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VASCULAR FUNCTION

Cardiovascular Magnetic Resonance Imaging for Non-Invasive Assessment of Vascular Function: Validation against Ultrasound

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ABSTRACT

Ultrasound is an established modality for quantification of vascular function in clinical studies of cardiovascular disease. We determined whether cardiovascular magnetic resonance imaging (CMR) can provide a comparable assessment of vascular function. In seventeen control subjects, we used CMR to quantify endothelium-dependent (flow mediated dilatation, FMD) and endothelium-independent dilatation of the brachial artery, brachial and carotid distensibility, aortic compliance, and pulse wave velocity. These were compared to brachial and carotid measurements obtained by established ultrasound protocols. Twelve of the volunteers then underwent repeated measurements with both modalities. There was good agreement between imaging modalities for measures of endothelial function and arterial structure in the same subjects (difference between CMR and ultrasound for FMD = 0.14 ± 6.8%, and brachial artery area = − 0.7 ± 2.2 mm², correlation between modalities for FMD = 0.62, p = 0.01 and for area = 0.87, p = <0.0001). Inter-study reproducibility was also similar (coefficient of variation (CV) for FMD: CMR = 0.3, ultrasound = 0.3, CV for brachial artery area: CMR = 0.1, ultrasound = 0.1). Comparability and reproducibility were not as strong for functional measures if repeated studies were several days apart (CV for FMD by ultrasound on the same day = 0.1 and several days apart = 0.4). CMR and ultrasound show good agreement for quantitative measures of vascular structure and function with good reproducibility for both modalities. The major advantage of CMR is that it allows *one-stop* integrated assessment of both peripheral and central measures of vascular function.

INTRODUCTION

Intermediate vascular phenotypes, such as flow mediated dilatation measures of endothelial function, arterial distensibility and pulse wave velocity, have been incorporated into clinical studies to investigate the development, progression and outcome of cardiovascular disease (1–6). The established modality over many years for these measurements has been ultrasound. We (7) and others (8) have recently demonstrated that cardiovascular magnetic resonance imaging (CMR) can also be used to assess parameters of vascular function.

CMR has the advantage of a wider field of view and allows assessment of central and peripheral vessels, as well as cardiac structure and function, in an integrated study. However, there is very limited information on how CMR assessment of vascular function compares with ultrasound evaluation. One study suggested CMR may be superior for assessment of endothelium-dependent flow mediated dilatation because CMR provides more reproducible measures (8). Ultrasound image quality is more dependent on subject anatomy (2). Furthermore, the alignment of the two dimensional image plane is dependent on operator experience. There is a risk of oblique views through vascular structures or movement effects between

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repeated measures, and the change in vessel size can only be measured in one direction. As vessels may not be circular (9), or respond uniformly, vascular dilatation would be underestimated. Magnetic resonance imaging allows three-dimensional anatomical positioning of image acquisition planes so that cross sectional planes can be set perpendicular to the artery and, as long as the arm is stable during image acquisition, may therefore allow more accurate assessment of artery cross sectional area. Nevertheless, in superficial arteries such as the brachial and carotid, magnetic resonance imaging is limited by inferior temporal and spatial resolution compared to ultrasound, image quality is affected by flow artefacts and automated methods for assessment of changes in vessel dimension have not been established, an integral part of functional measures (10, 11).

Therefore, we employed CMR to quantify a range of parameters of vascular structure and function in healthy control subjects and compared the measures, and their reproducibility, to those obtained by established ultrasound protocols.

METHODS

Overview

Seventeen control subjects without known cardiovascular disease and not on cardiovascular medication underwent CMR and ultrasound vascular imaging on different days. Images of the carotid and brachial artery were obtained with both modalities and aortic images with CMR only. These were used to assess brachial, carotid and aortic distensibility, aortic pulse wave velocity and endothelial dependent and independent responses of the brachial artery. Twelve of the subjects had repeated studies of the same measures on different days, and six underwent repeat brachial artery measures on the same day. All measurements were performed in temperature controlled rooms and subjects rested for ten minutes prior to the scans (2). The study was approved by the Local Research Ethics Committee and informed consent was obtained.

