Altered Age-Related Blood Pressure Pattern in Type 1 Diabetes

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Background—Pulse pressure (PP) increases with age as a result of arterial stiffening and is a powerful predictor of cardiovascular disease. Type 1 diabetes is associated with excessive cardiovascular mortality and increased arterial stiffness. We examined whether the age-related blood pressure changes in type 1 diabetic patients differ from those of the nondiabetic background population.

Methods and Results—We performed a cross-sectional, case-control study of 2988 consecutively selected diabetic subjects and 5486 randomly selected nondiabetic control subjects. Blood pressure was measured twice by mercury sphygmomanometry on a single occasion. Compared with controls, diabetic subjects had a higher systolic blood pressure in all age groups, whereas diastolic blood pressure was higher in those <40 years but lower in those >45 years of age. Consequently, diabetic subjects had a higher PP and a higher prevalence of isolated systolic hypertension. The early age-related rise in PP was more pronounced in subjects with diabetic nephropathy but was also evident in diabetic subjects with normal albumin excretion rate. In a multiple regression analysis, PP in diabetic patients was associated with age, male sex, duration of diabetes, and albuminuria.

Conclusions—A higher systolic pressure and an earlier decrease in diastolic pressure result in a higher and more rapidly increasing PP in type 1 diabetic patients. Our findings indicate accelerated arterial aging, which may contribute to the higher cardiovascular morbidity and mortality in these patients. (Circulation. 2004;110:1076-1082.)

Key Words: aging ■ arteriosclerosis ■ blood pressure ■ diabetes mellitus ■ hypertension

Aging is associated with several distinct blood pressure changes. Population-based studies have shown that systolic blood pressure (SBP) increases progressively with age, whereas diastolic blood pressure (DBP) rises until ∼60 years of age, after which it starts to decline.1,2 Consequently, pulse pressure (PP), the difference between SBP and DBP, increases steeply after that age. PP has relatively recently been recognized as an important predictor of cardiovascular disease (CVD),3 and there is evidence that PP is the most powerful blood pressure index in predicting cardiovascular end points in older persons.4,5 The increase in PP is a consequence of the age-induced stiffening of the large arteries.6 As arterial compliance declines, less energy is absorbed during systole and released during diastole, resulting in a widened PP.7 Thus, PP can be considered a surrogate marker of arterial stiffness, an entity strongly associated with CVD.8 Type 1 diabetes is associated with an excess of CVD. The risk is particularly elevated in patients with diabetic nephropathy but is also higher in type 1 diabetic patients without diabetic kidney involvement.9 It has been established that type 1 diabetic patients have stiffer arteries than do age-matched, nondiabetic control subjects and that the process of arterial stiffening is initiated before any signs of microvascular or macrovascular disease can be detected.10,11 The increase in stiffness seems to be correlated with the duration of diabetes, independent of age.12 However, it still remains unclear whether the age-induced blood pressure changes in type 1 diabetic patients with and without diabetic complications differ from those of the nondiabetic population. To address this issue, we studied whether an altered age-related blood pressure pattern, suggestive of accelerated arterial aging, could be detected in patients with type 1 diabetes. In addition, we examined factors associated with elevated PP in type 1 diabetic patients.
Type 1 Diabetic Subjects
This study is part of the Finnish Diabetic Nephropathy Study (FinnDiane), a multicenter, nationwide study of diabetic late complications. A total of 3025 patients with a diagnosis of type 1 diabetes with an age of onset <36 years and insulin therapy initiated within 1 year of diagnosis had, in a consecutive manner, been recruited at 59 hospitals and healthcare centers by October 31, 2002. All patients underwent a thorough physical examination between 1998 and 2002. Their medical history with regard to diabetes, diabetic complications, CVD, and data on the latest glycosylated hemoglobin (HbA1c) measurement were acquired from medical records. The analyses were limited to 2988 patients aged 18 to 64 years.

Every diabetic patient was classified according to diabetic renal involvement based on the urinary albumin excretion rate (AER) on at least 2 of 3 recent consecutive urine collections. Normalalbuminuric patients with a previously elevated AER who were currently receiving antihypertensive medication were classified by the AER before treatment. Normal AER was defined as <30 mg/24 h (<20 µg/min; n=1371), microalbuminuria as an AER of 30 to 300 mg/24 h (20 to 200 µg/min; n=352), macroalbuminuria as an AER ≥300 mg/24 h (≥200 µg/min; n=470), and end-stage renal failure (n=249) as dialysis treatment (n=64) or renal transplantation (n=185). Patients who did not fulfill any of these criteria because of missing (n=319), too few (n=157), or discordant (n=70) values were categorized as nonclassifiable (n=546).

