Impact of aortic stiffness by velocity-encoded magnetic resonance imaging on late gadolinium enhancement to predict cardiovascular events

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ABSTRACT

Background: Increased aortic stiffness has been established as a marker in various cardiovascular diseases. Previous reports revealed a significant correlation between aortic stiffness and myocardial scarring using the late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR). However, prognostic data concerning aortic stiffness combining myocardial scarring remains limited.
Method: A total of 402 patients who had undergone clinical CMR for the evaluation of cardiac function, LGE, and aortic pulse wave velocity (PWV) using velocity encoded-CMR (VE-CMR) were included. Patients were classified into 4 groups using mean PWV and the presence of LGE as elevated or non-elevated PWV and positive or negative LGE. Patients received follow-up for major adverse cardiovascular events (MACE) comprising cardiovascular death, non-fatal myocardial infarction, hospitalization for heart failure, coronary revascularization, and ischemic stroke. Predictors of MACE and hard cardiac events (cardiovascular death or non-fatal myocardial infarction) were evaluated.
Results: During the average follow-up period of 47.7 months, 58 MACE occurred. Patients who had elevated PWV and positive LGE experienced the highest rate of MACE compared to the group with non-elevated PWV and negative LGE (HR 11.90, p < 0.001). Among patients who had LGE, those who had elevated PWV experienced a 2.4-times higher rate of MACE compared to those who had non-elevated PWV. Multivariate analysis showed that PWV and LGE were independent predictors of MACE and hard cardiac events. PWV had excellent intra- and inter-observer reproducibility (intra-: ICC = 0.98, p < 0.001, inter-: ICC = 0.97, p < 0.001).
Conclusion: Aortic stiffness using VE-CMR had prognostic value to predict cardiovascular events, with the added benefits of LGE.
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1. Introduction

Arterial stiffness is one of the earliest detectable indicators of adverse structural and functional changes in the vessel wall. Various studies concerning a range of disease-specific and community-based cohorts have shown that increased arterial stiffness can be linked to a heightened risk for a first or repeated major cardiovascular event [1–3]. Arterial stiffness has been proven as an independent predictor when evaluated with traditional risk factors for cardiovascular morbidity and mortality [3–6].

Measurements for aortic stiffness can be undertaken using several methods such as carotid-femoral pulse wave velocity (PWV) with a tonometer, ultrasound, or cardiovascular magnetic resonance (CMR). Published research shows extensive use of a tonometer device; however, CMR is often the preferred method for several reasons. CMR-based PWV has the advantage of being able to assess almost any vessel while providing more accurate aortic distance estimates without geometric assumption. CMR has also been well-validated compared to invasive pressure recordings, with very high reproducibility [7].

Late gadolinium enhancement (LGE) is a unique CMR technique to detect and characterize myocardial scarring and fibrosis. The presence of LGE provides prognostic significance in various types of cardiomyopathy [8–10]. Previous studies revealed the association between aortic stiffness and myocardial remodeling, including increased left ventricular (LV) mass and myocardial scarring [11,12]. CMR can evaluate aortic stiffness and LGE in a single examination. However, no data exists for the prognosis of combined aortic stiffness and LGE.

This study sought to determine whether aortic stiffness assessed by CMR could add prognostic value to LGE for the prediction of cardiovascular events.

2. Methods

2.1. Study population

This was a retrospective, single-institution study. Males and females aged 18 years or older who were referred for clinical CMR to assess cardiac function, PWV, and LGE between November 2010 and January 2014 were enrolled. The main reasons for a scan were assessment of coronary artery disease (CAD)/chronic myocardial infarction, evaluation of heart failure/cardiomyopathy, and vascular study. In our institution, aortic stiffness measured by PWV has been routinely incorporated in the comprehensive CMR protocol. Detailed medical history was recorded on the same day as the CMR examination. History of hypertension, diabetes mellitus, hyperlipidemia, stable CAD, and stroke were defined by recent guidelines [13–16].

Exclusion criteria included (1) incomplete CMR examination, (2) patients who had diseases of the aorta involving PWV measurement (e.g. an aortic aneurysm), (3) poor CMR image quality, and (4) patients lacking follow-up data. The institutional ethics committee approved this retrospective study and waived the need for additional written informed consent.

2.2. CMR image acquisition

The CMR study was performed to assess cardiac function, PWV, and LGE using a 1.5 T Philips Achieva XR scanner (Philips Medical Systems, Best, The Netherlands). After a scout image to locate the cardiac axis, an electrocardiogram (ECG)-triggered, breath-hold, black blood, single shot sequence was acquired in the axial orientation covered the whole heart and thoracic aorta. The parameters were echo time (TE) 24 ms (ms), repetition time (TR) 1,400 ms, refocusing flip angle 90 degree, field of view (FOV) in × axis 240–360 mm, FOV in y axis 250–300 mm, slide thickness 8 mm, acquisition voxel size 1.75 × 1.75 mm, and reconstructed voxel size 0.64 × 0.64 mm.

