

# Increased Ambulatory Pulse Pressure Is a Strong Risk Factor for Coronary Endothelial Vasomotor Dysfunction

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| <b>OBJECTIVES</b>  | This study was aimed to determine the relationship between pulse pressure (PP) and coronary vasomotor dysfunction, a predictor of coronary events.                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>BACKGROUND</b>  | Pulse pressure is a strong risk factor for coronary artery disease (CAD). However, the mechanisms by which an increase in PP affects the pathogenesis of CAD are unclear.                                                                                                                                                                                                                                                                                                                                                                     |
| <b>METHODS</b>     | Ambulatory blood pressure (BP) monitoring for 24 h was performed in 103 consecutive patients with normal coronary angiograms (51 hypertensive and 52 normotensive; age 42 to 70 years). The relationship between changes in coronary arterial diameter and blood flow during an intracoronary infusion of acetylcholine (ACh) (5, 10, 50 $\mu$ g/min), and BP parameters, and other traditional risk factors was evaluated using univariate and multivariate linear regression analyses.                                                      |
| <b>RESULTS</b>     | With multivariate analyses, the 24-h PP showed an inverse correlation with the epicardial coronary dilator response to ACh independently of other covariates including age, smoking, and 24-h systolic BP in normotensive as well as hypertensive patients. Furthermore, multivariate analysis showed that the 24-h PP was inversely and independently correlated with the increase in coronary blood flow in response to ACh. The dilator response of epicardial coronary arteries to nitrate was not significantly correlated with 24-h PP. |
| <b>CONCLUSIONS</b> | Increased 24-h PP is independently associated with endothelial vasomotor dysfunction in conduit and resistance coronary arteries irrespective of the presence of hypertension. Increased ambulatory PP may have an intimate relation to coronary endothelial vasomotor dysfunction. (J Am Coll Cardiol 2005;45:1461–6) © 2005 by the American College of Cardiology Foundation                                                                                                                                                                |

Pulse pressure (PP), calculated as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), has been previously reported to be a stronger cardiovascular risk factor than SBP alone, especially in elderly hypertensive patients (1). Even in normotensive subjects, an increase in PP remains a powerful and independent predictor of cardiovascular risk, particularly for myocardial infarction (2). However, the underlying mechanisms by which an increase in PP plays a role in pathogenesis of coronary artery disease remain unclear. A recent report (3) showed that an increase in PP was associated with endothelial vasomotor dysfunction, an independent predictor of future coronary events, in the resistance vessels downstream from the brachial artery in hypertensive patients. However, there is no information on the effects of PP

on endothelial vasomotor functions in human coronary arteries in normotensive or hypertensive patients. Furthermore, the relationship between PP and endothelial vasomotor function in the coronary arteries may not be similar to the brachial artery because of the predominant role of DBP in the coronary circulation. Thus, the objective of this study was to determine whether an increase in PP might be associated with endothelial vasomotor dysfunction in the conduit and resistance vessels in the coronary circulation in both normotensive and hypertensive subjects.

## METHODS

**Study patients.** Study subjects consisted of a consecutive series of 103 patients. Characteristics of the study subjects are shown in Table 1. They underwent diagnostic coronary angiography for atypical chest pain (95 subjects) or ST-segment depression at rest or during exercise without chest pain (8 subjects) in Yamanashi University Hospital between January 2002 and January 2004. They fulfilled all of the following inclusion criteria: 1) angiographically normal coronary arteries (<5% narrowing after nitrate administration) and no coronary spasm (<50% decrease in epicardial

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#### Abbreviations and Acronyms

|     |                            |
|-----|----------------------------|
| ACh | = acetylcholine            |
| BP  | = blood pressure           |
| DBP | = diastolic blood pressure |
| HR  | = heart rate               |
| NO  | = nitric oxide             |
| PP  | = pulse pressure           |
| SBP | = systolic blood pressure  |

coronary diameter from baseline and neither chest pain nor ischemic electrocardiographic change) after the intracoronary infusion of acetylcholine (ACh); 2) normal left ventriculography; 3) no left ventricular hypertrophy, verified by both electrocardiography and echocardiography; and 4) no history of myocardial infarction, congestive heart failure, valvular heart disease, secondary hypertension, stroke, renal dysfunction (serum creatinine concentration >2.0 mg/dl) or other serious diseases. All medications that could have affected coronary vasomotor reactivity and blood pressure (BP) were withdrawn  $\geq 3$  days before the study. Hypertension was defined according to Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure-VI criteria (4): the averaged values of two or more BP measurements obtained on at least two separate occasions were >140 mm Hg SBP or >90 mm Hg DBP, with waking ambulatory BP measurements >135/85 mm Hg or sleeping ambulatory BP measurements >120/75 mm Hg. Written informed consent was obtained from all study subjects before the study. The study was approved by the ethics committee at our institution.

