DIABETES TECHNOLOGY & THERAPEUTICS
Volume 13, Number 12, 2011

DOI: 10.1089/dia.2011.0126

Pulse Wave Analysis and Cardiac Autonomic Neuropathy in Type 1 Diabetes: A Report from the Pittsburgh Epidemiology of Diabetes Complications Study

Aaron M. Secrest, Ph.D., M.P.H., Sara L. Marshall, M.P.H., Rachel G. Miller, M.S., Catherine T. Prince, Ph.D., M.P.H., and Trevor J. Orchard, M.D., M.Med.Sci.

Abstract

Background: The cross-sectional associations of cardiac autonomic neuropathy (CAN) with pulse wave analysis (PWA) measures (both arterial stiffness and myocardial perfusion) have not been explored in type 1 diabetes, despite recognition of an association of CAN with coronary artery disease.
Methods: Both CAN and PWA measures were obtained from 144 participants of the Pittsburgh Epidemiology of Diabetes Complications Study of childhood-onset type 1 diabetes at the 18-year follow-up examination. CAN was measured as variability in the R-R interval during deep breathing, and PWA was performed using SphgymoCor Px (AtCor Medical, Sydney, Australia). Other clinical and demographic factors were also assessed. Univariate and multivariable analyses for associations with CAN were performed for arterial stiffness measures (augmentation index [AIx] and augmentation pressure [AP]) and a myocardial perfusion measure (subendocardial viability ratio [SEVR]).
Results: Presence of CAN was univariately associated with all three PWA measures: AIx (odds ratio [OR] = 1.5, $P = 0.03$), AP (OR = 2.1, $P = 0.001$), and SEVR (OR = 0.4, $P < 0.001$). These relationships persisted after adjustment for potential PWA confounders. Adjusting for age and diabetes-related factors (glycosylated hemoglobin, systolic blood pressure, and overt nephropathy), CAN only remained significantly associated with SEVR (OR = 0.3, $P = 0.005$).
Conclusions: CAN is cross-sectionally associated with measures of both increased arterial stiffness and decreased myocardial perfusion in type 1 diabetes; however, only the association with decreased estimated myocardial perfusion persisted in fully adjusted models. These results provide potential insight into the CAN association with coronary artery disease.

Introduction

Cardiovascular disease causes 50% of the deaths worldwide in individuals with diabetes,[1] especially for young adults with type 1 diabetes, among whom the risk of coronary artery disease is increased by 10-fold.[2] Most of this excess risk can be attributed to atherosclerosis, which itself is strongly linked to vascular aging and health.[3,4] Several factors, including age and glycemic status, may influence vascular health, but of particular interest in diabetes is autonomic neuropathy (AN), a complication of diabetes shown to predict both cardiovascular events and mortality.[5] The autonomic nervous system regulates heart rate and vascular tone, and individuals with AN are likely to have increased arterial stiffness and decreased myocardial perfusion, which can be assessed using noninvasive pulse wave analysis (PWA). We recently described a relationship between cardiac AN (CAN) and both increased arterial stiffness and decreased estimated myocardial perfusion measured 18 years later, although because we did not have PWA measures at baseline, the temporal relationship between these and CAN is unclear.[6] In this report, we therefore further examine the cross-sectional association of CAN with these PWA measures to determine (1) whether an independent association exists beyond other potentially confounding or mediating variables like age, glycemic control, and renal disease and (2) whether the strength of the association varies according to the type of PWA measure.

Subjects and Methods

Study population

The sample for this analysis comes from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, comprising individuals diagnosed (or seen within 1 year of

Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania.

diagnosis) with childhood-onset (age <17 years) type 1 diabetes at Children's Hospital of Pittsburgh (Pittsburgh, PA) between 1950 and 1980 and placed on insulin therapy at discharge.[7,8] Baseline examination ($n=658$) occurred in 1986–1988, and the most recent examination (18-year follow-up, $n=309$) occurred between November 2004 and November 2006. The 309 participants at follow-up represents 70.4% of those alive and locally residing. The non-participants at the 18-year follow-up were significantly older, with longer duration of diabetes and higher glycosylated hemoglobin (HbA_{1c}) levels and complication rates ($P<0.001$ for all). Of note is that of the participants at baseline, 140 (21%) had died by the 18-year follow-up, and 79 (12%) had moved out of the area. This examination included PWA, which began part way through the examination period (after January 2006) and was performed on 144 participants. Comparisons between the PWA participants and non-participants have been published elsewhere.[6] No differences existed with respect to age, duration of diabetes, sex, HbA_{1c} level, or complication rates. The only difference was a slightly higher heart rate in PWA participants (76.0 vs. 73.1 beats/min, $P=0.04$). This study was approved by the University of Pittsburgh Institutional Review Board.

