Increases in Central Aortic Impedance Precede Alterations in Arterial Stiffness Measures in Type 1 Diabetes

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OBJECTIVE — Increased pulse pressure has been associated with increased cardiovascular risk in individuals with diabetes. Changes in central aortic properties can increase central pulse pressure and may adversely affect microvascular perfusion and cardiac performance. This study was performed to define early changes in central arterial properties in a group of young individuals with type 1 diabetes.

RESEARCH AND DESIGN METHODS — Seventeen individuals with type 1 diabetes and their nondiabetic control subjects who were participating in the Cardio-Diab Study had arterial stiffness and pulsatile hemodynamics measured with calibrated tonometry and pulsed Doppler. Aortic characteristic impedance (Z_c) was calculated from the ratio of change in carotid pressure and aortic flow in early systole. Pulse wave velocity (PWV) was assessed from tonometry and body surface measurements.

RESULTS — Duration of type 1 diabetes was 15.3 ± 0.7 (mean ± SD) years. In type 1 diabetic subjects, central pulse pressure was elevated (45 ± 11 vs. 36 ± 10 mmHg in control subjects, $P = 0.02$), as was peripheral pulse pressure (54 ± 13 vs. 43 ± 10 mmHg, $P = 0.002$). Z_c was elevated in type 1 diabetes (179 ± 57 vs. 136 ± 42 dynes × s/cm^5 in control subjects, $P = 0.004$), whereas PWV was not different (5.9 ± 0.9 vs. 5.9 ± 0.7 m/s in type 1 diabetic vs. control subjects, respectively; NS). There was a moderate correlation between Z_c and urinary albumin excretion (coefficient 0.39, $P = 0.02$).

CONCLUSIONS — Z_c appears to be increased early in type 1 diabetes, before elevation of PWV and is associated with higher pulse pressure, which may contribute to renal microvascular damage in diabetes.

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Cardiovascular disease (CVD) claims the lives of 65% of individuals with diabetes, ~150,000 deaths per year in the U.S. (1). Pulse pressure is a nontraditional marker of increased CVD risk that strongly predicts cardiovascular events in type 2 diabetes (2–4). Because stiffening of central arteries is associated with increased pulse pressure, understanding aortic changes in the natural history of diabetes is of interest and of particular importance because CVD risk in diabetes is not completely predicted by traditional cardiovascular risk factors and occurs at an early age (5). Improved understanding of the role played by central arterial stiffening in the pathophysiology of diabetes may shed light on the excess CVD mortality faced by these individuals.

There are multiple measures of arterial stiffness, reflecting different properties of the aorta and peripheral vessels. Prior studies have demonstrated conflicting results for stiffness changes in diabetic populations (6–14). These differences have been attributed to technical differences in studies, different ages and durations of diabetes in participants studied, and the presence of confounding conditions, such as hypertension (13,15). In addition, data on stiffness may differ, depending on whether regional or global measures of stiffness or wave reflection are assessed. In hypertensive patients, it has been shown that increased aortic impedance (Z_c) correlates with increased pulse pressure, with changes in pulse wave velocity (PWV) due primarily to changes in mean arterial pressure (MAP) rather than vessel stiffening (16). We sought to comprehensively assess arterial hemodynamics in a small cohort of young people with type 1 diabetes. We hypothesized that early changes in proximal aortic impedance in type 1 diabetes may play an important etiological role in later development of vascular complications.

RESEARCH DESIGN AND METHODS

— The Wisconsin Diabetes Registry Project was a population-based cohort of individuals with type 1 diabetes (17–21). The Cardio-Diab Study cohort included 155 of these individuals with no known CVD. Each subject with type 1 diabetes invited a sex- and race-matched nondiabetic sibling or cousin, or if neither was available, a friend, within 5 (preferably) or 10 years of his or her age to serve as a control. Twenty consecutive pairs participating in the Cardio-Diab Study in June 2004 through January 2005 were enrolled. The primary end point was the difference in aortic characteristic impedance between groups. The sample size gave us >80% power to detect a 30% difference in aortic impedance (16). The

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Abbreviations: CT, computed tomography; CVD, cardiovascular disease; ECG, electrocardiogram; LVOT, left ventricular outflow tract; MAP, mean arterial pressure; PWV, pulse wave velocity.

