

# Vascular Compliance Is Reduced in the Early Stages of Type 1 Diabetes

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**OBJECTIVE** — To determine whether arterial compliance of patients with type 1 diabetes is reduced before the development of clinically apparent diabetes complications.

**RESEARCH DESIGN AND METHODS** — Pulse-wave analysis was used to compare vascular compliance between patients with type 1 diabetes and nondiabetic control subjects. Analysis of covariance was used to determine differences between the two groups with adjustment for age if needed.

**RESULTS** — A total of 59 patients with type 1 diabetes were studied; age ranged from 17–61 years. Of the 59 patients, 32 had no evidence of diabetes complications and 27 had microvascular complications. The control group consisted of 57 healthy subjects ranging in age from 23–79 years. In the control group, large artery compliance (C1) and small artery compliance (C2) were inversely proportional to age ( $r = -0.55$  for C1 and  $-0.50$  for C2;  $P < 0.01$ ). When the control subjects were compared with type 1 diabetic patients without microvascular complications, C1 was  $1.51 \pm 0.04$  (SEM) for the control group and  $1.33 \pm 0.06$  (SE) ml/mmHg for the diabetic group, whereas C2 was  $0.080 \pm 0.005$  (SE) and  $0.065 \pm 0.005$  (SE) ml/mmHg for the control and diabetic subjects, respectively, when adjusted for age ( $P = 0.03$  for both C1 and C2).

**CONCLUSIONS** — Vascular compliance of both the large and small arteries is reduced in type 1 diabetic patients before any clinical complications from the diabetes are evident. This study serves to emphasize that vascular changes occur at an early point in the disease and may increase risk of cardiovascular events in patients with diabetes. Larger prospective studies are required to confirm this finding and to investigate the efficacy of medical intervention.

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**H**ypertension, hypercholesterolemia, and diabetes are well-recognized cardiovascular risk factors (1). Emerging evidence suggests that decreased vascular elasticity and storage capacity of the vessels, also known as vascular compliance, is associated with each of these conditions and may predispose patients to cardiovascular events (2,3). A reduction in arterial compliance is a marker for vascular disease and should prompt a more aggressive approach in managing cardiovascular risk

factors (3–6). Several studies have demonstrated diminished arterial compliance in patients with type 1 or type 2 diabetes, which may contribute, in part, to the excess cardiovascular morbidity and mortality associated with these conditions (7–11).

Noninvasive technology has enabled the measurement of pulse wave velocity and arterial pulse contour to assess vascular compliance (12,13). Doppler ultrasound has been used to measure pulse-wave velocity and aortic compliance, but

this method is operator-dependent and more prone to error (12). In addition, Doppler techniques only assess large arteries because measurements are taken from the aorta or the aorta-iliac junction (12). Pulse-wave contour analysis is a reproducible and objective method for determining compliance of both the large and small arteries by using radial artery tonometry to reliably estimate central artery aortic waveforms and pressure (14,15). This method enables simultaneous measurement of compliance of both large vessels (e.g., aorta) and small vessels (e.g., tissue bed vessels). The major advantage of using pulse-wave analysis over other techniques is that it can assess the compliance of small arteries, such as those that would be involved in the development of microvascular diabetic complications. In addition, this technique is noninvasive, operator-independent, and able to quickly obtain measurements, making it ideal for assessing effectiveness of therapy in the clinical setting.

Few studies have examined arterial compliance in patients with type 1 diabetes, and the published studies made use of either the Doppler or ultrasound techniques. Berry et al. (8) used Doppler flow volume to show a 29% reduction in systemic arterial compliance in type 1 diabetic patients compared with control subjects. Ryden-Ahlgren et al. (16) showed increased arterial stiffness in women with type 1 diabetes using ultrasound. In the present study, we used pulse-wave analysis to determine 1) the arterial compliance of patients with type 1 diabetes, 2) whether arterial compliance is reduced before clinically apparent microvascular complications, and 3) whether patients with known microvascular complications have diminished arterial compliance.

## RESEARCH DESIGN AND METHODS

### Patient population

Subjects with type 1 diabetes were recruited from the Diabetes Clinic at the University of Alberta Hospital, Edmon-

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**Abbreviations:** ANCOVA, analysis of covariance; C1, large artery compliance; C2, small artery compliance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ton, Alberta, Canada. To determine the presence of microvascular complications, patients were examined by an endocrinologist, underwent a yearly ophthalmologic evaluation, and underwent urinalysis for the presence of microalbuminuria. Out-patient charts were reviewed to obtain the medical history and the method of diabetes management. Control subjects were recruited from within the hospital and had no history of diabetes, cardiovascular disease, or hypertension and were taking no medication that could potentially interfere with vascular compliance. Consent was obtained before participation in the study.