Data collection

The PWA measures examined herein were augmentation index (AIx), augmentation pressure (AP), and subendocardial viability ratio (SEVR), which were derived via waveforms measured at the radial artery using a SphygmoCor Px version 7.01 (AtCor Medical, Sydney, Australia), as previously described.[9] In brief, a high-fidelity micromanometer with a frequency response of >2 kHz (Millar Instruments, Houston, TX) was gently pressed over the right radial artery until a consistent waveform was produced. Measurement was stopped after obtaining ≥20 sequential waveforms. Central pressure values were estimated from radial measurements using the software's mathematical transfer function,[9,10] the accuracy and reliability of which have been validated.[11] As the left ventricle contracts, the pressure wave moves forward in the major vessels until meeting sites of resistance, which reflect the wave backward. Stiffer artery walls result in earlier wave reflection.[12] When the reflected wave returns during systole rather than diastole, the systolic pressure is augmented, and this AP is the portion of the central systolic pressure contributed by the early reflected wave. AIx is expressed as a percentage of the pulse pressure (AIx = AP/pulse pressure × 100) and reflects the level of augmentation measured. Heart rate is inversely associated with AIx and AP.[13] SEVR, the ratio of the diastolic area under the curve of an arterial pulse wave to the systolic area under the curve,[14] is a ratio of myocardial perfusion (because coronary artery perfusion takes place primarily during diastole) to myocardial contraction, and it serves as a noninvasive, tonometric measure of myocardial perfusion relative to cardiac workload. Finally, the SphygmoCor device provides a quality index (QI), representing the reproducibility of the waveform. Only measures with a QI ≥80 were included in this study.

CAN was defined in the EDC as a history of an abnormal heart rate response to deep breathing (expiration–inspiration ratio of <1.1). Symptomatic AN (SAN) was defined by both an abnormal expiration–inspiration ratio (<1.1) and at least two positive responses to 21 questions asked during the EDC physician examination (using the Diabetes Control and Complications Trial clinical protocol) about symptoms of AN (e.g., gastroparesis, incontinence, impotence).[15] Other clinical variables of interest included systolic and diastolic blood pressure, heart rate, height, weight, and waist and hip circumferences, using standardized protocols previously described.[7] Body mass index and waist-to-hip ratio were then calculated from these measurements. Self-reported medication use, alcohol consumption (drinks/week), current and ever smoker status (≥100 cigarettes during lifetime), and physical activity were also obtained.[16] Some medications have been shown to have an effect on PWA measurements (angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, and nitrates) and were grouped as "pulse wave-influencing drugs" (PWIDs) for analysis.[17]

Blood samples drawn at the 18-year examination were used to obtain lipid, HbA_{1c}, and serum creatinine levels, as well as complete blood counts, based on standardized protocols. Urinary albumin levels from at least two validated timed collections were measured by immunonephelometry and used to calculate albumin excretion rates.[18]

Statistical analysis

Student's t test (or Mann–Whitney U test for nonparametric comparisons) and the χ^2 test were used as appropriate to compare by CAN status. Pearson's and Spearman's correlations were used for bivariate correlations for normal and non-normally distributed variables, respectively. For regression modeling, all continuous variables were converted to z-scores. Stepwise logistic regression was performed for prevalent CAN. Values of $P<0.05$ were considered statistically significant. SPSS version 18.0 (SPSS, Chicago, IL) was used for all analyses.

Results

Cross-sectional characteristics of the PWA population from the Pittsburgh EDC Study are listed by CAN status in Table 1. Overall, 54.2% ($n=78$) of this cohort had prevalent CAN, with a mean duration of type 1 diabetes of 36.4 years. CAN status did not differ by sex ($P=0.25$) or smoking history ($P=0.08$), but those with CAN were significantly older ($P<0.001$) and had a longer duration of diabetes ($P<0.001$). All three PWA measures significantly differed by CAN status as well: both AIx and AP were higher and SEVR was lower in the group with CAN.