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

protocol was approved by the University of Wisconsin Human Subjects Committee, and each participant gave separate informed consent for this substudy.

Participants were studied in the supine position after quiet rest (22–24). With a semiautomated, computer-controlled cuff, auscultatory blood pressure was obtained at 2-min intervals with a goal of obtaining three sequential readings within 5 mmHg for systolic blood pressure and diastolic blood pressure. Arterial tonometry was obtained from the brachial, radial, femoral, and carotid arteries in quick succession with a custom transducer. A limb-lead electrocardiogram (ECG) was recorded. Echocardiographic images of the left ventricular outflow tract were obtained in a parasternal long-axis view. Body surface measurements were assessed from suprasternal notch to brachial, radial, femoral, and carotid recording sites (22). Data were digitized during the primary acquisition, transferred to CD-ROM, and shipped to Cardiovascular Engineering (Waltham, MA) for analysis.

Noncontrast computerized tomography (CT) scans of the chest were performed using a GE HiSpeed Advantage spiral CT scanner (General Electric, Milwaukee, WI) using ECG gating. Scans were used to assess the outer diameter of the aorta 2 cm above the aortic valve. When the aorta was noncircular, the smallest dimension was used. A single timed urine collection was performed for determination of albumin concentration and creatinine clearance.

Tonometry waveforms were signal-averaged with the ECG used as a fiducial point (25). Average systolic and diastolic cuff pressures were used to calibrate the peak and trough of the signal-averaged brachial pressure waveform. Diastolic and integrated mean brachial pressures were used to calibrate other pressure tracings (26). Carotid-femoral PWV was calculated from transit time and body surface measurements corrected for parallel transmission as described previously (23). LVOT diameter was measured and used to compute cross-sectional area and to convert flow velocities to volume flows (27). The augmentation index was calculated using carotid waveforms (28). Aortic Z_c was estimated in the time domain as the pressure change associated with an increase in flow from 0 to 95% peak flow ($\Delta P/\Delta Q$). Proximal aortic compliance per unit length was calculated as described previously (29).

Table 1—*Characteristics of participants with and without type 1 diabetes*

Clinical characteristic	Type 1 diabetes	No type 1 diabetes
n	17	17
Female sex	13 (76)	13 (76)
White	17 (100)	17 (100)
Sibling control	NA	6 (35)
Age (years)	27.3 ± 7.7	28.2 ± 8.9
Duration of diabetes (years)	15.3 ± 0.7	NA
A1C (%) (normal range 4.3–6.0%)*	7.8 ± 1.5	5.0 ± 0.3
Hypertension (>140/90 mmHg)	1 (6)	1 (6)
Above blood pressure target for type 1 diabetes (130/80 mmHg)	1 (6)	4 (23)
Height (cm)	166.9 ± 14.0	170.0 ± 8.5
Weight (kg)	72.0 ± 19.7	72.6 ± 12.3
BMI (kg/m^2)	25.7 ± 5.7	25.1 ± 3.6
Waist-to-hip ratio	0.78 ± 0.04	0.77 ± 0.06
Current smokers	7 (41)	6 (35)
Use of antihypertensive medications	2 (12)	0
Use of lipid-lowering medications	1 (6)	0
Normoalbuminuria†	16 (100)	17 (100)
Urine albumin (μg/min)†	4.9 ± 2.2	4.2 ± 2.5

Data are *n* (%) or means ± SD. *$n = 15$ for no type 1 diabetes. †$n = 16$ for type 1 diabetes. NA, not applicable.

Baseline characteristics and hemodynamic data were compared using paired Student's *t* tests and Pearson correlations. Multivariable regression analyses were performed two ways. Correlations between impedance and other clinical variables of interest were explored in a regression analysis using matched pairs and thus controlling for diabetes effect. An unmatched multivariable regression analysis was also performed to determine which variables contained independent predictive value with regard to impedance and pulse pressure. Classical assumptions of linear regression analysis were satisfied for all analyses.

