

# The clinical usefulness of central hemodynamics to evaluate diastolic dysfunction in subjects without hypertension

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**Objective:** Diastolic dysfunction is associated with increased arterial stiffness in patients with hypertension. However, the role of arterial stiffness in diastolic dysfunction in subjects without hypertension has not been fully established.

**Materials and methods:** A total of 287 subjects (male:female ratio 121:166, mean age 53.0±14.4 years) without hypertension or any heart disease who simultaneously received transthoracic echocardiography and noninvasively semiautomated radial artery applanation tonometry (with an Omron HEM-9000AI) in the Department of Internal Medicine, St Vincent's Hospital, from July 2011 to September 2012, were enrolled in this study.

**Results:** A total of 147 subjects (male:female ratio 59:88, mean age 61.7±9.9 years), representing 51.2% of the 287 subjects, had diastolic dysfunction (defined as abnormal relaxation pattern of mitral inflow). There were significant differences in systolic blood pressure (BP), pulse pressure, late systolic peak pressure (SBP<sub>2</sub>), and radial augmentation index (RaAix) between normal diastolic function and diastolic dysfunction. ΔBP was defined as systolic BP minus SBP<sub>2</sub>, because of the difference in systolic BP between the two groups. ΔBP (odds ratio [OR] 1.059, 95% confidence interval [CI] 1.005–1.115; *P*=0.032) and RaAix (odds ratio 1.027, 95% CI 1.009–1.044, *P*=0.003) were associated with diastolic dysfunction. A receiver operating-characteristic curve showed that ΔBP (area under the curve 0.875, 95% CI 0.832–0.911) and RaAix (area under the curve 0.878, 95% CI 0.835–0.914) were associated with diastolic dysfunction.

**Conclusion:** We found that ΔBP and increased RaAix were associated with diastolic dysfunction in subjects without hypertension after adjustment for age and sex. Therefore, it is suggested that noninvasive estimation of central BP may be useful to reflect diastolic dysfunction in subjects with normal peripheral BP.

**Keywords:** central blood pressure, augmentation index, diastolic dysfunction

## Introduction

Diastolic dysfunction is the cardinal component for the diagnosis of heart failure with preserved left ventricular ejection fraction (LVEF). It has been suggested that patients who have heart failure with preserved LVEF tend to be older, female, and have a history of hypertension. Diastolic function is inversely correlated to arterial afterload, which is mainly determined by wave reflections arising from peripheral arteries and returning to the proximal aorta during mid-to-late systole.<sup>1,2</sup> Diastolic dysfunction is associated with increased arterial stiffness in patients with hypertension. In adults with hypertension, early return of the reflected wave may lead to increasing LV afterload and central pulse pressure (PP), which in turn promote LV hypertrophy and subendocardial ischemia.<sup>3</sup> When the arteries stiffen, accelerating the reflected wave increased central PP.<sup>4</sup>

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Systolic blood pressure (BP) is amplified when moving from the aorta to the periphery, unlike diastolic BP and mean pressures. Central BP relative to peripheral BP is significantly higher in people at risk of heart failure or disease compared with healthy people.<sup>5</sup> Central BP or PP appears to be clinically more useful than brachial BP measurement, because the reduction of wave reflection is important for LV mass regression.<sup>6</sup> It has been demonstrated that wide variation in brachial–aortic systolic BP difference occurs between patients with similar brachial systolic BP, especially for patients with cardiovascular risk factors.<sup>7</sup> However, the role of brachial–aortic systolic BP difference in diastolic dysfunction in subjects without hypertension is unclear.

The aim of the present study was to elucidate the association between brachial–aortic systolic BP difference and LV diastolic dysfunction in subjects without hypertension.