Cardiac functional study was performed using a steady state free precession (SSFP) technique in a vertical long axis, 2-chamber, 4-chamber, and multiple slice short axis views. The parameters were TE 1.8 ms, TR 3.7 ms, number of excitations 2, FOV 390 × 312 mm, matrix 256 × 240, reconstruction pixel 1.52 × 1.21, slice thickness 8 mm, and flip angle 70 degree.

PWV images were acquired during the waiting period between the administration of gadolinium contrast and LGE imaging. The image was determined with the free-breathing, velocity-encoded CMR (VE-CMR) technique as the through-plane flow in the mid-ascending and mid-descending thoracic aorta at the level of the pulmonary trunk. The parameters were TE 3.1 ms, TR 5.3 ms, refocusing flip angle 12 degree, FOV 250 × 210 mm, slide thickness 8 mm, typical matrix size 2.0 × 2.0 mm, reconstructed spatial resolution 1.12 × 1.12 mm, temporal resolution 10–20 ms, and velocity encoding 170 cm/s.

LGE images were acquired approximately 10 min after the injection of gadolinium-based contrast agent using a segmented inversion-recovery gradient-echo inversion-recovery technique in identical views as the SSFP images. Parameters were TE 1.25 ms, TR 4.1 ms, flip angle 15 degree, FOV 303 × 384 mm, matrix 240 × 256, in-plane resolution 1.26 × 1.5 mm, slice thickness 8 mm, and 1.5 Sensitivity-Encoding factor.

2.3. Cardiac function analysis

All analyses were performed by 2 experienced readers; if the readers' evaluations were not in agreement, a third reader also performed an analysis. Image analysis was performed on an independent Easy Vision workstation. CMR images in the short-axis view were classified as the basal, mid, or apical part of the LV. Segmentation of each slice was performed according to the recommendations of the American Heart Association, excluding the true apex [17]. The left ventricular ejection fraction (LVEF) was assessed by using end-systolic and end-diastolic volume calculated from the multiple slice short-axis images. The wall motion of each myocardial segment was recorded as the presence or absence of abnormal wall motion. Wall motion score index was calculated from the average of wall motion grades from all segments using the standard scoring system [18].

2.4. PWV analysis

Dedicated cardiovascular imaging software was applied for PWV analysis. PWV analyses were performed independently from the functional study and LGE. Using the VE technique, the contours of the mid-ascending and mid-descending thoracic aorta were drawn manually to achieve the flow (m/s) at those 2 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 for the linear extrapolation of the baseline and the steep early systolic stage. Aortic path length was determined by multiplanar reconstruction of axial half-Fourier acquisition from the steady stage image. With regard to 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 obtained in the VE images.

The PWV between the mid-ascending and mid-descending thoracic aorta was calculated using the following formula:

$$PWV = \Delta \times /\Delta T \ (m/s)$$

Where $\Delta \times$ indicated 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 those two corresponding levels (Fig. 1).

2.5. LGE analysis

Sixteen myocardial segments were defined for LGE analysis [17]. LGE images were analyzed using visual assessment by the consensus of 2 CMR-trained physicians. LGE was considered present only if confirmed on both short-axis and matching long-axis myocardial locations. Types of LGE (CAD and non-CAD patterns) as well as the number of LGE segments were also recorded.

2.6. Intra- and Inter-Observer reproducibility of PWV measurement

Forty patients were randomly selected in order to measure the variability of the first observer 4 weeks after the initial analysis and
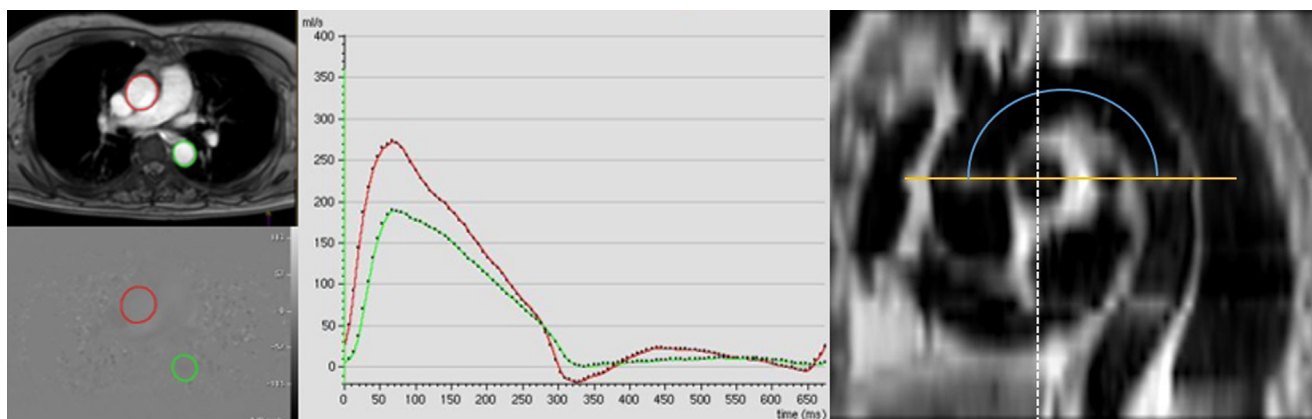
Fig. 1. Measurement of Time Delay between Pulse Waves and Aortic Path Length. Left: Through-plane VE-CMR at the mid-ascending (red circles) and mid-descending thoracic aorta (green circles). Middle: Corresponding flow measurement at the mid-ascending (red line) and mid-descending thoracic aorta (green line). Right: The measurement of aortic path length using a multiplanar reconstructed oblique sagittal view. VE-CMR = velocity-encoded cardiovascular magnetic resonance. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the variability of the second independent observer, who was blinded to the initial results.

