Pulsatile Stress in Middle-Aged Patients With Type 1 or Type 2 Diabetes Compared With Nondiabetic Control Subjects

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OBJECTIVE — Arterial pulse pressure is considered to be an independent cardiovascular risk factor. We compared pulse pressure during an active orthostatic test in middle-aged patients with type 1 diabetes and with type 2 diabetes and corresponding nondiabetic control subjects.

RESEARCH DESIGN AND METHODS — Forty patients with type 1 diabetes (mean age 50 years, diabetes duration 23 years, and BMI 23.0 kg/m^2) were compared with 40 nonhypertensive patients with type 2 diabetes (respectively, 50 years, 8 years, and 29.7 kg/m^2). Patients taking antihypertensive agents or with renal insufficiency were excluded. All patients were evaluated with a continuous noninvasive arterial blood pressure monitoring (Finapres) in standing (1 min), squatting (1 min), and again standing position (1 min). Patients with type 1 or type 2 diabetes were compared with two groups of 40 age-, sex- and BMI-matched healthy subjects.

RESULTS — Patients with type 1 diabetes and patients with type 2 diabetes showed significantly higher pulse pressure, heart rate, and double product of pulse pressure and heart rate (PP×HR) (type 1: 5,263 vs. 4,121 mmHg/min, $P = 0.0004$; type 2: 5,359 vs. 4,321 mmHg, $P = 0.0023$) levels than corresponding control subjects. There were no significant differences between patients with type 1 diabetes and type 2 diabetes regarding pulse pressure (59 vs. 58 mmHg), heart rate (89 vs. 88/min), and PP×HR (5,263 vs. 5,359 mmHg/min).

CONCLUSIONS — Patients with type 1 diabetes have increased levels of peripheral PP, an indirect marker of arterial stiffness, and PP×HR, an index of pulsatile stress, comparable to those of nonhypertensive patients with type 2 diabetes at similar mean age of 50 years.

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Arterial pulse pressure, a surrogate marker of large artery stiffness, was shown to be an independent cardiovascular disease (CVD) risk factor in several large longitudinal studies in patients with type 2 diabetes (1,2). In patients with type 1 diabetes of the Finnish Diabetic Nephropathy (FinnDiane) study (3), higher systolic blood pressure and an earlier decrease in diastolic blood pressure resulted in a higher and more rapidly increasing pulse pressure compared with those in nondiabetic control subjects. In the EURODIAB study (4,5), pulse pressure was also an independent risk factor for CVD and total mortality in patients with type 1 patients.

Middle-aged patients with type 1 diabetes are characterized by a long duration of the disease and therefore sustained exposure to chronic hyperglycemia, leading to accelerated progression of arterial stiffness and increased pulse pressure (6). In contrast, middle-aged patients with type 2 diabetes have a much shorter duration of diabetes but have other CVD risk factors such as abdominal obesity, insulin resistance, and metabolic syndrome, which could accelerate arterial stiffness (1,2). To our knowledge, no study has compared pulse pressure in patients with type 1 diabetes and in patients with type 2 diabetes at similar age. The primary aim of the present study was to investigate pulsatile stress in patients with type 1 diabetes and patients with type 2 diabetes at a similar mean age of 50 years. Each group of diabetic patients was compared with a group of nondiabetic control subjects, matched for age, sex, and BMI. Blood pressure and pulse pressure were monitored during an active postural test, the so-called squatting test, which has been shown by our group to amplify the pulse pressure increase according to diabetes duration in patients with type 1 diabetes (7,8).

RESEARCH DESIGN AND METHODS

— Forty patients (20 men and 20 women) with type 1 diabetes and 40 patients (20 men and 20 women) with type 2 diabetes were recruited among the patients followed in our department. Patients with arterial hypertension, renal insufficiency, or CVD or taking medications interfering with vascular reactivity (including any type of antihypertensive agents) were excluded from the study. All patients with type 1 diabetes received intensified insulin therapy with multiple daily insulin injections ($n = 36$) or continuous subcutaneous insulin infusion via a portable pump ($n = 4$). Patients with type 2 diabetes received various types of oral glucose-lowering therapies (metformin alone, sulfonylurea alone, or metformin-sulfonylurea combination) ($n = 25$) or insulin alone ($n = 5$) or combined with metformin ($n = 10$). Two groups of healthy subjects were used as control subjects and matched for BMI with either type 1 diabetic patients or type 2 diabetic patients (Table 1). The study was accepted by the ethics committee of our institution.

