>Baseline ejection fraction, %</td>
<td>61 ± 9</td>
<td>60 ± 9</td>
<td>0.22¹</td>
</tr>
<tr>
<td>Peak stress ejection fraction, %</td>
<td>71 ± 9</td>
<td>64 ± 14</td>
<td>0.03¹</td>
</tr>
<tr>
<td>Baseline stroke volume, ml</td>
<td>48 ± 14</td>
<td>50 ± 18</td>
<td>0.64¹</td>
</tr>
<tr>
<td>Peak stress stroke volume, ml</td>
<td>38 ± 12</td>
<td>40 ± 14</td>
<td>0.72¹</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (24)</td>
<td>13 (54)</td>
<td>0.08</td>
</tr>
<tr>
<td>Smoking history, never/former/current</td>
<td>16 / 2 / 3</td>
<td>8 / 10 / 5</td>
<td>0.02</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>17 (77)</td>
<td>19 (83)</td>
<td>0.91</td>
</tr>
<tr>
<td>Lipid lowering medications</td>
<td>16 (72)</td>
<td>19 (76)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or No. (%).

¹Adjusted for age and smoking history by multiple linear regression.

### Table 3. Hemodynamic parameters of patients undergoing dobutamine stress echocardiography at baseline and peak stress

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Nonischemic</td>
<td>Ischemic</td>
</tr>
<tr>
<td>Brachial diastolic BP, mm Hg</td>
<td>69 ± 13</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Brachial systolic BP, mm Hg</td>
<td>134 ± 20</td>
<td>132 ± 25</td>
</tr>
<tr>
<td>Central diastolic BP, mm Hg</td>
<td>71 ± 14</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>Central systolic BP, mm Hg</td>
<td>121 ± 22</td>
<td>121 ± 19</td>
</tr>
<tr>
<td>Tension time index, mm Hg/s per min</td>
<td>2413 ± 727</td>
<td>2352 ± 426</td>
</tr>
<tr>
<td>Diastolic pressure–time integral, mm Hg/s per min</td>
<td>3116 ± 528</td>
<td>2942 ± 419</td>
</tr>
<tr>
<td>Subendocardial viability ratio, %</td>
<td>139 ± 40</td>
<td>127 ± 19</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72 ± 14</td>
<td>69 ± 8</td>
</tr>
<tr>
<td>Ejection duration, ms</td>
<td>311 ± 21</td>
<td>324 ± 23</td>
</tr>
<tr>
<td>Pulse wave timing (Tr), ms</td>
<td>138 ± 9</td>
<td>139 ± 11</td>
</tr>
<tr>
<td>Central PP, mm Hg</td>
<td>50 ± 16</td>
<td>54 ± 15</td>
</tr>
<tr>
<td>Brachial PP, mm Hg</td>
<td>63 ± 20</td>
<td>60 ± 15</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation.

Abbreviations: BP, blood pressure; PP, pulse pressure.

¹Adjusted for age and smoking history by multiple linear regression.
LV subendocardial blood flow largely occurs during diastole, to maintain constant myocardial blood flow in the presence of low perfusion pressure, subendocardial autoregulation causes dilation of the deep-lying microvasculature to occur. The contractile nature of the myocardium ensures that this dilation is maximal throughout diastole, when the compressive forces exerted on the subendocardial vessels are removed, which allows blood to be drawn into the epicardial vessels though a suction wave generated by microcirculatory decompression. On the other hand, during systole the coronary microcirculation is compressed and global blood flow into the coronary circulation is reduced. Despite this, there remains some epicardial blood flow during systole, which is facilitated from contraction of the LV lumen and generates a forward-traveling pushing wave that directs blood into the coronary vessels. Negative systolic flow (backflow into the ascending aorta) may even occur when mean coronary perfusion pressures are severely reduced. Furthermore, the phasic components of coronary flow and the systolic–diastolic variations have been described as not solely due to varying resistances but rather by an active intramyocardial pump action. Thus, given the complex physiological interplay between pressure and flow, myocardial perfusion cannot be assumed from a single pressure point at end diastole without due consideration of the coronary flow profile throughout the duration of both systole and diastole.

