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Multi-modal magnetic resonance imaging quantifies atherosclerosis and vascular dysfunction in patients with type 2 diabetes mellitus

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Abstract

Vascular magnetic resonance imaging (MRI) is emerging as a powerful research tool. We studied 18 patients with type 2 diabetes mellitus and 20 controls (all with coronary artery disease). MRI measured distensibility, pulse wave velocity (PWV) and atherosclerosis in the aorta, and brachial artery flow-mediated dilatation (FMD). Patients with diabetes showed lower aortic distensibility (2.1×10^{-3} vs. 3.5×10^{-3} mmHg⁻¹, $p < 0.01$), faster PWV (8.8 vs. 6.2 m/s, $p < 0.01$) and impaired FMD (8.5% vs. 13.8%, $p < 0.05$). Diabetes was an independent negative predictor of distensibility. Aortic atherosclerosis was similar in the two groups. There was a negative correlation between aortic distensibility and atherosclerosis in control subjects only, suggesting that other factors such as protein cross-linking may explain lower aortic distensibility in diabetes. MRI provides comprehensive vascular phenotyping in patients with type 2 diabetes and is likely to be useful in studies of disease progression and drug therapy.

Keywords

magnetic resonance imaging; coronary artery disease; diabetes; distensibility; endothelial function; atherosclerosis

Introduction

Type 2 diabetes (DM) and the metabolic syndrome are increasing in prevalence – the World Health Organization estimates that by the year 2025 more than 300 million people worldwide will have diabetes.¹ These conditions carry substantially increased risk of atherosclerosis and its complications, yet the imaging techniques commonly employed clinically are biased towards the detection of severe, flow-limiting stenoses and are relatively poor at detecting early disease.² Consequently, the first presentation of arterial disease is often an acute event such as myocardial infarction or stroke. Multimodal

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assessment of arterial disease could enable earlier diagnosis, and precise targeting of treatment, and allow the effect of interventions to be monitored.

Ultrasound has been used extensively to study both arterial function and structure. Endothelial dysfunction has been demonstrated in at-risk individuals before the development of macroscopic atherosclerosis using brachial flow-mediated dilatation (FMD).³⁻⁵ In established disease, endothelial dysfunction of both peripheral⁶ and coronary⁷ arteries is associated with worse clinical outcome. Higher central arterial stiffness increases cardiovascular risk in both general populations⁸ and type 2 diabetes.^{9,10} Increased carotid wall thickness is associated with the presence of peripheral and cerebrovascular disease¹¹ and with the severity of coronary atherosclerosis on angiography.¹²

For vascular characterisation, ultrasound is relatively cheap and widely available, but the requirement for 'acoustic windows' limits assessment to superficial portions of vessels such as the carotid and brachial arteries. However, atherosclerosis is a systemic disease that affects large central arteries, including the aorta, although the precise distribution can be unpredictable. Magnetic resonance imaging (MRI) is not limited to assessment of superficial vessels and can provide extensive coverage of large arteries with high accuracy and reproducibility. It has been used to characterise atherosclerotic plaques in the aorta¹³ and to measure the response to therapy at multiple sites.¹⁴ In addition to structural information, MRI can acquire physiological data within the same vessels. We have developed techniques that enable pulse wave velocity, arterial distensibility and flow-mediated vasodilatation of the brachial artery to be measured in a single integrated examination and have used these to detect early vessel dysfunction in otherwise healthy young smokers.¹⁵ We hypothesised that multi-modality MRI would detect differences in arterial function and structure in patients with and without type 2 diabetes.

Methods

Study protocol

Thirty-eight coronary artery disease patients with a previous diagnosis of type 2 diabetes (n=18) and non-diabetic controls (n=20), matched for age, sex and serum total cholesterol, were evaluated. All patients had a diagnosis of coronary artery disease (CAD) based on coronary angiography or typical symptoms, with an exercise electrocardiogram that was positive for features of myocardial ischaemia. All subjects gave informed written consent and approval was granted by the local ethics committee. MRI was performed on a 1.5 Tesla Sonata system (Siemens, Erlangen) at constant temperature and after at least 20 minutes' quiet rest. Blood pressure was monitored throughout the study using a sphygmomanometer. Total imaging time was approximately 60 minutes.