## Materials and methods

### Study population

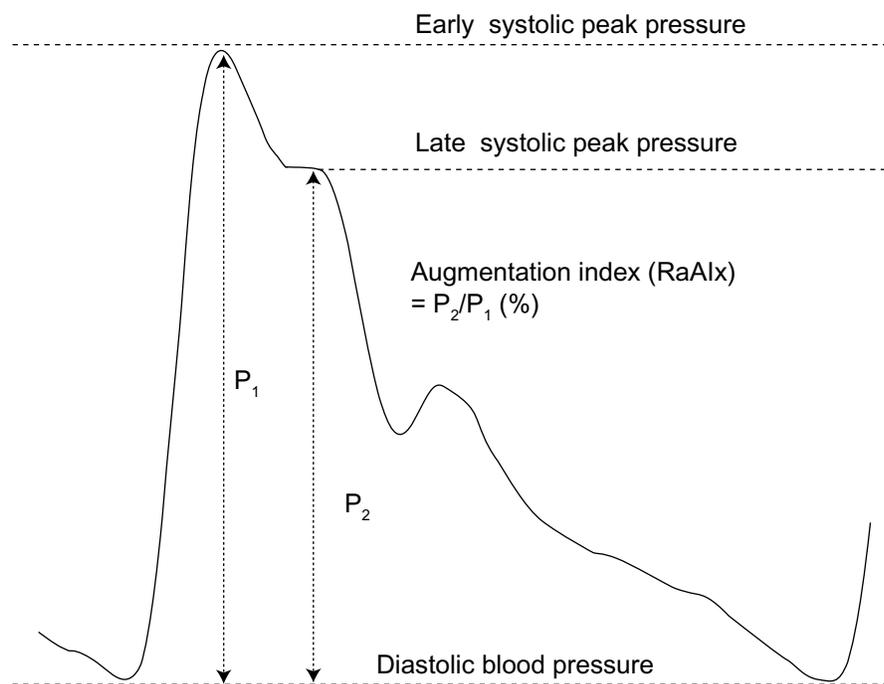
The study population consisted of subjects referred for echocardiography between July 2011 and September 2012. Among subjects who simultaneously underwent two-dimensional Doppler echocardiography and noninvasively semiautomated radial artery applanation tonometry (HEM-9000AI; Omron Healthcare, Kyoto, Japan) in the Department of Internal Medicine, St Vincent's Hospital, subjects without hypertension or any heart disease were enrolled in this study. Exclusion criteria included 1) history of hypertension or antihypertensive medication; 2) history or findings of cardiovascular disease, including heart-failure symptoms or systolic dysfunction (LVEF  $\leq$  50%), significant valvular heart disease (ie, greater than mild valvular insufficiency or stenosis), hypertrophic cardiomyopathy, and evidence of coronary artery disease (defined as history and/or treatment of angina and/or myocardial infarction, history of coronary artery revascularization procedures and/or coronary angiography with  $>$ 50% stenosis in one or more of the major coronary arteries, and/or regional wall motion abnormalities on rest echocardiography); 3) serum creatinine level  $>$ 1.4 mg/dL; 4) pregnant or lactating; 5) major systemic illness (ie, chronic inflammatory disease, active malignancy, and others); and 6) current atrial fibrillation (because radial tonometry is not accurate in these patients). There was no industry involvement in the design, conduct, or analysis of the study. The ethics committee approved the use of clinical data for this study, and all patients provided written informed consent.

### Measurement of central BP and brachial BP

All measurements were conducted in a quiet room kept at a constant temperature. After at least 10 minutes' rest and with the subject seated, brachial BP was measured using an HEM-907 automatic cuff oscillometric device (Omron Healthcare). The average of two readings was used to determine systolic BP, diastolic BP, mean arterial pressure, and PP. Next, the radial pulse wave was recorded by using an HEM-9010AI automated applanation tonometer (Omron Healthcare). This device consists of a sensor unit, pulse-measurement unit, and personal computer. The wristwatch-shaped sensor unit has a pressure sensor with an array of multiple 40 microtransducer elements on its inner surface. Once the sensor is placed on the left wrist over the radial artery, the device automatically flattens the artery, adjusts the applanation hold-down pressure, and selects an optimal sensing element to record the pulse wave appropriately. The obtained pressure signals are digitized at 500 Hz inside the pulse-measurement unit and then transmitted to the personal computer.<sup>8</sup> In this study, radial arterial pressure waveforms were recorded for 30 seconds. The radial augmentation index (RaAIx) (Figure 1) was calculated as follows: (second peak radial systolic pressure [SBP<sub>2</sub>] – diastolic pressure)/(first peak radial systolic pressure – diastolic pressure)  $\times$  100.<sup>9</sup> Systemic hypertension was defined as systolic pressure  $\geq$  140 mmHg and/or diastolic pressure  $\geq$  90 mmHg, based on more than three measurements or current use of antihypertensive drugs. The brachial–aortic systolic BP difference ( $\Delta$ BP) was calculated as systolic BP minus SBP<sub>2</sub>, because of differences in systolic BP.

