HHS Public Access

Author manuscript

J Diabetes Complications. Author manuscript; available in PMC 2021 October 01.

Published in final edited form as:

J Diabetes Complications. 2020 October ; 34(10): 107676. doi:10.1016/j.jdiacomp.2020.107676.

Cardiovascular Risk and Heart Rate Variability in Young Adults with Type 2 Diabetes and Arterial Stiffness: The SEARCH for Diabetes in Youth Study

Amy Sanghavi Shah, MD MS[1], **Mamta Jaiswal, MBBS PhD**[2], **Dana Dabelea, MD PhD**[3], **Jasmin Divers, PhD**[4], **Scott Isom, MS**[5], **Angela D Liese, PhD**[6], **Jean M Lawrence, ScD, MPH, MSSA**[7], **Grace Kim, MD**[8], **Elaine M. Urbina, MD MS**[1]

[1]Cincinnati Children's Hospital Medical Center and the University of Cincinnati

[2]Department of Neurology, University of Michigan, Ann Arbor MI

[3]Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Aurora, CO

[4]Division of Health Services Research, NYU Long Island School of Medicine, Mineola, NY

[5]Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC

[6]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC

[7]Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

[8]Seattle Children's Hospital, Seattle, WA

Abstract

Corresponding author: Amy Sanghavi Shah MD MS, Cincinnati Children's Hospital, Division of Endocrinology, 3333 Burnet Ave ML 7012, Cincinnati OH 45229.

CRediT author statement

Conceptualization: Mamta Jaiswal, Dana Dabelea, Elaine Urbina
Methodology: Dana Dabelea, Elaine Urbina, Amy Shah.
Software Programming: Scott Isom
Validation: Amy Shah, Scott Isom
Formal analysis: Scott Isom
Investigation: Dana Dabelea, Jean Lawrence, Elaine Urbina
Resources: Scott Isom, Jasmin Divers, Dana Dabelea, Jean Lawrence, Elaine Urbina
Writing: Dana Dabelea, Elaine Urbina, Amy Shah.
Writing: Review & Editing: All authors
Visualization: All authors
Supervision: Jasmin Divers, Dana Dabelea, Jean Lawrence, Elaine Urbina
Project administration: Jasmin Divers, Dana Dabelea, Jean Lawrence, Elaine Urbina
Funding acquisition: Jasmin Divers, Dana Dabelea, Jean Lawrence, Elaine Urbina

Conflicts of interest

The authors have no conflicts of interest to report.

Aims—To evaluate cardiovascular risk factors and heart rate variability (HRV) in young adults with type 2 diabetes and arterial stiffness and to explore the relationship between HRV and arterial stiffness.

Methods—We studied 185 young adults with youth-onset T2D enrolled in the SEARCH for Diabetes in Youth study. Cardiovascular risk factors and HRV were compared between individuals with and without type 2 diabetes and arterial stiffness (defined as a pulse wave velocity greater than the 90th percentile of healthy controls, >6.767 m/s). Semiparametric regression evaluated the independent relationship between HRV and PWV.

Results—Participants with T2D and arterial stiffness were more likely to be older, non-Hispanic Black, have higher systolic and diastolic blood pressure, greater adiposity and obesity-related dyslipidemia (higher triglycerides and lower HDL-C). Participants with T2D arterial stiffness also had lower overall HRV (lower SDNN) with parasympathetic loss (lower RMSSD and PNN50), $p<0.05$. Lower HRV tended to be but was not significantly associated with arterial stiffness after adjustment for age, race/ethnicity, sex and cardiovascular risk factors (beta coefficient = −1.11, $p=0.08$).

Conclusions—Youth with T2D and arterial stiffness have a worse cardiovascular risk profile, specifically risk factors related to the metabolic syndrome and lower HRV.

Keywords

type 2 diabetes; arterial stiffness; heart rate variability; pediatrics; adolescents

Introduction

Type 2 diabetes (T2D) is a risk for cardiovascular disease [1]. Prior work shows young adults with youth-onset T2D have a disproportionally higher rates of diabetes-related complications and an increased risk for mortality [2–5]. Rates of co-morbidities and complications are higher in youth with T2D compared to type 1 diabetes (T1D) despite similar glucose control and duration of diabetes [2–5]. For this reason, understanding the risk factors associated with early markers cardiovascular disease in young adults with T2D is important.

Arterial stiffness is an early marker of cardiovascular disease. In adults, higher arterial stiffness predicts greater cardiovascular morbidity and mortality [6, 7]. Pulse wave velocity (PWV) is the gold-standard method for assessing arterial stiffness. PWV is measured non-invasively and is therefore useful to assess cardiovascular risk in the pediatric and young adult population. Youth with T2D have higher PWV compared to their peers with T1D, as well as lean and obese controls [2, 7–9]. Older age, non-white race, higher blood pressure and greater BMI have been associated with higher PWV [8, 10].

