Original Article

Aortic Stiffness is Increased in Positive Adenosine Stress Cardiac Magnetic Resonance

Yodying Kaolawanich MD[1], Thananya Boonyasirinant MD[1]

[1] Division of Cardiology, Department of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Arterial stiffness is an independent predictor as well as a poor prognosticator for cardiovascular disease. Although abnormal arterial stiffness has been established in patients with ischemic cardiomyopathy, there are limited data on patients with less severe coronary artery disease. Adenosine stress cardiac magnetic resonance (CMR) imaging is a non-invasive test for the diagnosis of coronary artery disease.

Objective: To compare aortic stiffness of patients with positive and negative adenosine stress CMR.

Materials and Methods: Prospectively, 180 patients who were undergoing adenosine stress CMR were consecutively enrolled. Using CMR, aortic stiffness was measured as pulse wave velocity (PWV) by distance propagation divided by time delay between mid-ascending and mid-descending thoracic aorta. Adenosine stress CMR was evaluated as positive or negative along with the number of ischemic segments. The mean PWV of two groups was determined.

Results: The mean age was 66.8±10.8 years and 56.7% were female. Adenosine stress CMR was positive in 51 patients (28.3%). The mean PWV of all patients was 9.77±4.29 m/second and the mean ischemic segments from positive adenosine stress CMR patients was 6.35±3.81 segments. The mean PWV of positive adenosine stress CMR group was higher than negative adenosine stress CMR group significantly (11.13±5.40 m/second versus 9.23±3.65 m/second, *p*-value 0.01). As for the secondary outcomes, no correlation was found between PWV and the numbers of ischemic segments (r = 0.18, *p*-value 0.21). Nevertheless, after adjustment of other risk factors, PWV remained a significant predictor of myocardial ischemia (*p*-value 0.02, 95% CI 1.02 to 1.20).

Conclusion: Aortic stiffness measured by PWV is associated with positive adenosine stress CMR in patients with known or suspected coronary artery disease. PWV may become an integral part of coronary artery risk stratification and may affect future treatment.

Keywords: Aortic stiffness, Myocardial ischemia, Adenosine stress cardiac magnetic resonance

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Arterial stiffness describes a reduction of normal arterial compliance in response to pressure changes. It is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall. Increased arterial stiffness reflects arterial aging and damage. It has emerged as an important risk factor for cardiovascular disease.

From previous studies, a relationship between arterial stiffness and cardiovascular disease has been observed. Arterial stiffness is positively associated with hypertension[1,2], diabetes mellitus[3], coronary artery disease[4], atrial fibrillation[5], heart failure[6], stroke[7], and end-stage renal disease[8]. It is an independent predictor of all-cause and cardiovascular mortality[4].

Arterial stiffness can be assessed using several non-invasive and invasive methods, such as pressure wave form, Doppler ultrasound, computed tomography, and cardiac magnetic resonance (CMR). Doppler ultrasound is frequently used but CMR has several advantages for aortic stiffness measurement. In particular, it provides a high resolution, cross-sectional image. It can directly measure the length of the aorta without geometrical assumption, it has no ionizing radiation, and it can evaluate other aspects of the aorta, e.g., aortic wall strain and deformation[9,10].

Coronary artery disease is a leading cause of mortality and disability. Adenosine stress CMR is a non-invasive test to diagnose coronary artery disease. Adenosine stress CMR has several advantages, namely, high spatial resolution, no ionizing radiation, and reproducibility. The high accuracy of adenosine stress CMR in the diagnosis of coronary artery disease has been observed in several prior studies, with a sensitivity and specificity of 91% and 81%, respectively[11].

Some studies have established a correlation between aortic stiffness and coronary artery disease[12-14].

Correspondence to:

Boonyasirinant T. Division of Cardiology, Department of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: +66-2-4196104 ext. 5, **Fax**: +66-2-4127412
Email: drthananyaa@yahoo.com

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However, there are limited data between aortic stiffness and adenosine stress CMR. The aim of this study was to compare aortic stiffness measured by pulse wave velocity (PWV) in patients with positive adenosine stress CMR and negative adenosine stress CMR.

