

## Original Article

# Diagnostic accuracy of myocardial deformation indices for detecting high risk coronary artery disease in patients without regional wall motion abnormality

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**Abstract:** Background: The prediction of coronary artery disease (CAD) by conventional echocardiographic measurements is principally based on the estimation of ejection fraction and regional wall motion abnormality (RWMA). This study aimed to determine whether strain echocardiography of left ventricle measured by velocity vector imaging (VVI) method could detect patients with a high-risk CAD. Methods: In a prospective study, a total of 119 consecutive patients who were assessed for eligibility were categorized into three groups: (1) without CAD as normal (n=59), (2) 1- or 2-vessel disease as low-risk (n=29), and (3) left main and/or 3-vessel disease as high-risk (n=31). The peaks of systolic strain and strain rate from 18 curves of apical views were averaged as global longitudinal strain and strain rate (GLS and GLSR), respectively; the 6 systolic peaks of strain and strain rate at base- and mid-ventricular of short axis views were averaged as mean radial strain rate (MRSR). Results: GLS, GLSR, and basal MRSR of left ventricle were significantly lower in the high-risk group ( $P=0.047$ ,  $P=0.004$  and  $P=0.030$ , respectively). Receiver operating characteristics curve showed that the optimal values of GLS, GLSR, and basal MRSR for detecting the severe CAD were -17%,  $-1 \text{ s}^{-1}$ , and  $1.45 \text{ s}^{-1}$  with the sensitivities of 77%, 71%, and 71% and the specificities of 63%, 67%, and 62%, respectively. Conclusion: Decrements in the GLS, GLSR, and basal MRSR of the left ventricle can detect the high-risk CAD cases among patients without RWMA at rest.

**Keywords:** Coronary artery disease, global longitudinal strain, global longitudinal strain rate, mean radial strain rate, regional wall motion abnormality

## Introduction

It has been shown that the echocardiographic assessment of impact of coronary artery disease (CAD) on myocardium mainly relies on the evaluation of regional wall motion abnormality (RWMA) and left ventricular ejection fraction [1]. These methods are associated with some limitations, including being subjective and operator-dependent requiring the complete visualization of endocardium, being influenced by changes in cardiac loading and heart rate, and being the visual assessment of wall motion in apical views depending on the evaluation of inward myocardial motion. In contrast by these notions, deformation imaging as a non-invasive modality, including strain and strain rate imag-

ing, provides the complete assessment of functional components of myocardium [2, 3].

In order to overcome these limitations, some efforts have been applied to develop the indices of myocardial contractility, which are associated with acceptable interpretative variability to diagnose diseases even at its subclinical stages [4]. Recently, the 2-dimensional Speckle Tracking Echocardiography (STE) and its derivatives, including strain and strain rate imaging have been gained substantial clinical interest to surmount those limitations. The strain and strain rate imaging methods represent the magnitude and rate of myocardial deformations, respectively [1]. Based on the numerous studies, the majority of them support the existence

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of a significant correlation between the longitudinal strain and CAD [5-10]. However, such results have been inconsistent and only some studies have evaluated the correlation between the different types of strain and strain rate imaging consisting of longitudinal, circumferential, and radial in the patients without RWMA at rest [11, 12].

The main aim of our study was to determine whether the difference in fiber orientation and consequently the direction of motion can be used to identify changes in long and short axes of myocardial function (strain and strain rate) in CAD patients without RWMA at rest.

### Materials and methods

#### *Study population*

In a prospective study conducted in the Rajaie Cardiovascular Medical and Research Center, Tehran, Iran, a total of 285 consecutive patients were evaluated from October 2012 to October 2013, in which thirty six patients whose echocardiographic images were unsuitable for strain measurement were excluded subsequently. Therefore, 119 patients (46.1% recruitment rate) were entered into the study. These patients had no visual segmental RWMA and had undergone coronary angiography within 24 hours before enrolment in the study to be evaluated using echocardiography.

All patients whose left ventricular ejection fraction were less than 50% or had RWMA were excluded. Other exclusion criteria consisted of having a history of cardiomyopathy, significant valvular heart disease (more than mild), congenital heart disease, previous cardiac surgery, and heart rhythm except the sinus rhythm and left bundle branch block. This study was approved by our local ethics committee and institutional review board, and also written consent forms were obtained from all participants.