Cardiac autonomic dysfunction is another frequent and early but often under-recognized manifestation of T2D that confers a risk of arrhythmia, myocardial infarction and sudden death [11–15]. Cardiac autonomic dysfunction is associated with parasympathetic loss and sympathetic dysfunction [16, 17]. The autonomic nervous system is responsible for regulating

heart rate and vascular tone implying a potential pathophysiological link between cardiac autonomic function and arterial stiffness.

Thus, the aims of the present study were to 1) evaluate the cardiovascular risk factor profile and HRV in adolescents and young adults with youth-onset type 2 diabetes and arterial stiffness, and 2) to explore the independent relationship between HRV and arterial stiffness.

Subjects, Materials and Methods

This is a cross-sectional analysis of participants enrolled in the SEARCH for Diabetes in Youth study, a multi-center study examining the prevalence, incidence, and complications of youth-onset diabetes [18]. SEARCH has five sites in the United States (South Carolina; Cincinnati, Ohio and surrounding counties; Colorado with southwestern Native American sites; Seattle, Washington and surrounding counties; and Kaiser Permanente, Southern California). Participants included in this analysis were diagnosed with type 2 diabetes in 2002–2006 or 2008 and had a baseline visit at a mean of 9.3 ±6.4 months from their diabetes diagnosis. Participants (n=409) were eligible for a SEARCH study follow-up visit between 2011– 2015 when their duration of diabetes was at least ≥ 5 years [19]. Participants could have been up to five times over the 13 year period. Type 2 diabetes was defined as negative islet cell antibody titers and an insulin sensitivity score of <8.15, indicating insulin resistance [20]. Of the 409 eligible for a follow-up visit, 255 were seen for an in person study visit and 185 underwent arterial stiffness and heart rate variability testing. Institutional review boards at each site approved the study. All participants, the parent, adolescent or young adult, or both provided consent or assent.

Anthropometric, demographic and metabolic variables were collected similarly at each visit, as previously described [19]. Briefly, height and weight were measured in light indoor clothing without shoes and used to calculate BMI (kg/m^2). Waist circumference was measured twice in centimeters using the natural waist defined as midway between the lowest rib margin and the right iliac crest at the mid-axillary line. A third measurement was made if the second measure differed from the first by > 1.0 cm. The ratio of waist-to-height (WHtR) to quantify central obesity [21–23]. Blood and urine were collected after a minimum of an 8-hour fast and all samples (lipids, hemoglobin A1c, urine albumin, urine creatinine) were analyzed at the Northwest Lipid Metabolism and Diabetes Research Laboratories at University of Washington, Seattle, Washington [24]. Measurements of triglycerides and HDL cholesterol (HDL-C) were performed enzymatically on a Hitachi 917 autoanalyzer (Roche Molecular Biochemicals Diagnostics, Indianapolis, IN). LDL cholesterol (LDL-C) were calculated by the Friedewald equation for individuals with triglyceride concentrations <400 mg/dL and the Beta Quantification procedure for those with triglyceride ≥400 mg/dL. High-performance liquid chromatography (TOSOH Bioscience, Inc., San Francisco, CA) was used to measure Hemoglobin A1c. Urinary albumin and creatinine were measured from a first morning void.

At follow-up only, physical activity, hours of TV watching and smoking status were determined by a participant questionnaire. Two questions classified participants into “never”, “former”, and “current” smokers. If the participant answered “no” to the question “Have you ever tried cigarette smoking, even one or two puffs?” then the participant was classified as a

"never" smoker. If the participant answered "yes" to the above question, they were asked "During the past 30 days, on how many days did you smoke cigarettes?" If the participant answered "none" then they were classified as a "former" smoker. If the participant answered "yes" to ever smoking a cigarette and said they had smoked at least one day in the past 30 days then they were classified as a "current" smoker [25].

At the last follow-up visit, participants also underwent measurements of arterial stiffness and HRV testing, both measured by the SphygmoCor-Vx device (AtCor Medical, Sydney, Australia)[2]. All measurements occurred in the morning in a room with a stable room temperature, with the participant lying in the resting supine position for 10 min.

Arterial stiffness was assessed once at follow-up by a measuring carotid femoral pulse wave velocity (PWV). PWV calculates the speed of pressure waves generated by cardiac ejection to reach the periphery. Three ECG leads are applied to the torso of each participant. The distances from the lowest portion of the sternal notch to the carotid and femoral artery sites are then measured to the nearest 0.1 cm three times using a tape measure and averaged. A pressure waveform obtained from the proximal site (carotid artery) is recorded followed by a second arterial waveform recorded from the distal site (femoral artery) using a tonometer. Waveforms are also recorded on a simultaneous electrocardiogram. PWV is the difference in the carotid-to-femoral path distance divided by the time delay measured between the feet of the two waveforms reported in meters per second (m/s). The average of at least 10 beats was used in the analysis to cover a complete respiratory cycle. Three PWV recordings were obtained per participant and averaged. Repeat measures show a coefficient of variation of < 7%[26]. A PWV of 90th percentile or greater of controls from the SEARCH Cardiovascular Disease study defined arterial stiffness[2].