Orthostatic test

The squatting test (successively 1 min standing, 1 min squatting, and 1 min standing) is an original active orthostatic maneuver that leads to the most important and fast variations of the hydrostatic level with posture (9). Squatting produces a prompt increase in cardiac output and arterial blood pressure, essentially attributed to augmented venous return from compression of leg veins. These changes result in a significant increase in mean ar-

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Table 1—*Characteristics of middle-aged diabetic patients with type 1 diabetes, patients with type 2 diabetes, nondiabetic lean control subjects, and nondiabetic overweight/obese control subjects and average values recorded during the whole 3-min squatting test*

	T1DM	LC	T2DM	OC	*P* value T1DM vs. LC	*P* value T2DM vs. OC
n (men/women)	20/20	20/20	20/20	20/20		
Age (years)	50 ± 6	50 ± 6	50 ± 6	50 ± 6	0.8888	0.8971
Diabetes duration (years)	23 ± 11	—	8 ± 7	—	NA	NA
BMI (kg/m^2)	23.0 ± 2.0	22.2 ± 1.6	29.7 ± 3.7	28.6 ± 2.7	0.0642	0.1288
A1C (%)	8.4 ± 1.3	—	7.8 ± 1.6	—	NA	NA
Mean blood pressure (mmHg)	84 ± 13	85 ± 12	88 ± 13	86 ± 12	0.9719	0.5991
SBP (mmHg)	126 ± 21	120 ± 21	128 ± 20	122 ± 18	0.1649	0.1087
DBP (mmHg)	66 ± 11	68 ± 10	70 ± 13	70 ± 10	0.6195	0.1662
Pulse pressure (mmHg)	59 ± 13	52 ± 15	58 ± 16	52 ± 13	0.0160	0.0451
Pulse pressure-to-MBP ratio	0.703 ± 0.121	0.610 ± 0.139	0.677 ± 0.245	0.603 ± 0.152	0.0020	0.1082
Heart rate (bpm)	88 ± 13	80 ± 9	91 ± 10	84 ± 13	0.0029	0.0029
PP×HR product (mmHg · min^{-1})	5,263 ± 1,563	4,121 ± 1,120	5,359 ± 1,641	4,321 ± 1,277	0.0004	0.0023
SBP×HR product (mmHg · min^{-1})	11,120 ± 2,947	9,593 ± 1,771	12,082 ± 2,521	10,195 ± 2,291	0.0039	0.0008

Data are means ± SD. LC, nondiabetic lean control subjects; NA, not applicable; OC, nondiabetic overweight/obese control subjects; T1DM, patients with type 1 diabetes, T2DM, patients with type 2 diabetes.

terial blood pressure and pulse pressure (7,8), which is accompanied by an immediate decrease in heart rate and forearm vascular resistance, probably due to activation of cardiopulmonary and arterial baroreflexes, implicating the autonomic nervous system. Later on, the active transition from squatting to standing results in a profound initial blood pressure decrease inducing a reflex tachycardia, which can be used to detect diabetic cardiac autonomic neuropathy (CAN) (10,11) and assess baroreflex sensitivity (12).

Measurements

Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were measured continuously with a Finapres instrument (Ohmeda) that allows careful study of cardiovascular reflexes, especially during an orthostatic maneuver (13). The Finapres is based on servoplethysmomanometry, using the volume clamp technique at the finger level. A good concordance was reported between Finapres blood pressure measurements and direct intra-arterial measurements (13). Pulse pressure, i.e., SBP minus DBP, was automatically calculated throughout the test. Mean arterial blood pressure (MBP) was calculated by the formula (SBP + 2 × DBP)/3. To quantify the relative magnitude of the pulsatile to mean artery pressure ("pulsatility index"), we normalized the pulse pressure to the MBP and referred to this value as fractional pulse pressure (14). "Pulsatile stress" was defined as the double product of pulse pressure and heart rate (PP×HR)); it has been shown to be largely regulated by arterial stiffness and by sympathetic nerve activity and to be associated with a higher risk of (micro)albuminuria (15). We also calculated the SBP×HR double product, an index of cardiac load that has been shown to be associated with an increased CVD risk (16). For each variable or parameter, mean levels were calculated for each subject during the whole period of the test, during the initial standing position, and during the squatting position, after exclusion of the initial transition phase, as described previously (7,8).