Cardiovascular magnetic resonance imaging

MR imaging was performed on a 1.5T clinical MR scanner (Siemens Sonata, Erlangen, Germany) with subjects in the supine position, as previously described (7). Briefly, for aortic imaging, a combination of a 2-element array surface coil placed on the chest and a spine-coil-array within the patient bed was used. Carotid artery imaging was performed using a 2-element-array surface coil (Machnet, The Netherlands). For brachial artery imaging, a flexible surface coil was attached to the right elbow.

Vascular distensibility of the aorta and common carotid arteries was assessed using a TrueFISP (fast imaging with steady state precession) cine sequence with the following 7 parameters: aorta TR/TE 42 ms/1.4 ms, FOVread 380 mm, in-plane resolution 1.97 mm, slice thickness 7 mm, and carotid TR/TE 45.3 ms/2.4 ms, FOVread 200 mm, in-plane resolution 0.52 mm, and slice thickness 3 mm.

The imaging position for the brachial artery was chosen from a 3D angiographic pilot scan in order to align the imaging plane perpendicular to the artery. Cardiac gated TrueFISP cine images of the brachial artery were acquired with the following parameters TR/TE 56/3 ms, flip angle 66°, FOV 117 × 77 mm, matrix 384 × 252, 16 segments, 11–19 phases depending on heart rate.

For aortic flow and pulse wave velocity measurements, sagittal-oblique pilot images were acquired aligned with the aortic arch. A high-resolution gradient-echo pulse sequence with a velocity-encoding gradient for phase-contrast MRI was applied with TE 2.8 ms, effective TR 1 RR-Interval, flip angle 30°, matrix size 256 × 192, field of view 320 × 240 mm, slice thickness 5 mm, temporal resolution 11 ms per cine frame. Flow measurements in the aorta were made at 3 levels: the crossing of the pulmonary artery through [1] the ascending and [2] descending aorta and [3] at a level approx. 10 cm below the diaphragm. Distances between the levels were measured on the MR scanner console from the scout images of the aortic arch.

Blood pressure was measured from the left arm using an automated brachial artery sphygmomanometer during distensibility measurements of the aorta and carotid arteries and during brachial artery imaging.

Ultrasound imaging

Ultrasound imaging was performed by the same operator on an HP Sonos 5500 (Philips Medical Systems) with a linear array probe and digital image storage. Standard vascular imaging presets were used and the image was optimized using gain controls and zoom function. Parameters were not altered during a study.

The subject lay supine on a couch and longitudinal images of the carotid artery over five cardiac cycles at the site of the carotid bifurcation were stored. For brachial measures the forearm was stabilized in a pre-formed channel and the probe fixed in position with a stereo-tactic clamp. Longitudinal images of the brachial artery in B-mode, 5 to 10 centimeters above the antecubital fossa, were then stored over five cardiac cycles. Flow measures were taken using pulse-wave Doppler in the centre of the artery, aligned to the direction of the artery. Blood pressure was recorded using an automated device during carotid and brachial image acquisition.

Vascular data analysis

MR vessel dimensions were measured by manual delineation of inner vessel boundaries using CMR tools image post-processing software (Imperial College, London, UK). Ultrasound vessel dimensions were measured off line using automated wall tracking software (Vascular Imager, Medical Imaging Applications, Iowa). To compare ultrasound measures to the cross sectional MR area measures, vessel areas were calculated from the ultrasound diameter data assuming a uniformly circular artery.

Endothelial dependent and independent responses

Endothelium-dependent responses were calculated as both absolute (Area-post stimulus—Area pre-stimulus) and proportional change in end-diastolic vessel diameter or area ([Area-post stimulus—Area-pre stimulus]/Area-pre stimulus*100%) after forearm reactive hyperemia (flow mediated dilatation, FMD) induced by five minutes blood flow occlusion using a blood pressure cuff inflated on the proximal portion of the forearm to suprasystolic pressure. Endothelium-independent responses were calculated as the change in vessel size three minutes after a single sublingual spray of glyceryl trinitrate (GTN)(around 300 microgrammes) (GTN-induced dilatation, GTND).