#### *Echocardiographic evaluation*

We used a MyLab 60 echo machine (Esaote, Florence, Italy) equipped with a multi-frequency 2.5-3.4 MHz transducer. All participants underwent echocardiographic examination as were in left lateral decubitus position; all echocardiographic evaluations were carried out by a single operator who was unaware of clinical and angi-

ographic results. The harmonic image recordings of apical views, including four, three, or two chamber (4C, 3C, and 2C) views and short axis views at mitral and papillary muscle levels at frame rates of 45-64 frames per second, and good quality electrocardiogram signals were obtained and stored to be analyzed offline using Xstrain™ software.

For each of patients a clip with a best endocardial border was selected and proceeded as follows: A starting frame was chosen at the end of systole when the endocardial border being visible the best, meanwhile it was not mandatory since algorithm was designed to follow points tracked in any frame, and then, left ventricle endocardial surface was manually traced.

An epicardial surface tracing was automatically generated by the system of echo machine, creating a region of interest, which was manually adjusted to cover the full thickness of the myocardium. Before the images to be processed, a cine loop preview was used to confirm if the internal line of interest followed the endocardial border throughout the cardiac cycle.

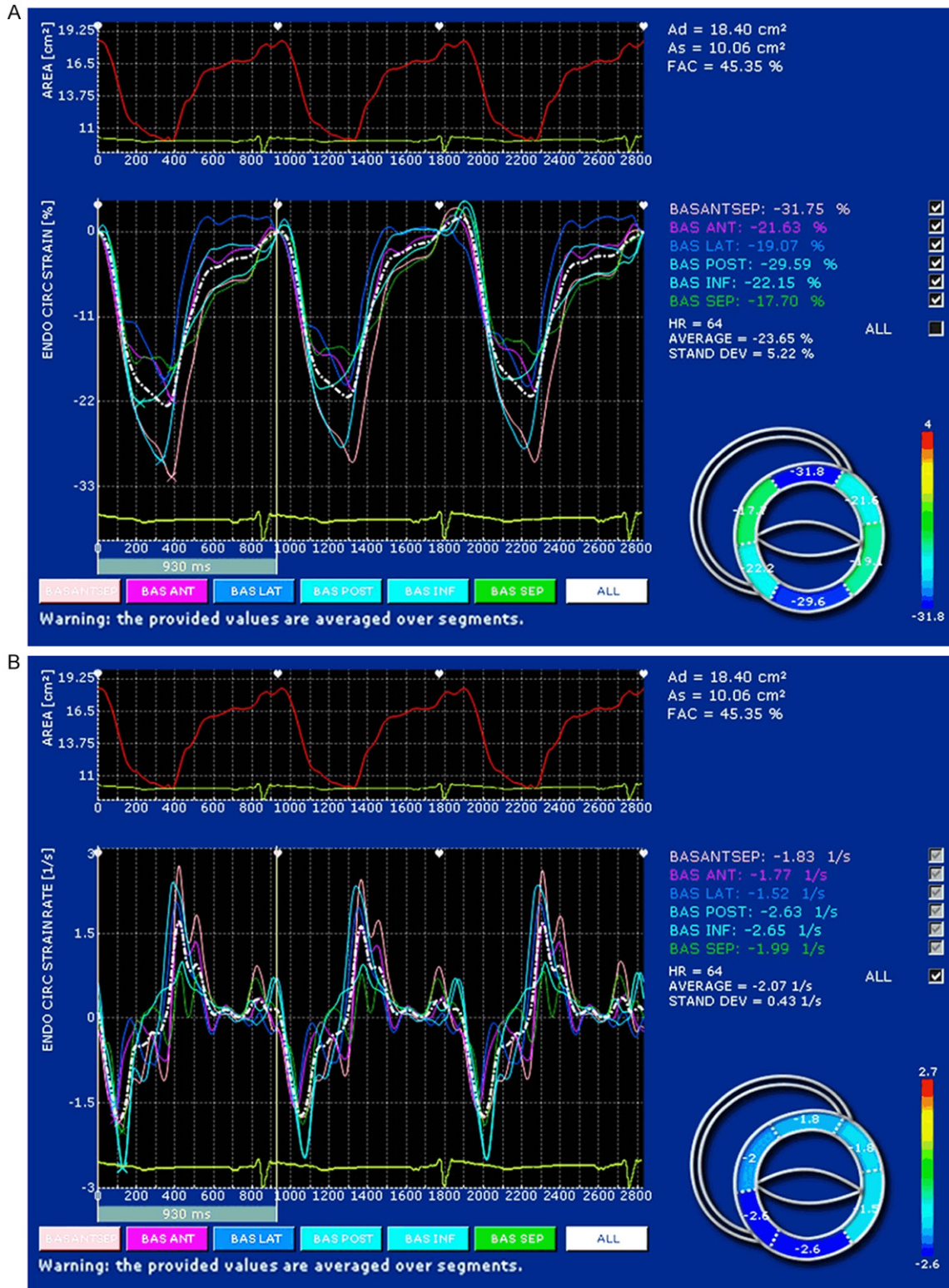
The strain and strain rate graphics for radial and circumferential views at short axis and for longitudinal view at long axis were automatically obtained by a velocity vector imaging (VVI) method, and average values for different parameters were calculated (**Figure 1**). Global longitudinal strain and strain rate (GLS and GLSR) values of the left ventricle were calculated by averaging 4C, 3C, and 2C values. The left ventricle end-diastolic and -systolic volumes were measured, and ejection fraction was calculated using a modified Simpson's biplane method either.