Magnetic resonance imaging

After initial pilot images two axial, ECG-gated, steady state free precession (SSFP) 'cine' images were acquired during breath-hold to determine aortic distensibility. The first was obtained at the level of the right pulmonary artery through the ascending and proximal descending aorta and the second through the distal aorta below the diaphragm (figure 1). Typical MRI parameters were: repetition time (TR) 2.8 ms, echo time (TE) 1.4 ms, in-plane resolution 2 mm, slice thickness 7 mm, temporal resolution 40 ms. Maximum and minimum aortic cross-sectional areas over the cardiac cycle were determined using semi-automated edge detection algorithms developed using Matlab software (Mathworks Inc.).¹⁶

Distensibility was then calculated by:
$$\frac{\text{relative change in area}}{\text{pulse pressure}}$$

To measure pulse wave velocity (PWV), an ECG-gated, spoiled gradient echo sequence with velocity-encoding gradient for phase contrast was applied during free breathing to the ascending and descending aorta at the same location as the first aortic cine. Parameters were: effective TR 1 RR-interval, TE 2.8 ms, in-plane resolution 1.3 mm, slice thickness 5 mm, temporal resolution 10 ms. Blood velocity was determined using Argus software (Siemens, Erlangen). The point of maximum change in blood velocity in the ascending and descending aorta was determined by fitting the differential of the velocity data with a Gaussian function. Pulse wave velocity was calculated by dividing the distance around the arch of the aorta by the time delay between maximum change in velocity at the two locations.

For assessment of atherosclerosis, a stack of 11 transverse black blood turbo spin echo (TSE) images covering the descending thoracic aorta was acquired during diastole. MRI parameters were: TR 750 ms, TE 11 ms, in-plane resolution 0.8 mm, slice thickness 5 mm. Images were contoured manually using CMRtools software (Imperial College, London) in order to define the inner and outer vessel wall boundaries, from which mean wall and lumen areas were obtained.

The approach to measuring brachial endothelial function using MRI has previously been described.¹⁷ This method was modified to employ a SSFP sequence: typical parameters TR 6 ms, TE 3 ms, in-plane resolution 0.3 mm, slice thickness 3 mm. Cross-sectional images of the brachial artery were acquired at baseline and following release of a cuff inflated to 50 mmHg above systolic blood pressure on the forearm for five minutes. After a 10-minute interval, further brachial artery images were acquired following administration of 400 micrograms of sublingual glyceryl trinitrate (GTN). Maximum percentage change in brachial artery cross-sectional area at end-diastole was used to determine the response to each stimulus.

Statistical analyses

Statistical analyses were carried out using SPSS version 12 (SPSS Inc.). Normal distribution of data was confirmed using the Kolmogorov-Smirnov test. Data are presented as mean $\pm$ standard error. Student's *t*-test and the Mann-Whitney U test were used to compare variables between groups as appropriate, while the chi-squared test was used for categorical variables. Statistical significance was assigned at $p < 0.05$. Stepwise multivariate analysis was undertaken with the MRI-measured vascular indices (aortic distensibility, wall area and brachial artery reactivity) as dependent variables and clinical factors (age, height, weight, diabetes, smoking, systolic blood pressure, diastolic blood pressure, total cholesterol levels, high-density lipoprotein [HDL]-cholesterol and triglyceride levels) as independent variables. Included in each multivariate model were independent variables that showed significant association with the dependent variables in univariate analysis at the 0.15 significance level. Backward elimination was applied in all multivariate models (using $p < 0.05$ as the threshold for removing a variable from the model). Coefficients of regression (β) are quoted as standardised values.

Results

Clinical and biochemical characteristics of the study population are shown in table 1. Median time from diagnosis of CAD to MRI scan was not significantly different between the groups: 15 months in patients with diabetes compared to 10 months for the control group

($p=0.55$). In subjects with diabetes, aortic distensibility was reduced compared to the controls (figure 1b): in the ascending aorta by 39% ($p<0.05$), in the proximal descending aorta by 41% ($p<0.01$) and in the distal descending aorta by 43% ($p<0.01$). PWV over the aortic arch was higher in subjects with type 2 diabetes than in controls ($8.8\pm0.8\text{ ms}^{-1}$ vs. $6.2\pm0.5\text{ ms}^{-1}$, $p<0.05$). In three subjects (one patient with diabetes and two controls), pulse wave velocity measurements were technically inadequate and they were excluded from analysis. Distensibility of each region of the aorta was strongly correlated within patients ($R>0.8$ for each region of aorta, $p<0.001$) and, importantly, was also correlated with PWV ($R>0.45$, $p<0.01$ for all regions).

