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Aortic Pathophysiology by Cardiovascular Magnetic Resonance in Patients with Clinical Suspicion of Coronary Artery Disease

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ABSTRACT

Purpose: **To correlate cardiovascular magnetic resonance (CMR)-based measurement of aortic pulse wave velocity (PWV) with serum markers for atherosclerosis and plaque burden in the thoracic aorta.** ***Method:*** **Individuals with risk factors for coronary atherosclerosis underwent CMR pulse wave velocity examination of the descending thoracic aorta and computed tomography for coronary calcium scoring. Inversion recovery images allowed quantification of aortic plaque. Serum lipids and c-reactive protein levels were measured.** ***Results:*** **Mean PWV did not correlate with presence of aortic plaque ($p = 0.55$). Subgroup analysis showed no significant correlation with PWV and total plaque. PWV and pulse pressure correlated (PP) (R^2 0.38, $p = 0.0003$), but PWV and other predictor variables did not. Total plaque area correlated with aortic diameter ($p = 0.0066$).** ***Conclusions:*** **In patients with suspected coronary artery disease, aortic pulse wave velocity reflects increased aortic stiffness demonstrated by elevated pulse pressure, but does not directly correlate with aortic plaque or serum markers for arterial disease.**

INTRODUCTION

Endothelial dysfunction occurs early in the development of arterial disease. Nitric oxide, prostacyclin, bradykinin, endothelin and angiotensin II act in equilibrium with tissue plasminogen activator, platelets and vascular smooth muscle cells to maintain normal vascular physiology (1). Endothelial damage disrupts this equilibrium, with resultant alteration of vessel wall mechanics characteristic of the atherosclerotic process (2, 3). Measurements of endothelial dysfunction underscore the systemic nature of the disease (4). In addition, aortic stiffness measured by validated noninvasive parameters has been correlated with variability in vessel wall gene expression (5), while other studies of pulse wave velocity suggest no correlation with extracoronary atherosclerosis (6).

There are many mathematical models describing this pathophysiology, each of which emphasizes the complex interaction of stress and strain on the vascular wall. Decreased large vessel compliance increases wave velocity of fluid traveling through the vessel, suggesting that measurement of aortic compliance could serve as a surrogate marker of vessel wall disease, most commonly atherosclerosis. Pulse wave velocity (PWV) is a well-accepted index of arterial compliance (7) and has shown a strong association with cardiovascular disease. Prior investigations using ultrasonography have demonstrated a clear relationship of decreased aortic compliance with coronary artery disease (8, 9), peripheral arterial atherosclerosis (10, 11) and cardiovascular mortality (12–14). In addition to ultrasound, cardiovascular magnetic resonance (CMR)-based techniques utilizing phase-contrast imaging and changes in transverse diameter have shown decreased aortic compliance in older patients (15), patients with Marfan syndrome (16, 17) and patients with diastolic heart failure (18). But to date, CMR-based PWV measurement has not been applied in patients with atherosclerosis.

Keywords: Aorta, Atherosclerosis, Cardiovascular Magnetic Resonance Imaging, Coronary disease.
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Table 1. Distribution of coronary artery disease (cad) severity by invasive coronary angiography

Severity of CAD	Number of patients (%)
No CAD	19 (47)
Mild	14 (35)
Moderate	3 (7.5)
Severe	4 (10)

A CMR technique to measure PWV employing a cylindrical excitation pulse has been developed and tested in a phantom flow model, normal volunteers and patients with connective tissue disease (19–21). We tested the hypothesis that MR-based PWV correlates with atherosclerotic plaque burden in the descending thoracic aorta as well as other established markers of atherosclerotic and aortic disease.

METHODS

Patient enrollment

Forty individuals (age 27-76, mean 56 years; 31% women) with risk factors and clinical suspicion for coronary atherosclerosis (CAD) referred for cardiac catheterization (Table 1) were prospectively enrolled to undergo cardiovascular magnetic resonance and computed tomography (CT) examination. All but four patients had symptoms such as chest pain or dyspnea suspected to be attributable to CAD. Written informed consent was obtained to participate in the Institutional Review Board-approved protocol. Brachial blood pressure was measured upon completion of CMR examination and used to calculate pulse pressure (PP). Serum c-reactive protein (CRP), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels were measured (Table 2).