Materials and Methods

This was a prospective, single-institution study. One hundred eighty patients undergoing adenosine stress CMR for the diagnosis and risk stratification of ischemic heart disease at Siriraj Hospital, Bangkok, Thailand between July 2015 and January 2016 were consecutively enrolled. The inclusion criteria were male or female patients above 18 years of age who were known or suspected coronary artery disease undergoing adenosine stress CMR and aortic stiffness measured by PWV. The exclusion criteria were an inability to perform due to ferromagnetic prosthesis, a magnetic resonance imaging (MRI) non-conditional cardiovascular implantable electronic device (CIED), an incomplete CMR examination, claustrophobia, pregnancy, and a disease of the aorta involving PWV measurement, e.g., aortic aneurysm.

The present study's protocol was approved by the Institutional Ethics Committee, and each subject gave written informed consent to participate.

Demographic data, including cardiovascular risk factors were obtained. The primary objective was to compare means of the PWV between patients with positive adenosine stress CMR and negative adenosine stress CMR. The secondary objective was to assess the correlation between PWV and the number of ischemic segments from positive adenosine stress CMR group.

CMR scanning[15]

A CMR study was performed using a 1.5 T Philips Achieva XR scanner (Philips Medical Systems, Best, the Netherlands). After taking a scout image to locate the cardiac axis, an electrocardiogram (ECG), triggered breath, hold black blood, single-shot sequence was acquired in the axial alignment for 30 slides, covering the whole heart and the thoracic aorta. The scanning parameters were echo time (TE) 24 milliseconds, repetitive time (TR) 1,400 milliseconds, refocusing flip angle 90°, field of view in x axis (FOVx) 240 to 360 mm, field of view in y axis (FOVy) 250 to 300 mm, slide thickness 8 mm, typical matrix size 124×192 mm, and typical acquired spatial resolution 2.4×1.8 mm.

PWV was assessed with the velocity encoded MRI (VE-MRI) technique as the through plane flow in the mid-ascending and descending thoracic aorta at the level of pulmonary trunk. Imaging parameters were TE 3.1 milliseconds, TR 5.3 milliseconds, refocusing flip angle 12°, FOVx 250 mm, FOVy 210 mm, slide thickness 8 mm, typical matrix size 128×256 mm, typical acquired spatial resolution 2.3×1.3 mm, temporal resolution 10 to 12 milliseconds, and velocity encoding 170 cm/second.

A myocardial first-pass perfusion study was determined immediately after an injection of 0.05 mmol/kg of gadolinium contrast agent (Magnevist; Bayer Schering Pharma, Berlin, Germany) beginning after 3-minutes of adenosine 0.56 mg/kg. The three short-axis slices of apical, mid, and basal left ventricular levels were acquired using an ECG-triggered, steady-state free precession (SSFP), inversion recovery, single-shot, turbo gradient-echo sequence. The image parameters were TE 1.32 milliseconds, TR 2.6 milliseconds, refocusing flip angle 50°, slide thickness; 8 mm, field of view (FOV) 270 mm, reconstructed FOV (RFOV) 320 mm, typical matrix size 256×240 mm, and reconstructed spatial resolution 1.52×1.21 mm. ECG monitoring was continuous, and 1-minute interval blood-pressure and oxygen-saturation monitoring were evaluated.

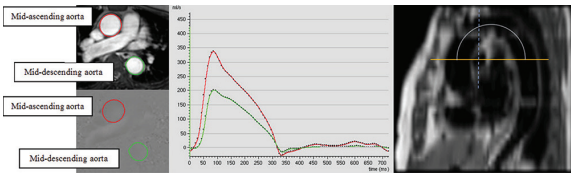
CMR analysis: PWV analysis

Cardiovascular imaging software (Extended Brilliance Workspace) was employed for the PWV analysis. The outlines of the mid-ascending and descending thoracic aorta were manually drawn to achieve the flow (m/second) in these two locations throughout all phases of the cardiac cycle. The corresponding flow time curve was generated. The arrival time of the pulse wave was measured as the point of interception of the linear extrapolation of the baseline and steep early systolic stage. The aortic path length was established by multiplanar reconstruction of the axial half-Fourier acquisition from steady state images. Regarding the reconstructed sagittal view, the path length was depicted as the centerline from the levels of the mid-ascending aorta to the mid-descending thoracic aorta, corresponding to the same level as the VE-MRI image was obtained (Figure 1).

