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

Jean-Christophe Philips, MD
Monique Marchand
André J. Scheen, MD, PhD

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/m²) were compared with 40 nonhypertensive patients with type 2 diabetes (respectively, 50 years, 8 years, and 29.7 kg/m²). 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. 5,399 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.

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-
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 servopletysmomonometer, 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 (MAP) 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 MAP 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 baseline values of both parameters (blood pressure and heart rate). 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) a 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.
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. 1A, 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...
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. 1B, 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 SqTv index (reflecting postquating tachycardia) but not the SqTs 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. 1C, Table 1). The transition 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 · mm⁻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-
Pulsatile stress in diabetes

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×CHR, 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 stiffening (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 shorter duration of the disease, but the association 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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