Cardiovascular magnetic resonance protocol

The CMR PWV protocol included a two-dimensional, respiratory-gated gradient echo pulse sequence to excite a cylindrical volume prescribed along the descending aorta in a sagittal plane. CMR acquisitions were completed on a 1.5 T system (Signa Lx, GE Healthcare, Milwaukee, WI, USA) with a four-channel cardiac receiver coil. A bipolar velocity-encoding gradient was then applied and stepped through a range of values to produce velocity traces throughout the cardiac cycle. Black blood imaging using a dual inversion recovery fast spin echo sequence was prescribed in serial axial planes for quantification of plaque in the descending thoracic aorta. Data sets were analyzed by three blinded reviewers with semi-automated postprocessing software (CineTool, GE Healthcare) using measurements of relative left-to-right propagation to quantify pulse wave velocity as well as to delineate endovascular and perivascular aortic borders (Figs. 1–4). The TSE and PWV scans were viewed in random order, not together for each patient. Contiguous short-axis steady-state free precession cine imaging was obtained to quantify left ventricular volumes and ejection fraction using standard techniques (22).

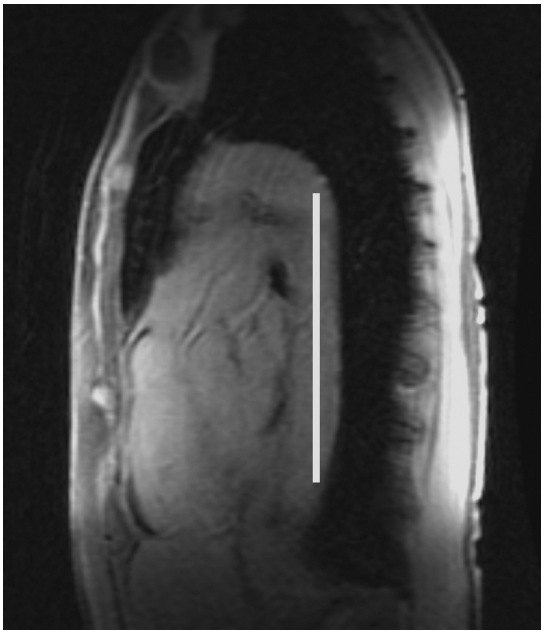

Figure 1. Sagittal scout image of descending aorta shows prescription for subsequent velocity sequence.

Table 2. Patient values for coronary disease risk factors

	Mean	SD	Median	Range
Avg PWV	4.87 m/s	1.22	4.90	2.37–8.93
Plaque Area	85.63 mm^2	53.68	63.79	21.5–198.2
Scores	256.88 mm^2	161.03	191.37	64.5–194.7
Aortic Diameter	22.58 mm	2.84	22.39	15.3–27.8
Index	0.14	0.037	0.13	0.092–0.35
Pulse pressure	57.83 mm Hg	14.56	52.50	38–95
CRP	5.47 mg/L	6.37	3.20	0.29–25.9
HDL	43.2 mg/dL	15.21	41.00	20–80
LDL	112.93 mg/dL	28.14	115.50	55–185
Ca score	427.5	669.41	108.50	0–2793

PWV = pulse wave velocity, CRP = c-reactive protein, HDL = high-density lipoprotein, LDL = low-density lipoprotein, Ca score = coronary artery calcium score.

Quantification of pulse wave velocity

Each patient's PWV sequence was loaded into the CineTool viewer with multiple frames demonstrating propagation of the wavefront from left to right (representing the patient's aorta in a head-to-toe configuration, respectively). An "analyze line" was placed parallel to the wavefront in each frame, crossing the zero velocity line (Fig. 3). Final quantification of PWV was determined by the rate of travel of the analyze line along the zero velocity line during the series of images. Values for each set of data were obtained independently by the reviewers. Each patient's final PWV measurement was determined after discarding the farthest outlier and averaging the remaining values.