During the transition from squatting to standing, there is an abrupt drop in blood pressure associated with a reflex tachycardia, which is followed by a rapid return to baseline values of both parameters (blood pressure increase and heart rate decrease). The mirror changes in heart rate and SBP allow the calculation of a baroreflex gain by plotting the pulse intervals (R-R) against SBP values, and the slope of this relation represents the baroreflex sensitivity (17). We also calculated both a vagal index (ratio between the baseline cardiac R-R interval and the longest R-R interval in the first 15 s of squatting [SqTv]) and a sympathetic index (ratio between the baseline cardiac R-R interval and the shortest R-R interval in the first 10–20 s of standing after squatting [SqTs]), as described previously (10,11). These indexes, based on heart rate reduction during squatting and reflex tachycardia during standing, were considered as markers of CAN: a higher SqtV value indicates a parasympathetic neuropathy, whereas a lower SqTs is an indicator of sympathetic neuropathy (10–12).

Concomitant A1C levels (normal values 4–6%) were measured to assess recent blood glucose control in diabetic patients; for each patient, the corresponding A1C mean level corresponded to the average of one to three measurements. Lipid profiles were also collected in diabetic patients and the prevalence of the metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III criteria) was calculated in patients with type 1 diabetes and in patients with type 2 diabetes.

Statistical analysis

The required sample size to have an 80% chance of detecting as significant (at the two-sided 5% level) 10 mmHg difference in pulse pressure between two different subgroups, with an assumed SD of pulse pressure of 14 mmHg, was 32 individuals. A difference of 10 mmHg was chosen as clinically significant because it has been shown to be associated with increased cardiovascular mortality in type 2 diabetes (1) and total mortality in the large EURODIAB cohort of patients with type 1 diabetes (5). Between-group differences were analyzed using unpaired *t* tests. The relationship between two variables, i.e., between pulsatile stress and baroreflex gain as a marker of CAN, was assessed with the Spearman correlation coefficient. Results are expressed as mean ± SD values for all continuous variables. $P < 0.05$ was considered significant.