### Clinical and biochemical assessment

Blood specimens were collected after a 12- to 14-hour fast (8 pm to 9.30 am) to reduce the influence of circadian variation. Total cholesterol and triglyceride concentrations were measured using standard enzyme methods. High-density lipoprotein cholesterol was measured after precipitation of very-low-density lipoproteins and low-density lipoprotein with phosphotungstic acid, and low-density lipoprotein was calculated using the Friedewald formula. Fasting glucose levels were enzymatically determined by the hexokinase method. A blood sample from every patient was drawn and centrifuged within 30 minutes. The serum samples were stored at  $-80^{\circ}\text{C}$ , and high-sensitivity C-reactive protein was determined using an immunoturbidity assay system (Liatest; Stago, Asnières-sur-Seine, France), with an interassay variability coefficient of variation of 6.25%.



**Figure 1** Definition of radial augmentation index (RaIx).  $P_1$  indicates the amplitude of the early systolic peak pressure, and  $P_2$  indicates the amplitude of the late systolic peak pressure. The radial AI was defined as the ratio of  $P_2$  to  $P_1$ .

## Transthoracic Doppler echocardiography

Two-dimensional, M-mode, pulsed Doppler, and tissue Doppler echocardiography were performed using a Vivid Seven ultrasound machine (GE Healthcare, Horten, Norway) with a 2.5 MHz transducer. Standard two-dimensional measurements (LV diastolic and systolic dimensions, ventricular septum and posterior wall thickness, and left atrial volume) were obtained as recommended by the American Society of Echocardiography.<sup>10</sup> From the apical window, a 1–2 mm pulsed Doppler sample volume was placed at the mitral valve tip, and mitral flow velocities from five to ten cardiac cycles were recorded. The mitral inflow velocities were traced, and the following variables were obtained: peak velocity of early diastolic mitral inflow (E), late diastolic mitral inflow (A), and deceleration time of the E velocity.<sup>11</sup> Stroke volume was measured from the LV outflow-tract diameter and the pulse-wave Doppler signal. Mitral annular velocities were measured by Doppler tissue imaging using the pulse-wave mode. The filter was set to exclude high-frequency signals, and the Nyquist limit was adjusted to a range of 15–20 cm/second. Gain and sample volume were minimized to allow a clear tissue signal with minimal background noise. Early diastolic mitral annular ( $E_m$ ), late diastolic ( $A_m$ ), and systolic velocities ( $S_m$ ) of the mitral annulus were measured from the apical four-chamber view with a 2–5 mm sample volume placed at the septal corner of the mitral annulus. According to the Euro-

pean Association of Echocardiography/American Society of Echocardiography recommendations<sup>11</sup> for the evaluation of LV diastolic function by echocardiography, there are three grades of diastolic dysfunction. In this study, all patients with diastolic dysfunction were grade I, or the abnormal relaxation pattern of mitral inflow.

## Statistical analyses

Continuous variables are presented as means  $\pm$  standard deviation, and categorical variables are presented as absolute and relative frequencies (%). Data for groups of diastolic function were compared using the Wilcoxon rank-sum test for continuous variables. Categorical variables were compared using the  $\chi^2$  test. The independent predictors of diastolic dysfunction were examined with multivariate logistic regression analysis after adjustment. All reported  $P$ -values were two-sided, and  $P$ -values  $\leq 0.05$  were considered to indicate statistical significance. A receiver operating-characteristic (ROC) curve was generated to determine the predictive power of central hemodynamics for diastolic dysfunction. All statistical analyses were conducted with SAS 9.1 statistical software (SAS Institute, Cary, NC, USA).

