Increase in Pulse Pressure Relates to Diabetes Mellitus and Low HDL Cholesterol, but Not to Hyperlipidemia in Hypertensive Patients Aged 50 Years or Older


Higher pulse pressure is associated with higher cardiovascular risk. We investigated the relationship between pulse pressure and known metabolic risk factors in hypertensive patients who had not experienced stroke or myocardial infarction. In a multicenter cross-sectional survey made in 1995, we registered 939 hypertensive patients aged 50 years. Of these, 734 had never experienced stroke or myocardial infarction. We divided these 734 patients into two groups based on the value of their pulse pressures: 396 patients with a pulse pressure $\geq 60$ mmHg, and 338 patients with a pulse pressure $< 60$ mmHg. The average pulse pressure value was 72 $\pm$ 12 mmHg in the former group, and 49 $\pm$ 8 mmHg in the latter group. The former group exhibited advanced age, a higher women-to-men ratio, lower high-density lipoprotein (HDL) cholesterol, and higher systolic and lower diastolic blood pressure. Diabetes mellitus (DM) and left ventricular hypertrophy were more frequently noticed in the former group than in the latter group. The prevalence of hyperlipidemia, however, was similar in the two groups. The association of pulse pressure with DM and low HDL cholesterol was statistically significant by multiple logistic analysis adjusted for age, sex, and other known cardiovascular risk factors. In conclusion, pulse pressure increases with advancing age. DM made a substantially larger contribution to the increase in pulse pressure than hyperlipidemia. (Hypertens Res 2002; 25: 335–341)

Key Words: pulse pressure, diabetes mellitus, hyperlipidemia, HDL-cholesterol

Introduction

Higher blood pressure (BP) is associated with larger risk of cardiovascular diseases (1, 2). The importance of pulse pressure as a major determinant of cardiovascular risk has been demonstrated by large-scale cohort studies (3–6) and randomized controlled studies in patients with hypertension (7–10) or left ventricular dysfunction (11). The importance of pulse pressure has also been demonstrated by analysis of BP obtained through automatic 24-h measurements (12). In aged patients, pulse pressure has been shown to have greater prognostic value than systolic or diastolic pressure (13, 14).

Pulse pressure increases along with stiffening of the vascular wall of large conduit arteries (15, 16). The arterial wall becomes stiffer with the progression of atherosclerosis, which involves calcifications, accumulation of large amounts of collagen, and fragmentation and rupture of elastic tissue. Therefore, pulse pressure may be a marker of systemic atherosclerosis. In addition to hypertension, diabetes mellitus...
(DM) and hyperlipidemia promote atherosclerosis. DM or insulin resistance has been associated with an increase in arterial stiffness or a decrease in vascular distensibility (17–21). Hyperlipidemia has also been associated with increased arterial stiffness (22, 23). Although it is plausible that DM and hyperlipidemia increase pulse pressure by increasing arterial stiffness, there has been no extensive exploration of the direct relationship between DM or hyperlipidemia and pulse pressure. In particular, the relative importance of DM and hyperlipidemia to the increase in pulse pressure remains unknown. In the present multicenter cross-sectional survey, we analyzed the relationship between these metabolic risk factors and pulse pressure in hypertensive patients aged 50 years or older.

