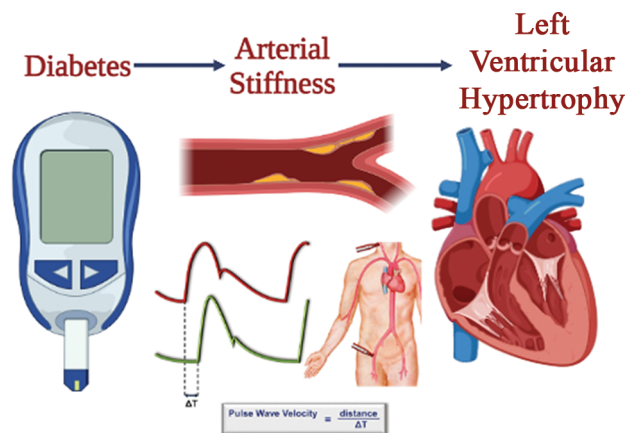


Association of Elevated Arterial Stiffness With Cardiac Target Organ Damage and Cardiac Autonomic Neuropathy in Young Adults With Diabetes: The SEARCH for Diabetes in Youth Study

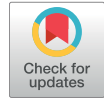
Elaine M. Urbina, Scott Isom, Dana Dabelea, Ralph D'Agostino Jr., Stephen R. Daniels, Lawrence M. Dolan, Giuseppina Imperatore, Eva Lustigova, Santica Marcovina, Amy Mottl, Catherine Pihoker, and Amy S. Shah

Diabetes Care 2023;46(4):786–793 | <https://doi.org/10.2337/dc22-1703>



ARTICLE HIGHLIGHTS

- Arterial stiffness is associated with cardiac structure and function.
- The relationships between arterial stiffness and cardiac target organ damage are similar in type 1 and type 2 diabetes.
- Cardiac autonomic neuropathy–induced arterial stiffness is not associated with cardiac abnormalities.



Association of Elevated Arterial Stiffness With Cardiac Target Organ Damage and Cardiac Autonomic Neuropathy in Young Adults With Diabetes: The SEARCH for Diabetes in Youth Study

Diabetes Care 2023;46:786–793 | <https://doi.org/10.2337/dc22-1703>

Elaine M. Urbina,¹ Scott Isom,²
Dana Dabelea,³ Ralph D'Agostino Jr.,²
Stephen R. Daniels,⁴ Lawrence M. Dolan,¹
Giuseppina Imperatore,⁵ Eva Lustigova,⁶
Santica Marcovina,⁷ Amy Mottl,⁸
Catherine Pihoker,⁹ and Amy S. Shah¹

OBJECTIVE

Adults with diabetes are at risk for cardiovascular (CV) events, possibly due to increased arterial stiffness (AS) and cardiac autonomic neuropathy (CAN). We sought to determine whether 1) AS is associated with cardiac target organ damage in young adults with youth-onset diabetes, 2) whether CAN is associated with AS, as one possible etiology for increased AS in this cohort, and 3) whether these relationships differ by type of diabetes.

RESEARCH DESIGN AND METHODS

Participants from the SEARCH for Diabetes in Youth Study (type 1 diabetes [T1D], $n = 222$; type 2 diabetes [T2D], $n = 177$; mean age 23 years) had clinical, echocardiographic, AS, and CAN assessed. Linear regression was performed to determine whether AS was associated with cardiac changes and CAN and whether relationships differed by diabetes type.

RESULTS

AS was significantly associated with cardiac structure (left ventricular mass index, $P < 0.0001$), systolic function (ejection fraction, $P = 0.03$) and diastolic function (transmitral peak early [E]/atrial [A] wave velocities ratio, $P = 0.008$; early [e']/atrial [a'] waves, $P = 0.02$) after adjustments for CV risk factors. The association between AS and CAN was not significant when other important covariates were added. These relationships were mostly similar in both T1D and T2D.

CONCLUSIONS

AS is associated with cardiac changes in young adults with diabetes. CAN-induced AS does not appear to be an etiology for cardiac abnormalities in this cohort.

Individuals with type 1 diabetes (T1D) and type 2 diabetes (T2D) have a higher risk of cardiovascular (CV) events compared with unaffected individuals (1). Cardiac autonomic neuropathy (CAN) is also known to develop at a higher frequency in adults with diabetes (2), and since the autonomic nervous system regulates vascular tone (smooth muscle contraction) (3), CAN may be one explanation for the observed increase in

¹Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH

²Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC

³Lifecourse Epidemiology of Adiposity and Diabetes (LEAD) Center, University of Colorado Anschutz Medical Campus (CU-Anschutz), Aurora, CO

⁴Department of Pediatrics, University of Colorado Anschutz Medical Campus (CU-Anschutz), Aurora, CO

⁵Division of Diabetes Translation, Centers for Disease Control and Prevention, Atlanta, GA

⁶Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

⁷Department of Medicine, University of Washington, Seattle, WA

⁸Division of Nephrology and Hypertension, University of North Carolina School of Medicine, Chapel Hill, NC

⁹Department of Pediatrics, University of Washington, Seattle, WA

Corresponding author: Elaine M. Urbina, elaine.urbina@cchmc.org

Received 31 August 2022 and accepted 9 January 2023

This article contains supplementary material online at <https://doi.org/10.2337/figshare.21892743>.