## Results

The baseline characteristics and comparison between normal and abnormal relaxation for diastolic function with regard to

clinical variables of the 287 subjects without hypertension or any structural heart disease are shown in Table 1. There were significant differences in age and body mass index (BMI) between the groups. There were no significant differences in LV end-systolic, end-diastolic dimensions, and LV ejection fraction between the two groups (Table 1). Subjects with diastolic dysfunction displayed a higher LV mass index, higher E/Em ratio, larger left atrial volume index, lower Em velocity of the mitral annulus, lower Sm and Em velocity, and higher deceleration time.

Table 2 shows the comparison of peripheral and central hemodynamics parameters and the indices of arterial stiffness according to diastolic function. There were significant differences in systolic BP, PP, SBP<sub>2</sub>, RaAIx, and ΔBP between the two groups. After adjusting for age, sex, and systolic BP, diastolic dysfunction correlated with heart rate, SBP<sub>2</sub>, and RaAIx. The results after adjustment for systolic BP seemed to be multicollinear only for SBP<sub>2</sub>, because SBP<sub>2</sub> was calculated by using directly measured systolic BP. In univariate analysis, diastolic dysfunction was associated with age (odds ratio [OR] 1.158, 95% confidence interval [CI] 1.119–1.199;  $P < 0.0001$ ),

BMI (OR 1.116, 95% CI 1.037–1.202;  $P = 0.004$ ), SBP<sub>2</sub> (OR 1.027, 95% CI 1.012–1.043;  $P = 0.001$ ), RaAIx (OR 1.027, 95% CI 1.009–1.044;  $P = 0.002$ ), diabetes mellitus (OR 3.841, 95% CI 1.240–11.894;  $P = 0.021$ ), and PP (OR 1.029, 95% CI 1.006–1.052;  $P = 0.012$ ). However, diastolic dysfunction was not associated with sex (OR 1.186, 95% CI 0.742–1.895;  $P = 0.477$ ). In multivariate logistic analysis, ΔBP (OR 1.073, 95% CI 1.013–1.137;  $P = 0.017$ ) was associated with diastolic dysfunction after adjusting age, sex, BMI, and PP. RaAIx was associated with diastolic dysfunction after adjusting for sex (OR 1.029, 95% CI 1.011–1.048;  $P = 0.003$ ) and after adjusting for age, sex, and systolic BP (OR 1.027, 95% CI 1.009–1.044;  $P = 0.003$ ), in multivariate logistic analysis. The OR estimate was based on a 1% increase in RaAIx.

An ROC curve demonstrated an association of ΔBP with diastolic dysfunction after adjusting for age and sex (Figure 2A). ROC curves showed that RaAIx was associated with diastolic dysfunction after adjusting for age and sex (Figure 2B). ΔBP and RaAIx were good predictive factors for diastolic dysfunction in subjects without hypertension and heart disease after adjusting confounding factors.