**Subjects and Methods**

**Patient Enrollment**

The survey was performed at 11 hospitals, where the members of the Research Group on Evaluation of the Effects of Drug Treatment on Hypertension and Other Disease Conditions in the Elderly or their collaborators had outpatient clinics. The subjects were primarily enrolled to a 1-year follow-up survey. The survey was performed in collaboration with the Research Group on Evaluation of the Effects of Drug Treatment on Hypertension and Other Disease Conditions in the Elderly. The primary aim of the survey was to assess 1) how elderly hypertensive patients are treated by Japanese physicians specializing in hypertension, and 2) the effects of BP on the activities of daily living (ADL). Details of the patient enrollment were described previously (24). In brief, we enrolled outpatients who were currently attending the outpatient clinics of the 11 hospitals described above. The patient enrollment was performed between June 1 and September 30 in 1995. Patients with DM were excluded if they had advanced complications, such as renal failure with serum creatinine > 2.0 mg/dl or orthostatic hypotension due to autonomic neuropathy. Outpatients aged 50 years or older were asked to fill out a questionnaire to evaluate their ADL. For each patient who consented to participate in this survey, the attending physicians filled out a case report form. Items included gender, personal history, clinical diagnosis, details of therapy, and physical findings such as height and body weight, BP, pulse rate, and laboratory data. A total of 1,163 outpatients were enrolled, and 939 patients had hypertension. The patients’ ages ranged from 50 to 94 years. Among the hypertensive patients, 198 had a prior history of stroke or myocardial infarction. Because retrospective analysis suggested a J-curve phenomenon between BP level and recurrence of stroke (25) or myocardial infarction (26), the goal blood pressure may have been affected by the presence of these cardiovascular complications. Therefore, we excluded these 198 patients. In addition, BP recording was not completed in 7 hypertensive patients. Thus the final study group consisted of 734 hypertensive patients.

**Case Report Form**

The attending physicians filled out a case report form for each patient. Items included gender, birth date, clinical diagnosis, medical history, lifestyle, physical findings, laboratory findings, and details of therapy. At each visit, the attending physician measured each patient’s BP twice using a standard mercury sphygmomanometer with the patient in a seated position. The average of the two readings was recorded as the BP for that day. The average of the BP readings taken on two consecutive visits was recorded in the case report form. Age was calculated by subtracting the birth date of the subject from the date of the survey. DM was diagnosed when the fasting plasma glucose concentration was ≥140 mg/dl, when the diagnosis was confirmed by a 75 g-oral glucose tolerance test, or when the patient was receiving an oral hypoglycemic agent or insulin. Hyperlipidemia was diagnosed when the serum total cholesterol concentration was ≥220 mg/dl, the serum triglyceride concentration was ≥150 mg/dl, or both, or when the patient was taking any antihyperlipidemic agent. In addition, when a patient showed a serum high-density lipoprotein (HDL) cholesterol concentration of less than 35 mg/dl, we regarded the patient as having low serum HDL cholesterol (27). Left ventricular hypertrophy was diagnosed based on an electrocardiographic criterion, i.e., SV1 + RV5 > 3.5 mV.

**Statistical Analysis**

Values are expressed as the mean ± SD. Pulse pressure was calculated by using the following formula: pulse pressure = systolic blood pressure - diastolic blood pressure. The data analysis was performed with the use of Statistical Analysis System (SAS) software (SAS Institute, Cary, USA) (28). Differences between groups were analyzed by an analysis of variance (ANOVA) followed by multiple comparison using Duncan’s multiple range test or, in comparisons of two groups, using Student’s t-test. Categorical data were analyzed by the χ²-test. To assess factors that related to the increase in pulse pressure, we performed multiple logistic analysis. P values less than 0.05 were considered to indicate statistical significance.

**Results**

**Patients Profile**

We divided the patients into two groups based on the value of their pulse pressures, i.e., 396 patients with a pulse pressure ≥60 mmHg and 338 patients with a pulse pressure < 60 mmHg (Fig. 1). Table 1 summarizes the clinical characteristics of each group of patients. The patient group with a pulse pressure ≥60 mmHg was characterized by a higher percent-
age of women and advanced age. The higher pulse pressure of this group was due to higher systolic blood pressure and lower diastolic blood pressure. Mean serum HDL cholesterol concentration was significantly lower in the patients with pulse pressure ≥60 mmHg. DM was significantly more prevalent in this patient group. The prevalence of low HDL-cholesterol was also higher in the patients with pulse pressure ≥60 mmHg than in the patients with pulse pressure < 60 mmHg, although the frequency of hyperlipidemia was similar in the two groups. Left ventricular hypertrophy was more frequently diagnosed in the patient group with a pulse pressure ≥60 mmHg, whereas serum creatinine concentra-

![Graph](image_url)

**Fig. 1.** Distribution of pulse pressure. Closed columns represent the patients with a pulse pressure < 60 mmHg, and open columns represent the patients with a pulse pressure ≥60 mmHg.