#### *Coronary angiography*

An experienced interventional cardiologist who was blinded to the patients' clinical and echocardiographic results assessed the angiograms and evaluated the location of lesions and diameter of stenosis for either of the coronary lesions.

Given the cut-off diameters of stenosis > 70% for three epicardial vessels and > 50% for the left main coronary artery as diseased artery, we defined the number of affected vessels. Accordingly, all patients were categorized into

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**Figure 1.** Values and curves of circumferential strain (A) and strain rate (B) of the base presented segment by segment.

three groups as follows: (1) no detected CAD, normal group; (2) 1- or 2-vessel CAD, low-risk

group; and (3) Left main and/or 3-vessel CAD, high-risk group.

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**Table 1.** Clinical characteristics of patients in the study groups by angiographic evaluation

	Total (n=119)	Normal (n=59)	Low-risk (n=29)	High-risk (n=31)	P-value
Male	64 (53.8)	33 (59.9)	15 (51.7)	16 (51.6)	0.897
Age (years)	56.4 ± 10.7	53 ± 10.4	60.5 ± 9.8*	59.1 ± 10.1*#	0.002
Height (m)	165.2 ± 11.1	167.4 ± 10.1	159.6 ± 14*	165.7 ± 9.3#	0.014
Weight (kg)	74.2 ± 11.1	75.1 ± 11	73.6 ± 10	74.8 ± 12.3	0.553
BSA (m <sup>2</sup> )	1.8 ± 0.18	1.84 ± 0.18	1.77 ± 0.18	1.80 ± 0.18	0.353
BMI (kg/m <sup>2</sup> )	27.3 ± 3.9	27.1 ± 4.2	27.8 ± 4.1	27.1 ± 3.2	0.715
Risk factors					
Diabetes mellitus	34 (28.6)	13 (22)	4 (13.8)	17 (54.8)	0.001
Hypertension	57 (47.9)	20 (33.91)	16 (55.2)	21 (67.7)	0.006
Dyslipidemia	54 (45.4)	21 (35.6)	14 (48.3)	19 (61.3)	0.063
Familial history	16 (13.4)	11 (18.6)	4 (13.8)	1 (3.2)	0.125
Smoking	26 (21.8)	12 (20.3)	7 (24.1)	7 (22.6)	0.915

\*P<0.05 when compared with normal group; #P<0.05 when compared with low-risk group (based on the Bonferroni's test). Data are presented as mean ± standard deviation and number (percentage). BMI, body mass index; BSA, body surface area.