2.7. Clinical Follow-Up

Based on the PWV and LGE results, patients were classified into 4 groups defined by elevated or non-elevated PWV (using mean PWV) and positive or negative LGE (group 1: non-elevated PWV with negative LGE, group 2: elevated PWV with negative LGE, group 3: non-elevated PWV with positive LGE, and group 4: elevated PWV with positive LGE).

Follow-up data for each group were collected from clinical visits and medical records. Patients received follow-up for major adverse cardiovascular events (MACE), defined as the composite outcomes of cardiovascular death, non-fatal myocardial infarction (MI), hospitalization for heart failure, coronary revascularization, and ischemic stroke. Cardiovascular death included death resulting from acute MI, heart failure, sudden cardiac death, stroke, or death due to complications from cardiovascular procedures [19].

CMR results may influence decisions regarding cardiovascular procedures such as percutaneous coronary intervention and coronary artery bypass surgery, leading to periprocedural events or death. Cardiovascular procedures that occurred within 6 months after the CMR study or periprocedural events that occurred during the same admission were not considered for analysis.

2.8. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA), with discrete data presented as numbers and percentages. Continuous data were expressed as mean ± standard deviation (SD) or median (25th to 75th percentile) if the data showed non-normal distribution. Continuous and categorical data were compared using Student's t-test and Fisher's exact test, respectively.

Kaplan-Meier event curves for the 4 groups of patients were constructed for MACE and compared by the log-rank test. To analyze the predictors of MACE and hard cardiac events (cardiovascular death or non-fatal MI), a Cox regression analysis was performed for the assessment of univariate predictors from the baseline characteristics, medications, and CMR parameters. Variables with p-value < 0.05 on univariate analysis were entered into a multivariate analysis to determine independent predictors for MACE and hard cardiac events. To assess the incremental prognostic values of significant predictors, global chi-square values were calculated

in hierarchical order after adding several predictors (clinical, clinical + LGE, and clinical + LGE + PWV). The intra- and inter-observer reproducibility of the PWV measurements were analyzed using the intraclass correlation coefficient (ICC) and Bland-Altman analysis.

The hazard ratios (HRs) and 95% confidence intervals (CIs) of the outcomes were calculated, with a p-value < 0.05 considered statistically significant.

3. Results

Four hundred and thirteen patients were enrolled in the study. We excluded patients with incomplete CMR examination (n = 1), patients who had an aortic aneurysm (n = 3), poor CMR image quality (n = 2) and patients who lacked follow-up data (n = 5). Thus, a total of 402 patients (208 men) were included in the final analysis. The average age was 68.3 years. The mean PWV was 12.01 m/s. Patients who had elevated PWV (PWV > 12.01 m/s) were older and had higher systolic blood pressure and pulse pressure. Patients who had elevated PWV also had a higher prevalence of hypertension and diabetes mellitus than those with non-elevated PWV. The average LVEF was 67.3%. LGE was detected in 88 patients (21.9%) with an average number of 4.4 LGE segments per patient. Among the 88 patients who had LGE, 79 had CAD pattern LGE (subendocardial and transmural LGE) and 9 had non-CAD pattern LGE.

There was no significant difference in left atrial (LA) diameter, LV mass index, the presence of wall motion abnormality, wall motion score index, the presence of LGE, and the type of LGE between the elevated and non-elevated PWV groups. Clinical characteristics and CMR variables of patients with elevated and non-elevated PWV are shown in Table 1.

3.1. Cardiovascular events

During the average follow-up period of 47.7 months, 58 MACE occurred. Table 2 shows all cardiovascular events during the follow-up. Patients who had non-elevated PWV with negative LGE (group 1) showed a significantly lower rate of MACE (1.37% per year). Using group 1 (non-elevated PWV with negative LGE) as the reference, patients who had elevated PWV and positive LGE (group 4) had the highest rates of MACE (HR 11.90, 95% CI 5.38–26.42, p-value < 0.001). Patients who had elevated PWV with negative LGE (group 2) and non-elevated PWV with positive LGE (group 3) also recorded significantly higher rates of MACE com-

Table 1
Baseline characteristics and CMR variables of patients with elevated and non-elevated PWV.