Heartbeats from an electrocardiogram were recorded for 10 minutes to determine HRV. The SphygmoCor-Vx device takes into account the normal heartbeats, ignoring ectopic beats, to derive a the normal R-R intervals (NN intervals) of the electrocardiogram and estimates several time-domain HRV indices. Both time- and frequency-domain HRV parameters are derived. Time domains include 1) the SD of the NN intervals (SDNN), 2) the root mean square differences of successive NN intervals (RMSSD), and 3) the percent of adjacent NN intervals with a difference greater than 50msec (PNN50). Frequency domains are calculated using Fast Fourier analysis which separates the heart rate spectrum into various components including: 1) normalized high frequency (HF) power, 2) normalized low frequency (LF) power, and 3) their ratio, LF: HF. SDNN is a measure of overall HRV. RMSSD and PNN50 represent the parasympathetic component of the HRV[16]. HF and LF power have traditionally been thought to represent parasympathetic and sympathetic components of HRV, respectively[27]. However, more recent literature suggests that is an over simplistic view as, LF and HF may be influenced by respiratory sinus arrhythmia, posture/movement, and other vagal components [28]. Tachograms and Poincare plots were examined at the time of conducting the study by study staff with the SphymaCor measurement repeated if needed. All data were checked to look for clinical or statistical outliers in the time and frequency domains and those with excessive artifact, were deleted.

Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC) and R: a language and environment for statistical computing. Differences in the characteristics and HRV of T2D youth with (PWV >6.767) and without arterial stiffness (PWV ≤ 6.767) were evaluated using Kruskal-Wallis tests for continuous outcomes and Chi-square tests for categorical outcomes. Cardiovascular risk factors over time were quantified by the area under the curve (AUC) where the area under the curve was calculated using trapezoidal rule with the time between measurements on the x-axis and the observed values of the risk factors of interest on the y-axis. Observed values used for the calculation of AUC variables were potentially collected at prior SEARCH visits (baseline, 1-, 2-, and 5-year follow up visits) and the visit that aligns with the arterial stiffness and HRV measurements.

We used semiparametric regression, where SDNN was modeled as a non-parametric function with linear terms for all the covariates to explore associations between overall heart rate variability (SDNN) and PWV. Several models were considered: (model 1, unadjusted) and then adjusted for covariates such as age, gender, race/ethnicity as black vs other (model 2), model 2 + systolic blood pressure (model 3), model 2 + BMI (model 4), model 2+ smoking as former/current vs never (model 5), model 2+ log (triglycerides) (model 6) and model 2 + hemoglobin A1c (model 7) to determine whether any one individual risk factor explained the association between HRV and PWV. The final model (model 8) adjusted for all covariates.

RESULTS

Characteristics of the 185 participants with T2D (62% female) who were included in these analyses are shown in Table 1. At the time of the PWV and HRV assessments participants were a median [Q1, Q3] age of 22.4 [19.4, 24.6] years, with a duration of T2D of 7.8 [6.5, 9.5] years. Individuals that comprised the cohort were Hispanic (23%), non-Hispanic black (40%), non-Hispanic white (29%) and other race/ethnicity (8%) which included Asian/Pacific Islander and Native American. Median [Q1,Q3] hemoglobin A1c was 9.1 [6.4, 11.8)], BMI was 33.5 kg/m^2 [27.3, 38.3], systolic blood pressure mean ± SD was 118±13 and diastolic blood pressure was 76.7±10.4. Thirty-three percent of the cohort reported being a current smoker, 29.4% reported being a former smoker, and 37.2% reported never smoking. Sixty-one percent reported <2 days of physical activity and 76% reported >2 hours of television watching per day. There were 22 (of the 185) that were on ACE inhibitors for either high blood pressure or microalbuminuria.

When stratified by the presence of arterial stiffness, defined as a PWV > 6.767m/s, participants with arterial stiffness were older, were more likely to be Non-Hispanic Black, had higher systolic and diastolic blood pressure, greater adiposity (BMI and waist to height ratio), and more obesity related dyslipidemia (higher triglycerides and lower HDL-C) compared to participants without arterial stiffness, all $p<0.05$ (Table 1). Non-Hispanic white participants were less likely to have arterial stiffness ($p=0.003$). Smoking status, days of physical activity, hours of television, hemoglobin A1c, duration of T2D, and urine microalbumin: creatinine ratio were not different between those with and without arterial stiffness.

Cumulative exposure to cardiovascular risk factors measured as AUC (area under the curve) shows that young adults with T2D and arterial stiffness also had higher AUC systolic and diastolic blood pressure, higher BMI AUC, higher waist to height ratio and triglycerides AUC, and lower HDL AUC compared to those without arterial stiffness, Table 2.

In unadjusted comparisons, youth with arterial stiffness also had overall lower HRV (median SDNN) and greater parasympathetic loss (lower median RMSSD and PNN50) compared to those without arterial stiffness, $p<0.05$. See Table 3. LF power, HF power and their ratio did not differ by arterial stiffness status.