**Table 2.** Echocardiographic parameters measured in the study groups

	Total (n=119)	Normal (n=59)	Low-risk (n=29)	High-risk (n=31)	P-value
LV end-diastolic diameter (cm)	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	0.875
LV end-systolic diameter (cm)	2.8 ± 0.5	2.8 ± 0.6	2.7 ± 0.5	2.8 ± 0.5	0.919
LV end-diastolic volume (ml)	88 ± 25	86 ± 28	91 ± 23	88 ± 21	0.638
LV end-systolic volume (ml)	35 ± 13	33 ± 12	36 ± 12	37 ± 15	0.316
LV ejection fraction (%)	60 ± 7	61 ± 6	60 ± 7	58 ± 7	0.245
GLS (%)	-16 ± 3	-17 ± 3	-16 ± 3	-15 ± 2	0.047
GLSR (s <sup>-1</sup> )	-1 ± 0.2	-1.1 ± 0.2	-1 ± 0.2	-0.9 ± 0.2*#	0.004
Basal CS (%)	-20 ± 5	-20 ± 5	-20 ± 6	-21 ± 4	0.651
Mid MCS (%)	-23 ± 7	-22 ± 6	-23 ± 7	-24 ± 7	0.783
Basal MCSR (s <sup>-1</sup> )	-1.3 ± 0.3	-1.3 ± 0.3	-1.3 ± 0.3	-1.3 ± 0.3	0.642
Mid MCSR (s <sup>-1</sup> )	-1.4 ± 0.5	-1.4 ± 0.5	-1.4 ± 0.5	-1.3 ± 0.4	0.833
Basal MRS (%)	27 ± 13	29 ± 13	25 ± 14	25 ± 12	0.300
Mid MRS (%)	30 ± 15	31 ± 16	25 ± 11	32 ± 16	0.161
Basal MRSR (s <sup>-1</sup> )	1.7 ± 0.7	1.8 ± 0.7	1.7 ± 0.6	1.4 ± 0.6*#	0.030
Mid MRSR (s <sup>-1</sup> )	1.7 ± 0.5	1.7 ± 0.6	1.6 ± 0.5	1.8 ± 0.6	0.650

\*P<0.05 when compared with normal group; #P<0.05 when compared with low-risk group (based on the Bonferroni's test). Data are presented as mean ± standard deviation. GLS, global longitudinal strain; GLSR, global longitudinal strain rate; LV, left ventricle; MCS, mean circumferential strain; MCSR, mean circumferential strain rate; MRS, mean radial strain; MRSR, mean radial strain rate.

