European Heart Journal – Cardiovascular Imaging (2014) **15**, 1263–1269
doi:10.1093/ehjci/jeu121

Subclinical diastolic dysfunction in young adults with Type 2 diabetes mellitus: a multiparametric contrast-enhanced cardiovascular magnetic resonance pilot study assessing potential mechanisms

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Received 8 March 2014; accepted after revision 29 May 2014; online publish-ahead-of-print 26 June 2014

Aims To assess the cardiac, vascular, anthropometric, and biochemical determinants of subclinical diastolic dysfunction in younger adults with Type 2 diabetes mellitus (T2DM) using multiparametric contrast-enhanced cardiovascular magnetic resonance (CMR) imaging.

Methods and results Twenty adults <40 years with T2DM [mean age 31.8(6.6) years, T2DM duration 4.7(4.0) years] and 20 age and sex-matched controls [10 obese non-diabetic controls and 10 lean controls (LC)] were studied. Cardiac volumes and function, circumferential strain and peak early diastolic strain rate (PEDSR), myocardial perfusion reserve, aortic stiffness (distensibility, pulse-wave velocity), focal fibrosis on late gadolinium enhancement, and pre- and post-contrast T1 mapping for contrast agent partition coefficient (subset, $n = 26$) were determined by CMR. In the T2DM cohort, mean aortic distensibility correlated with PEDSR ($r = 0.564$, $P = 0.023$) and diabetes duration correlated inversely with PEDSR ($r = -0.534$, $P = 0.015$) on univariate analysis. There was a close association between PEDSR and peak systolic strain ($r = -0.580$, $P = 0.007$).

Conclusion In young adults with T2DM, diabetes duration and aortic distensibility were associated with diastolic dysfunction. Interventional studies are required to assess whether cardiac dysfunction can be reversed in this phenotype of patients.

Keywords Cardiac magnetic resonance imaging • Diabetes mellitus • Diastolic dysfunction diabetes mellitus • Diabetic cardiomyopathies • Aortic distensibility • Diabetic diastolic heart failure

Introduction

Cardiovascular disease is the key cause of mortality in diabetes.[1] Diabetic cardiomyopathy occurs in up to 75% of older adults and is defined as myocardial dysfunction in the absence of valvular dysfunction, coronary artery disease, and hypertension.[2,3] Its pathogenesis involves metabolic, vascular, inflammatory, epigenetic, and neuroendocrine mechanisms.[2,4]

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Childhood obesity is reaching epidemic proportions worldwide. Of concern is the associated increase in young onset, Type 2 diabetes mellitus (T2DM).[5] T2DM in younger adults (age <40 years) is associated with an extreme phenotype characterized by a greater likelihood of Class II/class III obesity (≥35 kg/m^2), elevated hepatic adiposity, and a multigenerational family history of T2DM.[6] Younger adults with T2DM are at higher relative risk of cardiovascular complications including myocardial infarction and heart failure, and the 20-year mortality rate is as high as 11%.[7,8] The mechanisms leading to such high risk are not fully elucidated.

We recently demonstrated subclinical diastolic dysfunction on cardiovascular magnetic resonance (CMR) imaging in young adults with T2DM.[9] Peak early diastolic strain rate (PEDSR) was 23 and 11% lower than in age and sex-matched lean and obese non-diabetic controls, respectively.[9] Our study also demonstrated a strong trend towards reduced peak systolic strain (PSS).

CMR can uniquely characterize myocardial structure and function. However, there are no studies investigating tissue characterization, myocardial perfusion, or potential mechanisms of cardiac dysfunction in young adults with T2DM. Understanding the pathophysiology of early cardiovascular disease in patients with T2DM is important to identify potential therapeutic interventions to prevent or reverse myocardial dysfunction.

The aim of this study using multiparametric, contrast-enhanced CMR was to assess the cardiac, vascular, anthropometric, and biochemical associations with subclinical diastolic dysfunction in young adults with T2DM.