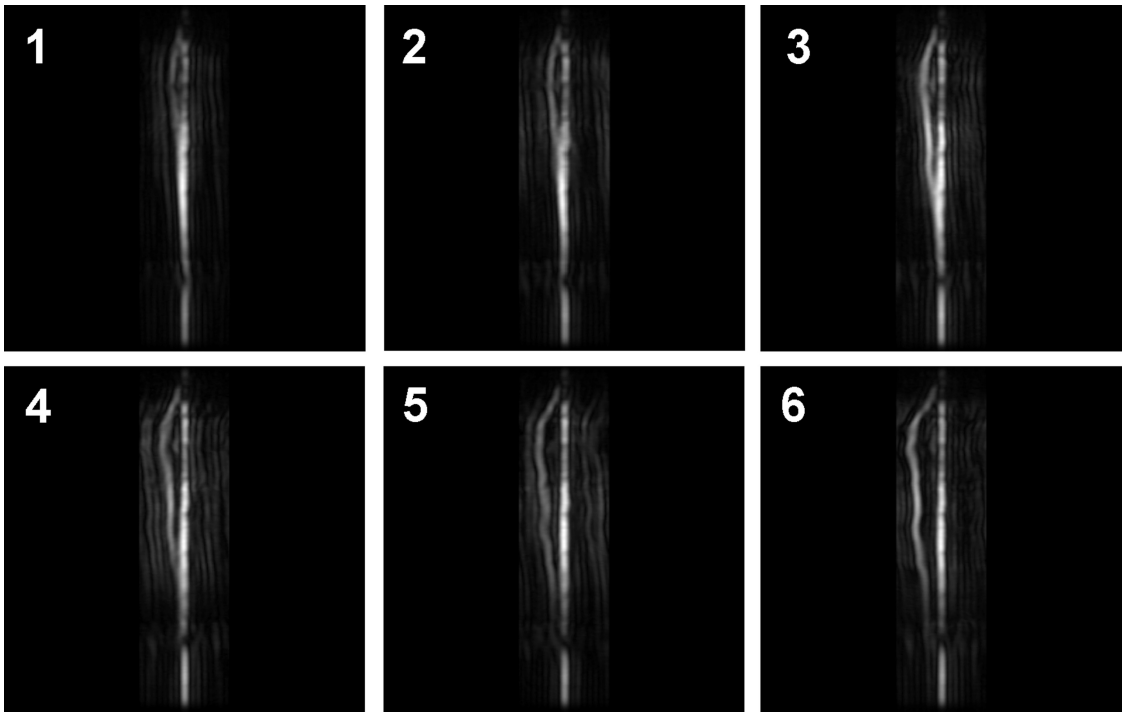

Figure 2. Propagating wavefronts during 6 serial phases of a cardiac cycle, starting approximately 73.920 ms after the onset of the R wave with 3.696 ms per frame, illustrated as one-dimensional spatial images along the aorta (head superior, feet inferior) with velocity along the aorta shown by the horizontal offset from the vertical bright line that represents stationary blood (zero velocity) and the tissue around the aorta inevitably excited by the two-dimensional RF pulse. Note the small curved section at the upper end caused by arch flow not aligned with velocity encoding.

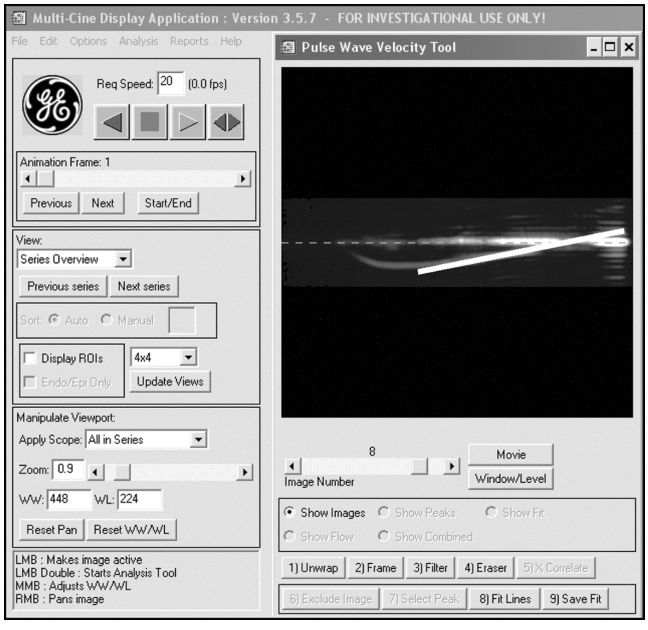

Figure 3. Screen capture of CineTool application (GE Global Research, Schenectady, NY, USA). Pulse wave travels from left to right in series of frames. A line drawn on each frame crosses the zero velocity line, allowing calculation of the pulse wave velocity.