RESULTS — Forty participants, 20 matched pairs, were sequentially studied. Complete arterial hemodynamic data were obtained from 17 pairs of participants. Seven type 1 diabetic subjects had related control subjects. The remaining 10 type 1 diabetic subjects had unrelated control subjects. Clinical characteristics of the participants are shown in Table 1. Although diabetes had been present on average for 15 years in the patients, the aggressiveness of diabetes management and control were demonstrated by the low prevalence of hypertension and microalbuminuria.

Arterial hemodynamic data are shown in Table 2. Systolic blood pressure and MAP were not statistically different in the two groups. Diastolic blood pressure was lower in the group with type 1 diabetes ($P = 0.05$). Both brachial and carotid pulse pressure were significantly elevated in the group with type 1 diabetes. Aortic Z_c was markedly elevated in patients with type 1 diabetes. Those with type 1 diabetes had larger forward pressure amplitude despite comparable peak flow (Fig. 1). PWV and the augmentation index, however, did not differ between type 1 diabetic and control subjects.

A decrease in aortic diameter could explain increased Z_c with no difference in PWV, given the strong dependence of impedance on vessel diameter. LVOT diameter determined by echocardiography and proximal aortic diameter determined by CT scan were both smaller in the group with type 1 diabetes, with the LVOT measurement reaching statistical significance (Table 2).

Correlation analysis was used to determine relations between both aortic impedance and pulse pressure and other clinical variables. Initial correlations were performed with matched pairs being preserved in the analysis, in effect controlling for diabetes. In addition to the presence of diabetes, urine albumin excretion, A1C, and female sex were significantly correlated with Z_c (Table 3). Multivariable analysis was performed using unmatched pairs but including diabetes as a variable. Urine albumin and LVOT diameter had independent predictive power in this

Table 2—*Arterial hemodynamics of participants with and without type 1 diabetes*

Hemodynamic parameter	Type 1 diabetes	No type 1 diabetes	*P* value
Heart rate (bpm)	69 ± 13	66 ± 13	0.52
Brachial systolic pressure (mmHg)	113 ± 13	108 ± 12	0.30
Brachial diastolic pressure (mmHg)	59 ± 9	65 ± 10	0.05
Mean pressure (mmHg)	79 ± 9	81 ± 11	0.48
Brachial pulse pressure (mmHg)	54 ± 13	43 ± 10	0.002
Carotid pulse pressure (mmHg)	45 ± 11	36 ± 10	0.02
PWV (m/s)	5.9 ± 0.9	5.9 ± 0.7	0.83
Augmentation index (%)	−1.5 ± 15.4	−4.8 ± 16.7	0.45
Aortic characteristic impedance, Z_c (dyne × s/cm^5)	179 ± 57	136 ± 42	0.004
Stroke volume (nl)	69 ± 12	72 ± 17	0.41
Peak aortic flow (ml/s)	329 ± 59	340 ± 67	0.60
Forward pressure wave amplitude (mmHg)	43 ± 11	34 ± 10	0.013
Reflected wave amplitude (mmHg)	12 ± 3	11 ± 3	0.21
Ratio of reflected to forward pressure wave amplitude	0.29 ± 0.06	0.32 ± 0.72	0.17
Mean peripheral resistance (dyne × s/cm^5)	1,395 ± 299	1,427 ± 277	0.72
LVOT diameter (cm)	2.04 ± 0.18	2.17 ± 0.19	0.01
Aortic diameter (cm)	2.70 ± 0.27	2.85 ± 0.28	0.30

Data are means ± SD. *P* value was determined by paired Student's *t* tests.

model, with an *F* statistic of 5.3 ($P = 0.003$); however, none of the individual *P* values in this model met the Bonferroni standard of $P = 0.0125$ for four comparisons. In multivariable analysis, only diabetes, impedance, and BMI remained independent predictors of central pulse pressure.