Those with prevalent CAN were more likely to have other co-morbidities (cardiovascular or renal disease) and were more likely to be taking a medication with potential effects on pulse wave measures, specifically, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers or calcium channel blockers (Table 1). Systolic blood pressure, albumin excretion rate, and serum creatinine were significantly higher in individuals with CAN ($P<0.001$ for all); however, HbA_{1c}, diastolic blood pressure, cholesterol levels, and body mass index did not vary by CAN status.

AIx, AP, and SEVR were all univariately associated with prevalent CAN (Table 2). These associations with CAN became stronger after adjusting for potential confounders (i.e., sex, heart rate, height [for AIx and AP only], and PWID use) in multivariable logistic regression modeling (Table 2, Model 1).

Table 1. Characteristics of the Pittsburgh Epidemiology of Diabetes Complications Pulse Wave Analysis Cohort by Cardiac Autonomic Neuropathy Status

Characteristic	*Overall*	*CAN status*	
		No CAN	*CAN*
% (*n*)	100.0 (144)	45.8 (66)	54.2 (78)
Demographic			
Female sex	50.7 (73)	45.5 (30)	55.1 (43)
Age (years)	44.6 ± 7.4	40.6 ± 6.0	48.1 ± 6.8***
Duration of diabetes (years)	36.4 ± 6.8	34.2 ± 5.8	38.3 ± 7.0***
Ever smoker	39.6 (57)	31.8 (21)	46.2 (36)
Key variable			
AIx (%)	23.0 ± 11.0	20.8 ± 10.7	24.9 ± 10.9*
AP (mm Hg)[a]	8.0 (5.0–12.0)	6.0 (3.8–9.3)	9.5 (6.0–14.0)***
SEVR (%)	142.2 ± 31.1	156.0 ± 30.0	130.5 ± 27.1***
Prevalent CAD	23.1 (33)	15.4 (10)	29.5 (23)*
Prevalent MA	60.1 (86)	43.9 (29)	74.0 (57)***
Prevalent ON	26.8 (38)	10.6 (7)	40.8 (31)***
Prevalent ESRD	9.0 (11)	0.0 (0)	16.2 (11)***
PWID use	62.5 (90)	47.0 (31)	75.6 (59)***
ACEI/ARB use	55.6 (80)	43.9 (29)	65.4 (51)**
ACEI use	44.4 (64)	36.4 (24)	51.3 (40)
ARB use	14.6 (21)	10.6 (7)	17.9 (14)
CCB use	12.5 (18)	1.5 (1)	21.8 (17)***
β-Blocker use	11.1 (16)	6.1 (4)	15.4 (12)
Nitrate use	3.5 (5)	1.5 (1)	5.1 (4)
Clinical variable			
HbA_{1c} (%)	7.4 ± 1.4	7.5 ± 1.3	7.4 ± 1.5
Systolic BP (mm Hg)	116 ± 16	110 ± 15	120 ± 17***
Diastolic BP (mm Hg)	67 ± 9	67 ± 8	66 ± 10
Hypertension (>140/90 mm Hg)	35.7 (51)	23.1 (15)	46.2 (36)**
Heart rate (beats/min)	76 ± 12	75 ± 13	77 ± 11
Non–HDL-c (mg/dL)	114 ± 33	115 ± 33	113 ± 33
HDL-c (mg/dL)	59 ± 17	57 ± 16	61 ± 17
Body mass index (kg/m^2)	27.1 ± 4.5	27.0 ± 4.5	27.2 ± 4.5
Waist-to-hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
AER ($\mu g/min$)[a]	6.4 (4.3–30.3)	5.3 (3.7–9.1)	12.1 (4.9–58.3)***
Serum creatinine (mg/dL)[a]	1.0 (0.9–1.1)	0.9 (0.8–1.1)	1.0 (0.9–1.2)***
eGFR-MDRD ($mL/min/1.73\,m^2$)	72 ± 20	81 ± 15	64 ± 20***
WBC count ($\times 10^{-9}/L$)	6.2 (5.1–7.4)	5.9 (4.9–7.1)	6.3 (5.2–8.2)