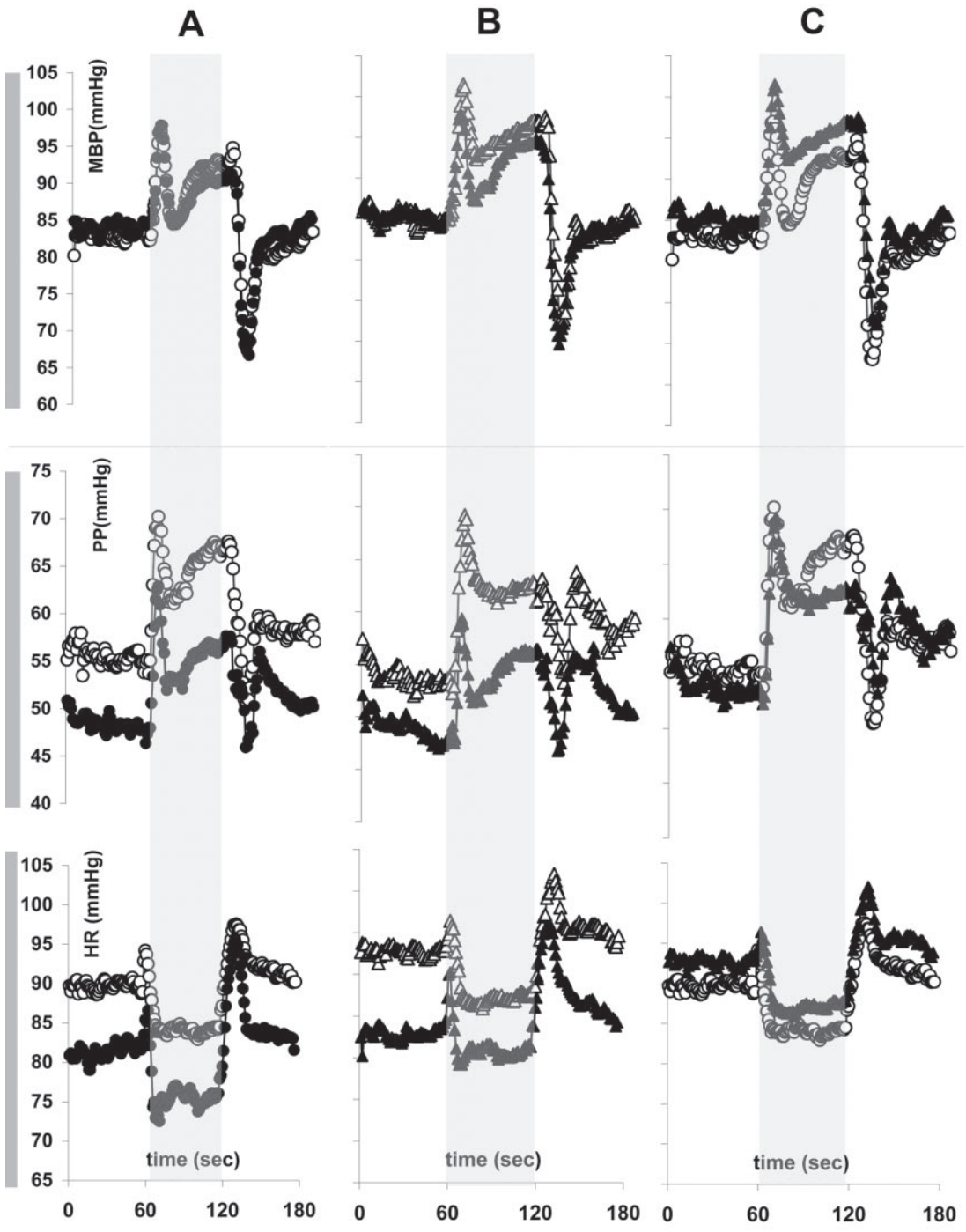

Figure 1—*Changes in MBP, pulse pressure (PP), and heart rate (HR) during a posture test (1 min standing, 1 min squatting [gray zone], 1 min standing).* A*: 40 patients with type 1 diabetes (○) versus 40 nondiabetic (●) subjects, matched for age, sex, and BMI.* B*: 40 patients with type 2 diabetes (△) versus 40 nondiabetic (▲) subjects matched for age, sex, and BMI.* C*: 40 patients with type 1 diabetes (○) versus 40 patients with type 2 diabetes (△) subjects, matched for age and sex.*

RESULTS

Patients with type 1 diabetes versus nondiabetic lean subjects

Compared with control subjects, patients with type 1 diabetes had similar MBP but were characterized throughout the test by significantly higher pulse pressure, heart rate, pulse pressure/MBP, PP×HR, and SBP×HR levels (Fig. 1*A*, Table 1). When squatting was compared with the initial standing position, a trend for higher increases in pulse pressure, PP/MBP, and PP×HR was observed in patients with type 1 diabetes than in control subjects, with a significantly higher increase in SBP×HR (Table 2). The baroreflex gain calculated during the transition from squatting to standing was markedly decreased in patients with type 1 diabetes compared with that in control subjects. SqTv and SqTs indexes were also significantly different in patients with type 1 diabetes compared with those in lean

Table 2—*Changes occurring during the transition from the initial standing position to the squatting position in middle-aged diabetic patients with type 1 diabetes, patients with type 2 diabetes, nondiabetic lean control subjects, and nondiabetic overweight/obese control subjects*

	T1DM	LC	T2DM	OC	*P* value T1DM vs. LC	*P* value T2DM vs. OC
N	40	40	40	40		
Δ MBP (mmHg)	8 ± 7	5 ± 4	10 ± 9	7 ± 8	0.0185	0.0875
Δ SBP (mmHg)	13 ± 11	8 ± 7	14 ± 14	9 ± 11	0.0101	0.0754
Δ DBP (mmHg)	3 ± 5	1 ± 4	6 ± 7	3 ± 7	0.0141	0.1391
Δ Pulse pressure (mmHg)	10 ± 8	7 ± 6	8 ± 11	6 ± 7	0.0705	0.1662
Δ Pulse pressure-to-MBP ratio	0.127 ± 0.110	0.087 ± 0.074	0.095 ± 0.133	0.065 ± 0.082	0.0593	0.2371
Δ Heart rate (/min)	−6 ± 7	−6 ± 6	−6 ± 7	−2 ± 7	0.7449	0.0123
Δ PP×HR product (mmHg · min^{-1})	557 ± 935	276 ± 532	449 ± 942	404 ± 743	0.1029	0.8132
Δ SBP×HR product (mmHg · min^{-1})	1,136 ± 1,270	601 ± 698	1,236 ± 1,440	963 ± 1,178	0.0227	0.3611
Baroreflex gain (mmHg · min^{-1})	2.20 ± 1.73	4.11 ± 2.26	2.05 ± 1.31	2.97 ± 2.18	0.0002	0.0351
SqTv index	0.88 ± 0.08	0.81 ± 0.13	0.90 ± 0.07	0.89 ± 0.09	0.0059	0.7553
SqTs index	1.13 ± 0.09	1.20 ± 0.11	1.13 ± 0.07	1.21 ± 0.10	0.0046	0.0004