Variables	Total (n = 402)	Elevated PWV (n = 145)	Non-elevated PWV (n = 257)	p-value
Male gender	208 (51.7)	82 (56.6)	126 (49.0)	0.15
Age, years	68.3 ± 10.8	72.9 ± 9.1	65.7 ± 10.8	<0.001
Body mass index, kg/sqm	26.7 ± 4.2	26.6 ± 4.2	26.8 ± 4.1	0.63
Systolic BP, mmHg	136.8 ± 19.073.8 ± 11.8	142.1 ± 18.6	33.9 ± 18.7	<0.001
Diastolic BP, mmHg	63.1 ± 17.2	73.3 ± 12.3	74.1 ± 11.5	0.49
Pulse pressure, mmHg	77.3 ± 13.6	68.9 ± 16.8	59.8 ± 16.6	<0.001
Heart rate, beats/minute		78.3 ± 14.9	76.7 ± 12.7	0.26
Medical history				
Hypertension	345 (85.8)	134 (92.4)	211 (82.1)	0.004
Diabetes mellitus	219 (54.5)	95 (65.5)	124 (48.3)	0.001
Hyperlipidemia	279 (69.4)	103 (71.0)	176 (68.5)	0.59
Stable CAD	63 (15.7)	28 (19.3)	35 (13.6)	0.13
History of myocardial infarction	13 (3.2)	3 (2.1)	10 (3.9)	0.39
History of heart failure	34 (8.5)	13 (8.9)	21 (8.2)	0.78
Stroke	18 (4.5)	6 (4.1)	12 (4.7)	0.81
Medications				
ACEI or ARB	180 (44.8)	80 (55.2)	100 (38.9)	0.002
Antiplatelet	196 (48.8)	72 (49.6)	124 (48.3)	0.79
Beta blocker	194 (48.3)	73 (50.3)	121 (47.1)	0.53
Calcium channel blocker	128 (31.8)	51 (35.2)	77 (29.9)	0.28
Statin	204 (50.8)	79 (54.5)	125 (48.6)	0.26
CMR variables				
LA diameter, mm	33.4 ± 4.2	33.2 ± 4.3	33.6 ± 4.1	0.44
LV mass index, g/sqm	52.3 ± 17.4	51.6 ± 14.4	52.6 ± 18.9	0.58
LVEF, %	67.3 ± 14.1	69.7 ± 13.8	65.9 ± 13.9	0.008
Wall motion abnormality	88 (21.9)	29 (20.0)	59 (22.9)	0.49
Average wall motion score index	1.54 ± 0.43	1.50 ± 0.49	1.57 ± 0.39	0.31
Presence of LGE	88 (21.9)	34 (23.5)	54 (21.0)	0.57
CAD pattern LGE	79 (19.7)	32 (22.1)	47 (18.3)	0.36
Non-CAD pattern LGE	9 (2.2)	2 (1.4)	7 (2.7)	0.49
Average number of LGE segments	4.4 ± 2.8	4.1 ± 2.3	4.5 ± 3.1	0.64
PWV, m/s	12.01 ± 7.80	18.59 ± 9.75	8.31 ± 1.92	< 0.001

Values are number (percentages) or mean ± standard deviation. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; PWV = pulse wave velocity.

Table 2
Cardiovascular events during follow-up.

Cardiovascular events	Total (n = 402)	Elevated PWV(n = 145)	Non-elevated PWV (n = 257)	HR (95% CI)	p-value
Cardiovascular death	8 (2.0)	4 (2.8)	4 (1.6)	2.07 (0.52–8.29)	0.31
Non-fatal myocardial infarction	20 (5.0)	12 (8.3)	8 (3.1)	3.11 (1.27–7.63)	0.01
Hospitalization for heart failure	36 (9.0)	22 (15.2)	14 (5.5)	3.35 (1.71–6.56)	< 0.001
Coronary revascularization	11 (2.7)	6 (4.1)	5 (2.0)	2.50 (0.76–8.21)	0.13
Ischemic stroke	10 (2.5)	8 (5.5)	2 (0.8)	8.58 (1.82–40.47)	0.005

Values are number (percentages). CI = confidence interval; HR = hazard ratio; PWV = pulse wave velocity.

pared to the reference group (HR 3.61, p-value < 0.001 and HR 4.38, p-value < 0.001, respectively). Among patients who had positive LGE (groups 3 and 4), the elevated PWV group (group 4) had a significantly higher rate of MACE than those who had non-elevated PWV (group 3) (HR 2.39, 95% CI 1.09–5.25, p-value 0.03). Kaplan-Meier survival curves for MACE are shown in Fig. 2. Patients with CAD scarring also had a significantly higher rate of MACE and hard cardiac events than those without scar (HR 3.32; 95% CI 1.97–5.60; p-value < 0.001 for MACE and HR 4.45; 95% CI 1.99–9.91; p-value < 0.001 for hard cardiac events).