Data are mean (±SD) value or percentage (*n*).
[a]Data are median value (interquartile range).
*P <0.05, **P <0.01, ***P <0.001.
ACEI, angiotensin converting enzyme inhibitor; AER, albumin excretion rate; AIx, augmentation index; AP, augmentation pressure; ARB, angiotensin II receptor blocker; BP, blood pressure; CAD, coronary artery disease; CAN, cardiac autonomic neuropathy; CCB, calcium channel blocker; eGFR-MDRD, estimated glomerular filtration rate by modification of diet in renal disease; ESRD, end-stage renal disease; HDL-c, high-density lipoprotein cholesterol; MA, microalbuminuria; ON, overt nephropathy; PWID, pulse wave-influencing drug; SEVR, subendocardial viability ratio; WBC, white blood cell.

Standardized unit increases in AIx and AP were associated with a twofold (odds ratio [OR] = 2.1; 95% confidence interval [CI] 1.3–3.4) and a threefold (OR = 3.0; 95% CI 1.7–5.4) increased chance of CAN, respectively, whereas a standardized unit increase in SEVR was associated with a significantly decreased (OR = 0.2; 95% CI 0.1–0.4) chance of CAN. On adjusting for other variables, it was noted that age eliminates the significant associations between both AIx and AP and prevalent CAN (Table 2, Model 2). However, although the addition of age diminished the statistical significance of the SEVR–CAN association, the relationship in the fully adjusted model remained highly significant (P = 0.005). Likewise, when individuals with SAN (n = 28) were excluded from analyses, the SEVR–CAN relationship remained in the final model (P = 0.006).

Because of the potential differential effect of the various PWIDs, multivariable models were performed after excluding each PWID use group, except for angiotensin converting enzyme inhibitor/angiotensin II receptor blocker use (as most participants [56%] reported angiotensin converting enzyme inhibitor/angiotensin II receptor blocker use). Participants reporting such use were analyzed separately (data not shown), and SEVR, but not AIx or AP, remained significant in fully adjusted models, similar to the findings in Table 2, Model 2. All of the exclusion models produced results similar to those in Table 2 except for models that excluded nitrate use, a finding we have previously seen in associations between PWA variables and coronary artery disease.[19] Higher AIx (OR = 1.8; 95% CI 1.1–3.1; P = 0.03) and AP (OR = 2.3; 95% CI 1.2–4.6; P = 0.02) were each significantly related to CAN in

Table 2. Unadjusted and Adjusted Odds Ratios for Cardiac Autonomic Neuropathy by Pulse Wave Analysis Measure Based on Multivariable Logistic Regression Models

	Unadjusted				*Model 1*[a]				*Model 2*[b]			
PWA measure	*OR*	*95% CI*	P	*−2LL*	*OR*	*95% CI*	P	*−2LL*	*OR*	*95% CI*	P	*−2LL*
Augmentation index	1.5	1.0–2.1	0.03	193.6	2.1	1.3–3.4	0.003	171.4	1.3	0.7–2.5	0.38	132.5
Augmentation pressure	2.1	1.4–3.4	0.001	184.3	3.0	1.7–5.4	<0.001	162.5	1.4	0.6–3.0	0.42	132.6
Subendocardial viability ratio	0.4	0.2–0.6	<0.001	172.4	0.2	0.1–0.4	<0.001	153.5	0.3	0.1–0.7	0.005	125.2

Odds ratios (ORs) are per standardized unit.
[a]Model 1: adjusted for potential confounders of sex, heart rate, height (for augmentation index and augmentation pressure only), and pulse wave-influencing drug use (use of at least one: angiotensin converting enzyme inhibitor/angiotensin II receptor blocker, calcium channel blocker, β-blocker, or nitrate).
[b]Model 2: adjusted for Model 1 variables and age, glycosylated hemoglobin, systolic blood pressure, and prevalent overt nephropathy.
CI, confidence interval; LL, log likelihood; PWA, pulse wave analysis.

fully adjusted models after exclusion of those taking nitrate medication ($n=5$). Consistent with the findings in Table 2, after exclusion of individuals taking nitrate medications ($n=5$), lower SEVR remained significantly associated with CAN (OR = 0.2; 95% CI 0.1–0.5; $P<0.001$).