The PWV between the mid-ascending and descending thoracic aorta was calculated with this formula:

$PWV = \Delta x / \Delta T$ (m/second)

Where Δx reflected the length of the aortic path between the mid-ascending and mid-descending thoracic aorta, and ΔT represented the time delay between the arrival of the foot of the pulse wave at



Left: Through-plane VE-MRI at mid-ascending (red circles) and mid-descending thoracic aorta (green circles)

Middle: Corresponding flow measurement at mid-ascending (red/above line) and mid-descending thoracic aorta (green/below line)

Right: Measurement of aortic path length from a multiplanar reconstructed oblique sagittal view

Figure 1. Measurement of time delay between pulse waves and aortic path length.

these two corresponding levels.

CMR analysis: adenosine stress test analysis[16]

CMR images in the short-axis view were classified as the basal, mid, or apical level of the left ventricle. The 16 myocardial segments for perfusion analysis were defined according to the standard recommendation of the American Heart Association (AHA), with the exclusion of segment 17. A myocardial perfusion defect was defined as positive when the perfusion delay persisted for at least five consecutive phases in at least one segment during the peak myocardial enhancement. The analyses were assessed by two experienced readers. If the results disagreed, a third experienced reader also performed the analysis.

Intra- and inter-observer variability

To assess the inter- and intra-observer variability, 20 patients were randomly selected to measure inter-observer and intra-observer variability by the same observer four weeks after an initial analysis, and by the second independent observer who was blinded to the initial results.

Statistical analysis

The statistical analyses were performed by SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, Ill., USA). Continuous data were expressed as mean ± standard deviation (SD). Discrete data were presented as numbers and percentages. Pearson's correlation coefficient was used to compare two continuous variables. The association of normally distributed variables was determined with Student's t-test to compare the mean between the two groups, and the association of the non-normally distributed variables with the Mann-Whitney U-test. A *p*-value smaller than 0.05 was considered statistically significant. Patient characteristics, underlying diseases and PWV were evaluated in univariate and multivariate analyses by binary logistic regression analysis (enter method). Intraclass correlation was used to evaluate intra- and inter-observer variability.

Results

Patient characteristics

Patient characteristics and CMR parameters are shown in Tables 1 and 2, respectively. The authors studied 78 men (43.3%) and 102 women (56.7%), with an average age of 66.8±10.6 years. Nineteen patients (10.6%) with known coronary artery disease were included. The left ventricular systolic function (LVEF) was preserved, the average LVEF was 66.66±14.90%.

PWV analysis

The average PWV was 9.77±4.29 m/second. PWV was associated with age (r = 0.43, *p*-value <0.001), body mass index (r = 0.19, *p*-value 0.01), hypertension

Table 1. Clinical characteristics of the study patients (n = 180)

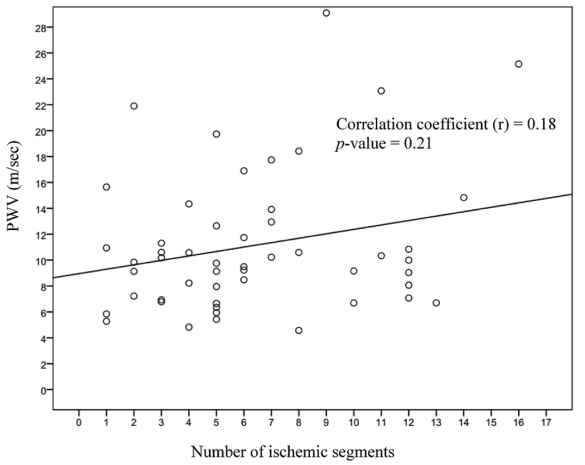
Variables	n (%) or mean ± SD
Age (year)	66.8±10.6
Men/women	78 (43.3)/102 (56.7)
Height (cm)	158.6±8.5
Weight (kg)	65.8±13
Body mass index (kg/m^2)	26.1±4.4
Systolic blood pressure (mmHg)	132.9±21.5
Diastolic blood pressure (mmHg)	68.9±11.5
Pulse pressure (mmHg)	68.8±20.9
Heart rate (bpm)	76.5±13.2
Smoking	11 (6.1)
Underlying disease	
Hypertension	134 (74.4)
Diabetes mellitus	70 (38.9)
Dyslipidemia	130 (72.2)
Coronary artery disease	19 (10.6)
Stroke	5 (2.8)
Medications	
Beta blocker	86 (47.8)
Calcium channel blocker	54 (30.0)
Angiotensin-converting enzyme inhibitor	74 (41.1)
Statin	97 (53.9)