Methods

Study population

We recruited 20 young adults with T2DM with no history of cardiovascular disease, aged 18–39 years, from primary and secondary care services. Ten age-matched lean controls (LC) and 10 age- and body mass index-matched obese non-diabetic controls were recruited. Exclusion criteria included body mass >150 kg and standard contraindications for CMR. The study was approved by the North Nottinghamshire Research Ethics Committee, conducted according to the Declaration of Helsinki, and all participants provided written informed consent.

Anthropometry and biochemical marker assessment

Participants attended fasted. Height, weight, and waist-to-hip ratio were measured. Serum triglycerides and HbA1c were assessed using standard enzymatic methods on an ADVIA System (Bayer, NY, USA). ELISA kits were used to determine plasma c-peptide concentration (Mercodia, Uppsala, Sweden).

CMR image acquisition

CMR was performed using a 1.5-T scanner (Siemens Avanto, Erlangen, Germany) with retrospective electrocardiographic gating and a 6-channel phased-array cardiac receiver coil. Cardiac volumes and function, adenosine stress and rest perfusion, and late gadolinium enhancement (LGE) imaging were performed using standard CMR techniques as previously described by our group.[10] Three short-axis tagged images were acquired at basal, mid-ventricular, and apical levels using a complementary spatial modulation of magnetization sequence with prospective ECG gating using steady-state free procession (SSFP) imaging. To achieve high temporal resolution (17 ms), a multiple breath-hold scheme was applied as previously described.[11] A retrospectively gated, high temporal resolution (TR 10 ms), phase-contrast velocity-encoding sequence was performed to calculate through-plane flow, perpendicular to the ascending and descending thoracic aorta at the level of the pulmonary artery bifurcation. This allowed assessment of aortic distensibility and pulse-wave velocity on SSFP and phase-contrast images, respectively. Three blood pressure readings were taken during this sequence using a Dinamap machine (GE, USA) and averaged to determine pulse pressure. The complete CMR protocol is summarized in *Figure 1*. In a subset [$n = 26$; 11 T2DM, 9 obese controls (OC), and 6 LC] of the cohort, images for T1 quantification were acquired using a single breath-hold Modified Look-Locker Inversion Recovery (MOLLI) series sequence at a mid-ventricular short-axis slice, before and 15–20 min after the final contrast agent dose.[12]

CMR image analysis

Analysis was performed offline blinded to patient details. Left ventricular (LV) volumes and function, myocardial perfusion reserve (MPR), and LGE were assessed using QMass 7.1 (Medis, Leiden, Netherlands). LV volumes and function were calculated by a single experienced operator (J.N.K.) as previously described.[10] Circumferential strain and strain rates were measured using inTag v1.0 (CREATIS, Lyon, France).[13] Global strain and strain rates were calculated as an average of the values obtained in basal, mid-cavity, and apical short-axis slices.

Myocardial perfusion reserve assessment

The epicardium and endocardium were contoured on the perfusion images at the basal, mid, and apical short-axis slices, along with a region of interest in the LV blood pool, to generate signal intensity vs. time curves. Quantitative perfusion estimates were obtained using Fermi-constrained deconvolution.[14] The arterial input function (contrast baseline) was taken from the basal slice for the analysis of all three slices. Automated methods described previously[15] were used to subtract the pre-contrast baseline from the curves, correct for differences in bolus arrival time and heart rate between the arterial input function and the myocardium, and to limit the data to the first pass of contrast through the heart. The MPR was calculated by dividing the absolute stress myocardial blood flow by the absolute rest myocardial blood flow estimate. Perfusion images were qualitatively assessed for focal and subendocardial perfusion defects (visible defect for ≥5 heartbeats). Since no focal perfusion defects were observed, reported MPR values are global averages from the three slices.

LGE imaging

LGE images were assessed for focal fibrosis, categorized as present or absent.