Data are means ± SD. Mean values of baroreflex gain as well as SqTv and SqTs indices of cardiac autonomic neuropathy are also presented for the four groups. There were 20 men and 20 women in each group. LC, nondiabetic lean control subjects; OC, nondiabetic overweight/obese control subjects; T1DM, patients with type 1 diabetes; T2DM, patients with type 2 diabetes.

control subjects (Table 2). There was a significant inverse correlation between pulsatile stress (PP×HR) and baroreflex gain in patients with type 1 diabetes ($r = -0.383$; $P = 0.023$) but not in lean control subjects ($r = -0.178$; NS).

Patients with type 2 diabetes versus nondiabetic overweight/obese patients

Compared with overweight/obese nondiabetic control subjects, patients with type 2 diabetes had similar MBP (hypertension was considered as an exclusion criterion in the present study). However, they showed higher pulse pressure, heart rate, pulse pressure-to-MBP ratio, PP×HR, and SBP×HR levels throughout the test (Fig. 1*B*, Table 1). Increases in pulse pressure, pulse pressure-to-MBP ratio, PP×HR, and SBP×HR when moving from standing to squatting were not significantly different in patients with type 2 diabetes and in overweight/obese nondiabetic control subjects (Table 2). The baroreflex gain was significantly decreased in patients with type 2 diabetes compared with that in control subjects. The SqTs index (reflecting postsquatting tachycardia) but not the SqTv index (a marker of bradycardia during squatting) was significantly lower in patients with type 2 diabetes than in overweight/obese nondiabetic control subjects (Table 2). There was a highly significant inverse correlation between pulsatile stress and baroreflex gain in patients with type 2 diabetes ($r = -0.719$; $P = 0.0001$) but not in overweight/obese control subjects ($r = -0.272$; NS). No significant differences in pulsatile markers and CAN indexes were noticed between the patients with type 2 diabetes treated with insulin and those not treated with insulin.

Patients with type 1 diabetes versus patients with type 2 diabetes

On average, MBP, pulse pressure, heart rate, pulse pressure-to-MBP ratio, PP×HR, and SBP×HR levels were comparable in middle-aged patients with type 1 and type 2 diabetes (Fig. 1*C*, Table 1). The transition from standing to squatting resulted in similar increases in MBP, pulse pressure, pulse pressure-to-MBP ratio, PP×HR, and SBP×HR in the two groups of diabetic patients (Table 2). Careful analysis of the two pulse pressure curves showed different kinetics in pulse pressure increases, with a second phase increase in pulse pressure in patients with type 1 diabetes that was not observed in patients with type 2 diabetes; however, the between-group difference during the second part of squatting did not reach statistical significance (Fig. 1*C*). The baroreflex gain was similar in patients with type 1 and type 2 diabetes. Accordingly, SqTv and SqTs indexes were not significantly different between the two diabetic groups (Table 2). Patients with type 1 diabetes had a much longer known disease duration (23 vs. 8 years; $P < 0.0001$) but a much lower prevalence of metabolic syndrome (3% vs. 42%; $P < 0.01$) than patients with type 2 diabetes.