SD = standard deviation

Table 2. Cardiac magnetic resonance parameters (n = 180)

Parameters	Mean ± SD
Left ventricular end-diastolic volume (LVEDV) (ml)	119.05±32.04
Left ventricular end-systolic volume (LVESV) (ml)	49.19±47.50
Left ventricular ejection fraction (LVEF) (%)	66.66±14.90
Pulse wave velocity (m/second)	9.77±4.29
Numbers of ischemic segments from adenosine stress CMR (n = 51)	6.35±3.81

SD = standard deviation; CMR = cardiac magnetic resonance



PWV, pulse wave velocity

Figure 2. Pearson's correlation of PWV and number of ischemic segments from positive adenosine stress CMR (n = 51).

(10.6±4.55 m/second versus 7.35±2.04 m/second, *p*-value <0.001), and LVEF (r = -0.23, *p*-value 0.002).

Adenosine stress CMR analysis

Adenosine stress CMR was positive in 51 patients (28.3%), and the mean number of ischemic segments from positive adenosine stress CMR patients was 6.35±3.81 segments.

Association between PWV and positive adenosine stress CMR

The mean PWV was higher significantly in patients with positive adenosine stress CMR group compared with negative adenosine stress CMR group (11.13±5.40 m/second versus 9.23±3.65 m/second, *p*-value 0.01, 95% CI 1.02 to 1.19).

As for the secondary outcomes, there was no correlation between PWV and the number of ischemic segments (r = 0.18, *p*-value 0.21) (Figure 2).

Predictors of myocardial ischemia

As demonstrated in Table 3, male gender, hypertension, known coronary artery disease and PWV were identified as potential predictors of myocardial ischemia from the univariate analysis (using *p*-value smaller than 0.20). In the multivariate analysis, only male gender and PWV remained significant predictors of myocardial ischemia.

Intra- and inter-observer variability

There was excellent intra-observer and inter-observer reproducibility for the PWV measurements. The mean PWV ± SD values were 8.86±2.53 m/second and 8.72±2.59 m/second (r = 0.99, *p*-value <0.001) for the first observer in the initial analysis and four weeks later, respectively, and 8.57±2.56 m/second (r = 0.98, *p*-value <0.001) for the second observer in the initial analysis.

Discussion

This is the first study to demonstrate a significant association between aortic stiffness measured by PWV and positive adenosine stress CMR. Furthermore, after adjustment for other risk factors, PWV remained a significant predictor of myocardial ischemia. Abnormal aortic stiffness may be a novel add-on parameter for risk stratification and may affect the future treatment of cardiovascular disease.

Arterial stiffness

Increasing arterial stiffness occurs as a consequence

Table 3. Predictors of myocardial ischemia

Clinical characteristic	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (year)	1.01 (0.98 to 1.05)	0.41	-	-
Male gender	2.15 (1.11 to 4.16)	0.02	2.54 (1.26 to 5.10)	0.01
Body mass index (kg/m^2)	1.03 (0.96 to 1.10)	0.48	-	-
Hypertension	1.88 (0.83 to 4.24)	0.13	1.39 (0.58 to 3.36)	0.46
Diabetes mellitus	1.28 (0.66 to 2.48)	0.46	-	-
Dyslipidemia	1.18 (0.56 to 2.46)	0.67	-	-
Coronary artery disease	2.55 (0.97 to 6.71)	0.06	2.37 (0.85 to 6.60)	0.10
Stroke	0.63 (0.07 to 5.73)	0.68	-	-
Smoking	2.23 (0.65 to 7.66)	0.20	-	-
PWV (m/second)	1.10 (1.02 to 1.19)	0.01	1.11 (1.02 to 1.20)	0.02

CI = confidence interval; PWV = pulse wave velocity

of aging and various pathological states such as atherosclerosis. Previous studies have found that arterial stiffness is significantly associated with various cardiovascular diseases, such as coronary artery disease[4], heart failure[6], atrial fibrillation[5], stroke[7], end-stage renal failure[8], and increased cardiovascular mortality[4].