**Table 1. Patients Profile**

<table>
<thead>
<tr>
<th></th>
<th>Patients with a pulse pressure</th>
<th></th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥60 mmHg (N = 396)</td>
<td>&lt; 60 mmHg (N = 338)</td>
<td></td>
</tr>
<tr>
<td>Men (%)</td>
<td>40.2</td>
<td>53.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years old)</td>
<td>68.4 ± 8.9</td>
<td>60.3 ± 8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>152.1 ± 13.1</td>
<td>132.5 ± 11.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80.5 ± 10.1</td>
<td>83.8 ± 8.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>104.4 ± 9.7</td>
<td>100.0 ± 9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>71.6 ± 11.6</td>
<td>48.7 ± 7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>70.6 ± 9.2</td>
<td>69.5 ± 9.7</td>
<td>0.118</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>22.2 (396)</td>
<td>15.7 (338)</td>
<td>0.025</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>53.5 (396)</td>
<td>53.6 (338)</td>
<td>0.997</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>5.85 ± 1.53 (341)</td>
<td>5.75 ± 1.41 (308)</td>
<td>0.349</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.32 ± 0.84 (390)</td>
<td>5.34 ± 0.82 (333)</td>
<td>0.677</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.36 ± 0.42 (379)</td>
<td>1.46 ± 0.43 (327)</td>
<td>0.005</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.60 ± 0.83 (354)</td>
<td>1.73 ± 1.21 (311)</td>
<td>0.092</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>80 ± 44 (391)</td>
<td>80 ± 18 (333)</td>
<td>0.176</td>
</tr>
<tr>
<td>LVH on ECG (%)</td>
<td>29.2 (360)</td>
<td>21.6 (324)</td>
<td>0.024</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>29.6 (392)</td>
<td>33.2 (334)</td>
<td>0.291</td>
</tr>
<tr>
<td>Habitual drinker (%)</td>
<td>39.4 (391)</td>
<td>51.2 (334)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP, blood pressure; MAP, mean arterial pressure; FPG, fasting plasma glucose concentration; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; ECG, electrocardiogram. Numbers in parentheses represent the number of patients for whom each type of laboratory data were available, or the number of patients for whom the presence or absence of each condition had been identified.
In the present study, pulse pressure was significantly associated with both DM and low serum HDL cholesterol concentration, but not with hyperlipidemia. The association of DM or low HDL cholesterol concentration and the increase in pulse pressure was independent of other confounding factors, including age, sex and mean arterial pressure. Thus DM and hyperlipidemia, the two major metabolic risk factors, made different contributions to the increase in pulse pressure.

**Pulse Pressure as a Marker of Cardiovascular Risk**

Previous studies have repeatedly demonstrated that an increase in pulse pressure was associated with higher cardiovascular morbidity and mortality (3, 8, 10, 11), a higher risk of coronary heart disease or myocardial infarction (4, 7, 9), a higher risk of heart failure (5, 6) or all-cause mortality (8). In the present cross-sectional survey, the prevalence of left ventricular hypertrophy was significantly higher in the group of patients with higher pulse pressure than in the group with lower pulse pressure. This finding also supports the notion that pulse pressure is a marker of cardiovascular risk.

**DM and Pulse Pressure**

Previous studies have suggested a close relationship between DM and arterial stiffening (17–21, 29). Aortic stiffness has been shown to increase in insulin-dependent diabetic patients of both sexes (17) or women (18). And it has been reported that the elastic carotid artery or coronary artery are stiffened in both insulin-dependent and non-insulin dependent diabetic patients (19–21). The arterial stiffening may increase the pulse wave velocity to augment the second systolic peak, resulting in an elevation of systolic blood pressure and an increase in pulse pressure (29).