T1 mapping

MOLLI sequences were analysed using *cmr42* (Circle Cardiovascular Imaging, Calgary, Canada). The endocardium and epicardium were contoured. A region of interest was drawn in the blood pool to correct for the concentration of blood contrast agent, and a heart rate correction algorithm applied. T1 relaxation time was calculated via a curve-fitting model using signal intensity vs. inversion time. To correct for confounders including body composition and renal function, the ratio of signal intensity change in myocardium to that in blood was calculated in order to estimate the contrast agent partition coefficient (λ). A higher λ implies a greater change in contrast concentration and thus fibrosis

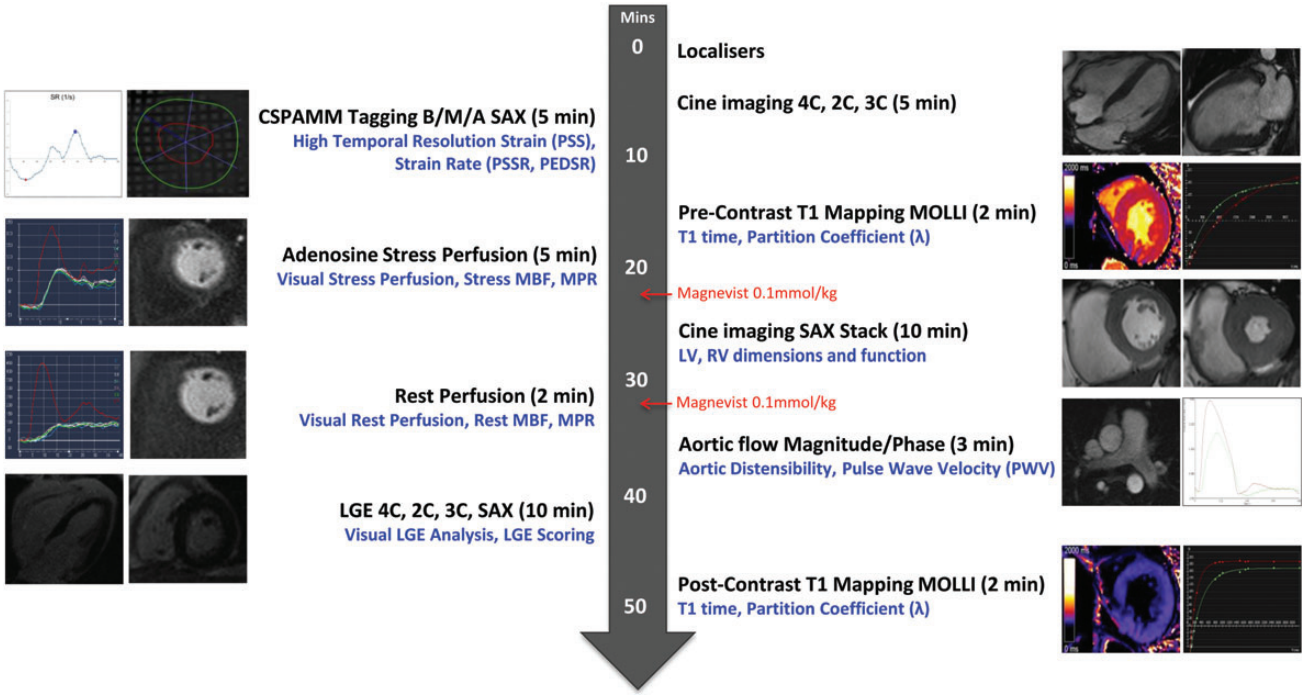

Figure 1 CMR protocol employed (1.5 T). MBF, myocardial blood flow; MPR, myocardial perfusion reserve; LGE, late gadolinium enhancement; RV, right ventricular; LV, left ventricular.

(interstitial space) in the myocardium. This was calculated from T1 values as follows:[16]

$$\lambda = \frac{[\text{T1 pre}_{(\text{myo})} - \text{T1 post}_{(\text{myo})}]}{[\text{T1 pre}_{(\text{blood})} - \text{T1 post}_{(\textit{blood})}]}.$$

Aortic distensibility and pulse-wave velocity

Aortic distensibility at the ascending and descending aorta was calculated as follows:[17]

$$\text{Aortic distensibility} = \frac{(A_{\max} - A_{\min})}{A_{\min} \times \text{Pulse pressure}},$$

where A is the aortic cross-sectional area. Pulse-wave velocity (PWV) was assessed using the in-house software (Java Image Manipulation). The time for the pressure wave to travel around the aortic arch was assessed from plots of blood volume flow rate measured in the ascending and descending aorta, by calculating the time lag for maximum cross-correlation. Aortic arch length was measured on the sagittal-oblique aortic cine image. PWV was then calculated as follows:[17]

$$\text{PWV} = \frac{\text{Distance between ascending and descending aorta}}{\text{time lag}}.$$