Results for brachial artery reactivity are shown in figure 2b. The endothelium-dependent brachial FMD response was lower in patients with diabetes ($p<0.05$), while the endothelium-independent response to GTN was similar ($p=\text{NS}$), as expected. No significant relationships were observed between brachial FMD and either aortic distensibility or aortic wall area in either group.

Mean aortic wall area, a measure of atherosclerotic plaque burden, was similar in patients with diabetes: $186\pm8\text{ mm}^2$ vs. $183\pm13\text{ mm}^2$ in controls ($p=\text{NS}$). Similarly, mean aortic lumen did not differ significantly in patients with diabetes: $453\pm21\text{ mm}^2$ vs. $435\pm22\text{ mm}^2$ in controls. There was a significant negative correlation between aortic wall area and aortic distensibility in the control subjects (figure 3b), but this was not the case in patients with diabetes, suggesting that the reduced distensibility in the latter group may be due to additional factors (discussed below).

In a multivariate model of distensibility in the proximal descending aorta, systolic blood pressure ($\beta=-0.60$, $p<0.001$), diabetes ($\beta=-0.29$, $p<0.01$) and age ($\beta=-0.26$, $p<0.05$) were independent predictors of distensibility ($R^2=0.70$, $p<0.001$ for model). The same factors were also independent predictors in the ascending and distal descending aorta, with similar levels of significance. Flow-mediated dilatation response in the brachial artery showed significant negative correlation with diabetes, body weight and fasting triglyceride levels. However, in multivariate analysis, only the presence of diabetes ($\beta=-0.36$, $p<0.05$) was an independent predictor of FMD ($R^2=0.22$, $p<0.05$ for model).

Despite the strong relationship between the presence of diabetes and both distensibility and FMD, these MR measures showed independence of $\text{HbA}_{1\text{C}}$.

Discussion

Multi-modal MRI was used for comprehensive vascular assessment in a single hour-long examination. Differences in aortic stiffness and brachial endothelial function were noted between patients with and without diabetes, using relatively small numbers of otherwise well matched patients.

Aortic stiffness is increasingly recognised as an independent predictor of cardiovascular risk⁸ and can be assessed using a variety of methods.^{18,19} Direct measurement of aortic dimensions using MRI is attractive due to the simplicity of the approach. Alternative methods include estimation of central arterial pressure by applying a 'transfer function' to the pressure waveform measured using tonometry at a more accessible artery, usually the radial. However, although these 'transfer functions' were developed from simultaneous peripheral and invasive aortic pressure recordings, whether they can be applied to all patients, including those with diabetes mellitus, has been debated.²⁰ Increased aortic stiffness in diabetes has been demonstrated previously in relatively large studies using measurements of pulse wave velocity.^{10,21} We confirm this finding, observing that patients with diabetes had significantly lower aortic distensibility and increased PWV. In

multivariate models diabetes remained an independent predictor of distensibility, along with age and systolic blood pressure. In our previous study of young smokers distensibility was similar throughout the aorta,¹⁵ while in this study of older patients we observed a differential reduction in aortic distensibility, more marked in proximal compared to distal segments. This is likely to be explained by age-related changes in the vessel wall,²² including loss of elastin fibres in the proximal aorta and their replacement with collagen.²³

Brachial FMD is a widely used, non-invasive measure of endothelial function and the impaired response to hyperaemia observed here in patients with diabetes is well recognised.⁴ A likely contributing factor is the adverse lipid profile observed in the group with diabetes, while other possible mechanisms include increased oxidative stress or inflammation.²⁴ Angiotensin-converting enzyme (ACE) inhibitors are known to improve endothelial function in diabetes mellitus.²⁵ Despite higher ACE inhibitor use in the group with diabetes, which would tend to reduce the difference between groups, we still observed impaired FMD in patients with diabetes. Central vessels, including the aorta, contain significant amounts of smooth muscle,²³ therefore aortic stiffness could also be influenced by endothelial function. Some investigators have reported a correlation between endothelial function and central arterial stiffness,²⁶ although none was observed in our study.