A total of 59 patients with type 1 diabetes (31 men, 28 women) were studied; age ranged from 17–61 years, and duration of diabetes was  $17.7 \pm 10.9$  years. Of the 59 patients, 32 had no evidence of diabetic complications, whereas 27 had microvascular complications (defined as presence of retinopathy, nephropathy, or neuropathy). The control group consisted of 57 healthy subjects (27 men, 30 women) ranging in age from 23–79 years.

#### Pulse-wave analysis

Large artery compliance, small artery compliance, blood pressure, and systemic vascular resistance were measured noninvasively using an HDI/Pulsewave Cardiovascular Profiling Instrument CR-2000 (Hypertension Diagnostics, Eagan, MN). Measurements were taken by a single operator after the subjects had been resting supine for 5 min in a quiet room and had not consumed any caffeine or smoked for at least 30 min. The theoretical basis and clinical validation of pulse-wave analysis have been described previously (15,17,18).

#### Statistical analysis

All statistical analyses were performed using SPSS statistical software (Version 10.0; SPSS, Chicago, IL). Analysis of variance was used to determine differences in characteristics between the control group, the entire diabetic group, and the subgroups of patients with and without microvascular complications. Variables tested and subsequently used in the analysis of covariance (ANCOVA), if a significant difference from the control was found, included age, gender, systolic and diastolic blood pressure, systemic vascular resistance, and smoking, because these factors have the potential to affect vascular compliance. The marginal mean age

**Table 1—Baseline characteristics of study participants**

Characteristic	Control subjects (n = 57)	Diabetic subjects (n = 59)
Age (years)	37.9 ± 12.6	31.2 ± 12.6*
Sex (M/F)	27/30	31/28
BMI (kg/m <sup>2</sup> )	24.8 ± 4.2	25.6 ± 3.8
Smokers	5	13
History of hypertension	—	17
Microvascular complications	—	27
Systolic blood pressure (mmHg)	123.1 ± 13.6	130.8 ± 12.6*
Diastolic blood pressure (mmHg)	69.1 ± 8.6	72.2 ± 10.2
Systemic vascular resistance (dyne · s · cm <sup>-5</sup> )	1,305.8 ± 231.1	1,354.9 ± 304.4

Data are n or means ± SEM. \*P = 0.005 versus control subjects.

between the control group and the comparison diabetic group was used in the ANCOVA for vascular compliance when the age between these two groups was statistically different. Data are expressed as the mean ± standard deviation unless otherwise noted. Univariate ANCOVA was used to test for significant differences;  $P < 0.05$  was considered significant. Linear regression was used to determine correlation coefficients.

**RESULTS**— The demographic data of the study participants are shown in Table 1. The diabetic patients were younger than the control subjects ( $31.2 \pm 12.6$  vs.  $37.9 \pm 12.6$  years,  $P = 0.005$ ) and had statistically higher systolic blood pressure, which was still within the accepted normal range ( $130.8 \pm 12.6$  vs.  $123.1 \pm 13.6$  mmHg,  $P = 0.005$ ).