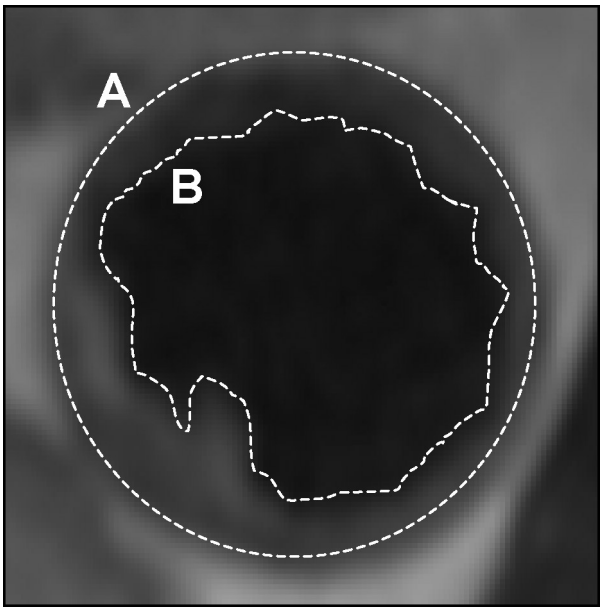

Figure 4. Dual inversion recovery fast spin echo image of descending thoracic aorta. The images with the greatest amount of plaque in each of the 3 aortic segments were selected. Aortic plaque area was calculated by subtracting endovascular area (B) from perivascular area (A).

Table 3. Aortic measurements

Patients with Aortic Plaque	Plaque Area: Proximal (mm^2)	Plaque Area: Mid (mm^2)	Plaque Area: Distal (mm^2)	Total Plaque Area (mm^2)	Aortic Diameter (mm)	Patient Height (cm)	Indexed Diameter/ Patient Height
1	83.78	98.72	0	182.5	26.67	170.2	0.0156
2	33.79	40.3	45.37	119.46	21.77	172.7	0.0126
3	30.96	70.16	0	101.12	23.13	165.1	0.0140
4	21.5	29.88	41.25	92.63	21.42	160	0.01339
5	63.79	32.8	18.59	115.18	24.06	165.1	0.01457
6	32.8	18.59	60.17	111.56	24.28	193	0.01258
7	59.77	26.09	35.1	120.96	21.63	154.9	0.01396
8	37.93	129.47	53.87	221.27	22.90	162.6	0.01408
9	101.46	112.97	74.4	288.83	28.05	177.8	0.01577
10	62.79	109.51	35.86	208.16	26.37	182.9	0.01441
11	55.59	99.56	44.66	199.81	25.17	188	0.01338
12	52.99	198.23	108.28	359.5	29.365	180.3	0.01628
13	57.58	46.1	47.07	150.75	22.70	162.6	0.01396
14	31.4	39.21	45.93	116.54	19.85	165.1	0.01202
15	114.46	192.59	140.29	447.34	25.04	170.18	0.01471
16	54.54	24.16	27.54	106.24	20.59	162.56	0.01267

Quantification of plaque area and presence of vessel remodeling

The descending thoracic aorta was divided into 3 sections: proximal, mid and distal. The single axial image demonstrating the greatest amount of plaque in each section was selected for aortic plaque area quantification. Black blood images of the selected axial slice of aorta were loaded into the CineTool viewer, allowing measurement of an area of interest. Plaque area was calculated as the difference between the areas enclosed by the endovascular and perivascular contours (Fig. 4). Aortic plaque score was calculated as the sum of the 3 sections and the perivascular aortic diameter was measured in the one segment with the largest plaque area and indexed to patient height in centimeters (Table 3).

CT protocol

Cardiovascular CT examination consisted of a noncontrast scan covering the heart obtained with a multi-detector scanner (Lightspeed16, GE Healthcare) to obtain a calcium (Ca) score.

STATISTICS

The mean PWV was compared with the presence of aortic plaque as a binary variable (0 = no plaque; 1 = plaque present) using a t-test. Regression analysis was performed in the aortic plaque subgroup with total plaque area from all 3 aortic segments as the independent variable, and PWV as the dependent variable.

Linear regression was then used to determine whether PP, CRP, HDL, LDL Ca Score, and plaque area could be used to predict PWV. Again, aortic plaque was assigned a binary variable (1 = presence of plaque and 0 = absence of plaque). R^2 and p values from the univariate regression were analyzed to check for presence of relationship between the dependent and independent variables. For the model building, forward selection process was used, beginning with the univariate relationship of each predictor variable against the outcome variable. Adjusted R^2 was used to determine which variable would be selected in the model. The variable that yielded the highest adjusted R^2 was selected in the model. Once the appropriate univariate model was identified, the appropriate multivariate model was found by adding individual variables to the univariate model.