Table 4 shows the association between overall HRV (SDNN) and arterial stiffness (PWV). Sequential regression models evaluated the association between HRV and PWV adjusted for age, race, sex and then systolic blood pressure z score, BMI z score, smoking, triglycerides and hemoglobin A1c. However, these risk factors did not account for the association between HRV and arterial stiffness. In the final model that included age, gender, race-ethnicity and all the risk factor covariates, lower HRV trended but was not significantly associated with higher PWV(beta coefficient = −1.11, $p=0.08$), Table 4, model 8.

DISCUSSION

This study found young adults with T2D and arterial stiffness were more likely to be older, Non-Hispanic Black, have a worse cardiometabolic profile and lower HRV. These findings also show youth with T2D and arterial stiffness also have abnormalities in heart rate variability or evidence of cardiac autonomic dysfunction.

We have previously shown in the SEARCH for Diabetes in Youth Study, by age 21 young adults with T2D not only have a high prevalence of arterial stiffness but also evidence of diabetic kidney disease, retinopathy, peripheral neuropathy, and hypertension [2, 29]. Rates of these complications were higher than the rates observed among participants with T1D -- especially for arterial stiffness, which was seen in nearly 50% of the cohort[2]. Prior work in youth with T2D also shows evidence of elevated left ventricular mass, abnormal cardiac geometry and impaired diastolic function, reduced cardiopulmonary fitness, abnormal limb blood flow, and cardiac autonomic dysfunction in adolescents with type 2 diabetes, all pointing to a group at high risk to develop cardiovascular disease [30–42]. For these reasons, it is important to understand whether the presence of arterial stiffness identifies participants with higher cardiovascular risk.

In the present study, we found that young adults with T2D and arterial stiffness had greater adiposity, higher blood pressure, and more obesity related dyslipidemia over time. These results point to a relationship between risk factors that are part of the metabolic syndrome constellation and arterial stiffness. The Young Finns Study has previously demonstrated a link between the metabolic syndrome in childhood and increased arterial stiffness in adulthood. Importantly, the Young Finns study showed that recovery from childhood metabolic syndrome was associated with decreased arterial PWV in adulthood. These findings highlight the importance of the prevention and/ or controlling metabolic risk factors early in life to prevent arterial stiffness in adulthood. It should be also noted that while

hemoglobin A1c, LDL cholesterol and microalbuminuria were not statistically different by arterial stiffness status in our study, the median values for each tended to be higher for individuals with arterial stiffness. As each is a known cardiovascular risk factor [8, 25, 38, 43, 44], comprehensive risk management is likely needed to reduce overall cardiovascular risk.

We found that HRV (SDNN) was lower in participants with arterial stiffness. In addition, time domains PNN50 and RMSSD were lower suggesting evidence of parasympathetic loss in those with arterial stiffness. Frequency domains HF power, LF power and their ratio did not differ by the presence of arterial stiffness. Recent data suggests LF and HF power may be influenced by respiration, vagal tone, and posture suggesting these are less sensitive measures of HRV[28]. Additionally, these frequency domains are best assessed on 24 hour HRV measurements which may also explain our findings.

HRV is thought to reflect baroreflex control, particularly vagal control [45]. As a result, stiffer vessels may lead to an attenuated baroreceptor function and thus decrease HRV. Additionally, changes in cardiac autonomic function (HRV) can affect the elasticity of the arterial wall by changing the smooth muscle tone of large arteries [46, 47]. Animal studies also show sympathectomized rats exhibit a significant reduction in the elastic properties of the aorta when compared with animals with intact sympathetic ganglia [48]. Thus, there is biological plausibility for a bi-directional relationship between HRV and arterial stiffness. A recent study published in young adults with T2D enrolled in the Treatment Options for Diabetes in Adolescents and Young Adults (TODAY) study found higher PWV in those with 3 or more abnormal HRV indices [38]. Similarly, Meyer et al reported that both central and peripheral PWV correlated with cardiac autonomic score in 45 adults with T2D [49]. A recent study in 290 adults with T2D also showed that impaired cardiac autonomic function was associated independently with abnormal PWV [50]. In SEARCH we have previously reported that increased PWV is associated with reduced heart rate variability in youth with type 1 diabetes but not in healthy controls [43, 51]. The relationship between HRV and arterial stiffness in patients with type 1 and now borderline (p=0.085) in T2D as demonstrated here but not controls suggests indirect support that link diabetes to cardiovascular disease.

Limitations of the current study include a single onetime assessment of arterial stiffness and HRV. However, follow-up HRV measurements and arterial stiffness are planned for this cohort. Second, HRV was limited to a relatively short length of recording (10 minutes), however, this method is considered standard clinical and research practice by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [52]. Strengths of the study include a large sample size, an ethnically diverse cohort, validated measures of arterial stiffness and cardiovascular autonomic neuropathy, and collection of longitudinal cardiovascular risk factors.

In summary, youth with type 2 diabetes and arterial stiffness have evidence of worse cardiovascular risk factors and lower heart rate variability. These findings suggest the presence of arterial stiffness may confer higher cardiovascular risk. However, long-term study of this cohort is needed to confirm this.