CONCLUSIONS — In this study we investigated changes in the large and medium arteries of young people with type 1 diabetes and demonstrated an increase in Z_c in type 1 diabetes, independent of MAP. Increased Z_c was associated with a higher level of pressure pulsatility in the diabetic aorta for a given level of flow. This increase in Z_c occurred before changes in more traditional measures of central arterial stiffness such as PWV, which has been shown to be elevated in more advanced stages of diabetes (6–8). The increase in Z_c was associated with increased central and peripheral pulse pressure in the patients with diabetes and was accompanied by a decrease in LVOT diameter. Although an increase in PWV and earlier return of reflected waves to the proximal aorta can cause an increase in central pulse pressure, particularly in younger people, premature wave reflection was not the mechanism of increased central or peripheral pulse pressure in our type 1 diabetic patients. Rather, the primary finding was an increase in incident pressure wave amplitude, indicating

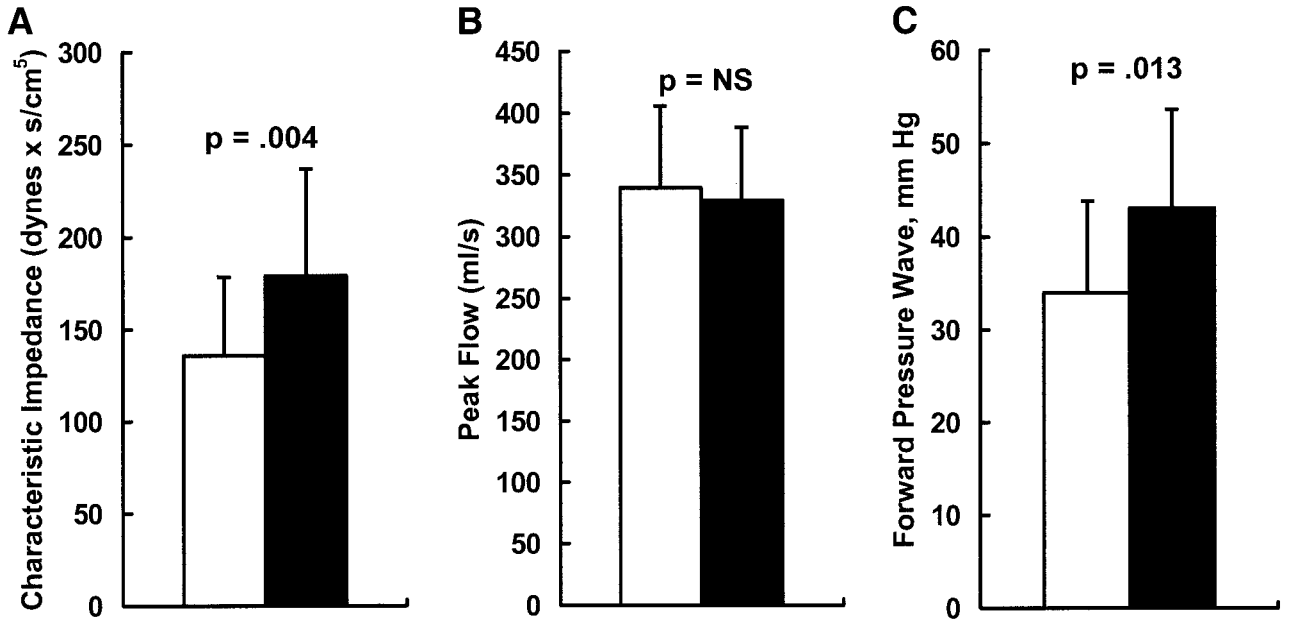

Figure 1— *Increased Z_c is present in type 1 diabetes* (A)*, despite similar aortic flow* (B)*. The increase in Z_c is explained by greater pressure development for a given amount of flow in the diabetic aorta* (C)*. □, control; ■, type 1 diabetes.*

Table 3—*Regression analysis of associations between Z_c of the aorta and clinical variables, analyzed as matched pairs*