Discussion

These analyses show that CAN is strongly associated with both arterial stiffness (measured by both AIx and AP) and reduced myocardial perfusion (measured by SEVR) in childhood-onset type 1 diabetes using noninvasive applanation tonometry. These associations remain after adjusting for potential confounders; however, adjusting for age and other risk factors of CAN (i.e., systolic blood pressure, HbA_{1c}) diminishes associations between CAN and all PWA measures. Both AIx and AP become nonsignificant, but SEVR (an estimate of myocardial perfusion) remains strongly associated with CAN.

These concurrent results contrast with our previous report that baseline CAN was more strongly predictive of both AIx and AP measured 18 years later, but less predictive of SEVR ($P=0.06$) in multivariable models.[6] This suggests that initially CAN may relate to future arterial stiffness and thereby arterio- and atherosclerosis risk, whereas in a contemporaneous setting (18 years later), when arterial stiffness is more prevalent, CAN reflects the later stage of decreased myocardial perfusion.

Decreased myocardial perfusion in response to a vasodilator (dipyridamole) has also been associated with CAN in type 1 diabetes.[20] These authors suggested that the pathophysiologic mechanism could be either impaired sympathetic-mediated vasodilatation of the coronary vessels, an inability to maintain mean blood pressure during concomitant systemic vasodilatation, or both.

Age, when added in multivariable analyses, diminishes the relationships between CAN and pulse wave measures (Model 2). Both AIx and AP became nonsignificant with age, but SEVR remained significant. We have shown that increased duration of diabetes (a proxy for age) is a major risk factor for CAN in type 1 diabetes.[5] Increased age is also associated with higher arterial stiffness measures.[21]

More than half (54.2%) of this cohort had a history of CAN (expiration–inspiration ratio of <1.1), but far fewer (19.4%) had a history of SAN. Analyses replacing SAN with CAN did not dramatically change results; however, because of a limited event rate ($n=28$ for SAN), fully adjusted models were not significant for any associations between PWA measures and SAN. Because no differences in multivariable analyses existed when individuals with SAN were excluded, we hypothesize that those with CAN are more likely to have decreased myocardial perfusion irrespective of concomitant symptoms.

Use of PWA-influencing medications was quite common in our cohort (62.5%), particularly in those with CAN (75.6%). Approximately 90% of PWID use was angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, both of which are very effective in reducing arterial stiffness indices.[22] Use of other medication classes (e.g., calcium channel blockers, β-blockers, and nitrates) was more frequent among those with CAN. Therefore, we examined the relationship between PWA measures and CAN in the absence of each PWID drug. Exclusion of calcium channel blockers and β-blockers had little effect. However, significant changes to multivariable models occurred by excluding participants on nitrates (only four participants with CAN were taking nitrates). Exogenous nitrate administration increases vasodilatation and arterial compliance and decreases systolic blood pressure.[23] In a double-blind randomized crossover study in elderly hypertensive participants, Stokes et al.[24] found that administration of isosorbide mononitrate decreased not only brachial systolic and diastolic blood pressures, but also aortic systolic blood pressure and AP. Another study by Stokes et al.[25] confirmed that isosorbide mononitrate alters PWA measures, decreasing systolic blood pressure by 16 mm Hg, pulse pressure by 13 mm Hg, and AIx by 4% in older hypertensive patients.

The sample size for this analysis was relatively limited. However, this is currently the largest type 1 diabetes study to assess PWA measures that we have identified. Also, survival bias exists in this population, as those who were either deceased or unable to attend the 18-year follow-up examination because of poor health may represent individuals with greater complication risk and/or individuals most affected by decreased myocardial perfusion. Also, compared with individuals without PWA measures at the 18-year exam, the PWA study group had significantly lower waist-to-hip ratio and albumin excretion rate measures, suggesting they represent a healthier segment of our type 1 diabetes population (data not shown). However, these limitations would more likely hinder discovering significant associations between CAN and PWA measures than demonstrate false relationships.

In conclusion, significant association between myocardial perfusion (as measured by SEVR) and CAN exists in this type 1 diabetes population, which might partially explain the increased risk of cardiovascular mortality in type 1 diabetes. Early identification of CAN (and more intensive management of cardiovascular risk) may reduce later cardiovascular morbidity and mortality in type 1 diabetes and is worthy of further evaluation.

Acknowledgments

This work was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (RO1-DK034818 and F30-DK082137 to A.M.S.).