3.2. Univariate and multivariate analyses of MACE and hard cardiac events

Univariate and multivariable analysis of predictors for MACE and hard cardiac events are shown in Table 3 and 4. Age, history of heart failure, and CMR variables such as LA diameter, LV mass index, LVEF, wall motion abnormality, LGE, and PWV were predictors for MACE from univariate analysis. History of heart failure, history myocardial infarction, and similar CMR variables were

predictors of hard cardiac events from univariate analysis. Multivariable analysis revealed that LV mass index, LGE, and PWV were independent predictors of MACE and hard cardiac events. Other independent predictors for MACE were age and history of heart failure. Another independent predictor for hard cardiac events was history of myocardial infarction.

When the prognosis was assessed in a hierarchical manner (clinical, clinical + LGE, clinical + LGE + PWV), LGE and PWV showed a significant increment in global chi-square for the prediction of MACE (Fig. 3A) and hard cardiac events (Fig. 3B).

3.3. Reproducibility of PWV measurement

Excellent intra- and inter-observer reproducibility were demonstrated for PWV measurements by VE-CMR. In 40 randomly selected patients, the mean PWV ± SD values were 9.77 ± 2.88 m/s and 9.78 ± 2.70 m/s by the first observer in the initial analysis and 4 weeks later, respectively (intra-observer ICC = 0.98; p < 0.001). The mean PWV ± SD value was 9.85 ± 2.77 m/s for the second observer (inter-observer ICC = 0.97; p < 0.001). There was no signif-
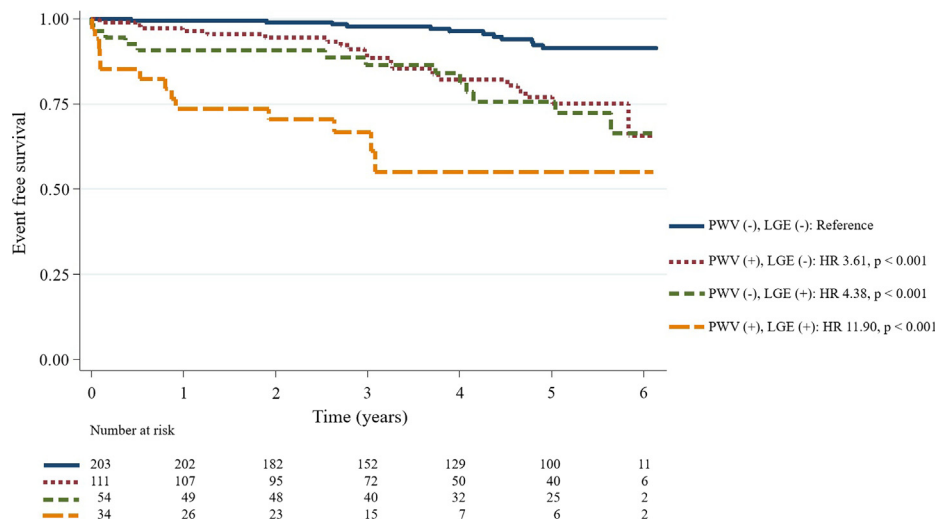
Fig. 2. Kaplan–Meier Event Curves for MACE. HR = hazard ratio; LGE = late gadolinium enhancement; PWV = pulse wave velocity.

Table 3
Univariate and multivariate analyses of variables for MACE.

Variables	Univariate analysis HR (95% CI)	p-value	Multivariate analysis HR (95% CI)	p-value
Male gender	1.21 (0.72–2.03)	0.46		
Age (per 10 years increment)	1.43 (1.10–1.86)	0.008	1.39 (1.06–1.82)	0.02
Systolic BP (per 10 mmHg increment)	1.003 (0.87–1.15)	0.96	3.09 (1.66–5.73)	< 0.001
Hypertension	2.49 (0.90–6.86)	0.08		
Diabetes mellitus	1.35 (0.80–2.27)	0.27		
Hyperlipidemia	1.08 (0.61–1.92)	0.80		
Stable coronary artery disease	1.62 (0.86–3.06)	0.14		
History of myocardial infarction	2.48 (0.90–6.86)	0.08		
History of heart failure	4.13 (2.29–7.44)	< 0.001		
Stroke	1.45 (0.52–4.01)	0.47		
ACEI or ARB	1.48 (0.89–2.49)	0.14		
Antiplatelet	1.21 (0.72–2.02)	0.47		
Beta blocker	1.06 (0.63–1.78)	0.82		
Calcium channel blocker	0.90 (0.51–1.58)	0.70		
Statin	1.26 (0.75–2.11)	0.38		
LA diameter (per 10 mm increment)	1.10 (1.04–1.17)	0.001		
LV mass index (per quartile)	1.66 (1.29–2.14)	< 0.001	1.34 (1.01–1.79)	0.04
LVEF (per 10% decrement)	1.38 (1.20–1.60)	< 0.001		
Wall motion abnormality	3.12 (1.86–5.23)	< 0.001		
Presence of LGE	3.49 (2.08–5.86)	< 0.001	2.74 (1.53–4.90)	0.001
PWV > 12.01 m/s	2.95 (1.75–4.98)	< 0.001	2.38 (1.36–4.17)	0.002

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CI = confidence interval; CMR = cardiovascular magnetic resonance; HR = hazard ratio; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; MACE = major cardiovascular events; PWV = pulse wave velocity.

icant bias (mean difference for intra-observer = 0.01 ± 0.53 m/s, p = 0.08, and for inter-observer = 0.07 ± 0.72 m/s, p = 0.66) (Fig. 4).