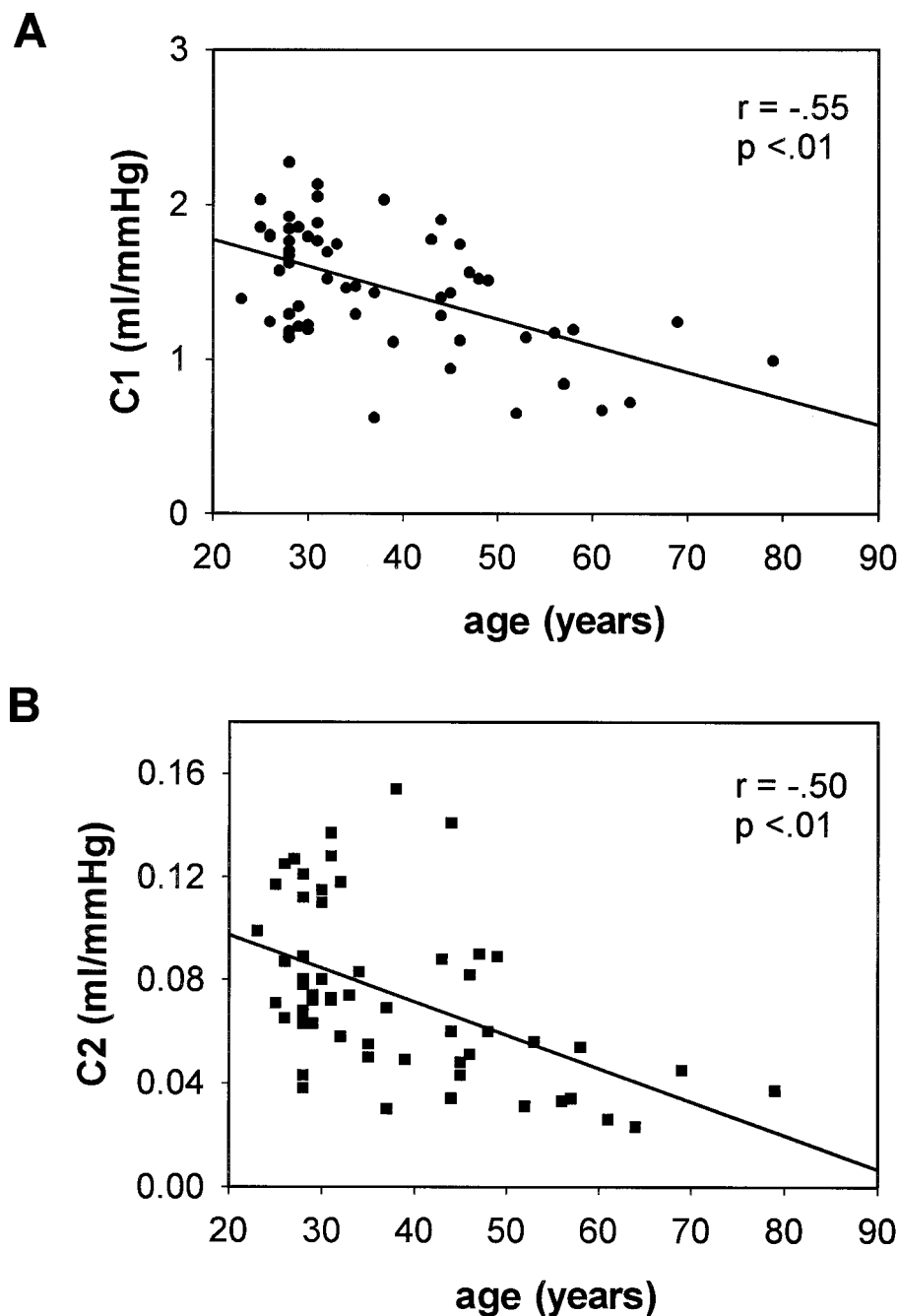
In the diabetic group, 17 patients had a history of hypertension and 22 were taking antihypertensive or antineuropathy medications; 19 patients were taking ACE inhibitors, 2 were taking angiotensin receptor blockers, 2 were taking calcium channel blockers, 2 were taking  $\beta$ -blockers, 4 were taking thiazide diuretics, and 2 were taking loop diuretics.

In the control group, large artery compliance (C1) and small artery compliance (C2) were inversely proportional to age ( $r = -0.55$  for C1 and  $-0.50$  for C2;  $P < 0.01$  (Fig. 1). In addition, men had greater C1 and C2 compared with women when controlled for age (C1 =  $1.65 \pm 0.32$  vs.  $1.30 \pm 0.38$  ml/mmHg, C2 =  $0.094 \pm 0.033$  vs.  $0.057 \pm 0.021$  ml/mmHg;  $P < 0.01$ , despite no differences in blood pressure or systemic vascular resistance.

ANCOVA was used to compare C1

and C2 between the control group and the diabetic group. No difference was observed between C1 or C2 in the two groups when the variables that also differed between the two groups (age, smoking, and systolic blood pressure) were added as covariables (C1,  $P = 0.39$ ; C2,  $P = 0.06$ ). When the diabetic patients without microvascular complications were examined, statistical differences with the control subjects were found for C1 and C2 when adjusted for age and systolic blood pressure, despite both groups being normotensive and having normal systemic vascular resistance (Table 2, Fig. 2). Using an age-adjusted model for the two groups, C1 was  $1.51 \pm 0.04$  for the control group and  $1.33 \pm 0.06$  ml/mmHg for the diabetic group ( $P = 0.03$ ), whereas C2 was  $0.080 \pm 0.005$  and  $0.065 \pm 0.005$  ml/mmHg for the control and diabetic groups, respectively ( $P = 0.03$ ) (Fig. 2).