Statistical analysis

Normality was assessed using Kolmogorov–Smirnov tests, histograms, and Q–Q plots. Continuous data were expressed as mean (standard deviation), if normally distributed. Non-parametric variables were expressed as median (25–75% interquartile range). Pearson's correlation coefficient and Spearman's rank correlation coefficient were used for normally and non-parametrically distributed data, respectively, when assessing potential mechanisms affecting the PEDSR. Statistical tests were performed using the SPSS v20.0 software.

Results

Baseline characteristics

The study group consisted of 20 T2DM subjects, 10 LC, and 10 OC. Detailed demographics, anthropometrics, and biochemical data for the three study groups have been published previously.[9] The mean duration of diabetes was 4.7(4.0) years. Age, sex, blood pressure, and ethnicity were similar in the groups (*Table 1*).

CMR data

LV function and circumferential strain

LV ejection fraction was preserved and similar across the groups. However, there was a strong trend towards reduced PSS in the T2DM group. PEDSR was significantly reduced in T2DM compared with lean and OC ($P = 0.04$) (*Table 1*).

Perfusion, LGE, and partition coefficients

No subjects had regional perfusion defects to suggest obstructive coronary artery disease. Global MPR was similar across the groups. On LGE imaging, right ventricular insertion point fibrosis was present in one obese control, five T2DM, and two LC. Mid-wall fibrosis and focal LGE (in a non-coronary distribution) were each present in one T2DM subject (*Figure 2*).

T1 mapping was undertaken on a subset of patients (11 T2DM, 6 LC, and 9 OC). Age, sex, blood pressure, and ethnicity were similar in the groups within the subset (see Supplementary data online, *Table S1*). Pre- and post-contrast T1 values and contrast partition coefficient (λ) did not differ between groups.

Aortic stiffness

Aortic distensibility and PWV did not differ significantly between groups. Data are summarized in *Table 1*.

CMR and bio-anthropometric associations with PEDSR in the T2DM cohort

A significant correlation was seen between mean aortic distensibility and PEDSR ($r = 0.564$, $P = 0.023$) and between diabetes duration and PEDSR ($r = -0.534$, $P = 0.015$, *Table 2*). On simple linear regression, each unit increase in aortic distensibility resulted in an increase in the PEDSR of 0.09 (*Figure 3A*). For each year of T2DM, PEDSR decreased by 0.032 (*Figure 3B*). There was a significant inverse association between PEDSR and PSS ($r = -0.580$, $P = 0.007$). The correlation of post-contrast T1 and PEDSR was moderate and of borderline significance ($n = 11$). There was no significant association between anthropometrics, inflammatory markers, HbA1c, LV mass, MPR, blood pressure, and PEDSR.

Discussion

This multiparametric, contrast-enhanced CMR-based pilot study demonstrated that aortic distensibility and diabetes duration were inversely related to PEDSR in young adults with T2DM.

Associations with PEDSR

Our observed association between PSS and PEDSR is consistent with the pathogenesis of heart failure.[18] The progression from Stage 1 (subclinical diastolic dysfunction) to stage 2 diabetic cardiomyopathy is characterized by the development of symptomatic systolic dysfunction.[3,19] Pathophysiological processes such as microvascular dysfunction, interstitial fibrosis, myocyte hypertrophy, lipotoxicity, and oxidative damage are known to contribute to both diastolic and systolic dysfunction in diabetic cardiomyopathy.[1–3] However, there is a paucity of studies assessing the pathophysiology of cardiac dysfunction in younger adults with T2DM, who represent an extreme phenotype.[6,9]