Variable	Regression coefficient (adjusted for diabetes)	SE	*P* value
Type 1 diabetes	43.4	13.0	0.004
Urine albumin excretion (μg/min)	17.1	6.2	0.01
A1C (%)	12.9	5.0	0.02
Female sex	121.0	47.8	0.02
LVOT diameter (cm)	−141.5	71.4	0.06
BMI (kg/m^2)	3.0	2.8	0.30
Carotid-femoral PWV (m/s)	16.3	17.1	0.35
Current smoking	−3.3	3.8	0.39
Augmentation index (%)	−0.5	1.0	0.64
Heart rate (bpm)	0.2	1.1	0.85

changes in the proximal aorta, leading to a greater pressure change for a given flow from the left ventricle.

Increased central arterial stiffness has been demonstrated previously in patients with type 2 diabetes (8–10). Early changes in diabetes and in type 1 diabetes in particular have not been as well characterized (11). Postmortem analysis demonstrated that aortas from individuals with type 1 diabetes were intrinsically stiffer than those from age-matched control subjects (12). In another study of participants with type 1 diabetes, diabetes was associated with increased aortic augmentation index in men but not in women (6). However, use of generalized transfer functions to calculate central pressure waveforms in diabetic subjects has been questioned, and changes in PWV and the augmentation index have not always correlated in studies of patients with diabetes (13,15). Furthermore, none of the foregoing studies measured Z_c.

Increased pulse pressure is known to be a marker of adverse clinical events in patients with diabetes (2,3), and pulse pressure is increased when impedance rises. From the waterhammer equation, Z_c is directly proportional to PWV and inversely proportional to vessel area (Z_c = PWV × ρ/area, where ρ is the density of blood). Impedance will thus be sensitive to changes in vessel diameter. Because PWV was not different between the two groups in our study, we suggest that a small decrease in aortic diameter could explain our data. This suggestion is supported by the decrease in LVOT area noted in the diabetic group in this study, which maintained significance in multivariable modeling. The failure to note a decrease in aortic diameter may result from use of noncontrast CT scans, allowing visualization of only the external vessel diameter. Eutrophic aortic remodeling results in a decreased internal lumen diameter due to vessel wall thickening, without a change in outer vessel diameter. If this sort of aortic remodeling were to occur in diabetes, leading to increased pulsatile pressure in the proximal aorta, it would be missed on a noncontrast scan. Decreases in internal aortic diameter have been noted previously in patients with diabetes (14) and those with hypertension (16). This decrease in aortic diameter with pathological conditions contrasts with the modest age-related increase in aortic diameter that has been observed in relatively healthy individuals. With aortic wall stiffening and aortic diameter increases, as in healthy aging, a predominant increase in PWV is observed because the increase in diameter offsets the effect of wall stiffening on Z_c (16). The present findings suggest that factors responsible for proper matching between aortic diameter and resting flow may be impaired in type 1 diabetes, indicating an active and potentially plastic vascular remodeling process at work in young patients with this disease process.

There are important implications of increased central arterial pulsatility early in the disease process of diabetes. The increased pulsatility with the change in Z_c is carried into the periphery, as manifest by increased brachial pulse pressure. The presence of higher pulse pressure in the central and peripheral circulation may lead to transmission of pressure pulsatility farther into the microcirculation than normally found and may precipitate microvascular damage. Evidence for microvascular damage is suggested by the correlation between increased Z_c and urine albumin levels in our study. Increased glomerular perfusion pressure, as might be seen if pressure pulsatility increases, is known to lead to renal microvascular damage (30). Our data suggest that changes in the central aorta may precipitate renal microvascular change or, conversely, that early microvascular damage in the kidney may contribute to increases in pressure and flow pulsatility at all levels of the circulation. The fact that the correlation with urine albumin is seen in the absence of overt microalbuminuria suggests that the aortic changes, which were substantial, may precede and contribute to the renal changes. In addition, our data suggest that once microalbuminuria develops, the relationship between arterial hemodynamics and renal vascular function may be altered, a concept supported by others (31). A similar relationship between pulse pressure or measures of central aortic stiffness and urine albumin excretion has been noted previously in type 2 diabetes (7,32,33), whereas urine albumin does not necessarily correlate with hyperinsulinemia (34), again suggesting the importance of hemodynamic changes in the development of renal microvascular disease. The link between pulse pressure or central arterial stiffness and urine albumin levels has also been demonstrated in patients with hypertension (16,35–41) and in healthy adults (42,43). In addition to damaging microvessels, the higher degrees of pressure pulsatility seen in type 1 diabetes may also increase tensile and shear stresses in the large and medium vessels and could contribute to early atherogenesis.