Acknowledgments

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

SEARCH 3/4: The authors wish to acknowledge the involvement of 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 number UL1 TR000062, 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 (DERC NIH grant number P30 DK57516); the University of Cincinnati, NIH/NCATS grant number UL1 TR000077, UL1 TR001425; and the Children with Medical Handicaps program managed by the Ohio Department of Health. 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.

Funding

Grant Support (SEARCH 3):

SEARCH for Diabetes in Youth is funded by the Centers for Disease Control and Prevention (PA numbers 00097, DP-05-069, and DP-10-001) and supported by the National Institute of Diabetes and Digestive and Kidney Diseases.

Grant Support (SEARCH 4):

The SEARCH for Diabetes in Youth Cohort Study (1UC4DK108173) 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.

The Population Based Registry of Diabetes in Youth Study (1U18DP006131, U18DP006133, U18DP006134, U18DP006136, U18DP006138, U18DP006139) is funded by the Centers for Disease Control and Prevention and supported by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Sites (SEARCH 1 through 4):

Kaiser Permanente Southern California (U18DP006133, U48/CCU919219, U01 DP000246, and U18DP002714), University of Colorado Denver (U18DP006139, U48/CCU819241-3, U01 DP000247, and U18DP000247-06A1), Cincinnati's Children's Hospital Medical Center (U18DP006134, U48/CCU519239, U01 DP000248, and 1U18DP002709), University of North Carolina at Chapel Hill (U18DP006138, U48/CCU419249, U01 DP000254, and U18DP002708), Seattle Children's Hospital (U18DP006136, U58/CCU019235-4, U01 DP000244, and U18DP002710-01), Wake Forest University School of Medicine (U18DP006131, U48/CCU919219, U01 DP000250, and 200-2010-35171)

References

1. Maahs DM, Daniels SR, de Ferranti SD, et al. Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. Circulation 2014;130: 1532–1558. [PubMed: 25170098]
2. Dabelea D, Stafford JM, Mayer-Davis EJ, et al. Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage Years and Young Adulthood. Jama 2017;317: 825–835. [PubMed: 28245334]
3. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, and Sellers EA Earlier onset of complications in youth with type 2 diabetes. Diabetes Care 2014;37: 436–443. [PubMed: 24130346]
4. Reynolds K, Saydah SH, Isom S, et al. Mortality in youth-onset type 1 and type 2 diabetes: The SEARCH for Diabetes in Youth study. J Diabetes Complications 2018;32: 545–549. [PubMed: 29685480]

5. Constantino MI, Molyneaux L, Limacher-Gisler F, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care 2013;36: 3863–3869. [PubMed: 23846814]
6. Vlachopoulos C, Aznaouridis K, and Stefanadis C Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55: 1318–1327. [PubMed: 20338492]
7. Urbina EM, Williams RV, Alpert BS, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. Hypertension 2009;54: 919–950. [PubMed: 19729599]
8. Urbina EM, Kimball TR, Khoury PR, Daniels SR, and Dolan LM Increased arterial stiffness is found in adolescents with obesity or obesity-related type 2 diabetes mellitus. J Hypertens 2010;28: 1692–1698. [PubMed: 20647860]
9. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27: 2588–2605. [PubMed: 17000623]
10. Wadwa RP, Urbina EM, Anderson AM, et al. Measures of arterial stiffness in youth with type 1 and type 2 diabetes: the SEARCH for diabetes in youth study. Diabetes Care 2010;33: 881–886. [PubMed: 20067960]
11. Vinik AI, Maser RE, Mitchell BD, and Freeman R Diabetic autonomic neuropathy. Diabetes Care 2003;26: 1553–1579. [PubMed: 12716821]
12. Maser RE, Mitchell BD, Vinik AI, and Freeman R The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care 2003;26: 1895–1901. [PubMed: 12766130]
13. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care 2017;40: 136–154. [PubMed: 27999003]
14. Benichou T, Pereira B, Mermillod M, et al. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. PLoS One 2018;13: e0195166. [PubMed: 29608603]
15. Cha SA, Park YM, Yun JS, et al. Time- and frequency-domain measures of heart rate variability predict cardiovascular outcome in patients with type 2 diabetes. Diabetes Res Clin Pract 2018;143: 159–169. [PubMed: 30006307]
16. Vinik AI and Ziegler D Diabetic cardiovascular autonomic neuropathy. Circulation 2007;115: 387–397. [PubMed: 17242296]
17. Spallone V, Ziegler D, Freeman R, et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 2011;27: 639–653. [PubMed: 21695768]
18. SEARCH for Diabetes in Youth: a multicenter study of the prevalence, incidence and classification of diabetes mellitus in youth. Control Clin Trials 2004;25: 458–471. [PubMed: 15465616]
19. Shah AS, Maahs DM, Stafford JM, et al. Predictors of Dyslipidemia Over Time in Youth With Type 1 Diabetes: For the SEARCH for Diabetes in Youth Study. Diabetes Care 2017;40: 607–613. [PubMed: 28126715]
20. Dabelea D, D'Agostino RB Jr., Mason CC, et al. Development, validation and use of an insulin sensitivity score in youths with diabetes: the SEARCH for Diabetes in Youth study. Diabetologia 2011;54: 78–86. [PubMed: 20886205]
21. World Health Organization (2011) Waist circumference and waist–hip ratio. Report of a WHO expert consultation, Geneva, 8–11 12, 2008.
22. Liu LL, Kahn HS, Pettitt DJ, et al. Comparing Two Waist-to-Height Ratio Measurements with Cardiometabolic Risk Factors among Youth with Diabetes. Int J Child Health Nutr 2016;5: 87–94. [PubMed: 28232855]
23. Pettitt DJ, Talton JW, Liese AD, et al. Comparison of two waist circumference measurement protocols: the SEARCH for diabetes in youth study. Pediatr Obes 2012;7: e81–85. [PubMed: 22991230]