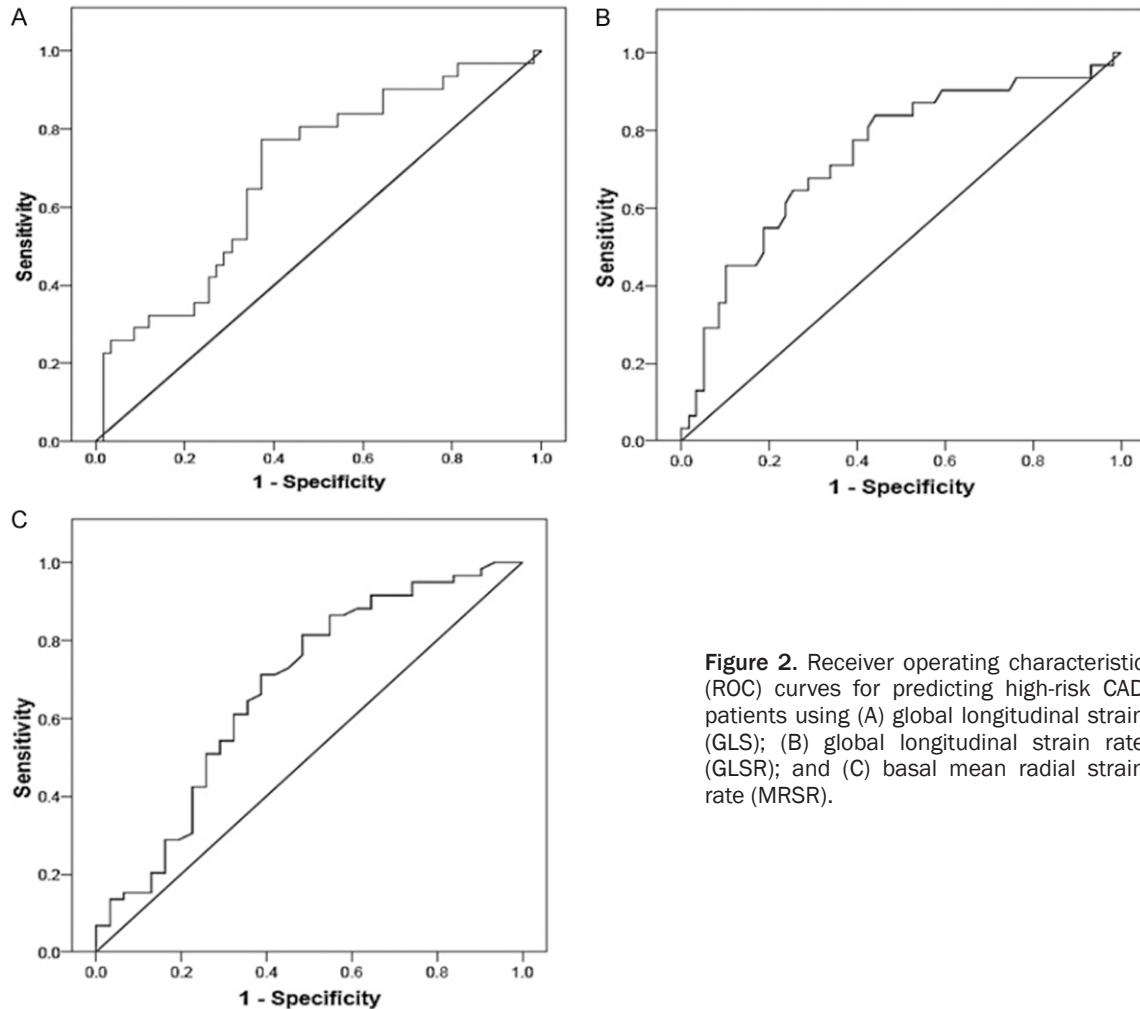
### Statistical analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables as number (percentage). The chi-square test and One-way ANOVA test were used for analyzing categorical and continuous variables, respectively. A post hoc test, Bonferroni's test, was also applied to compare the paired groups. Receiver operating characteristic (ROC) curve analysis was used to test the diagnostic accuracy of GLS, GLSR, and basal mean radial strain

rate (MRSR) for discriminating the high-risk patients from the two other groups, including low-risk and normal groups. To investigate intra-observer variability, measurements were done off-line on 20 randomly selected cases one month later and analysis was performed using Bland-Altman plot. Moreover, multivariate logistic regression analysis was conducted to identify the predictors of high-risk CAD; all variables with a P-value less than 0.05 in bivariate analysis were entered as dependent variables, and the status of angiographic evalua-



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**Figure 2.** Receiver operating characteristic (ROC) curves for predicting high-risk CAD patients using (A) global longitudinal strain (GLS); (B) global longitudinal strain rate (GLSR); and (C) basal mean radial strain rate (MRSR).

tion was considered as dependent variable. Three models were conducted, in which either of strain imaging values with significant *P* values was entered separately along with other variables. A two-tailed *P*-value of < 0.05 was considered statistically significant. All analyses were performed using the SPSS statistical software package, version 15.0 (SPSS Inc., Chicago, Illinois, USA).

### Results

A total of 119 patients were evaluated in the study, and those were categorized into three groups, including without CAD as normal group (*n*=59), 1- or 2-vessel CAD as low-risk group (*n*=29) and Left main and/or 3-vessel CAD as high-risk group (*n*=31). The baseline clinical characteristics of patients according to the study groups are presented in **Table 1**. The mean age of patients was  $56.4 \pm 10.7$  years,

and it was significantly different among groups (*P*=0.002). The mean of age differences between low- and high-risk groups with normal group were also significant based on Bonferroni's test (*P*=0.005 and *P*=0.025, respectively). The most of patients in three groups were males, but it was no significantly different (*P*=0.897). Of conventional risk factors, diabetes mellitus (55%) and hypertension (67%) were more frequent in the high-risk group when compared with low-risk and normal groups (*P*=0.001 and *P*=0.006, respectively). There was a trend toward the high-risk group to have more patients with dyslipidemia when compared with the normal and low-risk groups (*P*=0.063).