**Table 1** Clinical characteristics and baseline echocardiography findings

Variables	Total, n=287	Normal, n=140	Abnormal relaxation, n=147	P-value
Age, years	53.0±14.4	43.8±12.7	61.7±9.9	<0.0001
Males	121 (42.2)	62 (44.3)	59 (40.1)	0.477
Body mass index, kg/m <sup>2</sup>	23.8±3.4	23.2±3.5	24.4±3.1	0.0006
Hemoglobin A <sub>1c</sub> , %	6.7±1.7	6.4±1.1	6.8±1.9	0.986
Total cholesterol, mg/dL	191.2±42.2	188.0±43.8	193.3±41.2	0.288
Triglyceride, mg/dL	115.4±80.6	110.7±68.2	118.5±88.3	0.715
High-density lipoprotein, mg/dL	45.7±13.9	46.5±13.1	45.1±14.5	0.192
Low-density lipoprotein, mg/dL	116.8±36.9	117.0±34.2	116.7±38.6	0.936
High-sensitivity CRP, mg/dL	0.9±2.4	0.5±1.3	1.3±2.9	0.183
Smoking	40 (16.8)	19 (16.2)	21 (17.4)	0.818
Diabetes mellitus	19 (7.0)	19 (7.0)		–
Echocardiography				
LVEDD, mm	46.3±4.0	46.7±4.0	46.0±4.0	0.253
LVESD, mm	29.2±3.3	29.5±3.5	29.0±3.2	0.566
LV mass index, g/m <sup>2</sup>	98.8±21.8	93.4±21.4	104.0±21.1	<0.0001
LV ejection fraction, %	63.9±4.0	64.1±3.7	63.6±4.2	0.273
LV filling pressure, E/Em	8.6±4.2	7.8±4.8	9.4±3.3	<0.0001
Left atrial volume index, mL/m <sup>2</sup>	25.7±12.3	23.3±12.4	28.1±12.0	0.008
Transmitral E-wave velocity, cm/second	67.4±17.2	77.6±13.7	57.7±14.4	<0.0001
Transmitral A-wave velocity, cm/second	68.1±18.6	58.9±16.4	76.7±16.3	<0.0001
Transmitral E-wave/A-wave velocity	1.057±0.376	1.362±0.287	0.764±0.152	<0.0001
Systolic tissue velocity, cm/second	7.7±1.5	8.3±1.5	7.2±1.4	<0.0001
Early diastolic tissue velocity, cm/second	8.7±3.2	11±2.8	6.5±1.6	<0.0001
Late diastolic tissue velocity, cm/second	9.3±1.9	8.8±1.8	9.8±1.7	<0.0001
Transmitral E-wave deceleration time, millisecond	200.7±44.0	182.0±36.7	218.3±43.2	<0.0001

**Note:** Data presented as n (%) or means ± standard deviation.

**Abbreviations:** CRP, C-reactive protein; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; E, peak velocity of early diastolic mitral inflow; Em, early diastolic mitral annular.

**Table 2** Peripheral and central hemodynamic parameters according to diastolic function

Variables	Total, n=287	Normal, n=140	Abnormal relaxation, n=147	P-value	P-value*
Peripheral, mmHg					
Systolic blood pressure (BP)	125.6±15.5	123.1±13.9	128.0±16.5	0.009	
Diastolic blood pressure	76.7±10.4	75.7±9.8	77.5±10.9	0.143	
Pulse pressure	49.1±10.9	47.4±9.8	50.6±11.6	0.013	
Heart rate, beats/minute	73.8±12.5	73.5±12.7	74.1±12.4	0.723	<0.0001
Central					
Late systolic peak pressure (SBP <sub>2</sub> )	115.1±16.4	111.6±15.5	118.4±16.6	0.0005	0.040
Radial augmentation index, %	78.1±14.2	75.5±15.3	80.6±12.5	0.002	0.009
ΔBP, mmHg	10.5±7.3	11.6±7.8	9.6±6.6	0.021	

**Notes:** \*Adjusted for age, sex, systolic BP. Data presented as n (%) or means ± standard deviation.

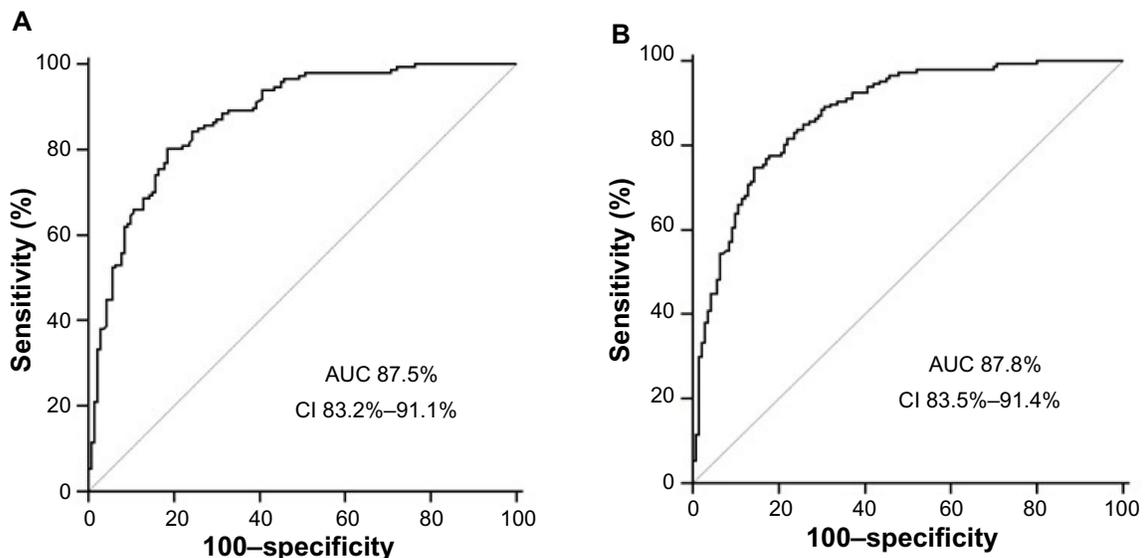
**Abbreviation:** ΔBP, brachial-aortic systolic BP difference.