Arterial stiffness can be assessed by several methods. Measurement of PWV using CMR in the present study is a preferred method for the evaluation of arterial stiffness for several reasons. Firstly, it provides high resolution images without ionizing radiation. It can also assess the pulse wave at the ascending and descending thoracic aorta at the same time, and then attenuate the error from an irregular heart rate during the measurement. Moreover, it can measure the distance between the ascending and descending thoracic aorta without geometrical assumption, unlike Doppler ultrasound.

Arterial stiffness and relationship to coronary artery disease

The relationship of arterial stiffness and myocardial ischemia is explained by hemodynamic and biochemical aspects. Arterial stiffness causes the early arrival of wave reflections in the systolic instead of the diastolic phase, and thus increases the systolic afterload while reducing the diastolic coronary perfusion pressure. Abnormal collagen turnover, cytokines, and metalloproteinase activity are common biochemical links between arterial stiffness and myocardial dysfunction[17].

Recent studies on arterial stiffness have found that abnormal arterial stiffness plays a role in the varied spectrum of coronary artery disease when evaluated by invasive and non-invasive methods. As for asymptomatic patients with cardiovascular risks, one study of 160 asymptomatic diabetic patients showed a strongly positive correlation of aortic stiffness measured by applanation tonometry and severe myocardial perfusion imaging defects from Single-photon emission computed tomography[14].

In patients with suspected stable coronary artery disease, some studies have reported that aortic stiffness is associated with the presence and the extent of coronary artery disease. A cross-sectional study of 92 patients with suspected coronary artery disease undergoing coronary angiography found there was a significant correlation between aortic stiffness using PWV from the left carotid-right femoral arteries by an automated machine and severity of coronary artery disease from coronary angiography[18]. Another study using coronary computed tomography angiography also demonstrated an association of PWV with the extent of coronary artery disease[13].

The present study has some advantages over previous studies. Firstly, PWV measurement using CMR can assess the aortic length accurately without geometrical assumption, unlike Doppler ultrasound. Moreover, by using CMR, aortic stiffness and myocardial ischemia can be evaluated simultaneously as a one-stop service. Finally, CMR can evaluate other aspects of coronary artery disease, such as myocardial viability or intracardiac thrombus.

With regard to the primary objective of our study, a significant association was found between aortic stiffness measured as PWV and positive adenosine stress CMR. Moreover, PWV was associated with age, body mass index, hypertension, and LVEF, which was consistent with previous studies[19,20].

However, in the case of the secondary outcomes, there was no correlation between PWV and the number of ischemic segments. This may be due to two reasons. Firstly, the patients had less ischemic severity of coronary artery disease than in previous studies. Furthermore, the left ventricular systolic function in the present study was preserved (the mean LVEF was 66.66±14.90%).

Conclusion

There was a significant association between aortic stiffness and positive adenosine stress CMR. This novel parameter may become an integrative risk stratification for coronary artery disease patients, and treatment with drugs lowering aortic stiffness may reduce cardiovascular events in the future.

Clinical implications and perspectives

A wider variety of severe diseases should be included to demonstrate the positive correlation of aortic stiffness with the severity of myocardial ischemia.

As aortic stiffness can be detected before the appearance of clinically apparent cardiovascular disease, it is likely that, in the future, measurement of arterial stiffness will become an increasingly important part of the cardiovascular risk assessment. It may possibly also improve the monitoring of therapy. This aspect warrants further investigation.

What is already known on this topic?

Aortic stiffness is an independent predictor of

cardiovascular diseases, including ischemic heart disease and increased cardiovascular mortality.

What this study adds?

There is a significant association between aortic stiffness assessed by CMR and positive adenosine stress CMR in patients with known or suspected coronary artery disease.

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Potential conflicts of interest

The authors declare no conflict of interest.

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