Vascular distensibility

Vascular distensibility ($mmHg^{-1}$) of the brachial and carotid artery—and aorta for MR measures—were calculated as relative change in cross-sectional area for a given pressure change according to formula: Distensibility = (Amax − Amin)/Amin* (Pmax − Pmin) where Amax = maximal (systolic) area (mm^2), Amin = minimal (diastolic) area (mm^2), Pmax = systolic blood pressure (mmHg), Pmin = diastolic blood pressure (mmHg) (4).

Pulse wave velocity

For the MR data, pulse wave velocity (m/s) was calculated as the ratio of distance between aortic measurement levels and time difference between arrival of the pulse wave at these levels. Arrival time of the pulse wave at each level was defined as the time point when the mean velocity reached half of its maximum value (8). Velocities were linearly interpolated between measured values enabling arrival time determination at higher temporal resolution than the imaging resolution. Curve fitting of velocity data was performed using Origin (Software Version 7, OriginLab Corporation, Northampton, MA).

Statistical analysis

Statistical analysis was performed using SPSS. All results are expressed as mean ± SD unless otherwise specified. Comparisons between the two modalities were made by correlations and Bland-Altman plots. For inter study variability, coefficients of variation were calculated for each parameter.

RESULTS

The characteristics of the study group are shown in Table 1. Both imaging techniques were well tolerated by all subjects. All scans were considered of good quality and full scans were obtained for all subjects. Total study time was around 30 minutes for ultrasound and 60 minutes for magnetic resonance imaging. Post processing of data was considerably longer for magnetic resonance imaging. However, magnetic resonance imaging included acquisition and analysis of aortic data. Figures 1 and 2 demonstrate the differences in appearance of artery images obtained by the two techniques.

Table 1. General characteristics of study group. Mean (SD)

	Male	Female	All
Number	10	7	17
Age in years (range)	33 (22–61)	32 (26–51)	32 (22–61)
Smokers in %	50	29	41
SBP in mmHg	113 (15)	118 (11)	115 (13)
DBP in mmHg	69 (8)	76 (7)	71 (8)
Height in cm	176 (10)	163 (9)	171 (10)
Weight in kg	74 (14)	61 (8)	68 (14)

Structural measurements

End-diastolic measures of brachial artery size at baseline, after cuff occlusion and following GTN were strongly correlated between modalities (Table 2 and Fig. 3). The variation in measures of brachial area between techniques was greater in those with smaller arteries (<12 mm^2) (Fig. 3). End-diastolic measurements of the carotid artery were also correlated, although