Total plaque area from all 3 segments was the independent variable in another regression, with indexed perivascular aortic diameter as the dependent variable. All statistics were analyzed using SAS software (SAS Institute, Cary, North Carolina, USA).

RESULTS

Mean PWV was not significantly different between the groups with and without measureable aortic plaque ($p = 0.55$). In the aortic plaque subgroup (15 patients), there was no significant correlation with PWV and total plaque area in all 3 aortic segments ($p = 0.57$).

The results of the univariate regression show a significant correlation between PWV and pulse pressure (PP) (R^2 0.38 and $p = 0.0003$) (Table 4); there was no significant correlation between PWV and any other predictor variables (Figs. 5–6). Predictor variables were regressed against the outcome variable to find the best univariate model and the assumptions were checked. PP was found to have the highest adjusted R^2 (0.36). When the univariate model was found, each of the remaining predictor

Table 4. Results of univariate regression

Predictor Variable	R^2	adjusted R^2	P > F
Pulse pressure	0.3794	0.3572	0.0003
CRP	0.0060	−0.0295	0.6834
HDL	0.0604	0.0268	0.1906
LDL	0.0313	−0.0033	0.3496
Ca score	0.0122	−0.0231	0.5616
Presence of Ao plaque	0.0093	−0.0168	0.5539

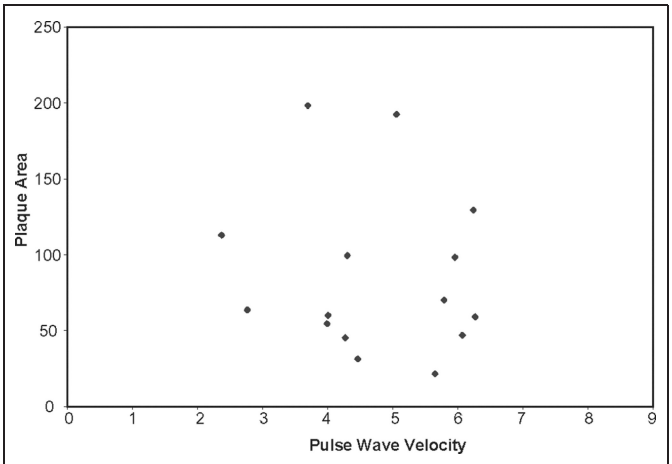

Figure 5. Graph of pulse wave velocity versus plaque area. There was no significant correlation between these measurements.

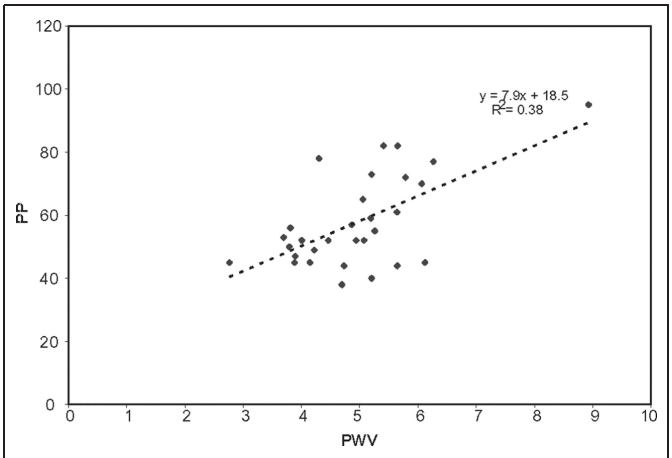

Figure 6. Pulse wave velocity (PWV) data plotted versus pulse pressure (PP) indicates validity of MRI PWV measurement.

variables were added to the model one at a time. The presence of aortic plaque was observed to yield the highest adjusted R^2 (0.44), so plaque area was added to the model. When this procedure was repeated, only Ca score yielded the highest adjusted R^2 (0.45); but the p value for t-statistics was not significant (0.30) (Table 5). Total plaque area demonstrated a positive correlation with indexed aortic diameter ($R^2 = 0.42$, $p = 0.0066$) (Fig. 7).