Overweight/obese versus lean subjects without diabetes

On average, MBP, pulse pressure, heart rate, pulse pressure-to-MBP ratio, PP×HR, and SBP×HR levels were comparable in obese and lean nondiabetic individuals in the present study (Table 1). The postural change from standing to squatting resulted in similar increases in MBP, pulse pressure, pulse pressure-to-MBP ratio, and PP×HR in overweight/obese and lean subjects, with only a trend for a higher increase in SBP×HR (+963 ± 1,178 vs. + 601 ± 698 mmHg · min^{-1}; $P = 0.0991$) in presence of obesity (Table 2). The baroreflex gain was significantly lower in overweight/obese subjects than in lean individuals (2.97 ± 2.18 vs. 4.11 ± 2.26 mmHg · min^{-1}; $P = 0.0332$), even in absence of diabetes. The SqTv index was higher in obese subjects than in lean control subjects ($P = 0.0011$), whereas the SqTs index was almost similar in the two nondiabetic groups (Table 2).

CONCLUSIONS

— The main findings of the present study are *1*) higher pulse pressure, pulse pressure-to-MBP ratio, PP×HR, and SBP×HR levels in middle-aged patients with type 1 diabetes compared with those in lean control subjects, in agreement with higher pulsatile stress and cardiac workload in patients with long-standing type 1 diabetes, *2*) similarly, higher pulse pressure, pulse pressure-to-MBP ratio, PP×HR, and SBP×HR levels in middle-aged nonhy-

pertensive patients with type 2 diabetes compared with those in overweight/obese nondiabetic control subjects, *3*) the absence of significant differences in pulse pressure, pulsatile index, pulsatile stress, and double product between patients with type 1 diabetes and with type 2 diabetes matched for age (50 years on average); and *4*) indexes of CAN as shown by lower baroreflex gain and altered SqT indexes during squatting in both patients with type 1 diabetes and type 2 diabetes compared with those in nondiabetic control subjects. Therefore, middle-aged patients with type 1 diabetes or with type 2 diabetes are exposed to comparable pulsatile stress, a known cardiovascular and renal risk marker (1–5,15,16). In patients with type 1 diabetes, the negative influence of a much longer diabetes duration (23 years on average in the present study) might be at least partially compensated for by the positive influence of lower BMI, less insulin resistance, and a much lower prevalence of metabolic syndrome compared with those for patients with type 2 diabetes. On the contrary, middle-aged patients with type 2 diabetes are exposed to high pulsatile stress despite a shorter known duration of diabetes (8 years on average in our population), presumably because of the presence of other concomitant cardiovascular risk factors (even if hypertension were excluded in the present study), as shown by a much higher prevalence of metabolic syndrome compared with that for patients with type 1 diabetes.

The observation of higher pulse pressure levels in patients with type 1 diabetes compared with control subjects in the age range 40–60 years is in agreement with previous studies from our group, demonstrating an earlier pulse pressure increase with age in this population (7,8) and with the observational data of the large cross-sectional, case-control FinnDiane study (3). Because pulse pressure is considered an indirect marker of arterial stiffness, these higher pulse pressure results are in agreement with accelerated vascular aging in the population with type 1 diabetes (6), especially patients with chronic poor glucose control (18). In the FinnDiane study, the ambient level of glucose was not associated with increased pulse pressure, but the time of exposure to hyperglycemia seemed to play a fundamental role in the process of premature arterial stiffening in patients with type 1 diabetes (3). In the EURODIAB Prospective Complications Study, pulse pressure was significantly associated with all-cause mortality and a mean 12 mmHg higher pulse pressure was observed in patients with type 1 diabetes who died compared with that of those who survived (5).

Decreased baroreflex gain was observed in our patients with type 1 diabetes, reflecting the presence of CAN after >20 years of diabetes (19). This result was confirmed by altered SqTs and SqTv indexes during the squatting test, markers of parasympathetic and sympathetic dysfunction, respectively (10). CAN exposes diabetic patients to an increased mortality risk (19). There may be some connection between pulse pressure and CAN (8), between aortic stiffness and CAN (20), and between arterial stiffness, cardiovagal baroreflex sensitivity, and postural blood pressure changes (21). Increased SBP was identified as a factor associated with an increased risk of developing CAN in the cohort of patients with type 1 diabetes of the EURODIAB Prospective Complications study (22). The pathophysiological mechanism linking CAN to arterial stiffness in patients with type 1 diabetes remains unknown, but this association persisted after adjustment for potential confounders such as baseline A1C, HDL cholesterol, and smoking history (23). In the present study, we found a significant relationship between pulsatile stress and baroreflex gain as a marker of CAN in patients with type 1 diabetes. In patients with type 2 diabetes, markers of CAN are also present (11), although less marked than in patients with prolonged type 1 diabetes (7). The relationship between pulse pressure and CAN is less well known in patients with type 2 diabetes even if associations between autonomic neuropathy, vascular dysfunction, and hyperinsulinemia have been demonstrated (24). Interestingly, a remarkable significant inverse correlation was noted between pulsatile stress and baroreflex gain in the group of patients with type 2 diabetes in our study. Several mechanisms may underlie the association between arterial stiffness and impaired cardiovagal baroreflex sensitivity. The stiffness of the carotid arteries and the aorta, where the arterial baroreceptors are located, may affect the stretch-sensitive receptors and hence baroreflex sensitivity. In addition to structural vascular changes, functional mechanisms associated with endothelial dysfunction may also contribute to the impairment of baroreflex sensitivity associated with arterial stiffness (21).