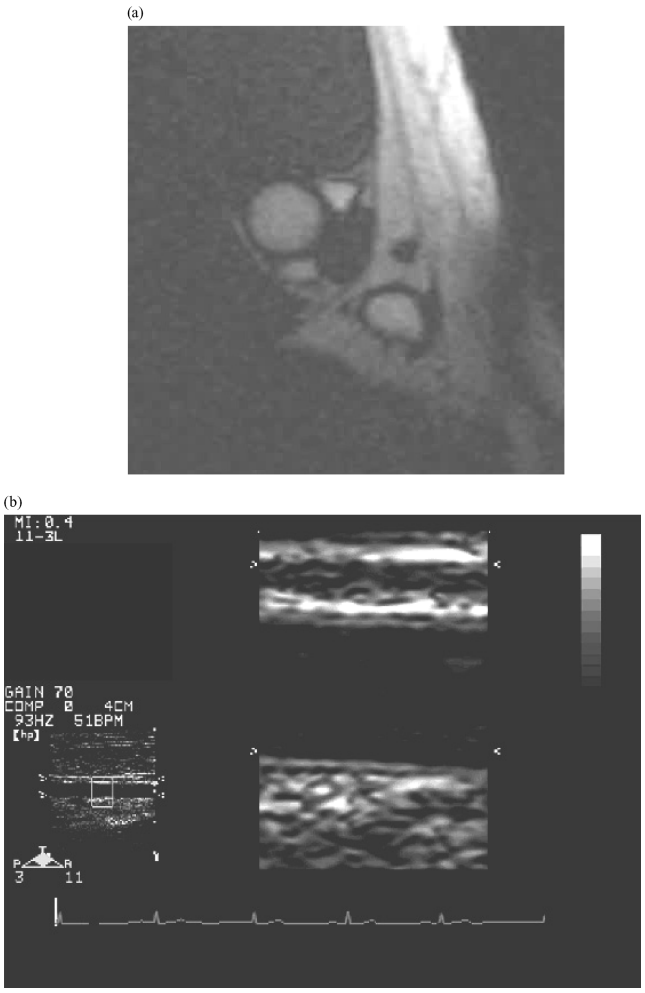

Figure 1. Cross sectional and longitudinal brachial artery images obtained between 5 and 10 centimetres proximal to the antecubital fossa. (a) Cardiovascular magnetic resonance imaging; (b) Ultrasound.

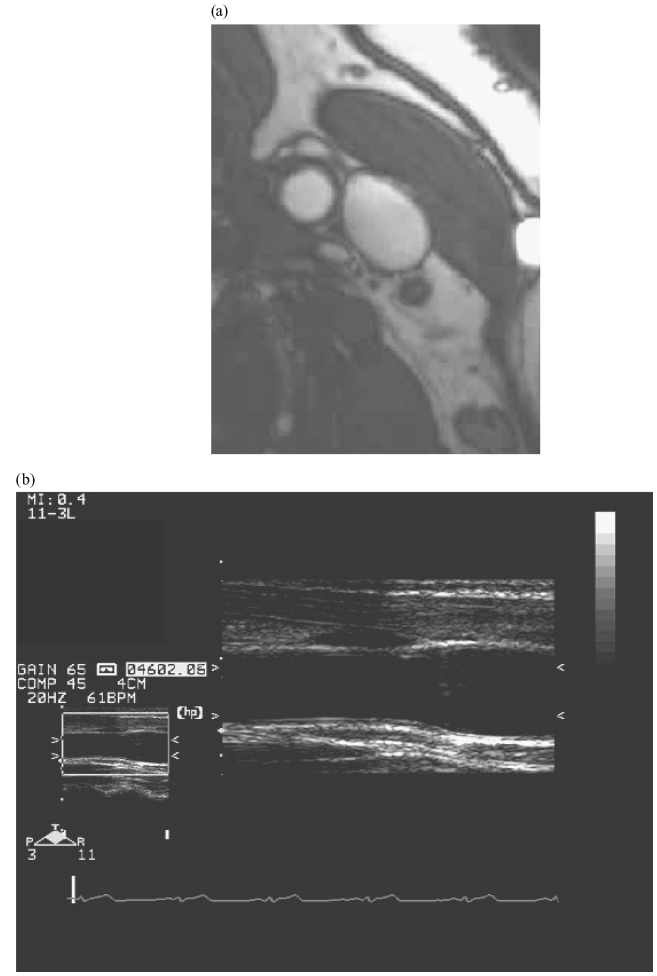

Figure 2. Cross sectional and longitudinal carotid artery images acquired by the different modalities at the level of the carotid bifurcation. (a) Cardiovascular magnetic resonance imaging; (b) Ultrasound.

not as strongly (Table 2). For both arteries, the calculated cross sectional area tended to be greater with ultrasound than the directly measured area obtained from magnetic resonance imaging (Table 2), but these differences did not reach significance (p for difference between baseline end-diastolic areas of brachial artery by each modality = 0.7).