DISCUSSION

This study represents the first investigation of a cylindrical excitation MR technique measuring pulse wave velocity as part of a comprehensive examination of the aorta in patients with varying degrees of coronary artery atherosclerosis. Mean PWV did not differ significantly between patients with versus those without measureable aortic plaque, nor did PWV correlate significantly with extent of CAD. Also, in the plaque subgroup, PWV did not correlate with total measured aortic plaque area. PWV did show a significant relationship with brachial pulse pressure and the presence of aortic plaque when assessed as cumulative variables. Pulse pressure is directly reflective of vessel wall stiffness and is a highly significant prognostic indicator, with high values showing correlation with increased risk of adverse cardiovascular end points as well as total mortality (23, 24).

These data also show evidence of positive arterial remodeling, with a larger aortic diameter indexed to height in those patients with significant plaque burden. Remodeling is a known compensatory phenomenon, seen throughout the arterial system, and is associated with vessel inflammation and increased protease activity (25). It is not known if the presence of remodeling has a distinct relationship with cardiovascular morbidity or mortality.

Limitations of this study include the small sample size, although we feel the distribution of coronary disease reflects the population presenting for noninvasive evaluation in clinical practice. There was an absence of selection bias as these were patients chosen by cardiologists as having a higher than normal pretest likelihood of having obstructive CAD. A larger cohort would perhaps demonstrate a significant relationship between aortic plaque burden and aortic stiffness measured by PWV, as aortic plaque should diminish the elasticity of the aorta.

In addition, there are likely significant effects of medications on aortic physiology and PWV that were not taken into account in this study. Antihypertensives, in particular beta-receptor antagonists, calcium channel antagonists and

Table 5. Additive model of univariate regression

		Number of Variables in the Model		
		1	2	3
Predictor Variable	DF	Adj. R^2	Adj. R^2	Adj. R^2
Pulse pressure	1	0.3572	—	—
CRP	1	−0.0295	0.3360	0.4285
HDL	1	0.0268	0.3393	0.4241
LDL	1	−0.0033	0.3360	0.4379
Ca score	1	−0.0231	0.3446	0.4469
Presence of Ao plaque	1	−0.0168	0.4443	—

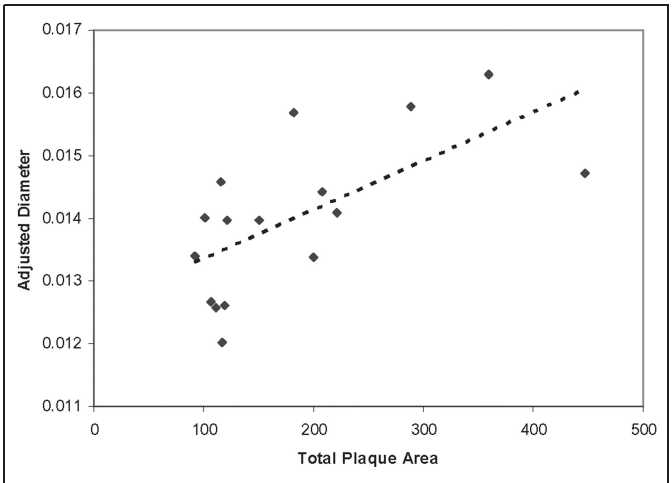

Figure 7. Total area of plaque (mm^2) vs. adjusted diameter (aortic diameter in cm/patient height in cm).

angiotensin-converting enzyme inhibitors, have been shown to increase aortic compliance and affect PWV in normal patients, patients with hypertension, and patients with Marfan Syndrome (26, 27).

The reason for the lack of association with CRP and aortic PWV is unclear. Prior comparisons of carotid and aortic arterial physiology and CRP have demonstrated significantly higher values in patients with visualized atheroma (28). There was a large variability of measured CRP in our patient cohort that could be secondary to a number of causes. CRP has a known association with elevated body mass index, cigarette smoking, diabetes, estrogen/progesterone use, chronic infections and rheumatologic disease (29); none of which were controlled for in this group of subjects. The mean CRP was 5.47 mg/L, which is above the level of 3.0 mg/L currently considered high relative risk for cardiovascular disease. If patients with extremely high levels of CRP ($\geq$10 mg/L) are excluded (n = 5) in calculation, the remaining 25 patients have a mean CRP of 2.9 mg/L.

In summary, this first *in vivo* MR-based evaluation of aortic pulse wave velocity in relation to aortic atherosclerosis in patients with risk factors and clinical suspicion for coronary artery disease showed correlation of PWV with pulse pressure, a known measure of aortic stiffness. While this provided validity of the technique, we did not find association with aortic plaque or serum markers of atherosclerosis. The validation of this technique supports further study in a larger patient cohort with additional measures of endothelial function and coronary artery disease.

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