© 2023 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <https://www.diabetesjournals.org/journals/pages/license>.

arterial stiffness (AS) seen in adults with diabetes (4). The increased stiffness, in turn, is associated with measures of cardiac target organ damage (TOD) in adults (5), and cardiac damage, such as increased left ventricular (LV) mass (LVM) and systolic and diastolic dysfunction, is associated with hard CV events (myocardial infarction, stroke, heart failure) later in life (6). Whether increased AS is associated with the presence of CAN and whether AS is associated with TOD in adolescents and young adults with youth-onset diabetes is not well described. Our aims were to 1) determine whether AS is associated with cardiac TOD after adjustment for other CV risk factors, 2) explore whether the presence of CAN is associated with AS and may be one etiology for increased AS in this cohort, and 3) determine whether these relationships differ by diabetes type.

RESEARCH DESIGN AND METHODS

Description of Study Participants

Individuals in this analysis were part of the SEARCH for Diabetes in Youth Study (SEARCH) who were enrolled in 2002–2006 or 2008 and had AS, CAN, and echocardiographic parameters examined in 2015–2019. Diabetes type was defined based on measures at the baseline visit (etiologic diabetes type), with participants who were insulin sensitive or antibody positive characterized as having T1D ($n = 194$) and those who were insulin resistant and islet cell antibody negative as having T2D ($n = 158$). For the 47 participants where islet cell antibodies or insulin sensitivity measures were not available, diabetes type was based on their provider diagnosis (28 with T1D, 19 with T2D). Prior work in SEARCH has shown good agreement between etiologic diabetes type and provider-diagnosed diabetes type (7). All participants or parent/guardians provided written informed consent and assent, as appropriate by age. The institutional review boards at each site approved this study.

Data Collection

Detailed descriptions of the cohort and methods have been published previously (8). SEARCH has used consistent protocols to measure anthropometric, demographic, metabolic, and AS variables over time (8,9). Blood was collected after a minimum fast of 8 h, and all samples (lipids, glycosylated hemoglobin A_{1c} [HbA_{1c}] and C-reactive protein at follow-up) were analyzed at the Northwest Lipid Metabolism

and Diabetes Research Laboratories at the University of Washington, Seattle, Washington.

Pulse wave velocity (PWV), a measure of central AS, was measured using the SphygmoCor-Vx device (AtCor Medical, Sydney, NSW, Australia; PWV femoral) (8). Three PWV recordings were obtained per participant at each site and averaged. Repeat measures showed a coefficient of variation of $<7\%$. The augmentation index (Alx) is a measure of wave reflections related to AS. The average of three Alx measurements was used in the analysis (8). Reproducibility studies in our laboratory demonstrated intraclass correlation coefficients between 0.7 and 0.9. For both PWV and Alx, a higher value indicates greater stiffness.

Heart rate (HR) variability (HRV), a reflection of sympathetic and parasympathetic influence on the heart (8), was measured by the SphygmoCor with a 10-min electrocardiogram strip. After filtering out ectopic beats, the device derives the normal R-R intervals (N-N intervals) of the electrocardiogram and estimates time-domain parameters including 1) the SD of the N-N intervals (SDNN), 2) the root mean square differences of successive N-N intervals (RMSSD), and 3) the percent of adjacent N-N intervals with a difference >50 ms (PNN50). In addition to describing changes in HR (N-N interval) as a function of time (time domain measures such as PNN50), HR fluctuations over time can also be described as the sum of the oscillatory components defined by their frequency and amplitude (10). Fast Fourier analyses is used to identify high-frequency (HF) and low-frequency (LF) oscillations in the HR over time providing 1) normalized HF power, 2) normalized LF power, and 3) the LF-to-HF ratio. HF and LF power have traditionally been thought to represent parasympathetic and sympathetic components of HRV, but recent literature suggests that LF and HF may be influenced by respiratory sinus arrhythmia, position, movement, and other vagal components (8). Time and frequency domain measures are correlated. SDNN is a measure of overall HRV and correlates with total power. RMSSD and PNN50 represent the parasympathetic component of the HRV and are correlated with HF (11). Thus, parasympathetic loss is quantified by the reduction in PNN50, RMSSD, and HF power. These relationships have been

previously demonstrated in animal and human studies (10).

Echocardiography

M-mode of the LV was performed in the long- and short-axis views to calculate LVM. Traditional and tissue Doppler imaging of mitral inflow was obtained for evaluation of diastolic function. Echocardiograms were read by a single technician blinded to diabetes type at the central Echocardiography Reading Center (Cincinnati Children's Hospital Medical Center) on Digiview (Digisonics, Houston, TX) for LV structure and LV diastolic function. Global longitudinal LV strain, stroke volume, and ejection fraction (EF) were obtained from the apical four-chamber view on the TOMTEC system (Unterschleissheim, Germany) using a speckle tracking technique. Coefficients of variation for LV structure and diastolic function measures were $\leq 5.7\%$, with intraclass correlation coefficients ≥ 0.89 (9).

LVM was calculated by the standard formula (12) and then indexed (LVMI) to height in meters raised to 2.7 to minimize the effects of age, sex, and race (13). Measures of diastolic function included the ratio of the transmitral peak early (E) and atrial (A) wave velocities, with lower E/A indicating mild and elevated E/A indicating severe, restrictive physiology. The velocity of relaxation of the heart at the level of the mitral valve annulus at both the septum and free wall (early $[e']$ and atrial $[a']$ waves) was obtained to calculate E/e' (higher indicates diastolic dysfunction) and e'/a' ratio (lower indicates diastolic dysfunction). These noninvasive measures of diastolic function correlate well with invasive measures of diastolic function (time constant of relaxation $[\tau]$) and LV end-diastolic pressure (9).