Control Subjects
The control group was obtained from a national, population-based health survey, Health 2000. This survey consists of a randomly drawn, nationally representative sample of persons aged 30 years or older who attended a comprehensive health examination at the local health center or comparable premises during the years 2000 and 2001. All 5486 subjects younger than 75 years without self-reported diabetes were included in the analyses.

Blood Pressure Measurement and CVD
Blood pressure was measured by identical techniques and equipment in diabetic and control subjects. After the patient had rested for at least 5 minutes, blood pressure was measured twice in a sitting position by a trained nurse using a mercury sphygmomanometer. SBP was recorded at phase I and DBP at phase V of Korotkoff sounds. The mean of the 2 recordings was used in the study. Essential hypertension was defined as an SBP ≥140 mm Hg, a DBP ≥90 mm Hg, or use of antihypertensive medication in controls and in diabetic patients with a normal AER. Isolated systolic hypertension was defined as an SBP ≥140 mm Hg and a DBP <90 mm Hg, irrespective of antihypertensive medication use. CVD was defined as a history of stroke, myocardial infarction, or angina pectoris based on self-reported disease, medical records, and clinical examination.

Statistical Analysis
The difference in blood pressure levels between diabetic and control subjects was analyzed in matching age groups. When male and female subjects were analyzed together, a statistical model that gave both sexes equal weight in each age group was used. Comparisons were made with the χ² test, t test, Mann-Whitney U test, or ANOVA with SPSS software, version 11.0 (SPSS, Inc). The rate of PP increase with age was calculated by means of simple linear regression. A multiple linear regression analysis with backward, stepwise elimination was used to identify factors associated with PP. Results are expressed as mean±SEM or the 95% confidence interval (CI). Values of P<0.05 were considered statistically significant.

Results
Clinical Characteristics
The clinical characteristics of the subjects are described in Table 1. Diabetic patients, on average, were younger, had a lower body mass index, and had more CVD than did controls.

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetic Subjects</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>Entire group 2988</td>
<td>5486</td>
<td>...</td>
</tr>
<tr>
<td>Age 30–64 y</td>
<td>2164</td>
<td>4755</td>
<td>...</td>
</tr>
<tr>
<td>Men, %</td>
<td>Entire group 51.7</td>
<td>46.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 30–64 y</td>
<td>52.0</td>
<td>47.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>Entire group 37.5±0.2</td>
<td>49.2±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 30–64 y</td>
<td>42.6±0.2</td>
<td>46.1±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>Entire group 25.1±0.1</td>
<td>26.8±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 30–64 y</td>
<td>25.3±0.1</td>
<td>26.6±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>Entire group 24.7</td>
<td>23.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Age 30–64 y</td>
<td>23.7</td>
<td>25.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td>Entire group 40.1</td>
<td>14.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 30–64 y</td>
<td>49.6</td>
<td>11.1</td>
<td>&lt;0.001</td>
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<tr>
<td>CVD, %</td>
<td>Entire group 7.2</td>
<td>6.1</td>
<td>0.02</td>
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<tr>
<td>Age 30–64 y</td>
<td>9.7</td>
<td>3.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Duration of diabetes, y</td>
<td>Entire group 22.4±0.2</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Age 30–64 y</td>
<td>26.2±0.2</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>Entire group 8.5±0.0</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Age 30–64 y</td>
<td>8.4±0.0</td>
<td>...</td>
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</tbody>
</table>

Abbreviations are as defined in text. Values are mean±SEM.

The proportion of smokers was similar, whereas the use of antihypertensive medication was more common in the diabetic group. The prevalence of antihypertensive treatment in normalalbuminuric diabetic subjects aged 30 to 64 years was 18.3%.

Systolic Blood Pressure
With the exception of men aged 60 to 64 years, diabetic subjects had a higher SBP than did controls in all age categories (Figure 1). When subjects receiving antihypertensive medication were excluded, the SBP of diabetic patients was higher in the age categories <50 years.

Diastolic Blood Pressure
Compared with the control subjects, diabetic male subjects <35 years and diabetic female subjects <40 years had a higher DBP, whereas DBP was lower in diabetic men and women in age groups >45 years. In the diabetic group, the highest DBP was found in the age group 40 to 44 years (82±1 mm Hg), whereas the peak in the control group was observed in the age group 55 to 59 years (85±0 mm Hg). The pattern of DBP being higher in the young and lower in the middle-aged diabetic patients was also evident in the analysis of untreated subjects.
Pulse Pressure
PP was higher in both diabetic male and female subjects of all age categories. Similar PP levels were observed to 20 years earlier in diabetic than in control subjects. The PP of diabetic men increased at an average rate of 0.89 mm Hg/y (95% CI, 0.72 to 1.05) between 35 and 59 years, whereas the increase in male controls in the same age span was only 0.37 mm Hg/y (95% CI, 0.29 to 0.42). Not until after 55 years of age (55 to 74) did the male control PP increment reach a comparable rate of 0.87 mm Hg/y (95% CI, 0.67 to 1.07). In diabetic women, PP increased at an average rate of 1.10 mm Hg/y (95% CI, 0.92 to 1.29) between 30 and 64 years. The corresponding rate in female controls was 0.61 mm Hg/y (95% CI, 0.56 to 0.66). In the analysis that excluded subjects who were taking a blood pressure–lowering medication, diabetic subjects had a higher PP in all age categories.