**Protocol for coronary angiography.** After baseline angiography, incremental doses of ACh (5, 10, and 50  $\mu$ g/min) were infused directly into the left coronary artery through the Judkins catheter for 2 min with a 5-min interval between each dose (5). Hemodynamic measurements and coronary angiography were repeated before and during each of the ACh infusions. After an additional 15 min, intracoronary injection of isosorbide dinitrate (1 mg) was per-

formed; 2 min after that, coronary angiography was performed in multiple projections in all study subjects.

**Ambulatory BP measurements.** Systolic BP, DBP, PP, and heart rate (HR) during daily activities were measured every 30 min for 24 h, by the oscillometric method, using a noninvasive ambulatory BP monitoring system (TM-2425, A&D, Tokyo, Japan) (6). The daytime and nighttime mean values of SBP, DBP, PP, and HR during the 24-h period were analyzed after reviewing the patients' diaries. We defined daytime as the period from the time they awoke to the time they went to sleep, and nighttime as the period during which they were sleeping (7). The daytime, nighttime, and 24-h SBP, DBP, PP, and HR were the averages of all of the values obtained at 30-min intervals. Non-dipper hypertension was defined by the absence of the fall (>10%) in the nighttime mean SBP, and/or in DBP from the respective daytime values (7).

**Quantitative coronary angiography and the measurement of coronary blood flow.** A quantitative coronary angiographic study was performed in all of the study subjects with the Judkins technique in the morning when the patients were fasting, in the same manner as described previously (5). Measurement of luminal diameter of the left anterior descending coronary artery at the midsegment was performed quantitatively by use of a computer-assisted coronary angiographic analysis system (Cardio 500, Kontron Instruments, Munich, Germany) by two observers blinded to the study protocol. Responses of the coronary artery diameter to infusions of ACh and nitrates were expressed as percent changes from baseline diameter measured on angiograms taken just before each infusion.

Blood flow velocity was measured in a subgroup of 56 consecutive subjects using a 0.014-inch wire equipped with a Doppler crystal at its tip (Flow Wire, Cardiometrics, Mountain View, California), which was advanced through the Judkins catheter and carefully positioned in a straight proximal segment of the left anterior descending coronary artery to obtain a stable flow velocity signal (5). The stable peak flow velocity signals at baseline and during a 2-min

**Table 1.** Study Patients' Characteristics

|                                      | All Patients<br>(n = 103) | Hypertensive Patients<br>(n = 51) | Normotensive Patients<br>(n = 52) |
|--------------------------------------|---------------------------|-----------------------------------|-----------------------------------|
| Age (yrs)                            | 62 $\pm$ 11               | 63 $\pm$ 11                       | 61 $\pm$ 12                       |
| Male (%)                             | 45                        | 45                                | 44                                |
| Body mass index (kg/m <sup>2</sup> ) | 24 $\pm$ 4                | 25 $\pm$ 5                        | 24 $\pm$ 3                        |
| Smoking (%)                          | 45                        | 49                                | 41                                |
| Total cholesterol (mg/dl)            | 205 $\pm$ 36              | 206 $\pm$ 39                      | 203 $\pm$ 33                      |
| Diabetes mellitus (%)                | 26                        | 30                                | 22                                |
| Hypertension (%)                     | 50                        | —                                 | —                                 |
| Non-dipper (%)                       | 31                        | 62*                               | —                                 |
| Ambulatory daytime PP (mm Hg)        | 50 $\pm$ 11               | 54 $\pm$ 13                       | 47 $\pm$ 8†                       |
| Ambulatory daytime SBP (mm Hg)       | 127 $\pm$ 17              | 140 $\pm$ 16*                     | 119 $\pm$ 12*†                    |
| Baseline coronary diameter (mm)      | 3.3 $\pm$ 0.8             | 3.4 $\pm$ 1.0                     | 3.2 $\pm$ 0.6                     |
| Baseline coronary flow (ml/min)      | 83 $\pm$ 39               | 85 $\pm$ 40                       | 80 $\pm$ 39                       |

Data are expressed as mean  $\pm$  SD and percentage. \*p < 0.05 vs. all patients; †p < 0.05 vs. hypertensive patients.

PP = pulse pressure; SBP = systolic blood pressure.

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