Statistics

Summary statistics for characteristics of participants were computed using means and SDs, median and interquartile range, or count and percentages. Tests comparing diabetes types (T1D vs. T2D) were done using t tests, Kruskal-Wallis tests, or χ^2 tests, depending on the distribution, with $P < 0.05$ indicating a significant difference between groups. The presence of increased AS was defined as a carotid-femoral PWV at the 90th percentile or greater for a healthy control subject from a SEARCH Cardiovascular Disease Study

(8). These control subjects ($n = 171$) did not have diabetes, were a mean age of 19.3 ± 3.3 years, 52% female, and 77% non-Hispanic White, with a mean BMI 24.8 ± 6.2 kg/m². CAN was defined as abnormalities in three or more HRV measures using age- and sex-specific cut points (SDNN, RMSSD, HF, LF, HF-to-LF ratio). Data from the same control participants were used to calculate frequency domains (3).

Multivariable linear regression models were performed to determine whether increased AS was associated with cardiac structure and function. The initial model included a measure of AS, age at diabetes diagnosis, race, ethnicity, sex, and study site. Additional models included mean arterial pressure (MAP) to adjust for baseline distending pressure, diabetes type, BMI z score, duration of diabetes, HbA_{1c}, LDL-cholesterol (C), triglyceride (TG)-to-HDL-C ratio, and hsCRP from the CV imaging visit. HR was added to the models for PWV and height for the models for Alx. A sensitivity analysis was done adding smoking and medication use (blood pressure [BP], lipid, oral diabetes agent, and/or insulin). Neither parameter altered the models, so these items were not included in the final models. Measures of diet, physical activity, and sedentary behavior were omitted due to incomplete data for the majority of participants. Models were repeated, stratified by diabetes type, as an exploratory analysis.

Additional models were constructed to explore whether CAN was associated with AS. The prevalence of CAN was low (12.5%), and PNN50 had the highest correlation with AS measures. Owing to the short recording time (10 min), calculation of frequency domain measures was less robust, likely accounting for lower correlations with the outcomes. Therefore, PNN50 was included as the key independent variable with the same covariates as for the models relating AS to cardiac measures. The interaction of AS and PNN50 measures and diabetes type were checked during the modeling process. PNN50 had an interaction for several outcomes, so the analysis of PNN50 was stratified by diabetes type. Finally, we examined the relationship between CAN and cardiac structure and function.

Data and Resource Availability

All data and materials are available upon reasonable request.

RESULTS

The study population (Table 1) was 22.8 ± 5.1 years, with a duration of diabetes of 10.8 ± 3.2 years on average (62.7% female, 13.5% Hispanic, 33.1% non-Hispanic Black, 45.4% non-Hispanic White; 8.0% other). Overall, the cohort had obesity, with a BMI 30.6 ± 8.9 kg/m², and 44% ($n = 177$ of 399) had T2D. In general, those with T2D had a more adverse CV risk factor profile than those with T1D. We also examined the characteristics of the cohort by the presence of elevated AS and by the presence of CAN (Supplementary Tables 1 and 2).

Overall, CV parameters (Table 1) were in the clinically normal range for LVMI (13), systolic function (global longitudinal strain, EF) (14) and diastolic function (E/A, E/e', e'/a') (15–17). When stratified by diabetes type, those with T2D had greater AS (PWV) and more adverse time domain HRV measures (lower SDNN, PNN50, RMSSD all $P \leq 0.0001$) but did not differ by frequency domain measures (Table 1). The prevalence of increased AS (75.7% vs. 23.4%) and CAN (16.9% vs. 9.0%, both $P \leq 0.02$) was higher in T2D versus T1D. Participants with T2D had higher LVMI (37.4 vs. 28.9 g/m^{2.7}), lower systolic function (strain -18.6 vs. -20.7% ; EF 53.5 vs. 57.5%), and lower diastolic function (lower E/A: 1.6 vs. 1.9 , higher E/e': 7.5 vs. 6.2 , and lower e'/a' 1.6 vs. 1.9) than those with T1D (all $P \leq 0.0001$) (Table 1 and Fig. 1).

We evaluated the relationship between AS and cardiac structure and function adjusted for age, race, ethnicity, sex, and study site for the overall cohort. We found that PWV was associated with global longitudinal strain ($P = 0.0004$) and E/e' ($P < 0.0001$). PWV remained significantly associated with LVMI ($\beta = 1.95$, $P < 0.0001$), systolic function (EF, $\beta = -0.77$, $P = 0.03$) and diastolic function (E/A ratio, $\beta = -0.052$, $P = 0.008$; e'/a' $\beta = -0.048$, $P = 0.02$) after adjustment for these demographics, BP, HR, diabetes type, diabetes duration, BMI z score, HbA_{1c}, lipids, and inflammation (Supplementary Table 2, all models $P \leq 0.0001$). Although PWV was significantly associated with global longitudinal strain and E/e' initially (data not shown), PWV became nonsignificant with

the addition of HR and MAP, suggesting these parameters may have a more pronounced effect on these parameters compared with AS in this population. In the full models, diabetes type only had a significant association with E/e'.

In stratified models by diabetes type (Table 2), PWV was associated with LVMI for participants with T1D and T2D with similar β estimates (T1D $\beta = 1.41$, T2D $\beta = 1.67$, both $P \leq 0.005$). PWV was not significant in the models for EF or strain for either diabetes type, likely due to smaller sample size. PWV was significant for E/A for T2D and e'/a' for T1D (Table 3). There were differences by diabetes type in the other covariates that remained significant in the models, but the patterns were not consistent across cardiac measures. Therefore, with the smaller sample size in the stratified models, it is difficult to discern which CV risk factors are driving any diabetes-type related differences.