4. Discussion

Our results demonstrated that (1) aortic stiffness assessed by VE-CMR and LGE were independent predictors of MACE and hard cardiac events, (2) the combination of aortic stiffness and LGE provided a significant improvement in prognostic predictions, and (3) VE-CMR showed excellent reproducibility for aortic stiffness measurement.

Arterial stiffening is a hallmark of the aging process and atherosclerosis, with a reduction in arterial wall compliance and distensibility. Arterial stiffness is affected by complex interactions between vascular smooth muscle cells and the extracellular matrix containing elastin, collagen, and fibrillin fibers. Furthermore, numerous potential signaling events contribute to age- and disease-related arterial stiffness such as oxidative stress, inflammation, and decreased expression of endothelial nitric oxide synthase activity. Increased aortic stiffness has been established as contributory to various conditions such as aging, hypertension, diabetes mellitus, dyslipidemia, and smoking [20–27]. Similarly, patients in our study with elevated PWV were older and had a higher prevalence of cardiovascular risk factors including hypertension and diabetes mellitus.

Aortic stiffness is strongly associated with cardiovascular diseases. Recent studies have shown that aortic stiffness is positively correlated with CAD, stroke, heart failure, atrial fibrillation, and end-stage renal disease [3,4,28–30]. Aortic stiffness is also an independent predictor of vascular morbidity and mortality [3,4]. A meta-analysis of 17 longitudinal studies that evaluated PWV, with follow-up of 15,877 subjects for a mean of 7.7 years, found that an increase in PWV by 1 m/s corresponded to a risk increase of 15% in all-cause mortality [31].

Table 4
Univariate and multivariate analyses of variables for hard cardiac events.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male gender	1.12 (0.50–2.49)	0.78	4.58 (1.24–16.85)	0.02
Age (per 10 years increment)	1.01 (0.98–1.05)	0.49		
Systolic BP (per 10 mmHg increment)	1.002 (0.98–1.02)	0.87		
Hypertension	2.03 (0.48–8.64)	0.34		
Diabetes mellitus	1.23 (0.55–2.77)	0.61		
Hyperlipidemia	1.01 (0.42–2.43)	0.99		
Stable coronary artery disease	2.14 (0.84–5.39)	0.11		
History of myocardial infarction	4.95 (1.48–16.63)	0.01		
History of heart failure	3.05 (1.14–8.16)	0.03		
Stroke	N/A	N/A		
ACEI or ARB	1.32 (0.59–2.94)	0.49		
Antiplatelet	1.69 (0.74–3.85)	0.22		
Beta blocker	1.18 (0.53–2.65)	0.69		
Calcium channel blocker	1.08 (0.46–2.52)	0.86		
Statin	1.45 (0.64–3.26)	0.37		
LA diameter (per 10 mm increment)	1.14 (1.05–1.24)	0.002		
LV mass index (per quartile)	1.03 (1.02–1.04)	< 0.001	1.03 (1.01–1.04)	0.003
LVEF (per 10% decrement)	0.97 (0.95–0.99)	0.003		0.02
Wall motion abnormality	4.61 (2.06–10.29)	< 0.001		0.002
Presence of LGE	5.28 (2.36–11.81)	< 0.001	3.18 (1.26–8.05)	
PWV > 12.01 m/s	2.66 (1.19–5.96)	0.02	3.99 (1.67–9.50)	

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CI = confidence interval; CMR = cardiovascular magnetic resonance; HR = hazard ratio; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; N/A = not available; PWV = pulse wave velocity.
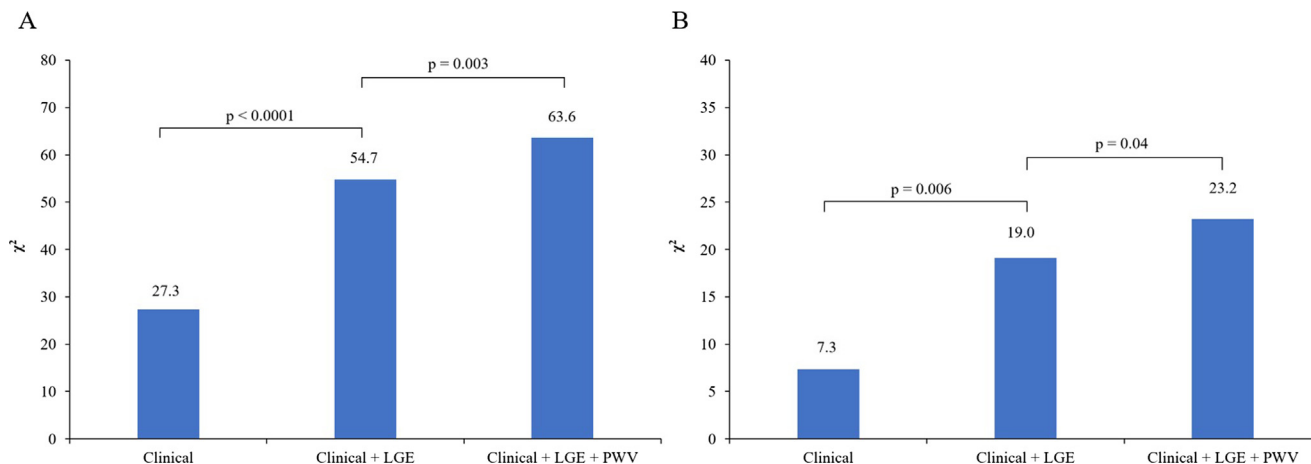