The work of Buckberg et al. almost 40 years ago, revealed that the ratio DPTI/TTI (the SEVR) is analogous to subendocardial oxygen supply and demand and thus coronary perfusion. It is known that myocardial ischemia may occur with disturbance to the oxygen balance in the LV subendocardium. We, therefore, suggested that if brachial DBP was a nonischemic response. Critically, if brachial DBP were a suitable marker of myocardial perfusion, then we should have observed a concomitant reduction in brachial DBP in patients with inducible ischemia at peak stress. However, DBP remained unchanged despite the reduction in SEVR and the induced ischemia. To our knowledge, such a finding has never been described before and highlights that brachial DBP is not analogous to myocardial perfusion and cannot be  to be more pronounced in CAD patients, in whom coronary stenosis may impair autoregulatory processes and coronary flow reserve in the presence of low perfusion pressures. Although the presence of LV hypertrophy may cause an upward shift in the lower range of coronary autoregulation, in the absence of significant stenosis, autoregulation remains effective over a large range of perfusion pressures, and coronary flow reserve only becomes exhausted (subendocardial vessels become maximally dilated) when coronary driving pressures reach a critical low point. Furthermore, SEVR was largely unchanged across quartiles of brachial DBP, even at DBP values <70 mm Hg (a value in the range suggested as the nadir of the DBP and mortality J-curve, in both control subjects and CAD patients. Thus, our data suggest that myocardial ischemia is unlikely to be related to low brachial DBP values in the physiological range shown to correlate with increased CV mortality. Although some investigators have suggested that vascular parameters including elevated aortic stiffness and widened PP may contribute to the increased mortality risk associated with low DBP, we found no relationship of these parameters with brachial DBP in this study.

Further evidence for the lack of connection between brachial DBP and myocardial perfusion was highlighted by our results in the setting of dobutamine stress testing. With the positive chronotropic effect of dobutamine, it was expected that diastolic duration would shorten, thus lowering the DPTI (and SEVR) and potentially contributing to an ischemic response. In agreement with this theory, SEVR at peak dobutamine stress was significantly reduced in patients in whom ischemia was induced compared with those with a nonischemic response. Critically, if brachial DBP were a suitable marker of myocardial perfusion, then we should have observed a concomitant reduction in brachial DBP in patients with inducible ischemia at peak stress. However, DBP remained unchanged despite the reduction in SEVR and the induced ischemia. To our knowledge, such a finding has never been described before and highlights that brachial DBP is not analogous to myocardial perfusion and cannot be
the prevailing mechanism to explain the DBP J-curve relationship with mortality.

Noninvasive, rather than direct, measures of myocardial perfusion were used in this study. However, SEVR derived from arterial tonometry has been directly compared with invasive measurement and shown to be a valid technique under conditions of rest and elevated heart rate, whereas others have shown SEVR to be highly correlated with subendocardial perfusion. On the other hand, a study by Smulyan et al. showed that although central systolic BP acquired by radial artery tonometry closely approximated ascending aortic systolic pressure at low dobutamine doses, this was underestimated at higher infusion rates. This potential error may have resulted in a systematic underestimation of true SEVR at higher dobutamine doses. Although our study population was representative of a wide range of brachial DBP values, there were few participants with extremely low brachial DBP (e.g., <50–60 mm Hg), and it could be argued that a stronger relationship between SEVR and brachial DBP may have been evident in these participants. Nevertheless, coronary autoregulation still occurs in the presence of mean perfusion pressures approximating 60 mm Hg or less, and studies describing the brachial DBP J-curve relationship with mortality have highlighted that the nadir of the brachial DBP J-curve is at or below 70 mm Hg. Thus if increased risk associated with low brachial DBP was indicative of myocardial ischemia, we should have noted a relationship with SEVR in our lowest quartile of DBP (<73 mm Hg), but this was not the case. This study was not designed to assess J-curve relationships, and, as such, the sample sizes are relatively small. This may have limited the power to determine whether there was an effect modification by age and sex on the association of a low DBP with SEVR and adverse central hemodynamics. Finally, we cannot rule out the possibility that vasoactive medications or the presence of cardiovascular risk factors may have influenced the observed hemodynamic comparisons between control subjects and CAD participants.

The pathophysiological mechanisms underlying the J-curve relationship between DBP and mortality are incompletely understood. The current belief suggests that poor myocardial perfusion as a result of low brachial DBP plays a significant role underlying the increased mortality risk. The results of this study refute this assertion as a plausible physiological explanation because we have demonstrated that brachial DBP is a poor marker of myocardial perfusion and ischemia. Indeed, the coronary vasculature is capable of autoregulation across a wide range of perfusion pressures, and ascribing causality of myocardial ischemia from a single pressure point in the cardiac cycle (low DBP) appears to be a simplification of the complex physiological interplay involved in coronary hemodynamics. Our results also demonstrated that low DBP was not associated with adverse central hemodynamic variables, including increased aortic stiffness, widened central PP, or elevated augmentation index. Thus, further effort should be directed toward exploring other potential mechanisms contributing to the increased risk associated with low DBP to ultimately allow appropriate and targeted therapeutic strategies to be employed.

**DISCLOSURE**

Dr Sharman has received research funding from AtCor Medical. All other authors declared no conflict of interest.

**REFERENCES**