Alx was associated with diastolic function (E/e' $\beta = 0.019$, $P = 0.04$; e'/a' $\beta = -0.007$, $P = 0.003$) in the fully adjusted model for the overall cohort (Supplementary Table 4). Alx was no longer associated with LVMI or EF when MAP and height were added, and no association was seen with strain. Alx remained significant for E/A until laboratory values were added. This suggests that wave reflections (Alx) may affect diastolic function, while central AS (PWV) may affect cardiac structure and systolic and diastolic function. Looking at E/A by diabetes type the effect of Alx is significant for T2D ($\beta = -0.007$, $P = 0.03$), but not for T1D ($\beta = 0.003$, $P = 0.5$). The effect of Alx on e'/a' is similar for both T1D ($\beta = -0.007$, $P = 0.06$) and T2D ($\beta = -0.007$, $P = 0.05$).

In models investigating whether altered autonomic tone may affect AS and wave reflections in the overall cohort we examined the relationship between PNN50 and AS. An interaction term for PNN50 * diabetes type was significant for both PWV and Alx models (data not shown). In models stratified by diabetes type and adjusted for the presence of other risk factors (Table 4), PNN50 was significantly associated with PWV for both T1D ($\beta = -0.01$, $P = 0.01$) and T2D ($\beta = -0.01$, $P = 0.04$). PNN50 was only associated with Alx for participants with T2D ($\beta = -0.11$, $P = 0.03$), suggesting that autonomic imbalance only has an effect on wave reflections in participants with T2D. Finally, we examined whether the presence of CAN

Table 1—Description of the study population

Parameter	Overall All (n = 399)	Diabetes type		P value
		T1D (n = 222)	T2D (n = 177)	
Age (years)	22.8 (5.1)	21.3 (5.3)	24.6 (4.2)	<0.0001
Duration of diabetes (years)	10.8 (3.2)	11.2 (2.9)	10.3 (3.5)	0.0037
Female sex, n (%)	250 (62.7)	122 (55.0)	128 (72.3)	0.0004
Race/ethnicity, n (%)				<0.0001
Hispanic	54 (13.5)	28 (12.6)	26 (14.7)	
Non-Hispanic Black	132 (33.1)	36 (16.2)	96 (54.2)	
Non-Hispanic White	181 (45.4)	136 (61.3)	45 (25.4)	
Other	32 (8.0)	22 (9.9)	10 (5.6)	
Diabetes type, n (%T2D)	222 (44.3)	—	—	
BMI (kg/m ²)	30.6 (8.9)	25.5 (5.2)	37.0 (8.4)	<0.0001
BMI z score	1.3 (1.0)	0.7 (0.9)	1.9 (0.6)	<0.0001
Waist-to-height ratio	0.5 (0.5; 0.6)	0.5 (0.4; 0.5)	0.6 (0.6; 0.7)	<0.0001
Systolic BP (mmHg)	115.4 (15.3)	110.0 (11.9)	122.1 (16.5)	<0.0001
Systolic BP z score	−0.1 (1.2)	−0.6 (1.0)	0.4 (1.2)	<0.0001
Diastolic BP (mmHg)	75.1 (11.5)	71.7 (10.5)	79.3 (11.4)	<0.0001
Diastolic BP z score	0.8 (1.0)	0.5 (1.0)	1.2 (0.9)	<0.0001
MAP (mmHg)	88.5 (12.0)	84.5 (10.2)	93.6 (12.3)	<0.0001
LDL-C (mg/dL)	106.5 (36.8)	101.6 (32.2)	112.5 (41.0)	0.0034
TG-to-HDL-C ratio	2.0 (1.2; 3.6)	1.4 (1.0; 2.2)	3.4 (2.1; 5.0)	<0.0001
C-reactive protein (mg/dL)	0.3 (0.1; 0.8)	0.1 (0.0; 0.4)	0.6 (0.2; 1.2)	<0.0001
HbA _{1c} (%)	9.2 (2.5)	8.9 (1.9)	9.6 (3.0)	0.0116
Insulin use, n (%)	311 (78.5)	212 (95.9)	99 (56.6)	<0.0001
Diabetes medications, n (%)†	351 (90.2)	218 (98.6)	133 (79.2)	<0.0001
Hypertension medications, n (%)	59 (15.8)	26 (12.0)	33 (21.0)	0.0819
Lipid medications, n (%)	29 (7.8)	11 (5.1)	18 (11.5)	0.0233
PWV (m/s)	6.9 (1.8)	6.0 (1.2)	8.0(1.7)	<0.0001
SDNN	51.5 (34.9; 73.2)	55.9 (40.3; 84.6)	44.9 (27.8; 59.8)	<0.0001
PNN50	17.5 (2.7; 43.1)	27.4 (6.9; 46.2)	10.3 (0.8; 31.9)	<0.0001
RMSSD	42.0 (24.1; 68.2)	48.9 (30.7; 74.2)	34.5 (17.2; 57.5)	<0.0001
LF power	47.6 (19.0)	46.8 (17.9)	48.6 (20.2)	0.364
HF power	52.4 (19.0)	53.2 (17.9)	51.4 (20.2)	0.364
LF-to-HF ratio	0.9 (0.5; 1.6)	0.9 (0.5; 1.5)	0.9 (0.6; 1.8)	0.4769
LVMI (g/m ^{2.7})	32.5 (9.3)	28.9 (6.7)	37.4 (10.0)	<0.0001
Peak longitudinal strain (%)	−19.8 (4.0)	−20.7 (4.1)	−18.6 (3.5)	<0.0001
Peak longitudinal strain rate (/ms)	−1.0 (0.2)	−1.0 (0.2)	−0.9 (0.2)	<0.0001
EF (%)	55.8 (7.8)	57.5 (7.6)	53.5 (7.5)	<0.0001
E/A ratio	1.8 (0.5)	1.9 (0.5)	1.6 (0.5)	<0.0001
E/e' ratio	6.8 (2.0)	6.2 (1.4)	7.5 (2.3)	<0.0001
e'/a' ratio	1.8 (0.6)	1.9 (0.6)	1.6 (0.5)	<0.0001
Presence of CAN, n (%)	50 (12.5)	20 (9.0)	30 (16.9)	0.0173
Presence of elevated AS, n (%)	186 (46.6)	52 (23.4)	134 (75.7)	<0.0001