Figure 1. Age-specific mean blood pressure indices for diabetic and control males (A), females (B), both sexes combined (C), and for subjects of both sexes without antihypertensive treatment (D). Filled symbols indicate diabetic subjects; hollow symbols, controls; squares, systolic blood pressure (SBP); circles, diastolic blood pressure (DBP); triangles, PP. Abbreviations are as defined in text. *P<0.05, **P<0.001 for SBP; †P<0.05, ‡P<0.001 for DBP; P<0.001 for PP between all corresponding age categories.
Age-related PP in diabetic subjects stratified by AER is demonstrated in Figure 2. In the age categories 30 to 54 years, patients with macroalbuminuria had the highest PP, followed by microalbuminuric and normoalbuminuric diabetic patients. Control subjects had significantly lower PP than normoalbuminuric diabetic subjects in all age categories. When the diabetic group was stratified by age of onset of diabetes, PP differed between diabetic subgroups in all age groups between 25 and 59 years. In a similar analysis that included only diabetic patients with a normal AER, the difference was significant in the age groups 30 to 34 and 35 to 39 years (not shown). No major PP differences were observed between age- and sex-specific tertiles of HbA1c within the diabetic group. Diabetic subjects free of CVD had

<table>
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<tr>
<th></th>
<th>Controls</th>
<th>DM microalbuminuria</th>
<th>DM normo AER</th>
<th>DM macroalbuminuria</th>
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<tr>
<td></td>
<td>n</td>
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<td>39</td>
<td>104</td>
<td>83</td>
</tr>
<tr>
<td>DM, micro, n</td>
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<td>47</td>
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<tr>
<td>DM, normo, n</td>
<td>259</td>
<td>175</td>
<td>207</td>
<td>210</td>
</tr>
<tr>
<td>Controls, n</td>
<td>-</td>
<td>695</td>
<td>733</td>
<td>712</td>
</tr>
</tbody>
</table>

Significance: *P*<0.05 between diabetic subgroups; †P<0.01 for diabetic subjects with normal AER vs controls; ‡P<0.01 for diabetic subjects without CVD vs controls.

**Figure 2.** Age-specific mean PP stratified by AER (A), age at onset of diabetes (B), tertiles of HbA1c (C), and CVD (D). Nonclassifiable and end-stage renal failure diabetic subjects were omitted from A. Because of small numbers of patients (n < 5) in diabetic subgroups, age groups of 60 to 64 years in B and of 18 to 29 years in D were omitted. DM indicates diabetes mellitus (type 1). All other abbreviations are as defined in text.
a higher PP than did controls in all age groups and a lower PP than did diabetic subjects aged 40 to 49 with a history of cardiovascular complications. Furthermore, we noted that there were no differences in PP between smokers and nonsmokers (not shown).

The variables sex, age, duration of diabetes, AER, body mass index, smoking, and HbA1c were entered into a backward, multiple linear regression analysis with PP as the dependent variable. In the final model, male sex, age, duration of diabetes, and AER were independently associated with PP in diabetic patients (Table 2).

### Hypertension
With the exception of patients aged 50 to 59 years, essential hypertension was significantly more frequent in diabetic patients with a normal AER compared with control subjects (Figure 3). In a corresponding comparison, isolated systolic hypertension was approximately 3 times more common in normoalbuminuric diabetic subjects of all ages.

### Discussion
As a new finding, this study shows that the age-related blood pressure changes in individuals with type 1 diabetes differ markedly from those of nondiabetic subjects. As a result of a higher SBP and a DBP that starts to decline at a younger age, diabetic men and women have a higher and more rapidly increasing PP. This premature rise in PP is strongly related to the time of exposure to hyperglycemia and to the development of diabetic kidney disease. However, it also characterizes type 1 diabetic patients with a persistently normal urinary AER.