There are limitations to our study. The group studied was small and may not be representative of people with type 1 diabetes. In addition, by necessity, this exploratory analysis of stiffness involved multiple comparisons, and spurious significant values are possible. The study was powered for the primary end point only, and other significant findings must be interpreted as exploratory rather than definitive. With the small sample size, outliers may significantly influence the data and lead to spurious findings. The urine albumin determination is based on a single timed collection rather than on an average of repeated collections. Our conclusion that aortic diameter is reduced because Z_c is increased but PWV is not assumed that Z_c and PWV are measured at the same point. Z_c assesses the proximal aortic root whereas carotid-femoral PWV

evaluates the spatially averaged properties of the descending thoracic and abdominal aorta and iliac artery. Thus, regionally heterogeneous changes in arterial properties, rather than a difference in aortic diameter, may explain elevated Z_c with unchanged carotid-femoral PWV. These data are cross-sectional. Longitudinal data on a larger group of subjects would be required to demonstrate aortic remodeling and the relationship to changes in impedance and other measures of stiffness over time.

In summary, we have shown increased pulse pressure in young individuals with type 1 diabetes, resulting from changes in aortic characteristic impedance at similar MAPs. The changes in Z_c may be related to decreased aortic diameter. Z_c correlates with urine albumin levels, which suggests a link between central arterial properties, increased central and peripheral pulse pressures, and microvascular damage at an early stage in the pathophysiology of diabetic vascular disease. We suggest that increased vessel pulsatility, delivered distally in the circulation, may expose organs to greater degrees of small vessel pulsatile flow than is optimal, leading to microvascular damage and organ dysfunction.