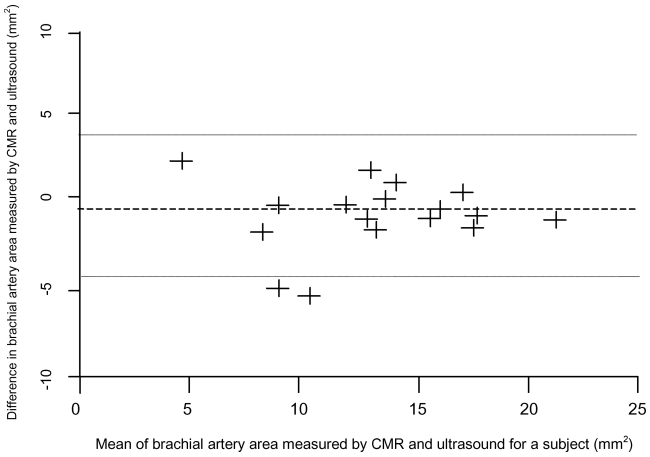

Figure 3. Difference in end diastolic brachial artery cross sectional area measured by CMR and ultrasound. Mean difference is −0.7 mm^2 and outer lines represent 2SDs.

Functional measurements

There was good agreement between the measures of endothelium-dependent and independent function by magnetic resonance imaging and ultrasound (Table 3 and Fig. 4). FMD and GTND were larger with magnetic resonance imaging than ultrasound, which probably reflected the smaller baseline area measurements. Use of cross sectional area to quantify vascular function was associated with greater reported percentage FMD and GTND (mean FMD based on diameter for ultrasound group = 4.74% and mean FMD based on area = 9.79%). Associations between both brachial and carotid distensibility measures were weaker (Table 3).

Interstudy reproducibility

Both modalities had good reproducibility for all measures of artery area performed several days apart (Table 4) and almost identical reproducibility for measures of endothelium-dependent and independent function and carotid distensibility. Brachial artery distensibility had poor reproducibility in the magnetic resonance imaging group. Reproducibility of aortic distensibility was similar to the reproducibility of brachial and carotid functional measures. The most reproducible functional

Table 2. Comparison of brachial and carotid artery measures. Difference between CMR and ultrasound represents the mean (SD) of the differences in the vascular measures obtained by CMR and ultrasound in each individual. Results are presented as Mean (SD)

	CMR	Ultrasound	Difference between CMR & ultrasound	Correl[n]	P for correl[n]
Resting diastolic brachial area in mm^2	12.6 (4.3)	13.3 (4.4)	−0.7 (2.2)	0.87	<0.0001
Resting systolic brachial area in mm^2	13.7 (5.0)	14.1 (4.6)	−0.4 (2.1)	0.90	<0.0001
Post-cuff diastolic brachial area in mm^2	13.7 (4.5)	14.5 (4.9)	−0.8 (2.6)	0.85	<0.0001
Post-GTN diastolic brachial area in mm^2	19.3 (4.5)	18.3 (5.4)	1.0 (2.7)	0.96	<0.0001
Carotid diastolic area in mm^2	35.5 (9.6)	37.9 (6.7)	−2.4 (7.7)	0.60	0.02
Carotid systolic area in mm^2	42.8 (10.6)	44.6 (8.2)	−1.8 (7.8)	0.72	0.01

Table 3. Comparison of vascular structure and function measures. Difference between CMR and ultrasound represents the mean (SD) of the differences in the vascular measures obtained by CMR and ultrasound in each individual. Results are presented as Mean (SD)

	CMR	Ultrasound	Difference between CMR & ultrasound	Correl^n	P for correl^n
FMD absolute diameter change in mm	—	0.185 (0.12)	—	—	—
FMD relative diameter change in %	—	4.74 (3.19)	—	—	—
FMD absolute area change in mm^2	1.22 (0.87)	1.10 (0.94)	0.12 (0.9)	0.60	0.02
FMD relative area change in %	9.93 (8.43)	9.79 (6.74)	0.14 (6.8)	0.62	0.01
GTN absolute diameter change in mm	—	0.67 (0.17)	—	—	—
GTN relative diameter change in %	—	17.20 (7.03)	—	—	—
GTN absolute area change in mm^2	6.37 (1.72)	4.66 (1.51)	1.71 (1.1)	0.79	0.001
GTN relative area change in %	52.7 (19.5)	37.8 (17.13)	14.9 (7.5)	0.76	0.01
Brachial distensibility in mmHg^{-1}	3.52 (2.27)	1.73 (0.48)	1.79 (2.2)	0.46	0.12
Carotid distensibility in mmHg^{-1}	5.22 (2.92)	8.85 (2.00)	−3.28 (0.8)	0.49	0.21