Some investigators have failed to detect any significant increase in the stiffness of the elastic artery in diabetic patients (30, 31). In these studies, however, the distensibility of the muscular femoral artery was decreased in young uncomplicated insulin-dependent diabetic patients (30), and brachial arterial waveform analysis revealed a decrease in distal but not in larger artery compliance (31). Therefore, in diabetic patients, atherosclerotic change seems to be initiated at the muscular or more distal arteries. In the present study, we examined hypertensive patients with and without DM aged 50 years or older. Hence, we did not observe the early stage of the atherosclerotic process.

Although the findings of the present study did not permit us to specify the mechanism by which DM contributed to the increase in pulse pressure, it is noteworthy that several patients having pulse pressure ≥60 mmHg were receiving insulin therapy (Table 2). Exogenous insulin has been reported to impair the ability of plasma to promote cellular cholesterol efflux, probably via decreasing plasma phospholipid transfer protein activity (32). Because the removal of cholesterol from peripheral vascular cells is an important defense...
mechanism against atherosclerosis, impairment of this process would result in arterial stiffening. Thus, use of insulin may be a factor that mediates the increase in pulse pressure in diabetic patients. In addition, insulin resistance has been nominated as a factor to mediate stiffening of arterial wall (20, 33). An association between insulin resistance and arterial stiffness was reported in healthy young women (33) and patients with non-insulin dependent DM (20). Unfortunately, we did not measure the serum insulin level or urinary excretion of C-peptide in subjects of the present study. Hyperglycemia has also been suggested to increase cardiovascular stiffness through formation of advanced glycosylation endproducts (AGEs) (34, 35). Both decreasing the formation of AGEs (36) and breaking the cross-link of AGEs (37) reportedly restored large artery properties in experimental diabetic rats. In the present study, there was no significant difference in fasting plasma glucose concentrations between the patients with a pulse pressure ≥60 mmHg and the patients with a pulse pressure < 60 mmHg. However, the present study was cross-sectional, and we did not have precise information about the duration of DM or long-term control of blood glucose in the participants.

Hyperlipidemia and Pulse Pressure

Although a previous study reported a significant positive correlation between serum cholesterol concentration and pulse pressure (12), we found no significant association between hyperlipidemia and pulse pressure. In the present study subjects, the average values of total cholesterol concentration were within the normal range, and were substantially lower than those reported in a previous study (12). Furthermore, in that study (12), the correlation between low-density lipoprotein cholesterol and pulse pressure was not significant. Several studies have demonstrated an association between hyperlipidemia and arterial wall stiffness (22, 23). These studies examined patients with familial hypercholesterolemia characterized by extremely high serum cholesterol levels. Earlier studies have also reported an absence of significant association between arterial stiffness and hyperlipidemia (38, 39). One of these studies (38) examined hypercholesterolemic children at the age of 3 to 14 years. In these subjects, the shorter duration of exposure to hypercholesterolemia might have prevented the increase in arterial stiffness.

We do not exclude the possibility that mild hypercholesterolemia affects the properties of the vascular wall. In normotensive and essential hypertensive patients, no significant differences in the carotid arterial wall properties were found between patients with a total cholesterol concentration ≤240 mg/dl and patients with a total cholesterol concentration > 240 mg/dl (39). However, carotid intimal-medial thickness was significantly related to cholesterol levels in the whole population (39). Furthermore, improvement of the stiffness of the large arteries has been observed after cholesterol-lowering therapy (40).

Low HDL Cholesterol and Increase in Pulse Pressure

We found a significant association between low HDL cho-

Table 3. Factors Relating to an Increase in Pulse Pressure by Single Logistic Analysis