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References

1. National diabetes statistics fact sheet: general information and national estimates on diabetes in the United States [article online], 2005. Available from http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm. Accessed 19 January, 2007
2. Schram MT, Chaturvedi N, Fuller JH, Stehouwer CD: Pulse pressure is associated with age and cardiovascular disease in type 1 diabetes: the Eurodiab Prospective Complications Study. *J Hypertens* 21: 2035–2044, 2003
3. Schram MT, Kostense PJ, Van Dijk RA, Dekker JM, Nijpels G, Bouter LM, Heine RJ, Stehouwer CD: Diabetes, pulse pressure and cardiovascular mortality: the Hoorn Study. *J Hypertens* 20:1743–1751, 2002
4. Cockcroft JR, Wilkinson IB, Evans M, McEwan P, Peters JR, Davies S, Scanlon MF, Currie CJ: Pulse pressure predicts cardiovascular risk in patients with type 2 diabetes mellitus. *Am J Hypertens* 18:1463–1467, 2005; discussion 1468–1469
5. McEwan P, Williams JE, Griffiths JD, Baqust A, Peters JR, Hopkinson P, Currie CJ: Evaluating the performance of the Framingham risk equations in a population with diabetes. *Diabet Med* 21:318–323, 2004
6. Brooks B, Molyneaux L, Yue DK: Augmentation of central arterial pressure in type 1 diabetes. *Diabetes Care* 22:1722–1727, 1999
7. Smith A, Karalliedde J, De Angelis L, Goldsmith D, Viberti G: Aortic pulse wave velocity and albuminuria in patients with type 2 diabetes. *J Am Soc Nephrol* 16: 1069–1075, 2005
8. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG: Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 15 106:2085–2090, 2002
9. Brooks BA, Molyneaux LM, Yue DK: Augmentation of central arterial pressure in type 2 diabetes. *Diabet Med* 18:374–380, 2001
10. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR: Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: the ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation* 91:1432–1443, 1995
11. Wilkinson IB, MacCallum H, Rooijmans DF, Murray GD, Cockcroft JR, McKnight JA, Webb DJ: Increased augmentation index and systolic stress in type 1 diabetes mellitus. *Q J Med* 93:441–448, 2000
12. Oxlund H, Rasmussen LM, Andreassen TT, Heickendorff L: Increased aortic stiffness in patients with type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 32:748–752, 1989
13. Lacy PS, O'Brien DG, Stanley AG, Dewar MM, Swales PP, Williams B: Increased pulse wave velocity is not associated with elevated augmentation index in patients with diabetes. *J Hypertens* 22:1937–1944, 2004
14. Ryden Ahlgren A, Lanne T, Wollmer P, Sonesson B, Hansen F, Sundkvist G: Increased arterial stiffness in women, but not in men, with IDDM. *Diabetologia* 38: 1082–1089, 1995
15. Mather K, Lewanczuk R: Measurement of arterial stiffness in diabetes: a cautionary tale. *Diabetes Care* 27:831–833, 2004
16. Mitchell GF, Lacourciere Y, Ouellet JP, Izzo JL Jr, Neutel J, Kerwin LJ, Block AJ, Pfeffer MA: Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. *Circulation* 108:1592–1598, 2003
17. Palta M, Shen G, Allen C, Klein R, D'Alessio D: Longitudinal patterns of glycemic control and diabetes care from diagnosis in a population-based cohort with type 1 diabetes: the Wisconsin Diabetes Registry. *Am J Epidemiol* 144:954–961, 1996
18. Palta M, LeCaire T, Daniels K, Shen G, Allen C, D'Alessio D: Risk factors for hospitalization in a cohort with type 1 diabetes: Wisconsin Diabetes Registry. *Am J Epidemiol* 146:627–636, 1997
19. Allen C, LeCaire T, Palta M, Daniels K, Meredith M, D'Alessio DJ: Risk factors for frequent and severe hypoglycemia in type 1 diabetes. *Diabetes Care* 24:1878–1881, 2001
20. Allen C, Shen G, Palta M, Lotz B, Jacobson R, D'Alessio D: Long-term hyperglycemia is related to peripheral nerve changes at a diabetes duration of 4 years: the Wisconsin Diabetes Registry. *Diabetes Care* 20: 1154–1158, 1997
21. Lecaire T, Palta M, Zhang H, Allen C, Klein R, D'Alessio D: Lower-than-expected prevalence and severity of retinopathy in an incident cohort followed during the first 4–14 years of type 1 diabetes: the Wisconsin Diabetes Registry Study. *Am J Epidemiol* 164:143–150, 2006
22. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vesan RS, Levy D: Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 43:1239–1245, 2004
23. Mitchell GF, Izzo JL Jr, Lacourciere Y, Ouellet JP, Neutel J, Qian C, Kerwin LJ, Block AJ, Pfeffer MA: Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the Conduit Hemodynamics of Omapatrilat International Research Study. *Circulation* 105: 2955–2961, 2002
24. Mitchell GF, Tardif JC, Arnold JM, Marchiori G, O'Brien TX, Dunlap ME, Pfeffer MA: Pulsatile hemodynamics in congestive heart failure. *Hypertension* 38:1433–1439, 2001
25. Mitchell GF, Pfeffer MA, Westerhof N, Pfeffer JM: Measurement of aortic input impedance in rats. *Am J Physiol* 267: H1907–H1915, 1994
26. Kelly R, Fitchett D: Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. *J Am Coll Cardiol* 20:952–963, 1992
27. Zoghbi WA, Quinones MA: Determination of cardiac output by Doppler echocardiography: a critical appraisal. *Herz* 11:258–268, 1986
28. Murgo JP, Westerhof N, Giolma JP, Al-