No statistical differences were apparent in the diabetic subgroup with microvascular complications (C1 =  $1.33 \pm 0.41$ , C2 =  $0.059 \pm 0.035$  ml/mmHg) compared with the control group (C1 =  $1.47 \pm 0.39$ , C2 =  $0.074 \pm 0.033$  ml/mmHg) when blood pressure and systemic vascular resistance were added as covariables to the ANCOVA (C1,  $P = 0.14$ ; C2,  $P = 0.23$ ) (Table 2). Of note, 20 of the 27 diabetic patients with microvascular complications were on medical therapy for hypertension or nephropathy. Of the 20 medically treated patients, 18 were taking ACE inhibitors and 1 was taking an angiotensin receptor blocker. The seven patients who were not taking medication for hypertension or nephropathy had only peripheral neuropathy and were normotensive.



**Figure 1**—Vascular compliance decreases with age in the control subjects. A: Large artery compliance (C1). B: Small artery compliance (C2).

**CONCLUSIONS** — In this study, we demonstrated by pulse-wave analysis that young, normotensive subjects with type 1 diabetes have diminished large artery and small artery compliance despite having no microvascular or macrovascular complications. These findings provide further evidence that changes in the vascular wall occur before clinical complications are clinically apparent in seemingly healthy

diabetic individuals. No such changes in compliance were found in patients with established microvascular complications. However, 20 of these 27 patients were taking medications that are known to affect compliance.

Several other studies have also found decreased vascular compliance in diabetic patients. Berry et al. (8) used flow velocity Doppler measurements to also show that

type 1 diabetic patients without diabetic complications had a 29% reduction in systemic arterial compliance when compared with control subjects. This effect was independent of glycemic control and altered lipid levels. Echo tracking sonography has also been used to show increased aortic stiffness in women with type 1 diabetes (16). Postmortem aortic samples from patients with type 1 diabetes also show reduced extensibility and increased wall thickness (9).

Pulse waveform analysis of diabetic patients has demonstrated similar results. Duprez et al. (19) studied 31 diabetic patients on insulin therapy and found an inverse correlation between small artery compliance and duration of diabetes. No such correlation was seen for large artery compliance. McVeigh et al. (20) used intra-arterial brachial artery waveforms in 28 patients with type 2 diabetes to demonstrate diminished small artery compliance. Of these patients, 12 had retinopathy, 3 had microalbuminuria, and 2 had impaired sensation of vibration. Pulse wave velocity was also higher in type 2 diabetic patients, indicating greater arterial stiffness (21).

The patients with established microvascular disease did not demonstrate a reduction in vascular compliance. The unadjusted data for C1 and C2 seem to show lower compliance values in this diabetic group compared with the control subjects (Table 2). However, when analysis of variance is performed with blood pressure and systemic vascular resistance as covariables, there were no statistical differences in compliance between these two groups. This could represent the beneficial effect of medical therapy on the vasculature, because 74% of these patients were receiving treatment and 70% were using an ACE inhibitor or an angiotensin II receptor blocker. It has recently been shown that in hypertensive individuals on chronic antihypertensive therapy, vascular compliance is indistinguishable from normotensive subjects when measured by pulse-wave analysis (13). Treatment with ACE inhibitors is known to affect smooth muscle proliferation and improve endothelium-dependent vasodilatation by stimulating production of nitric oxide (22). Arcaro et al. (23) found improved vessel wall dilatation and endothelium mediated flow in diabetic patients randomized to treatment with captopril or enalapril. Therefore, it is not

Table 2—Arterial compliance, blood pressure, and systemic vascular resistance of diabetic patients with and without microvascular complications compared with control subjects

Characteristic	Control group (n = 57)	Diabetic group with no microvascular complications (n = 32)	Diabetic group with microvascular complications (n = 27)
Age (years)	37.9 ± 12.6	23.4 ± 8.5*	40.4 ± 10.4
C1 (ml/mmHg)	1.47 ± 0.39	1.47 ± 0.33*	1.33 ± 0.41
C2 (ml/mmHg)	0.074 ± 0.033	0.075 ± 0.021*	0.059 ± 0.035
C1 (ml/mmHg) [age adjusted]	1.51 ± 0.04	1.33 ± 0.06*	—
C2 (ml/mmHg) [age adjusted]	0.080 ± 0.005	0.065 ± 0.005*	—
Systolic blood pressure (mmHg)	123.1 ± 13.5	125.6 ± 10.5*	136.9 ± 17.5*
Diastolic blood pressure (mmHg)	69.1 ± 8.6	68.5 ± 8.6	76.5 ± 10.4*
Systemic vascular resistance (dyne · s · cm <sup>-5</sup> )	1,305 ± 231.1	1,215.7 ± 175.6	1,519.8 ± 343.4*

Data are n or means ± SEM. \*P < 0.05 versus control group.

surprising that the patients with microvascular complications had vascular compliance similar to the control subjects, because most were taking medications that improve vascular compliance. However, the lack of a difference in compliance between these two groups could still be due to type 2 error, considering the small sample size of this diabetic group and the inherent added variability caused by the treatment of this group of patients with different antihypertensive or renal protective agents. Another study assessing the vascular compliance in a larger group of such subjects before the addition of medical therapy would address this issue.