24. Shah AS, Wadwa RP, Dabelea D, et al. Arterial stiffness in adolescents and young adults with and without type 1 diabetes: the SEARCH CVD study. Pediatr Diabetes 2015;16: 367–374. [PubMed: 25912292]
25. Shah AS, Dabelea D, Talton JW, et al. Smoking and arterial stiffness in youth with type 1 diabetes: the SEARCH Cardiovascular Disease Study. J Pediatr 2014;165: 110–116. [PubMed: 24681182]
26. Urbina EM, Khoury PR, McCoy C, Daniels SR, Kimball TR, and Dolan LM Cardiac and vascular consequences of pre-hypertension in youth. J Clin Hypertens (Greenwich) 2011;13: 332–342. [PubMed: 21545394]
27. Fagard RH, Pardaens K, Staessen JA, and Thijs L Power spectral analysis of heart rate variability by autoregressive modelling and fast Fourier transform: a comparative study. Acta Cardiol 1998;53: 211–218. [PubMed: 9842406]
28. Hayano J and Yuda E Pitfalls of assessment of autonomic function by heart rate variability. J Physiol Anthropol 2019;38: 3. [PubMed: 30867063]
29. Hamman RF, Bell RA, Dabelea D, et al. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. Diabetes Care 2014;37: 3336–3344. [PubMed: 25414389]
30. Specht BJ, Wadwa RP, Snell-Bergeon JK, Nadeau KJ, Bishop FK, and Maahs DM Estimated insulin sensitivity and cardiovascular disease risk factors in adolescents with and without type 1 diabetes. J Pediatr 2013;162: 297–301. [PubMed: 22921593]
31. Snell-Bergeon JK and Nadeau K Cardiovascular disease risk in young people with type 1 diabetes. J Cardiovasc Transl Res 2012;5: 446–462. [PubMed: 22528676]
32. Nadeau KJ and Reusch JE Cardiovascular function/dysfunction in adolescents with type 1 diabetes. Curr Diab Rep 2011;11: 185–192. [PubMed: 21336845]
33. Bjornstad P, Truong U, Pyle L, et al. Youth with type 1 diabetes have worse strain and less pronounced sex differences in early echocardiographic markers of diabetic cardiomyopathy compared to their normoglycemic peers: A RESistance to InSulin in Type 1 ANd Type 2 diabetes (RESISTANT) Study. J Diabetes Complications 2016;30: 1103–1110. [PubMed: 27133451]
34. Bjornstad P, Snell-Bergeon JK, Nadeau KJ, and Maahs DM Insulin sensitivity and complications in type 1 diabetes: New insights. World J Diabetes 2015;6: 8–16. [PubMed: 25685274]
35. Bjornstad P, Cree-Green M, Baumgartner A, et al. Renal function is associated with peak exercise capacity in adolescents with type 1 diabetes. Diabetes Care 2015;38: 126–131. [PubMed: 25414156]
36. Cree-Green M, Bergman BC, Cengiz E, et al. Metformin Improves Peripheral Insulin Sensitivity in Youth With Type 1 Diabetes. J Clin Endocrinol Metab 2019;104: 3265–3278. [PubMed: 30938764]
37. Nadeau KJ, Zeitler PS, Bauer TA, et al. Insulin resistance in adolescents with type 2 diabetes is associated with impaired exercise capacity. J Clin Endocrinol Metab 2009;94: 3687–3695. [PubMed: 19584191]
38. Shah AS, El Ghormli L, Gidding SS, et al. Prevalence of arterial stiffness in adolescents with type 2 diabetes in the TODAY cohort: Relationships to glycemic control and other risk factors. J Diabetes Complications 2018;32: 740–745. [PubMed: 29936086]
39. Bjornstad P, Truong U, Dorosz JL, et al. Cardiopulmonary Dysfunction and Adiponectin in Adolescents With Type 2 Diabetes. J Am Heart Assoc 2016;5: e002804. [PubMed: 26994128]
40. Bacha F, Gidding SS, Pyle L, et al. Relationship of Cardiac Structure and Function to Cardiorespiratory Fitness and Lean Body Mass in Adolescents and Young Adults with Type 2 Diabetes. J Pediatr 2016;177: 159–166 e151. [PubMed: 27499218]
41. Levitt Katz L, Gidding SS, Bacha F, et al. Alterations in left ventricular, left atrial, and right ventricular structure and function to cardiovascular risk factors in adolescents with type 2 diabetes participating in the TODAY clinical trial. Pediatr Diabetes 2015;16: 39–47. [PubMed: 24450390]
42. Shah AS, Khoury PR, Dolan LM, et al. The effects of obesity and type 2 diabetes mellitus on cardiac structure and function in adolescents and young adults. Diabetologia 2011;54: 722–730. [PubMed: 21085926]
43. Dabelea D, Talton JW, D'Agostino R Jr., et al. Cardiovascular risk factors are associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. Diabetes Care 2013;36: 3938–3943. [PubMed: 24101697]