## Discussion

The objective of the present study was to examine whether the difference in brachial–aortic systolic BP was associated with LV diastolic dysfunction in subjects without hypertension or any heart disease. The role of brachial–aortic systolic BP difference in diastolic dysfunction in subjects with similar and normal pressure of peripheral artery is contentious. The present study demonstrates that ΔBP was associated with diastolic dysfunction in subjects after adjusting for age, sex, BMI, and PP. The amplification of systolic BP when moving from the aorta to the periphery was correlated with diastolic dysfunction in subjects without hypertension. Noninvasive estimation of central BP by automated applanation tonometry is a simple and inexpensive test. Therefore, the measurement of central BP may play a useful role in reflecting diastolic dysfunction despite normal BP at the brachial artery.

The results of the present study are similar to those of an earlier report that central PP derived from the second shoulder of the radial waveform, which does not require a generalized transfer function to radial waves, is associated with cardiovascular target-organ changes independent of brachial BP.<sup>12</sup> Another study reported that arterial wave reflection was independently associated with incident cardiovascular events and strongly associated with incident congestive heart failure.<sup>13</sup> The Strong Heart Study demonstrated that noninvasively determined central PP was related more strongly to vascular hypertrophy, extent of atherosclerosis, and cardiovascular events than brachial BP in the general population.<sup>14</sup>

To our knowledge, diastolic dysfunction is associated with older age, female sex, and a history of hypertension. Despite similar peripheral PP, the central hemodynamics reflecting arterial stiffness differ between men and women.<sup>15</sup>



**Figure 2** A receiver-operating characteristic curve, showing that the difference in central and brachial blood pressure (A) and radial augmentation index (B) were associated with diastolic dysfunction after adjusting for age and sex.

**Abbreviations:** AUC, area under the curve; CI, confidence interval.

In this study, diastolic dysfunction was not associated with sex.

In the present study, subjects with diastolic dysfunction displayed higher RaAIx values than those without diastolic function. Diastolic dysfunction correlated with RaAIx after adjusting for age, sex, and systolic BP. The results of the present study were similar to those of an earlier report on the association between increased aortic and carotid arterial augmentation index (AI) and risk of cardiovascular disease.<sup>16</sup> AI was also correlated with age in healthy subjects.<sup>16</sup> Kohara et al demonstrated that radial AI can be a simple and easily obtainable index of vascular aging.<sup>9</sup>

There are some limitations to the present study. This study was cross-sectional, so the causal relationship between  $\Delta$ BP and diastolic dysfunction remains to be fully established by prospective studies. The study did not analyze whether subjects take antihypertensive medication because of no history of hypertension. However, disparities in central versus peripheral BP responses to vasoactive drugs have been reported,<sup>17,18</sup> and the individual responses to the medication were variable. Also, brachial systolic BP was relatively unchanged, whereas there was significant central systolic BP decrease.<sup>19</sup> AI was obtained directly from radial pressure waveforms instead of aortic or carotid pulse waves. However, RaAIx has been significantly associated with carotid AI in an adult population with a wide age range, and gives equivalent information to carotid AI measurements.<sup>20</sup>

In conclusion, differences in brachial and central BP and increased RaAIx were associated with diastolic dysfunction in subjects without hypertension after adjusting for age and sex. Therefore, it is suggested that noninvasive estimation of central BP may reflect diastolic dysfunction in subjects with normal peripheral BP.

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## Disclosure

The authors report no conflicts of interest in this work.

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