The association between aortic distensibility and PEDSR is similar to that demonstrated in the Multi-Ethnic Study of Atherosclerosis (MESA) substudy with carotid stiffness.[20] If aortic stiffness is an important determinant of PEDSR in this cohort of patients, it is surprising that we did not see significant differences in the mean values of distensibility and PWV in the T2DM and control groups. However, it may be that aortic stiffening occurs mainly in older T2DM patients and in those with longer diabetes duration.[21,22] Similar to our tagging results, Tissue Doppler echocardiography has also shown a linear relationship between diabetes duration and worsening diastolic function.[23] Patil *et al.*[24] demonstrated that diastolic dysfunction develops relatively early, with a diabetes duration of ≥4 years being its strongest independent predictor. It is intriguing to speculate

Table 1 Demographic and CMR data

				P-value	
	T2DM ($n = 20$)	LC ($n = 10$)	OC ($n = 10$)	T2DM vs. LC	T2DM vs. OC
Age	31.8 (6.6)	30.0 (6.7)	30.9 (5.6)	0.477	0.699
Sex	45% M, 55% F	50% M, 50% F	60% M, 40% F	1.000	0.700
BMI	33.9 (5.8)	21.9 (1.7)	33.4 (2.4)	<0.001	0.618
LVEDM (g)	85.2 (76.4, 102.9)	80.8 (70.9, 85.5)	76.2 (65.8, 111.6)	0.002	0.601
LVEDMI (g/m^2)	41.75 (7.73)	44.40 (6.34)	40.39 (9.02)	0.423	0.961
LVEDMI/height$^{1.7}$ (g/m)	36.16 (7.05)	31.25 (5.38)	35.16 (8.47)	0.013	0.988
LVEDM/LVEDV (g/mL)	0.54 (0.45, 0.61)	0.45 (0.42, 0.51)	0.54 (0.48. 0.60)	0.029	0.862
LVEDVI (mL/m^2)	79.8 (11.5)	94.2 (9.2)	80.5 (11.0)	0.004	0.949
LVESVI (mL/m^2)	36.0 (6.6)	41.9 (5.4)	37.6 (8.3)	0.037	0.562
LV ejection fraction (%)	54.9 (5.0)	55.5 (3.5)	53.6 (4.5)	0.727	0.481
Left atrial volume (mL)	79.28 (3.33)	81.22 (20.14)	88.88 (13.73)	0.993	0.174
LAVI (mL/m^2)	36.36 (9.19)	46.99 (8.95)	42.61 (5.95)	0.005	0.069
Tagging					
PSS (%)	−21.20 (2.75)	−23.48 (2.36)	−23.30 (2.62)	0.077	0.076
PEDSR (1/s)	1.51 (0.24)	1.97 (0.34)	1.78 (0.39)	0.001	0.042
MPR	3.37 (1.33)	3.68 (1.57)	3.03 (0.75)	0.728	0.516
T1 mapping	$n = 11$	$n = 6$	$n = 9$		
Pre-contrast T1 (ms)	944.03 (93.00)	985.52 (86.63)	962.27 (116.06)	0.465	0.457
Post-contrast T1 (ms)	454.33 (82.67)	428.10 (98.14)	432.50 (81.01)	0.801	0.496
Partition coefficient (λ)	0.443 (0.06)	0.442 (0.06)	0.443 (0.05)	0.112	0.778
Aortic stiffness					
Pulse-wave velocity (m/s)	4.37 (1.02)	3.97 (0.80)	4.02 (0.85)	0.449	0.342
Mean aortic distensibility (10^{-3} mmHg^{-1})	5.78 (4.34, 7.15)	5.92 (4.64, 7.48)	6.30 (4.39, 8.00)	0.484	0.897
Ascending aortic distensibility (10^{-3} mmHg^{-1})	6.51 (4.74, 7.67)	6.36 (4.41, 8.10)	7.16 (4.90, 8.01)	0.586	0.938
Descending aortic distensibility (10^{-3} mmHg^{-1})	5.24 (3.95, 5.83)	5.97 (4.10, 7.11)	5.60 (3.85, 8.00)	0.391	0.262

Mean (SD) or median (25th, 75th percentiles) for non-parametric data.
LV, left ventricular; LVEDM, left ventricular end-diastolic mass; LAVI, left atrial volume index; I, indexed to BSA; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; PSS, peak systolic strain; PEDSR, peak end-diastolic strain rate.