A higher burden of atherosclerosis is generally observed in patients with diabetes.²⁷ In this study all patients had coronary artery disease, diagnosed either by ECG treadmill testing or coronary angiography. Therefore, a possible limitation of the study is that pre-selection for coronary atherosclerosis diminished potential differences in atherosclerosis burden. However, assessment of atheroma burden using coronary angiography is imperfect,² and increasingly investigators are measuring atherosclerosis in other arterial territories, including the aorta.^{13,14,28} Additionally, all patients in our study were established on statin treatment for at least one year, which has been shown using MRI to reduce aortic atherosclerosis over a similar timeframe¹⁴ and could have affected our ability to detect a difference in atherosclerosis between groups.

Despite similar plaque burden and duration of coronary artery disease, clear differences were observed between the groups for distensibility and FMD, highlighting the value of measuring multiple parameters using MRI. Negative correlation was observed between wall area and distensibility in the aorta of control subjects, suggesting that an increased burden of atherosclerosis adversely influences distensibility. However, the lack of similar correlation in the diabetes group suggests that compositional changes within the arterial wall, such as cross-linking of collagen by glycation, could also contribute to aortic stiffening²⁹ and represent another possible therapeutic target.³⁰

In summary, we demonstrate that MRI can successfully assess both central and peripheral arteries in patients with diabetes. As expected, significant differences were detected in the vascular function of patients with diabetes compared to controls, and importantly the number of subjects needed to detect a difference was small. This technology may prove useful by reducing the numbers of patients required for clinical trials. In addition, measurement of multiple parameters may provide further insights into diabetic vascular disease and allow better stratification of risk, since within patients the functional and structural measures did not always vary together. More precise characterisation of disease may also allow targeting of specific therapies according to the stage of disease and pathological process.

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Figure 1.

Aortic distensibility. (a): sagittal pilot image of the aorta is used to select two transverse planes (indicated by white lines) for ECG-gated steady state free precession (SSFP) cine acquisitions. Still images of the ascending (AA), proximal descending (PDA) and distal descending aorta (DDA) are shown during diastole and systole. (b): distensibility

Figure 2. Brachial artery reactivity. (a): transverse image of arm; higher magnification shows brachial artery (BA) at baseline and after hyperaemia due to cuff release. (b): brachial artery responses to flow-mediated dilatation (FMD) and glyceryl trinitrate (GTN).

Figure 3.

Aortic wall area. (a): high-resolution transverse image of aortic plaque – inner and outer wall boundaries are contoured to derive wall and lumen areas. (b): Aortic wall area vs. distensibility. Blue squares and solid regression line, control subjects ($R = -0.61$, $p < 0.01$); yellow triangles and dashed regression line, subjects with diabetes ($R = -0.18$; $p = \text{ns}$)

Table 1
Selected clinical and biochemical characteristics of the study participants

	Diabetes	Control	P
Number of subjects	18	20	-
Age (years)	65.9±1.7	63.2±2.2	NS
Height (m)	1.74±0.01	1.74±0.02	NS
Weight (kg)	90.4±3.3	84.0±3.2	NS
Body mass index (kg/m ²)	29.8±1.0	27.9±1.1	NS
HbA _{1C} (%)	8.2±0.3	6.0±0.2	<0.01
Systolic BP (mmHg)	136.5±2.9	127.6±4.0	NS
Diastolic BP (mmHg)	76.6±2.1	78.6±1.4	NS
Pulse pressure (mmHg)	59.9±3.2	49.1±4.1	NS
Total cholesterol (mmol/L)	3.76±0.14	4.15±0.21	NS
LDL cholesterol (mmol/L)	2.41±0.12	2.68±0.17	NS
HDL cholesterol (mmol/L)	0.92±0.03	1.17±0.07	<0.01
Triglycerides (mmol/L)	2.16±0.12	1.40±0.26	<0.05
Number with history of smoking	10	14	NS
Number using ACE inhibitor	16	11	<0.05
Number using beta-blocker	12	16	NS
Number using aspirin	18	20	NS
Number using statin	18	20	NS
Diabetic patients using			
- insulin	7	-	-
-oral agents	11	-	-

Key: HbA_{1C} = haemoglobin A_{1C}; BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ACE = angiotensin-converting enzyme