The diminished vascular compliance

found in diabetes is believed to be multifactorial. Hyperglycemia activates the polyol pathway and protein kinase C and causes the formation of advanced glycosylation end products (24). Each of these pathways interferes with endothelial relaxation induced by either nitric oxide or acetylcholine. Johnstone et al. (25) found diminished forearm vasodilation in response to methacholine in diabetic patients compared with control subjects. In addition, diabetes is associated with increased levels of oxygen-derived free radicals, which may inactivate nitric oxide or act as a vasoconstrictor (26). Oxidized LDL also inhibits endothelium-dependent relaxation and may be a contributing factor in diabetic patients (14).

The structure of the blood vessels is also altered in patients with diabetes. There is an increase in type IV collagen, fibronectin, and laminin, which leads to changes in the elastic properties of the basement membrane. The extracellular matrix proteins become glycosylated, leading to increased collagen cross-linking (24). Furthermore, insulin is believed to contribute to smooth muscle cell proliferation and increased synthesis of extracellular matrix proteins, which could reduce vessel compliance.

There are several limitations to this study. First, the cross-sectional design did not allow us to follow the patients prospectively to determine whether compliance improved or worsened with further therapeutic intervention. Second, data were not available to assess the degree of glycemic control (HbA<sub>1c</sub>); however, others have found that HbA<sub>1c</sub> did not correlate with vascular compliance (8,27). Data on the lipid status of the subjects were also not available from the review of the chart. If the lipid profiles of the diabetic group were abnormal, this would only emphasize the need to aggressively control all cardiovascular risk factors, even early in the course of diabetes.

Diabetes is a risk factor for cardiovascular disease (1). We have shown that vascular compliance of both large and small vessels is reduced in patients with type 1 diabetes before any clinical complications from the disease are evident. This study serves to emphasize that vascular changes occur at an early point in the disease and may increase risk of cardiovascular events in diabetic patients. Larger prospective studies are required to

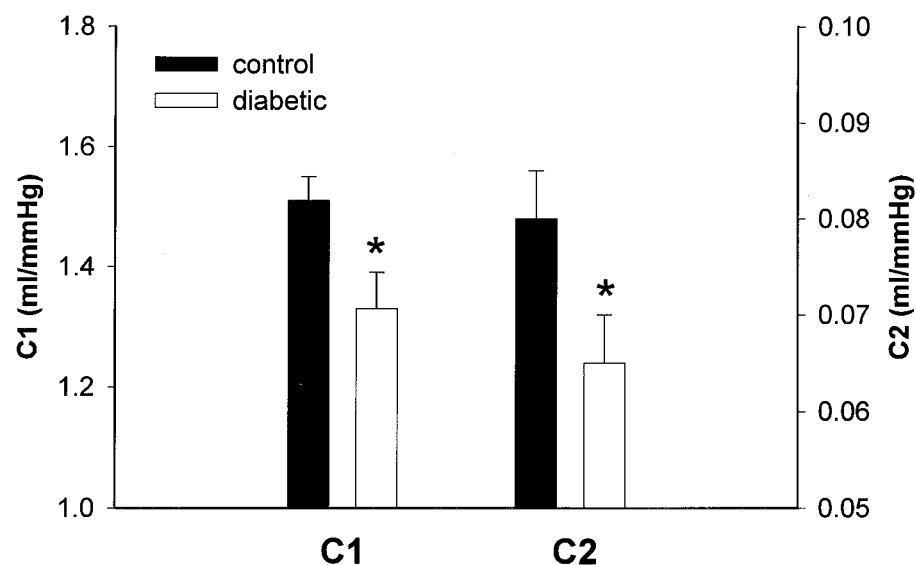


Figure 2—Age-adjusted large artery compliance (C1) and small artery compliance (C2) for the control group and diabetic patients without microvascular complications. \*P = 0.03.

confirm this finding and to investigate the efficacy of medical intervention.

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