Data are presented as mean (SD), as median (interquartile range), or as n (%), as indicated. †Includes medications classified as second- or third-generation sulfonylureas, amylin analog, biguanide, and dipeptidyl peptidase 4 inhibitors.

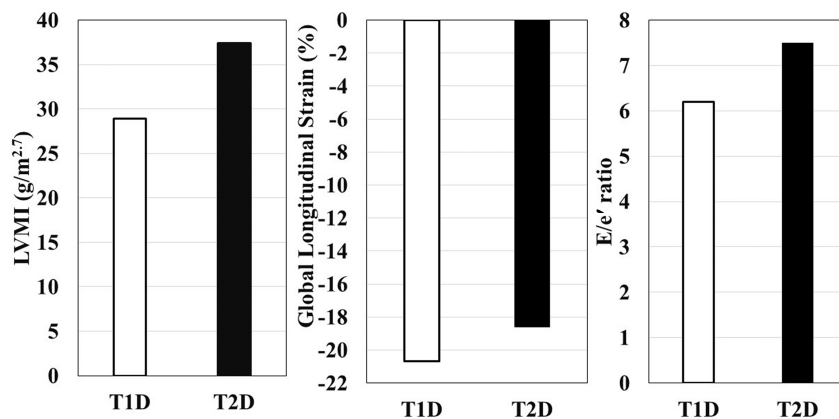


Figure 1—Cardiac structure and function stratified by diabetes type. T1D differs from T2D, all $P = 0.0001$.

and AS or whether CAN was related to cardiac outcomes. In models with demographics, MAP, and HR, there was no significant association of the presence of CAN with either AS or cardiac outcomes. This is likely due to limited power as only 12.5% of the sample met the CAN definition.

CONCLUSIONS

In this study examining the relationship between increased AS and cardiac TOD, we found that central AS (PWV) remained a significant determinant of cardiac structure (LVMI) and systolic (EF) and diastolic function (E/A, e'/a'), even after adjustment for demographics and CV risk factors, including a term for diabetes type. The significance of PWV

persisted in models stratified by diabetes type for LVMI (both T1D and T2D), e'/a' ratio (T1D only), and E/A (T2D only) but, due to smaller sample size, lost significance for the other parameters. In contrast, wave reflections (Alx) only remained associated with diastolic function (E/ e' , e'/a') after adjustments, suggesting that distinct arterial parameters have different effects on cardiac TOD. Finally, we also showed the relationship between increased central stiffness and cardiac structure and function was similar by diabetes type.

In adults, the relationship between altered arterial parameters and cardiac structure and function is well documented, but few patients with T2D were studied (18). The Framingham Heart Study found a significant relationship between PWV and

LVMI ($N = 6,203$) in their population cohort, with increased odds for LV hypertrophy with higher PWV (odds ratio 1.27; 95% CI 1.16–1.39) that was attenuated but persisted after adjustment for clinic BP (19). In a Flemish cohort ($N = 1,233$), higher PWV was associated with higher E/ e' ratio, a robust measure of diastolic dysfunction (20). There was no association between central stiffness and LV systolic radial strain, but longitudinal strain, the more commonly measured parameter obtained in this study, was not analyzed (20). One smaller study ($N = 142$) evaluated adults with T1D ($n = 70$) and T2D ($n = 72$) and found that PWV was independently associated with E/A, E/ e' , and the grade of LV diastolic dysfunction (21). These studies did not, however, evaluate for differences by diabetes type. Alx is also correlated with LVMI in individuals treated for hypertension ($N = 512$) after correction for BP (22) and with diastolic function in a community-based sample ($N = 983$) (23). However, more advanced arterial testing has demonstrated that the forward and backward waves separated from the composite Alx may provide stronger correlations with LVMI ($N = 4,145$, Multi-Ethnic Study of Atherosclerosis [MESA] study) (24).

Fewer studies are available relating AS to cardiac TOD in youth. In African American adolescents ($N = 120$, age 13–18 years), Alx did not correlate with LVMI, but in an adjusted model, for every 10% change in Alx there was a 0.01-mm change

Table 2—Multivariable models relating PWV to LVMI and systolic function stratified by diabetes type

Parameter	LVMI		EF		LV systolic strain	
	T1D	T2D	T1D	T2D	T1D	T2D
Intercept	27.13 (5.35)		66.53 (6.82)	64.23 (7.88)	−29.06 (3.7)	−28.35 (3.54)
PWV (m/s)	1.41 (0.46)	1.67 (0.58)				
Age at diabetes diagnosis (years)			0.34 (0.13)			0.31 (0.11)
Female (REF = male)	−2.11 (0.96)		3.10 (1.22)	3.57 (1.41)		−1.41 (0.63)
Non-Hispanic White (REF = other race)	−1.29 (1.00)			3.22 (1.46)		
HR (bpm)	−0.10 (0.04)			−0.13 (0.06)		
BMI z score	2.77 (0.53)	4.97 (1.35)				
Diabetes duration (years)			0.41 (0.2)			
TG-to-HDL-C ratio†	−0.68 (0.34)					
R^2	0.33	0.34	0.21	0.22	0.20	0.27
Model P value	<0.0001	<0.0001	<0.0001	0.0016	0.0001	<0.0001

Data are β (SE) estimates, and only significant values ($P \leq 0.05$) are shown. All models were adjusted for all parameters listed, study site, and ethnicity, MAP, LDL-C, \ln (C-reactive protein), and HbA_{1c} , which were not significant in all models. R^2 , coefficient of determination.