measure over time was pulse wave velocity by magnetic resonance imaging. In the ultrasound group, who had measures on the same day, reproducibility of functional measures was greater than for those who had measures several weeks apart (CV for FMD by ultrasound on the same day = 0.1 and several days apart = 0.4).

DISCUSSION

Ultrasound and magnetic resonance imaging show good agreement for quantitative measures of vascular structure and endothelial function, with good reproducibility for both modalities.

A previous study of in vivo endothelial function suggested CMR had a superior reproducibility for flow mediated dilatation measures compared to ultrasound, largely due to poor reproducibility of ultrasound measures (8). Our reported reproducibility is an accurate representation of both techniques in our hands and further reports of reproducibility by different centres will be useful to determine consistent measures by different observers. Our ultrasound reproducibility is consistent with recently reported coefficients of variation for the measure of between 0.3 (12) and 0.4 (13).

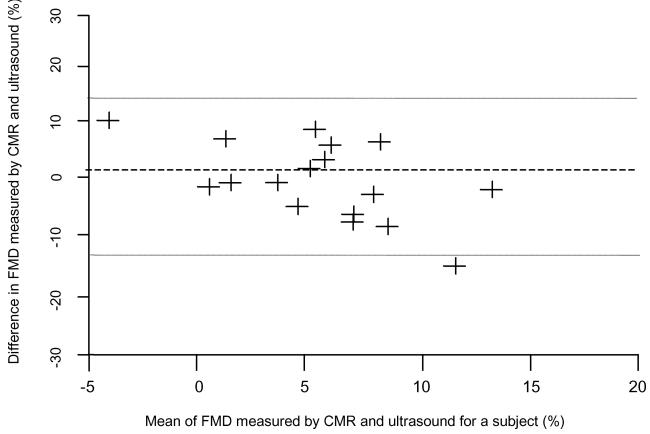

Figure 4. Difference in flow mediated dilatation of brachial artery (based on relative change in cross sectional area) measured by CMR and ultrasound. Mean difference is 0.14% and outer lines represent 2SDs.

An advantage proposed for the use of CMR in assessment of artery endothelial function and distensibility is the ability to assess change in artery area. An ultrasound study based on phantoms and a control subject suggested cross-sectional images might provide more sensitive measures of change in size after reactive hyperaemia (14). Furthermore, intravascular ultrasound has been used to demonstrate that the resting brachial artery is oval, which is not accounted for in longitudinal imaging (9). The standard ultrasound technique could be adapted to acquire routinely cross sectional images rather than longitudinal images (14). However, our study suggests any increase in accuracy of estimated artery area from the use of cross sectional images does not have a major impact on reproducibility of either structural or functional measures in the brachial artery.

A major factor in the reproducibility of functional measures appears to be physiological variability over time. Our study demonstrated functional measures were more reproducible when repeated on the same day compared to several days apart. Structural measures, less affected by physiological variability, were also better correlated and more reproducible than functional measures. Temperature (2), time of day (15) and diet (16) have been shown to influence functional measures and, although our study included controls for these factors, improvements in area measurements may have a very small impact relative to the effect of physiological variability in clinical studies. It will also be of interest to determine the variability in functional measures between techniques in patients with disease as they may have a different stress response to the two imaging modalities, which might influence vascular responses.