Elevated blood pressure is frequently present in individuals with type 2 diabetes and constitutes an important modifiable risk factor for cardiovascular end-organ damage. In type 1 diabetes, blood pressure derangements, resulting in an increased risk of microvascular and macrovascular complications, have generally been thought of as isolated to the subgroup of patients who develop diabetic kidney disease. This view is largely based on the influential work of Nørgaard et al, who reported a prevalence of essential hypertension in type 1 diabetic patients without diabetic kidney disease that was similar to that of the general population. Our study sheds new light on this important issue: Compared with the nondiabetic general population, type 1 diabetes is, even in the absence of diabetic kidney disease, associated with a deleterious blood pressure pattern. Our observations may to some extent explain the grossly elevated risk of CVD observed in type 1 diabetic patients with diabetic nephropathy. However, because recent research has identified PP as a powerful, independent predictor of CVD and mortality in type 1 diabetic patients, a premature rise in PP could be one explanation behind the increased risk of CVD in type 1 diabetic patients without diabetic kidney disease.

Although aging changes the blood pressure indices in subjects with and without diabetes in a parallel manner, the changes seem to be shifted to a 15- to 20-year younger age in type 1 diabetic subjects, suggesting accelerated vascular aging. This study does not explore the mechanisms behind the premature arterial stiffening, but according to one hypothesis, deposition of advanced glycation end products and cross-linking of collagen molecules in the arterial wall may contribute to the increased arterial stiffness in diabetic patients. Another mechanism that could be involved is endothelial dysfunction, which has been associated with both diabetes and arterial stiffness.

The fact that the prevalence of diabetic kidney complications increases with the duration of diabetes can certainly to some extent explain the observation that patients with a young age of onset of diabetes showed an earlier increase in PP than did patients with a later onset. The observation of a similar difference in the analysis including merely normoalbuminuric patients and the results of the multiple regression analysis indicate that disease duration per se has a considerable impact on arterial stiffness, independent of age and renal involvement. Thus, although the ambient level of glycemic control was not associated with increased PP, the time of exposure to hyperglycemia seems to play a fundamental role in the process of premature arterial stiffening.

The finding that not only PP but also essential hypertension is more common in type 1 diabetic patients than in the control group is in conflict with the prevailing perception that the prevalence of essential hypertension in type 1 diabetic pa-
tients is similar to that of the nondiabetic population. In the study by Nørgaard et al., SBPs and DBPs were not assessed separately, and hypertension was defined by considerably higher blood pressure values than are presently used. Because the higher prevalence of essential hypertension in our diabetic patients was largely due to a higher prevalence of isolated systolic hypertension, one can speculate that this discrepancy with previous results is caused by the fact that a large proportion of the patients with moderate, isolated systolic hypertension would not have been identified by the more restrictive criteria used by Nørgaard et al. Given that the study was published in 1990, any comparison will, however, be complicated by the more aggressive blood pressure treatment practiced today.

In view of the fact that effective antihypertensive treatment substantially lowers the greatly increased risk of cardiovascular events caused by isolated systolic hypertension and that this risk reduction is even greater in diabetic patients, we would like to emphasize the increased occurrence of isolated systolic hypertension observed in younger middle-aged patients with type 1 diabetes without any signs of diabetic nephropathy.

Some limitations of this study should be noted. The fact that we used blood pressure recordings from a single occasion will most likely result in an overestimation of hypertension when compared with measurements on several occasions. This circumstance is nevertheless unlikely to generate any considerable differences between groups because both groups were examined in the same manner. The diabetic patients were mainly recruited from hospitals, thus constituting a potential referral bias. However, the sample is one of the largest of type 1 diabetic patients ever studied and corresponds to 10% of all individuals with type 1 diabetes in Finland. Because the care of type 1 diabetic patients in Finland has traditionally been hospital based, a major effect of a referral bias does not seem likely.

A potential problem in the interpretation of the results is the higher rate of antihypertensive medication in the diabetic group. However, because most of the commonly used antihypertensive agents reduce PP, this circumstance will in fact lead to an underestimation of the difference between groups. This will, to a lesser degree, affect the results of normoalbuminuric diabetic patients, whose rate of antihypertensive medication use was only slightly higher than that of the controls, but it may be a considerable confounder in patients with diabetic kidney disease. Because the PP of untreated diabetic patients was higher than that of untreated controls in all age groups, we can safely exclude the possibility that the difference between groups was caused by blood pressure-lowering medication.

Diabetic neuropathy is another factor that might influence the results, because aortic stiffness in type 1 diabetic subjects has been shown to be correlated with autonomic neuropathy, independent of diabetes duration. On the other hand, there is evidence that diabetic neuropathy is associated with elevated DBP, but not with elevated SBP, which would cause a reduced, not an increased, PP.

In conclusion, even in the absence of diabetic kidney involvement, type 1 diabetic patients have a higher PP that increases earlier and more rapidly compared with the nondiabetic background population. This is suggestive of accelerated arterial stiffening and may explain the higher cardiovascular risk of these patients.

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