†TG-to-HDL-C values were winsorized due to outlying values.

Table 3—Multivariable models relating PWV to diastolic function stratified by diabetes type

Parameter	E/A		E/e'		e'/a'	
	T1D	T2D	T1D	T2D	T1D	T2D
Intercept	4.18 (0.44)	3.96 (0.38)	3.18 (1.26)		4.84 (0.42)	4.63 (0.43)
PWV (m/s)		−0.07 (0.02)				
Age at diabetes diagnosis (years)		−0.03 (0.01)			−0.03 (0.01)	−0.05 (0.01)
Female (REF = male)			0.52 (0.23)		−0.17 (0.07)	
Hispanic (REF = non-Hispanic/unknown)	0.28 (0.12)					−0.27 (0.12)
MAP (mmHg)				0.05 (0.02)		
HR (bpm)	−0.01 (0.00)	−0.01 (0.00)			−0.02 (0.00)	−0.01 (0.00)
BMI z score			0.35 (0.12)			
Diabetes duration (years)		−0.03 (0.01)			−0.03 (0.01)	−0.05 (0.01)
HbA _{1c} (%)				−0.14 (0.07)		
ln(hsCRP)				0.33 (0.15)		
R ²	0.34	0.46	0.24	0.23	0.45	0.47
Model P value	<0.0001	<0.0001	<0.0001	0.0004	<0.0001	<0.0001

Data are β (SE) estimates, and only significant values ($P \leq 0.05$) are shown. All models were adjusted for all parameters listed, study site, and race, LDL-C, and TG-to-HDL-C ratio, which were not significant in all models. R², coefficient of determination.

in LV relative wall thickness ($P = 0.05$), a measure of LV geometry (25). One cohort that included one-third healthy weight, one-third with obesity, and one-third youth with both obesity and T2D (total $N = 670$, age 10–24 years) found an independent

relationship between vascular compromise (increased carotid intima-media thickness, higher PWV and Alx) and cardiac TOD, including increased LVMI and systolic and diastolic function (26–28). In the Treatment Options for Type 2 Diabetes

in Adolescents and Youth (TODAY) Study ($N = 388$, all T2D) (29), a composite AS measure was constructed from PWV, Alx, and brachial artery distensibility z scores at baseline and compared with echocardiograms obtained 2 years later. The

Table 4—Multivariable models relating cardiac autonomic function to AS stratified by diabetes type

Parameter	PWV				Alx			
	T1D		T2D		T1D		T2D	
	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
Intercept	2.79 (0.91)	0.002	−3.67 (1.34)	0.01	−28.96 (11.77)	0.01	−38.89 (11.96)	0.002
PNN50	−0.01 (0)	0.01	−0.01 (0.01)	0.04	0.03 (0.04)	0.54	−0.11 (0.05)	0.03
Age at diagnosis (years)	0.10 (0.01)	<0.0001	0.13 (0.04)	0.002	0.26 (0.20)	0.18	0.48 (0.37)	0.20
Female (REF = male)	0.15 (0.14)	0.28	0.73 (0.23)	0.002	8.55 (1.80)	<0.0001	10.83 (2.07)	<0.0001
Hispanic (REF = non-Hispanic/unknown)	−0.16 (0.23)	0.47	0.32 (0.37)	0.39	−2.25 (2.94)	0.45	1.94 (3.48)	0.58
Non-Hispanic White (REF = other race)	−0.09 (0.16)	0.57	−0.19 (0.26)	0.47	−4.38 (2.07)	0.04	−3.17 (2.40)	0.19
MAP	0.01 (0.01)	0.10	0.07 (0.01)	<0.0001	0.22 (0.09)	0.02	0.38 (0.08)	<0.0001
BMI z score	0.16 (0.08)	0.04	0.54 (0.18)	0.004	−1.37 (1.01)	0.18	−5.33 (1.57)	0.001
Diabetes duration	0.08 (0.02)	0.001	0.12 (0.03)	<0.0001	0.50 (0.31)	0.10	1.33 (0.26)	<0.0001
HbA _{1c}	0.04 (0.04)	0.30	0.05 (0.04)	0.23	−0.40 (0.49)	0.42	−0.02 (0.35)	0.96
LDL-C	0.003 (0)	0.53	0.01 (0)	0.02	0.05 (0.03)	0.13	0.04 (0.02)	0.07
TG-to-HDL-C ratio†	0.16 (0.05)	0.002	0.05 (0.05)	0.23	0.32 (0.66)	0.63	−0.43 (0.40)	0.28
ln(C-reactive protein)	0.07 (0.06)	0.18	−0.04 (0.09)	0.69	0.58 (0.71)	0.42	0.02 (0.81)	0.98
R ²	0.51		0.53		0.27		0.50	
Model P value	<0.0001		<0.0001		<0.0001		<0.0001	

R², coefficient of determination. †TG/HDL values were winsorized due to outlying values.

composite measure did remain significantly associated with LVM index and diastolic function but did not relate to systolic function (29). No studies including both cardiac structure and function have been conducted in young adults with T1D, and no comparative studies between participants with youth-onset T1D and T2D have previously been performed.