Measures of distensibility in the brachial and carotid arteries were not as well correlated as those of endothelial function. Distensibility depends on measurement of small changes in vessel diameter over the cardiac cycle. CMR image quality, particularly of the brachial artery, is reduced in systole due to flow artefacts and brachial artery distensibility had the poorest reproducibility. However, measures of absolute vessel area in diastole and systole were well correlated between techniques, which would suggest the artefact may not be a significant factor. Variability

Table 4. Repeat measures of vascular structure and function by CMR and ultrasound. Difference in measures represents the mean (SD) of the difference between repeated vascular measures in each individual. Results are presented as Mean (SD)

	Difference in CMR measures	Coefficient of variation	Difference in ultrasound measures	Coefficient of variation
Brachial artery area in mm^2	−0.91 (1.31)	0.07	0.72 (1.57)	0.1
Carotid artery area in mm^2	−1.75 (2.44)	0.1	−0.97 (4.61)	0.1
Asc Aorta area in mm^2	−29.1 (56)	0.1	—	—
Desc Aorta area in mm^2	−14.5 (27)	0.1	—	—
Distal Aorta area in mm^2	−6.2 (19)	0.1	—	—
FMD absolute in mm^2	−0.5 (0.59)	0.4	−0.006 (0.08)	0.4
FMD relative in %	−3.2 (6.76)	0.3	−0.97 (1.73)	0.3
Brachial distensibility in $mmHg^{-1}$	−0.30 (2.12)	0.6	−0.24 (0.31)	0.2
Carotid distensibility in $mmHg^{-1}$	1.52 (2.30)	0.3	3.16 (3.95)	0.3
Asc Aorta dist in $mmHg^{-1}$	1.55 (2.83)	0.3	—	—
Desc Aorta dist in $mmHg^{-1}$	2.10 (2.97)	0.4	—	—
Distal Aorta dist in $mmHg^{-1}$	1.36 (3.05)	0.3	—	—
PWV in ms^{-1}	0.35 (0.45)	0.1	—	—

could arise from the blood pressure measurement required for calculation of distensibility. We used a validated technique of automated sphygmomanometer blood pressure measurements in the contra-lateral brachial artery but this is only a surrogate measure of intra-arterial pressure (5).

Pulse wave velocity is less dependent on blood pressure and image quality. We used aortic flow velocity to represent aortic pulse wave velocity (8). In our study pulse wave velocity reproducibility was superior to that of other compliance measures, which is in keeping with reports on the reproducibility of pulse wave velocity using different techniques (18). CMR would provide a means to combine vascular distensibility measures assessed by pulse wave velocity with brachial endothelial measures.

There were some general variations in measurements between techniques. Ultrasound tended to record larger areas likely to be because CMR delineated the internal artery diameter whereas ultrasound diameter was taken as the intima-media boundary. Also, the ultrasound plane is set in the maximal arterial diameter and calculated circular cross sections would overestimate the area of oval arteries. This difference had the effect of slightly lower calculated proportional changes in artery size. However, there was no statistically significant systematic difference between groups. Structural carotid measures were not as well correlated as those of the brachial artery, which may be because the carotid vessel area is more variable along its length. Small differences in measurement point between modalities might lead to greater disparity in vessel area. Also variation in area measures appeared to be greater in smaller vessels. This is likely to reflect the fact that a small absolute error in diameter measurement in a small vessel will have a greater effect on calculated area than the same absolute difference in diameter in larger vessels.

CMR measures can be improved further. Artery areas were measured by manual delineation compared to automated vessel wall tracking with ultrasound. Concerns have also been raised about the flow artefact secondary to reactive hyperaemia in CMR images, which appear after cuff occlusion (17). Although these are minimal at end-diastole when measures are taken they could obscure boundaries and might be reduced further by different arm positions or CMR settings.

Previous studies have used magnetic resonance imaging for assessment of atherosclerotic pathology within the aorta, carotid or coronary arteries (19–23). Functional measures provide additional information on underlying differences in vascular biology, and have been widely applied in ultrasound-based studies, as markers of disease or risk factor development (1–6, 24–27). They have been instrumental in understanding the emergence of cardiovascular disease from early in life within populations. Our study demonstrates CMR can also now be used to provide accurate, reproducible measures of endothelial function, as good as the best ultrasound techniques, and raises the possibility of combining pathological or structural cardiac and vascular assessment, with physiological vascular parameters in a single non-invasive investigation.

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