Fig. 3. Incremental Prognostic Value of LGE and PWV. When prognosis was assessed in a hierarchical manner, LGE and PWV showed significant increment in the global chi-square for the prediction of MACE (A) and hard cardiac events (B). Clinical = age, male gender, history of myocardial infarction, and history of heart failure.

Defining the thresholds and normative values for PWV measurement is challenging. An expert consensus recommended that a carotid-femoral PWV value of over 10 m/s should be defined as a fixed cut-off [32]. However, a fixed threshold has several limitations. The variability of PWV with age and cardiovascular disease risk factors prompted an interest in establishing reference values for various segments of the population. In our study, the mean PWV was used as a cut-off level. This method is simple and reflects the overall PWV value; however, this threshold may not be feasible for other patient populations.

Aortic stiffness can be non-invasively measured by several modalities such as applanation tonometer, Doppler ultrasound, and CMR. Carotid-femoral PWV using a tonometer is generally accepted as a simple and inexpensive method to measure aortic stiffness. This technique is the measure used in most clinical studies and is a strong predictor of cardiovascular events [3,4,6]. However, this method has a limitation regarding the measurement of aortic length. The aortic distance is measured by a tapeline

between the carotid and radial arteries, leading to a potential error. PWV measurement using CMR is one of the preferred methods to evaluate aortic stiffness. This technique can assess PWV accurately across any segment of the aorta. Unlike applanation tonometry, CMR can measure the distance of the aorta without geometrical assumptions. Moreover, CMR-based PWV measurements have been well-validated and compared to invasive pressure recordings with high reproducibility [7]. The PWV measured by CMR in this study also demonstrated excellent images with significantly high reproducibility, consistent with previous studies [7].

Age-associated alterations in aortic morphology and stiffness have been shown to be linked to LV remodeling and scarring. This mechanism of augmented central arterial volume may initially compensate for the stress-induced alteration of aortic function and elasticity but may also gradually lead to chronically increased LV afterload and stimulate LV hypertrophy, remodeling, and dysfunction over time [33]. A previous study demonstrated the relationship between PWV measured by CMR and changes in LV
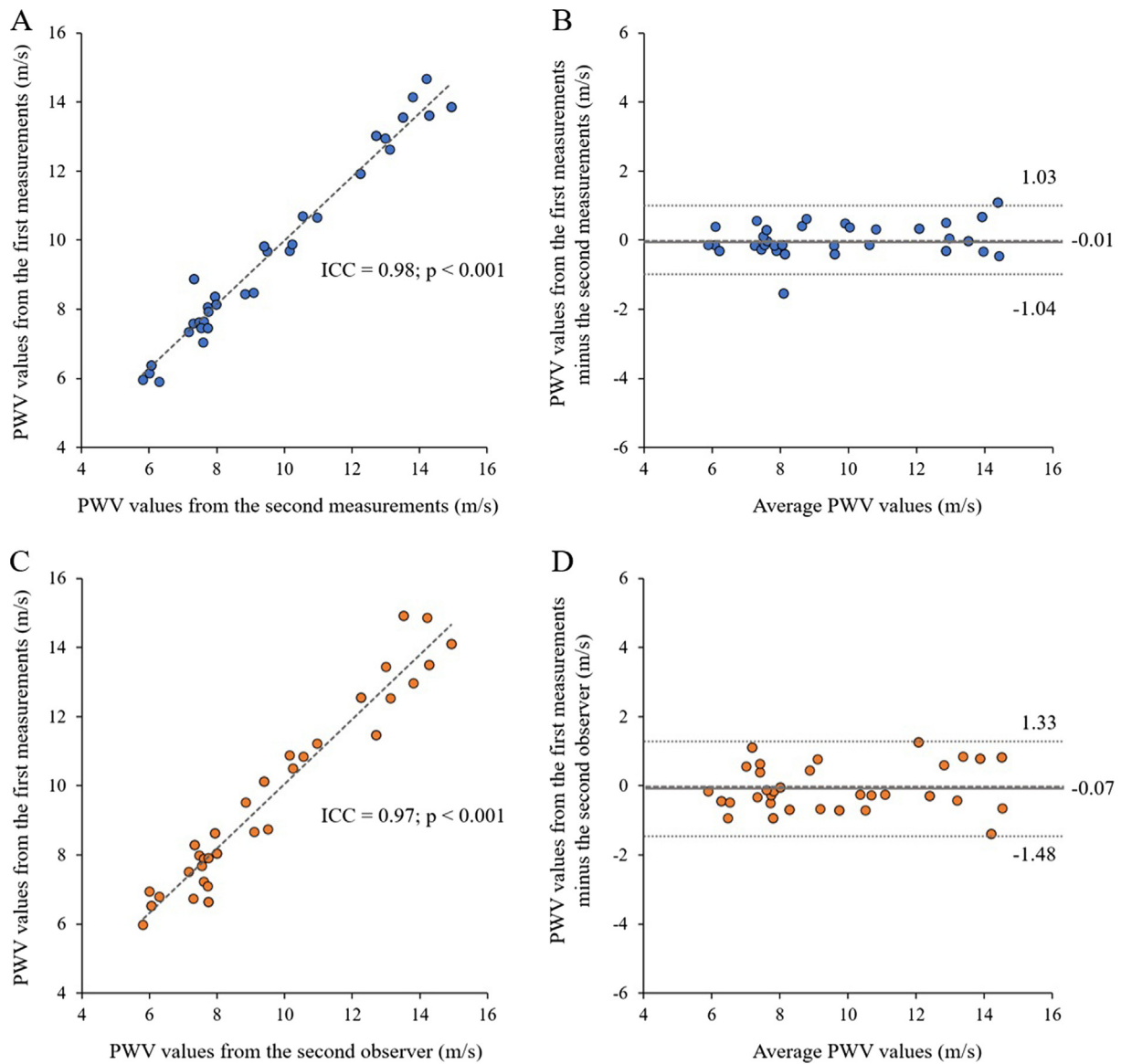
Fig. 4. Reproducibility of PWV measurement. The intraclass correlation (A for intra-observer and C for inter-observer) and Bland–Altman plot (B for intra-observer and D for interobserver). ICC = intraclass correlation coefficient, PWV = pulse wave velocity.