Author Disclosure Statement

No competing financial interests exist.

References

1. International Diabetes Federation: Diabetes Atlas, 4th ed. 2009. www.diabetesatlas.org (accessed July 4, 2011).
2. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC: Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia 2003;46:760–765.
3. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A: Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236–1241.
4. Shokawa T, Imazu M, Yamamoto H, Toyofuku M, Tasaki N, Okimoto T, Yamane K, Kohno N: Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Circ J 2005;69:259–264.
5. Orchard TJ, Lloyd CE, Maser RE, Kuller LH: Why does diabetic autonomic neuropathy predict IDDM mortality? An analysis from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Res Clin Pract 1996;34(Suppl): S165–S171.
6. Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ: Cardiovascular autonomic neuropathy, HDL cholesterol, and smoking correlate with arterial stiffness markers determined 18 years later in type 1 diabetes. Diabetes Care 2010;33:652–657.
7. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Ellis D, LaPorte RE, Kuller LH, Wolfson SK Jr, Drash AL: Factors associated with avoidance of severe complications after 25 yr of IDDM. Pittsburgh Epidemiology of Diabetes Complications Study I. Diabetes Care 1990;13:741–747.
8. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH: Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. Diabetes 1990;39:1116–1124.
9. Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, Kass DA: Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation 1997; 95:1827–1836.
10. O'Rourke MF, Pauca A, Jiang XJ: Pulse wave analysis. Br J Clin Pharmacol 2001;51:507–522.
11. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ: Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998;16:2079–2084.
12. O'Rourke MF: Wave travel and reflection in the arterial system. J Hypertens Suppl 1999;17:S45–S47.
13. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ: The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol 2000; 525:263–270.
14. Buckberg GD, Archie JP, Fixler DE, Hoffman JI: Experimental subendocardial ischemia during left ventricular hypertension. Surg Forum 1971;22:124–125.
15. The Diabetes Control and Complications Trial Research Group: DCCT Manual of Operations. Publication No. 93-183382. Springfield, VA: National Technical Information Service, Department of Commerce, 1993.
16. Kriska AM, LaPorte RE, Patrick SL, Kuller LH, Orchard TJ: The association of physical activity and diabetic complications in individuals with insulin-dependent diabetes mellitus: the Epidemiology of Diabetes Complications Study—VII. J Clin Epidemiol 1991;44:1207–1214.
17. Morgan T, Lauri J, Bertram D, Anderson A: Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens 2004;17:118–123.
18. Ellis D, Buffone GJ: New approach to evaluation of proteinuric states. Clin Chem 1977;23:666–670.
19. Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ: Pulse wave analysis and prevalent cardiovascular disease in type 1 diabetes. Atherosclerosis 2010;213: 469–474.
20. Taskiran M, Fritz-Hansen T, Rasmussen V, Larsson HB, Hilsted J: Decreased myocardial perfusion reserve in diabetic autonomic neuropathy. Diabetes 2002;51:3306–3310.
21. Lambert J, Smulders RA, Aarsen M, Donker AJ, Stehouwer CD: Carotid artery stiffness is increased in microalbuminuric IDDM patients. Diabetes Care 1998;21:99–103.
22. Pannier BM, Guerin AP, Marchais SJ, London GM: Different aortic reflection wave responses following long-term angiotensin-converting enzyme inhibition and beta-blocker in essential hypertension. Clin Exp Pharmacol Physiol 2001;28:1074–1077.
23. Simon AC, Levenson JA, Levy BY, Bouthier JE, Peronneau PP, Safar ME: Effect of nitroglycerin on peripheral large arteries in hypertension. Br J Clin Pharmacol 1982;14:241–246.
24. Stokes GS, Ryan M, Brnabic A, Nyberg G: A controlled study of the effects of isosorbide mononitrate on arterial blood pressure and pulse wave form in systolic hypertension. J Hypertens 1999;17:1767–1773.
25. Stokes GS, Bune AJ, Huon N, Barin ES: Long-term effectiveness of extended-release nitrate for the treatment of systolic hypertension. Hypertension 2005;45:380–384.

Address correspondence to:
Trevor J. Orchard, M.D., M.Med.Sci.
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh
3512 Fifth Avenue, 2nd Floor
Pittsburgh, PA 15213

E-mail: orchardt@edc.pitt.edu