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>p value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (women)</td>
<td>0.530</td>
<td>0.0004</td>
<td>1.70</td>
<td>1.27–2.28</td>
</tr>
<tr>
<td>Age (every 1 year)</td>
<td>0.074</td>
<td>&lt; 0.0001</td>
<td>1.08</td>
<td>1.06–1.10</td>
</tr>
<tr>
<td>MAP (every 1 mmHg)</td>
<td>0.049</td>
<td>&lt; 0.0001</td>
<td>1.05</td>
<td>1.03–1.07</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.431</td>
<td>0.0253</td>
<td>1.54</td>
<td>1.05–2.25</td>
</tr>
<tr>
<td>Low HDL-cholesterol</td>
<td>0.907</td>
<td>0.0051</td>
<td>2.48</td>
<td>1.31–4.67</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.001</td>
<td>0.9939</td>
<td>1.00</td>
<td>0.75–1.34</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>- 0.169</td>
<td>0.2917</td>
<td>0.84</td>
<td>0.62–1.16</td>
</tr>
<tr>
<td>Drinking habit</td>
<td>- 0.479</td>
<td>0.0015</td>
<td>0.62</td>
<td>0.46–0.83</td>
</tr>
<tr>
<td>Use of insulin</td>
<td>15.094</td>
<td>0.9748</td>
<td>&gt; 99</td>
<td>&lt; 0.01–999 &lt;</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; HDL, high-density lipoprotein. 95% CI: 95% confidence interval.

Table 4. Factors Relating to an Increase in Pulse Pressure by Multiple Logistic Analysis

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>p value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>0.780</td>
<td>0.0008</td>
<td>2.18</td>
<td>1.38–3.45</td>
</tr>
<tr>
<td>Low HDL-cholesterol</td>
<td>1.144</td>
<td>0.0018</td>
<td>3.14</td>
<td>1.53–6.43</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>- 0.186</td>
<td>0.3089</td>
<td>0.83</td>
<td>0.58–1.19</td>
</tr>
<tr>
<td>Drinking habit</td>
<td>0.046</td>
<td>0.8406</td>
<td>1.05</td>
<td>0.67–1.63</td>
</tr>
</tbody>
</table>

Results are adjusted for age, sex and mean arterial pressure. HDL, high-density lipoprotein. 95% CI: 95% confidence interval.
lesterol and increase in pulse pressure. This finding would seem to be reasonable, since low HDL cholesterol is a well-established risk factor of arteriosclerosis. However, a significant positive correlation between serum HDL cholesterol and clinic or 24-h mean ambulatory pulse pressure has also been reported (41). The relevance of low HDL cholesterol to increase in pulse pressure should be further examined in future studies.

**Relationship of Smoking and Use of β-Blocker to Pulse Pressure**

Although smoking is a major cardiovascular risk factor, there was no significant association between smoking and pulse pressure in this study. In an earlier study (42), smoking one cigarette caused short-term increases in arterial wall stiffness in habitual smokers, while no obvious long-term effect of smoking was observed on arterial stiffness. The present findings are consistent with this previous observation (42). The fact that the prescription rate of β-blocker was significantly lower in the patient group with a pulse pressure ≥60 mmHg than in the patient group with a pulse pressure < 60 mmHg (Table 2) would seem to suggest that the β-blocker influenced pulse pressure. However, multiple logistic analysis failed to detect a significant association between non-use of a β-blocker and the increase in pulse pressure. β-Blockers have been reported to be weaker than the other classes of antihypertensive drugs in decreasing pulse pressure (43). Furthermore, a previous study showed an absence of effect of conventional antihypertensive drugs on the aging-related increase in pulse pressure (44).

In conclusion, in Japanese elderly hypertensive patients of the present study, DM and low HDL-cholesterol, but not hyperlipidemia, were significantly related to increased pulse pressure. In the risk stratification by the Joint National Committee (45), the World Health Organization and International Society of Hypertension (46) and the Japanese Society of Hypertension (47), DM is considered to constitute a more serious risk than the other risk factors. The strong association of DM and pulse pressure demonstrated in the present study is consistent with this notion.

**References**

beta of the common carotid and femoral arteries are associated with insulin resistance in NIDDM. *Diabetes Care* 1998; 21: 1178–1182.


32. Dullaart RPF, van Tol A: Twenty four hour insulin infusion impairs the ability of plasma from healthy subjects and Type 2 diabetic patients to promote cellular cholesterol efflux. *Atherosclerosis* 2001; 157: 49–56.