tobelli SA: Aortic input impedance in normal man: relationship to pressure wave forms. *Circulation* 62:105–116, 1980
29. Mitchell GF, Pfeffer MA, Finn PV, Pfeffer JM: Equipotent antihypertensive agents variously affect pulsatile hemodynamics and regression of cardiac hypertrophy in spontaneously hypertensive rats. *Circulation* 94:2923–2929, 1996
30. Giunti S, Barit D, Cooper ME: Mechanisms of diabetic nephropathy: role of hypertension. *Hypertension* 48:519–526, 2006
31. Zatz R, Brenner BM: Pathogenesis of diabetic microangiopathy: the hemodynamic view. *Am J Med* 80:443–453, 1986
32. Knudsen ST, Poulsen PL, Hansen KW, Ebbehoj E, Bek T, Mogensen CE: Pulse pressure and diurnal blood pressure variation: association with micro- and macrovascular complications in type 2 diabetes. *Am J Hypertens* 15:244–250, 2002
33. Palmas W, Moran A, Pickering T, Eimicke JP, Teresi J, Schwartz JE, Field L, Weinstock RS, Shea S: Ambulatory pulse pressure and progression of urinary albumin excretion in older patients with type 2 diabetes mellitus. *Hypertension* 48:301–308, 2006
34. Cubeddu LX, Hoffmann IS, Aponte LM, Nunez-Bogesits R, Medina-Suniaga H, Roa M, Garcia RS: Role of salt sensitivity, blood pressure, and hyperinsulinemia in determining high upper normal levels of urinary albumin excretion in a healthy adult population. *Am J Hypertens* 16:343–349, 2003
35. Cirillo M, Stellato D, Laurenzi M, Panarelli W, Zanchetti A, De Santo NG: Pulse pressure and isolated systolic hypertension: association with microalbuminuria: the GUBBIO Study Collaborative Research Group. *Kidney Int* 58:1211–1218, 2000
36. Tsakiris A, Doumas M, Lagatouras D, Vyssoulis G, Karpanou E, Nearchou N, Kouremenou C, Skoufas P: Microalbuminuria is determined by systolic and pulse pressure over a 12-year period and related to peripheral artery disease in normotensive and hypertensive subjects: the Three Areas Study in Greece (TAS-GR). *Angiology* 57:313–320, 2006
37. Wiinberg N, Bang LE, Wachtell K, Larsen J, Olsen MH, Tuxen C, Hildebrandt PR, Rokkedal J, Ibsen H: 24-h Ambulatory blood pressure in patients with ECG-determined left ventricular hypertrophy: left ventricular geometry and urinary albumin excretion—a LIFE substudy. *J Hum Hypertens* 18:391–396, 2004
38. Pedrinelli R, Dell'Omo G, Penno G, Bandinelli S, Bertini A, DiBello V, Mariani M: Microalbuminuria and pulse pressure in hypertensive and atherosclerotic men. *Hypertension* 35:48–54, 2000
39. Schillaci G, Pirro M, Mannarino MR, Pucci G, Savarese G, Franklin SS, Mannarino E: Relation between renal function within the normal range and central and peripheral arterial stiffness in hypertension. *Hypertension* 48:616–621, 2006
40. Tsioufis C, Tzioumis C, Marinakis N, Toutouzas D, Kallikazaros I, Stefanadis C, Toutouzas P: Microalbuminuria is closely related to impaired arterial elasticity in untreated patients with essential hypertension. *Nephron Clin Pract* 93:c106–c111, 2003
41. Munakata M, Nunokawa T, Yoshinaga K, Toyota T: Brachial-ankle pulse wave velocity is an independent risk factor for microalbuminuria in patients with essential hypertension—a Japanese trial on the prognostic implication of pulse wave velocity (J-TOPP). *Hypertens Res* 29:515–521, 2006
42. Kohara K, Tabara Y, Tachibana R, Nakura J, Miki T: Microalbuminuria and arterial stiffness in a general population: the Shimanami Health Promoting Program (J-SHIPP) study. *Hypertens Res* 27:471–477, 2004
43. Knight EL, Kramer HM, Curhan GC: High-normal blood pressure and microalbuminuria. *Am J Kidney Dis* 41:588–595, 2003