The data of echocardiographic examination are summarized in **Table 2**. No significant differences were found among three groups concerning conventional echocardiographic parameters. The GLS of the left ventricle was signifi-

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**Table 3.** Multivariate logistic regression analyses showing predictors of high-risk patients

	Model 1*			Model 2*			Model 3*		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.038	1.000-1.078	0.047	1.040	1.002-1.079	0.039	1.044	1.005-1.084	0.023
Height	0.984	0.955-1.013	0.296	0.980	0.951-1.010	0.211	0.981	0.952-1.012	0.234
Hypertension	2.236	1.068-4.684	0.033	2.350	1.116-4.948	0.024	2.182	1.033-4.606	0.041
Diabetes mellitus	2.871	1.266-6.506	0.012	2.333	1.023-5.323	0.044	2.645	1.165-6.007	0.020
GLS	1.110	0.996-1.237	0.057						
GLSR				7.440	1.621-34.129	0.010			
Basal MRSR							0.524	0.299-0.918	0.024

\*The GLS, GLSR, and basal MRSR were entered separately into each model of 1, 2, and 3 along with the other variables, respectively. CI, confidence interval; GLS, global longitudinal strain; GLSR, global longitudinal strain rate; MRSR, mean radial strain rate; OR, odds ratio.

cantly lower in the high-risk group when compared with that in the low-risk or normal groups ( $-15 \pm 2$  vs.  $-16 \pm 3$  and  $-17 \pm 3$   $s^{-1}$ , respectively,  $P=0.047$ ). The GLSR was also significantly lower in the high-risk group when compared with the low-risk and normal groups ( $-0.9 \pm 0.2$ ,  $-1 \pm 0.2$  and  $-1.1 \pm 0.2$   $s^{-1}$ , respectively,  $P=0.004$ ). Among short axis parameters, only the basal MRSR was lower in the high-risk group when compared with other groups ( $1.4 \pm 0.6$ ,  $1.7 \pm 0.6$  and  $1.8 \pm 0.7$   $s^{-1}$ , respectively,  $P=0.030$ ). According to the post hoc test, the mean of GLSR and basal MRSR were significantly different between high-risk group and normal group ( $P=0.003$  and  $P=0.025$ , respectively).

The ROC curve analysis was constructed to detect the patients with high-risk CAD. Based on the ROC curve analysis, the optimal cut-off values for GLS, GLSR, and basal MRSR of the left ventricle for the detection of patients diagnosed with high-risk CAD were -17% (sensitivity 77% and specificity 63%, **Figure 2A**),  $-1$   $s^{-1}$  (sensitivity 71% and specificity 67%, **Figure 2B**) and  $1.45$   $s^{-1}$  (sensitivity 71% and specificity 62%, **Figure 2C**), respectively. Intra-observer variability for long-axis and short-axis strain and strain rate was at acceptable range of 5% and no significant variability was seen among all the parameters by Bland-Altman plot analysis.

In the multivariate logistic regression analyses, the variables with  $P$ -value  $< 0.05$ , including age, height, hypertension, and diabetes mellitus along with either of strain values consisting of GLS, GLSR, and basal MRSR were entered separately into three models. Among the measured strain imaging parameters, the GLSR

(odds ratio [OR] 7.440, 95% confidence interval [CI] 1.621-34.129,  $P=0.010$ ) and basal MRSR (OR 0.524, 95% CI 0.299-0.918,  $P=0.024$ ) were the independent predictors of high-risk patients (**Table 3**).

### Discussion

In the present study, we found that despite the lack of detecting visual segmental wall motion abnormality in patients with CAD, the echocardiographic parameters, including GLS, GLSR and basal MRSR were significantly lower in the high-risk CAD group when compared with those in low-risk CAD and control groups.

Our findings in terms of GLS and GLSR were in agreement with previous studies [5, 9, 11, 13]. However, the populations whom were evaluated and strain parameters analyzed varied in previous studies. Valocik et al. [5] showed a significant reduction in the mid-ventricle MRSR of patients with multi-vessel CAD. In our study, we also showed that among short axis parameters examined, only the basal MRSR significantly declined in the high-risk group. In another study, Deng et al. [11] revealed that the peak systolic longitudinal strain was significantly reduced in myocardial segments subtended by coronary arteries with greater than 75% stenosis when compared with controls.