44. Shah AS, Dolan LM, Gao Z, Kimball TR, and Urbina EM Racial differences in arterial stiffness among adolescents and young adults with type 2 diabetes. Pediatr Diabetes 2012;13: 170–175. [PubMed: 21790919]
45. Piepoli M, Sleight P, Leuzzi S, et al. Origin of respiratory sinus arrhythmia in conscious humans. An important role for arterial carotid baroreceptors. Circulation 1997;95: 1813–1821. [PubMed: 9107168]
46. MacFadyen RJ and Lim HS Emergence of structural arterial stiffness in diabetes and the role of abnormalities of autonomic tone in the sequence of events. J Hum Hypertens 2004;18: 755–756. [PubMed: 15254562]
47. Pfeifer MA, Weinberg CR, Cook DL, et al. Autonomic neural dysfunction in recently diagnosed diabetic subjects. Diabetes Care 1984;7: 447–453. [PubMed: 6499637]
48. Lacolley P, Glaser E, Challande P, et al. Structural changes and in situ aortic pressure-diameter relationship in long-term chemical-sympathectomized rats. Am J Physiol 1995;269: H407–416. [PubMed: 7653604]
49. Meyer C, Milat F, McGrath BP, Cameron J, Kotsopoulos D, and Teede HJ Vascular dysfunction and autonomic neuropathy in Type 2 diabetes. Diabet Med 2004;21: 746–751. [PubMed: 15209768]
50. Chorepsima S, Eleftheriadou I, Tentolouris A, et al. Pulse wave velocity and cardiac autonomic function in type 2 diabetes mellitus. BMC Endocr Disord 2017;17: 27. [PubMed: 28526073]
51. 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. [PubMed: 23435158]
52. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93: 1043–1065. [PubMed: 8598068]

Highlights

- Arterial stiffness is a marker of CVD that predicts morbidity and mortality
- Decreased HRV confers higher CV risk and may regulate arterial stiffness
- Youth with T2D and arterial stiffness have a worse CV risk profile and lower HRV.

Table 1.

Characteristics of the youth with type 2 diabetes overall and stratified by their arterial stiffness status collected at the follow-up visit (2011–2015)

Variable	All N= 185	PWV ≤6.767 m/sec N= 88	PWV >6.767 m/sec N= 97	p-value
Age, years	22.4 (19.4, 24.6)	21.7 (18.66, 23.8)	23.3 (20.3, 25.0)	0.013
Female, %	62%	56%	68%	0.08
Duration, years	7.8 (6.5, 9.5)	8.1 (6.3, 9.2)	7.8 (6.9, 9.6)	0.44
Race/ethnicity				
Non-Hispanic Black, %	40%	32%	47%	0.031
Non-Hispanic White, %	29%	40%	20%	0.0026
Hispanic, %	23%	17%	29%	0.057
Other, %	8%	11%	4%	0.063
Current smoker, %	33%	31%	35%	0.60
Former smoker,%	29%	30%	29%	0.82
Never smoker, %	37%	38%	36%	0.76
Systolic BP, mm Hg	118±13	114±11	122±14	<0.0001
Diastolic BP, mm Hg	76.7±10.4	73.8±9.0	79.4±10.8	0.0012
Waist to Height ratio	0.6 ± 0.11	0.5 ± 0.11	0.77 ± 0.11	<0.0001
BMI (kg/m^2)	33.5 (27.3, 38.3)	28.2 (25.1, 34.1)	36.4 (32.5, 41.5)	<0.0001
BMI z score	1.8 (1.2, 2.2)	1.3 (0.7, 1.9)	2.1 (1.8, 2.3)	<0.0001
Hemoglobin A1C (%)	9.1 (6.4, 11.8)	8.7 (6.0, 11.88)	9.5 (6.6, 11.99)	0.35
HDL-cholesterol, mg/dL	40.0 (34, 47)	42.5 (37, 49)	39.0 (33, 44)	0.0034
LDL cholesterol, mg/dL	100.0 (79, 130)	99.0 (76, 117)	106.0 (81, 136)	0.068
Triglycerides, mg/dL	122.0 (80, 207)	105.0 (74, 179)	141.0 (88, 255)	0.015
Total Cholesterol, mg/dL	177.0 (144, 210)	171.0 (139, 198)	183 (145, 223)	0.086
Albumin: Creatinine ratio, mg/g	8.6 (4.6, 30.2)	7.4 (4.1, 23.9)	9.9 (4.9, 35.8)	0.17
Percent with microalbuminuria	25%	21%	29%	0.33
Days of physical activity				0.86
0-2	61%	60%	61%	
3-7	39%	40%	39%	
Hours/ day of television watching				0.23
< 2 hours	24%	28%	21%	
2 or more hours	76%	72%	79%	