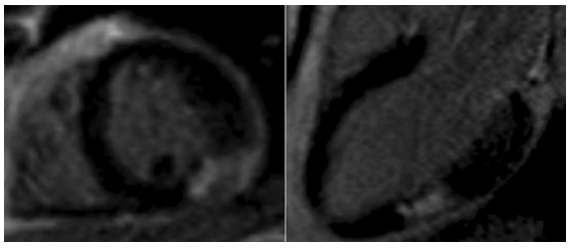

Figure 2 LGE. Images are from the same T2DM subject demonstrating significant focal mid-wall LGE in the inferolateral wall, indicative of fibrosis (subject had diabetes duration of 6 years).

that interventional studies targeting arterial stiffness and reversing diabetes will result in improvements in diastolic dysfunction.[25]

Our perfusion results are in keeping with several other studies. The MESA study did not demonstrate reduced MPR in asymptomatic patients with diabetes.[26] Two separate studies have also shown a lack of correlation between MPR and diastolic dysfunction in diabetes.[27,28] In younger type 1 diabetic patients, MPR was only lower in those with diabetes duration of >10 years,[27] suggesting that microvascular dysfunction is a relatively late phenomenon and is therefore unlikely to be primary mechanism to explain diastolic dysfunction, which occurs early.

The association between HbA1c levels and diastolic function[29,30] is not a universal finding.[31] Also consistent with our results is the finding that diastolic function may be unchanged despite improved glycaemic control.[32] These data suggest that factors in addition to advanced glycation end-products are likely to contribute to diastolic dysfunction. Another potential reason for the lack of association may be that HbA1c was only mildly elevated (median 7.1%) in our subjects, with the majority having values of 5–8%.

Role of myocardial steatosis

Myocardial steatosis results from excessive free fatty acid respiration due to insulin resistance. Myocardial steatosis has been confirmed in

T2DM using magnetic resonance spectroscopy and correlates strongly with diastolic indices, including PEDSR.[28,33–35] Given that experimental models have confirmed that steatosis[36] is associated with toxic metabolites that cause myocardial function and cause apoptosis, it is likely that steatosis occurs before fibrosis in T2DM.

Table 2 Correlation coefficients of PEDSR and its potential determinants

Variable correlated with PEDSR	*r*-value	*P*-value
CMR parameter		
LVEDM[a]	0.053	0.824
LVEDM/LVEDV[a]	0.283	0.227
Pre-contrast T1	−0.318	0.341
Post-contrast T1	−0.583	0.060
Partition coefficient	−0.180	0.597
Global MPR	−0.071	0.779
Mean aortic distensibility	**0.564**[a]	***0.023***[a]
Pulse-wave velocity	−0.134[a]	0.622[a]
PSS	**−0.580**	***0.007***
Biochemical biomarkers		
HbA1c	−0.045	0.856
Serum triglycerides	−0.181	0.445
C-peptide	0.280[a]	0.246[a]
Anthropometric variables		
Duration of diabetes	**−0.534**	***0.015***
BMI	−0.113	0.636
Waist:hip ratio	−0.028	0.905

LV, left ventricular; LVEDM, left ventricular end-diastolic mass; I, indexed to BSA; LVEDV, left ventricular end-diastolic volume; PSS, peak systolic strain; PEDSR, peak end-diastolic strain rate; BMI, body mass index.
[a]Analysed using Spearman's rank correlation coefficient, all other correlations using Pearson's correlation coefficient.
Bold and italic values indicate the variables where *p*-value was significant ($p < 0.05$).

Myocardial steatosis lowers pre-contrast T1 values due to the low T1 of fat (≈300 ms) and post-contrast T1 values will be higher than normal.[37] Steatosis may therefore explain the unexpected moderate inverse correlation we saw between post-contrast T1 and PEDSR ($r = -0.583$, $P = 0.06$ despite $n = 11$).