Few studies have examined the relationship between AS and autonomic tone in youth. In SEARCH, lower SDNN was associated with higher PWV and Alx in participants with T1D (8) and T2D, but the relationship was attenuated after adjustment for CV risk factors (30). In the TODAY Study, CAN was present in 8% of the cohort, and those participants had greater PWV (31). Our work adds to the literature by evaluating the relationship between central AS (PWV), wave reflections (Alx), and HRV or CAN stratified by diabetes type. While we found a relationship between PWV and individual measures of HRV, PNN50 was associated with PWV for both T1D and T2D, and PNN50 was associated with Alx for participants with T2D only, we did not find an association between CAN and PWV. We postulated this may be due to power (low percentage of CAN in the overall cohort) and therefore cannot conclude that CAN-induced AS is associated with cardiac abnormalities.

Limitations and Strengths

We collected HRV data over only a 10-min period. Although this method is considered acceptable practice by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, the short measurement period may under detect HRV abnormalities and/or CAN (11). For this reason, we also did not analyze the SD of the 5-min average N-N intervals index, which measures HR changes due to cycles >5 min. In addition, our study is cross-sectional, so we cannot determine whether altered autonomic tone led to the increased AS or the stiffness led to cardiac TOD. We also were unable to assess the impact of diet, exercise, and smoking due to missing data, but our previous work showed a weak relationship of these CV risk factors to AS, HRV, and cardiac damage (3,9).

Primary strengths are the large number of young people with T1D and with T2D, an inclusion of central stiffness,

wave reflections, and autonomic tone, and assessing the relationship to both cardiac structure and function and by diabetes type. These findings may not be generalizable to a population without diabetes.

Conclusion

AS is associated with cardiac structure and function in a similar fashion in both T1D and T2D. Although we did see an association between HRV and AS, due to a low prevalence of CAN, we cannot prove that CAN-induced AS is an etiology for cardiac abnormalities. However, since the presence of AS, CAN, and cardiac TOD as observed in this study predict CV events in adults (32), strategies for prevention are logical steps to prevent future CV disease.

Acknowledgments. The SEARCH for Diabetes in Youth Study is indebted to the many youth, their families, and their health care providers, whose participation made this study possible.

Funding. This study received funding from the Kaiser Permanente Southern California's Clinical Research Center (funded by Kaiser Foundation Health Plan and supported in part by the Southern California Permanente Medical Group), the South Carolina Clinical & Translational Research Institute, at the Medical University of South Carolina, NIH/National Center for Advancing Translational Sciences (NCATS) grant numbers UL1 TR000062 and UL1 TR001450, Seattle Children's Hospital and the University of Washington, NIH/NCATS grant number UL1 TR00423, University of Colorado Pediatric Clinical and Translational Research Center, NIH/NCATS grant number UL1 TR000154, the Barbara Davis Center at the University of Colorado at Denver (Diabetes Endocrinology Research Center [DERC] NIH grant number P30 DK57516), the University of Cincinnati, NIH/NCATS grant numbers UL1 TR000077 and UL1 TR001425, and the Children with Medical Handicaps program managed by the Ohio Department of Health. SEARCH 4, the SEARCH for Diabetes in Youth Cohort Study, is funded by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, and supported by the Centers for Disease Control and Prevention (1R01DK127208-01, 1U4DK108173). The Population Based Registry of Diabetes in Youth Study (project numbers 1U18DP006131, 1U18DP006133, 1U18DP006134, 1U18DP006136, 1U18DP006138, and 1U18DP006139) is supported by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases and funded by the Centers for Disease Control and Prevention (DP-15-002). SEARCH 1, 2, 3 is supported by National Institute of Diabetes and Digestive and Kidney Diseases and funded by the Centers for Disease Control and Prevention (PA numbers 00097, DP-05-069, and DP-10-001) and supported by the Kaiser Permanente Southern California (U48/CCU919219, U01 DP000246, and

U18DP002714), University of Colorado Denver (U48/CCU819241-3, U01 DP000247, and U18DP000247-06A1), Cincinnati's Children's Hospital Medical Center (U48/CCU519239, U01 DP000248, and 1U18DP002709), University of North Carolina at Chapel Hill (U48/CCU419249, U01 DP000254, and U18DP002708), Seattle Children's Hospital (U58/CCU019235-4, U01 DP000244, and U18DP002710-01), and Wake Forest University School of Medicine (U48/CCU919219, U01 DP000250, and 200-2010-35171).

This study includes data provided by the Ohio Department of Health, which should not be considered an endorsement of this study or its conclusions. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Diseases.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. E.M.U. designed the analysis plan and wrote the manuscript. S.I. conducted the data analysis and edited the manuscript. D.D., S.R.D., L.M.D., G.I., E.L., S.M., A.M., and C.P. designed the study and edited the manuscript. R.D. helped with statistical analysis and interpretation of the findings. A.S.S. designed the analysis plan, interpreted the results, and edited the manuscript. All authors gave final approval of this version of the manuscript to be published. The authors consented to the publication of this manuscript. E.M.U. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented as an oral presentation at the 82nd Scientific Sessions of the American Diabetes Association, virtual and at New Orleans, LA, 3–7 June 2022.