All data are represented as mean± SD or median (IQR) or %. BP: blood pressure, BMI: body mass index, high density lipoprotein, LDL: Low density lipoprotein. p indicates the difference between those with and without arterial stiffness. Microalbuminuria was defined as an albumin: creatinine ratio >30 mg/g

Table 2.

Longitudinal risk factor profile assessed as area under the curve (AUC) of youth with T2D overall and stratified by arterial stiffness status

Variable	All	PWV <=6.767	PWV >6.767	P-value
Systolic BPAUC	116(111. 122)	115 (109. 118)	119 (113. 126)	<0.0001
Diastolic BPAUC	73.0 (69.0. 78.2)	71.5 (66.8. 76.0)	75.3(70.7. 80.4)	0.0002
Waist to Height Ratio AUC	0.6±0.1	0.55 ±0.067	0.65 ±0.094	<0.0001
Body mass index z score AUC	2.0 (1.4. 2.3)	1.6 (1.2, 2.1)	2.2 (1.9. 2.5)	<0.0001
Hemoglobin Ale AUC	8.5±2.4	8.4 ±2.5	8.5 ±2.3	0.63
HDL cholesterol AUC	41±9	43±10	40 ±8	0.043
LDL cholesterol AUC	103±30	9S±27	108 ±328	0.067
Total cholesterol AUC	174 (147. 198)	166 (146. 195)	181 (148. 209)	0.15
Triglycerides AUC	131 (88. 201)	123 (83.5. 175.0)	147 (92. 209)	0.048
Albumin: Creatinine ratio AUC	9.0 (5.0. 37.2)	9.2 (4.7. 23.7)	8.8 (5.5, 43.9)	0.72

All data are represented as mean ± SD or median(IQR) and are adjusted for time in the study. The p value indicates the difference between those with and without arterial stiffness

Table 3.

HRV indices of the youth with type 2 diabetes overall and stratified by their arterial stiffness status collected at the followup visit (2011–2016)

Variable	All	PWV <=6.767	PWV>6.767	P-value
Total Power	1277 (615. 3264)	1666 (888. 4340)	961 (460. 2282)	0.002
HF Power	393 (141. 1256)	632 (234. 1798)	268 (85. 920)	0.001
LF Power	373 (180. 892)	405 (241. 1227)	299 (131. 559)	0.003
HF Power Normalized (hz) (lower is worse)	52.4 (38.2, 64.2)	54.4(41.7, 65.0)	51.2 (35.6, 64.1)	0.17
LF Power Normalized (hz) (higher is worse)	47.6(35.8, 61.8)	45.6 (35.0, 58.3)	48.8 (35.9, 64.4)	0.17
LF: HF ratio (%. higher is worse)	0.9 (0.6. 1.6)	0.8 (0.5. 1.4)	0.9 (0.6, 1.8)	0.17
PNN50 (%. lower worse)	14.4(3.5, 42.6)	25.1 (5.9, 46.9)	9.2 (2.1, 32.8)	0.002
RMSSD (inssec, lower is worse)	40.2 (24.9, 65.5)	48.5 (27.8, 78.8)	33.1(215 57 1)	0.003
SDNN msec, lower is worse)	46.1 (33.4, 71.7)	51.9 (36.9, 79.3)	41.9 (29.2, 61.8)	0.002

All data are median (IQR). HF: high frequency, LF: low frequency, PNN50: percent of adjacent NN intervals with a difference greater than 50msec, RMSSD: root mean square difference of successive normal RR intervals. SDNN: standard deviation of normal RR interval. The p value indicates the unadjusted difference between those with and without arterial stiffness.

Table 4.

Linear regression models for association between SDNN (overall heart rate variability) and PWV (arterial stiffness)

Variable	β Estimate	SE	p-value
Model 1: Unadjusted relationship between PWV and SDNN	−2.91	0.71	0.00006
Model 2 : Model 1 + Age. Sex. Race (black vs other)	−2.44	0.70	0.00058
Model 3 : Model 2 + Systolic BP z score	−2.03	0.68	0.0034
Model 4 : Model 2 + BMI z score	−2.32	0.61	0.00019
Model 5 : Model 2 + Smoking	−2.36	0.72	0.0012
Model 6 : Model 2 +Triglycerides (log transformed)	−1.55	0.71	0.030
Model 7 : Model 2 + Hemoglobin A1c	−2.08	0.72	0.0046
Model 8 : PWV= SDNN + Age+ Sex +Race + systolic BPz-BMIz + smoking + log triglycerides + Hemoglobin A1c	−1.11	0.64	0.085