Importantly, both liver and cardiac triglyceride can be reduced in response to a very low calorie diet[38] and appear to be associated with improved diastolic filling in T2DM.[25] We observed no correlation between serum triglycerides and PEDSR, consistent with the lack of correlation between serum and myocardial triglyceride content seen in previous studies.[34] Further work should be undertaken in larger cohorts with T2DM to assess the relationship between pre-/post-contrast T1, extracellular volume, and steatosis in T2DM.

Limitations

The small sample size renders multivariate analysis inappropriate and only a subset of patients had T1 mapping. Coronary angiography was not performed, but the absence of regional stress perfusion defects supports the absence of obstructive coronary artery disease.

Conclusions

The duration of T2DM and mean aortic distensibility were associated with PEDSR in this young cohort of young adults with T2DM. Further work is required to determine whether interventions that improve arterial stiffness and glycaemic control in this young, extreme cohort can reverse myocardial dysfunction.

Authors' contributions

M.J.D., M.A.N., G.P.M., and T.Y. conceived the idea for the study and developed the initial protocol. E.G.W. and M.L. developed study documents, managed the trial, and recruited patients. E.G.W., M.L., and G.P.M. were present at study visits. J.N.K., A.S., M.A.H., and J.B.

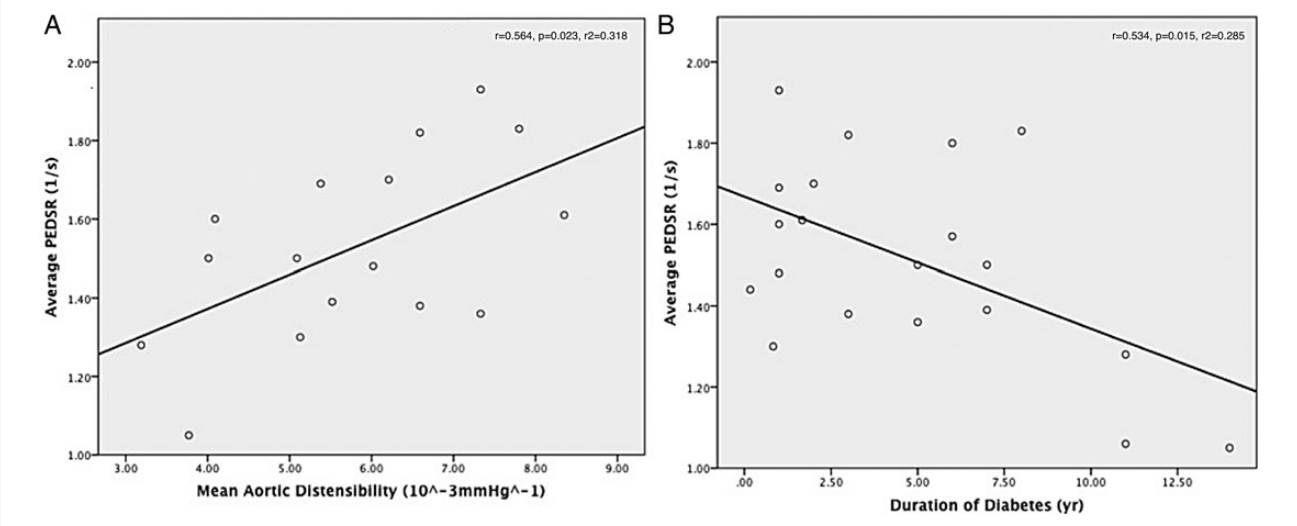

Figure 3 (*A*) Correlation between mean aortic distensibility and PEDSR. (*B*) Correlation between diabetes duration and PEDSR.

performed the CMR analyses. J.N.K. wrote the paper and performed statistical analysis, which all authors critically reviewed.

Conflict of interest: none declared.

Funding

This study is part of the research portfolio supported by the NIHR Leicester Cardiovascular and the NIHR Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Units at the University Hospitals of Leicester NHS Trust, University of Leicester, and Loughborough University. The study was funded by a Medical Research Council Interdisciplinary Bridging Award. G.P.M.C. is supported by a NIHR Postdoctoral research fellowship.

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