geometry, including increased LV mass and concentric remodeling in 100 healthy subjects [11]. Another recent study showed the association between PWV and myocardial fibrosis, measured by scar imaging and native T1 mapping in patients with known dilated cardiomyopathy [12]. The correlation between aortic stiffness and myocardial scarring was evidenced by these study results. Therefore, aortic stiffness combined with myocardial scarring may have a prognostic role in patients with cardiovascular diseases.

Myocardial scarring and fibrosis have been demonstrated as common features in a broad variety of cardiac diseases and lead to ventricular remodeling and dysfunction [34]. CMR can uniquely characterize the type and extent of myocardial scarring by LGE technique. LGE provides strong predictive values for future cardiovascular events in a wide range of patient populations, including those with ischemic and non-ischemic heart diseases [8–10]. In our study, the prevalence of LGE was 21.9%. There was no difference in the prevalence of both CAD and non-CAD type myocardial scarring between patients with and without elevation of PWV. However, the number of patients with non-CAD scarring in our

study was limited. Overall LGE as well as CAD pattern LGE also provided a significant prognostic value in this study.

Increased aortic stiffness was shown to have prognostic significance in healthy subjects and patients who had cardiovascular diseases, including CAD and non-ischemic cardiomyopathy such as hypertrophic cardiomyopathy [3–5,35]. A few studies demonstrated the prognostic value of aortic stiffness assessed by CMR for patients with stable CAD or post STEMI [36,37]. However, research focusing on the prognostic value of combined aortic stiffness and LGE is lacking. Given that a comprehensive CMR study can provide data for both aortic stiffness and myocardial scarring in a single examination, we sought to demonstrate the prognostic value of combining aortic stiffness and myocardial scarring to predict future cardiovascular events. Our study showed that non-elevated PWV and negative LGE are associated with a very low risk for cardiovascular events, while patients who had elevated PWV and positive LGE had the highest rate of MACE. Moreover, increased PWV can provide additional prognostic value for patients with LGE.

Novel CMR techniques to detect diffused myocardial fibrosis, including native T1 mapping, have proven the association with aortic stiffness [12,38]. However, prognostic data regarding these techniques combined with aortic stiffness requires further evaluation and may play a significant role in the near future.

4.1. Study limitations

This study had some limitations. Firstly, the most prevalent type of myocardial scarring in our patient population was CAD pattern. Thus, this result is not advisable for utilization in non-ischemic cardiomyopathy patients. Secondly, abnormal PWV in this study was defined by the mean PWV value. Consequently, this threshold PWV may not be employed in other studies. Thirdly, this study had a relatively low event rate, and some degree of overfitting may have occurred in the multivariable analyses. Finally, our study was retrospective in its methodology and some confounding factors could not be completely eliminated.

5. Conclusion

This is the first study to demonstrate the prognostic value of combining aortic stiffness using VE-CMR and myocardial scarring. Assessment of aortic stiffness may become an integrated component in future comprehensive CMR examinations.

Declaration of Competing Interest

The authors confirm that there are no conflicts of interest, including related consultancies, shareholdings, and funding grants.

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