In the majority of studies carried out in patients with ischemic heart disease, the power of site specificity of strain and strain rate imaging was employed. This segmental analysis includes some limitations as follows: 1) presenting normal reference values for different myocardial segments are problematic [5], because in normal population the longitudinal and circumfer-

ential strain and strain rate increase from the base of ventricle to its apex [14, 15]; and 2) The area with impaired function is not necessarily aligned with the standard segmental division of the left ventricle [13]. In an experimental study of coronary stenosis, coronary artery narrowing led to both local decline and the global decline of myocardial function with reduced contractility at remote regions, ischemia at distance [16].

In addition, we assessed global long axis deformation and average short axis indices by VVI, which was a simple and rapid analysis. We presented the cut-off values for strain and strain rate that could be used easily and reproducibly in clinical practice. The cut-off value of GLS (-19.4%) presented by Choi et al. [8] for the identification of high-risk CAD patients differed from value calculated in this study (-17%). This difference may be caused by the fact that measuring STE modality in their study had been accomplished by Automated Function Imaging (AFI), while in our study the measurement was performed using VVI method. Comparing the different techniques of 2-dimensional STE, Bansal et al. [17] showed that the measured values for longitudinal strain were underestimated by VVI method when compared with the AFI method.

Although exercise or pharmacologic stress echocardiography has a higher sensitivity to detect ischemia in a 3-vessel/left main CAD, the global hypokinesia induced by stress or a lack of hyperdynamic response to exercise due to balanced ischemia may mask the detection of CAD [18]. Thus decrement in the deformation indices at rest may provide an important diagnostic clue to high pretest probability for the presence of high-risk CAD.

The exact mechanism for the subclinical impairment of myocardial function in patients with CAD has been remained unknown. Chio et al. [8] investigation revealed that repetitive insults to myocardium due to severe coronary stenosis could reduce systolic longitudinal function, while resting regional wall motion remained normal. Edvarsen et al. [19] suggested another hypothesis that subclinical myocardial damage could be a marker of coronary atherosclerosis even in the absence of overt myocardial infarction, mainly due to small-vessel microembolization, endothelial dysfunction and chronic ischemia. In another study Geer et al. [20] describ-

ed morphological changes in subendocardial myocardium that appeared to be caused by severe and chronic subendocardial ischemia in patients without the evidences of myocardial infarction. These hypotheses could imply that how deformation imaging can recognize the early subclinical myocardial dysfunction and damage.

It has been reported that patients with hypertension and/or diabetes mellitus had the reduced global or regional strain [21, 22]. Hypertension and diabetes mellitus were found to be the two important confounding variables in our study. However, in the present study, we used the multivariate regression analysis and showed that the GLSR and basal MRSR were the predictors of high-risk patients. According to the findings of Hoit et al. [1], the major limitations of strain imaging for routine clinical use consist of variable cut-off values and algorithms, softwares ongoing changes, and a paucity of normal reference values. Finally, although the temporal and magnitude markers of segmental strain are important in specific situations such as stress echocardiography, the GLS which correlates with left ventricular ejection fraction has been shown to be potential for becoming a routine measurement in the evaluation of CAD [1]. We believe that despite all limitations considered for strain modalities, these parameters can be used as routine examinations for diagnosing and risk stratification of CAD patients; further prospective large-scale studies will be of great benefit for clarifying the importance of these findings and those implementation in our clinical practice.

### *Study limitations*

Our study has been subjected to some limitations. First, the number of patients enrolled in the study was relatively small. Secondly, decreases in the strain and strain rate values may not be specific for severe CAD, and may also be present in other cardiomyopathic conditions; hence, we tried to deal with this problem by implementing our exclusion criteria. Thirdly, although we used the VVI method for deformation imaging, it seems that the AFI method is preferable and is likely to be associated with a higher accuracy compared with the VVI method [17]. Fourthly, the number of patients excluded from the study due to poor image quality was

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relatively high (n=36). Meanwhile, this did not impose any adverse effect on the study, because the number of patients in the CAD and the control groups remained well matched.

### Conclusions

Our study demonstrated that in the patients suspecting to have CAD without RWMA at rest, the decrement in the GLS, GLSR and basal MRSR of the left ventricle can be used as non-invasive diagnostic tools to identify the high-risk CAD cases.

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### Disclosure of conflict of interest

None.

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