References

1. Sattar N, Rawshani A, Franzén S, et al. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. *Circulation* 2019;139:2228–2237
2. Grassi G, Biffi A, Dell'Oro R, et al. Sympathetic neural abnormalities in type 1 and type 2 diabetes: a systematic review and meta-analysis. *J Hypertens* 2020;38:1436–1442
3. Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability among youth with type 1 diabetes: the SEARCH CVD study. *Diabetes Care* 2013;36:157–162
4. Prince CT, Secret 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
5. Alonso-Domínguez R, Sánchez-Aguadero N, Patino-Alonso MC, et al.; EVA Investigators. Association between measurements of arterial stiffness and target organ damage in a general Spanish population. *Ann Med* 2021;53:345–356
6. Cuspidi C, Facchetti R, Bombelli M, et al. Risk of mortality in relation to an updated classification of left ventricular geometric abnormalities in a

- general population: the Pamela study. *J Hypertens* 2015;33:2133–2140
7. Crume TL, Hamman RF, Isom S, et al.; SEARCH for Diabetes in Youth Study Group. The accuracy of provider diagnosed diabetes type in youth compared to an etiologic criteria in the SEARCH for Diabetes in Youth Study. *Pediatr Diabetes* 2020;21:1403–1411
 8. Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability is associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. *Diabetes Care* 2013;36:2351–2358
 9. Shah AS, Isom S, Dabelea D, et al.; SEARCH for Diabetes in Youth Study Group. A cross sectional study to compare cardiac structure and diastolic function in adolescents and young adults with youth-onset type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. *Cardiovasc Diabetol* 2021;20:136
 10. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991;84:482–492
 11. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996;93:1043–1065
 12. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57:450–458
 13. de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992;20:1251–1260
 14. Yang H, Wright L, Negishi T, Negishi K, Liu J, Marwick TH. Research to practice: assessment of left ventricular global longitudinal strain for surveillance of cancer chemotherapeutic-related cardiac dysfunction. *JACC Cardiovasc Imaging* 2018;11:1196–1201
 15. Carvalho JC, Farand P, Do HD, Brochu MC, Bonenfant F, Lepage S. Effect of age and sex on echocardiographic left ventricular diastolic function parameters in patients with preserved ejection fraction and normal valvular function. *Cardiol J* 2013;20:513–518
 16. Eidem BW, McMahon CJ, Cohen RR, et al. Impact of cardiac growth on Doppler tissue imaging velocities: a study in healthy children. *J Am Soc Echocardiogr* 2004;17:212–221
 17. Kasner M, Westermann D, Steendijk P, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. *Circulation* 2007;116:637–647
 18. Alem MM, Alshehri AM. Inter-relationships between left ventricular mass, geometry and arterial stiffness. *J Int Med Res* 2020;48:1–15
 19. Vasan RS, Short MJ, Niiranen TJ, et al. Interrelations between arterial stiffness, target organ damage, and cardiovascular disease outcomes. *J Am Heart Assoc* 2019;8:e012141
 20. Cauwenberghs N, Knez J, Tikhonoff V, et al. European Project On Genes in Hypertension (EPOGH) Investigators. Doppler indexes of left ventricular systolic and diastolic function in relation to the arterial stiffness in a general population. *J Hypertens* 2016;34:762–771
 21. Roos CJ, Auger D, Djaberi R, et al. Relationship between left ventricular diastolic function and arterial stiffness in asymptomatic patients with diabetes mellitus. *Int J Cardiovasc Imaging* 2013;29:609–616
 22. Matsui Y, Ishikawa J, Eguchi K, et al. The influence of wave reflection on left ventricular hypertrophy in hypertensive patients is modified by age and gender. *Hypertens Res* 2008;31:649–656
 23. Russo C, Jin Z, Palmieri V, et al. Arterial stiffness and wave reflection/novelty and significance. *Hypertension* 2012;60:362–368
 24. Zamani P, Bluemke DA, Jacobs DR Jr, et al. Resistive and pulsatile arterial load as predictors of left ventricular mass and geometry: the multi-ethnic study of atherosclerosis. *Hypertension* 2015;65:85–92
 25. DeLoach SS, Daskalakis C, Gidding S, Falkner B. Central blood pressures are associated with left ventricular mass index among African-American adolescents. *Am J Hypertens* 2012;25:41–45
 26. Urbina EM, Dolan LM, McCoy CE, Khoury PR, Daniels SR, Kimball TR. Relationship between elevated arterial stiffness and increased left ventricular mass in adolescents and young adults. *J Pediatr* 2011;158:715–721
 27. Madsen NL, Haley JE, Moore RA, Khoury PR, Urbina EM. Increased arterial stiffness is associated with reduced diastolic function in youth with obesity and type 2 diabetes. *Front Pediatr* 2021;9:781496
 28. Mehta S, Khoury PR, Madsen NL, Dolan LM, Kimball TR, Urbina EM. Arterial thickness and stiffness are independently associated with left ventricular strain. *J Am Soc Echocardiogr* 2018;31:99–104
 29. Shah AS, Gidding SS, El Ghormli L, et al.; TODAY Study Group. Relationship between arterial stiffness and subsequent cardiac structure and function in young adults with youth-onset type 2 diabetes: results from the TODAY Study. *J Am Soc Echocardiogr* 2022;35:620–628.e4
 30. Shah AS, Jaiswal M, Dabelea D, et al. Cardiovascular risk and heart rate variability in young adults with type 2 diabetes and arterial stiffness: the SEARCH for Diabetes in Youth Study. *J Diabetes Complications* 2020;34:107676
 31. Shah AS, El Ghormli L, Vajravelu ME, et al. Heart rate variability and cardiac autonomic dysfunction: prevalence, risk factors, and relationship to arterial stiffness in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study. *Diabetes Care* 2019;42:2143–2150
 32. Bluemke DA, Kronmal RA, Lima JA, et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 2008;52:2148–2155