Patients with type 2 diabetes also showed increased pulse pressure, pulsatility index, and pulsatile stress compared with those for overweight/obese nondiabetic individuals matched for BMI, age, and sex. This result was observed despite the absence of hypertension and a much shorter duration of diabetes compared with those in the population with type 1 diabetes analyzed in the present study. It is well known, however, that type 2 diabetes remains silent during an average of 10 years before diagnosis and initiation of treatment in most cases. Thus, selected patients may have a longer duration of type 2 diabetes than the average 8-year known duration noted in the present population. To avoid the potential bias of hypertension and the interferences of antihypertensive agents, we deliberately selected type 2 diabetic patients without hypertension. Despite normal MBP, middle-aged patients with type 2 diabetes had higher pulse pressure and pulsatile stress and higher SBP×HR, two CVD risk markers (16). Increased pulse pressure levels have been repeatedly demonstrated in large longitudinal studies in patients with type 2 diabetes and shown to be associated with a higher incidence of cardiovascular events (1,2).

Some limitations of the present study should be discussed. Several studies have demonstrated that absolute brachial and finger pulse pressure measurements are not identical with larger differences in SBP. However, the differences were generally small and not considered of clinical relevance (13). Furthermore, some studies have shown a good concordance between periphery (finger, as in the present study) and central (aortic, now recognized as the most important risk factor) blood pressure measurements (25). Nevertheless, pulse pressure measured at the finger site may not necessarily reflect central pulse pressure because of the amplification phenomenon. Second, glucose control of patients with type 1 diabetes evaluated in the present study was far from optimal, despite intensified insulin therapy. Therefore, our results could not necessarily be extrapolated to patients with near normoglycemia for many years because chronic hyperglycemia seems to play a major role in accelerating arterial stiffness (18). Third, patients with type 2 diabetes selected in the present study did not have hypertension. Therefore, the similar results in markers of pulsatile stress in middle-aged patients with type 1 and type 2 diabetes should be interpreted in this context. We cannot exclude the

possibility that overweight/obese patients with type 2 diabetes and hypertension may be exposed to higher vascular stress than lean normotensive patients with type 1 diabetes at the same age. This would certainly be the case for SBP×HR but may also be true for the various pulsatility markers. Fourth, very few patients had positive microalbuminuria in the two diabetic cohorts analyzed in the present study, because we excluded patients with hypertension or those taking antihypertensive agents. Therefore, we were not in a position to study the possible relationship between pulsatile stress and early renal alterations as shown in previous studies (15).

In summary, middle-aged patients with a long duration of type 1 diabetes have similarly increased pulsatile stress compared with age-matched patients with type 2 diabetes characterized by a shorter duration of the disease, but the presence of other vascular risk factors such as obesity and insulin resistance and no hypertension. In addition, both diabetic groups have markers of CAN with a reduced baroreflex gain compared with nondiabetic control subjects. The combination of these risk factors may contribute to increase the CVD risk in type 1 diabetic patients with a long exposure to chronic hyperglycemia in a fashion similar to that of patients with type 2 diabetes whose high CVD risk is well known.

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J.-C.P. contributed to the concept and design of the study; acquired, analyzed, and interpreted data; outlined the structure of the manuscript; and reviewed/edited the manuscript. M.M contributed to the concept and design of the study; acquired, analyzed, and interpreted data; outlined the structure of the manuscript; and reviewed/edited the manuscript. A.J.S. contributed to the concept and design of the study, outlined the structure of the manuscript, wrote the manuscript, and reviewed/edited the manuscript.

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