Chapter 8

Incremental Value of Subclinical Left Ventricular Systolic Dysfunction for the Identification of Patients With Obstructive Coronary Artery Disease

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ABSTRACT

Background. Left ventricular (LV) diastolic dysfunction and subclinical systolic dysfunction may be markers of coronary artery disease (CAD). However, whether these markers are useful for prediction of obstructive CAD is unknown.

Methods. A total of 182 consecutive outpatients (54±10 years, 59% males) without known CAD and overt LV systolic dysfunction underwent 64-slice multislice computed tomography (MSCT) coronary angiography and echocardiography. The MSCT angiograms showing atherosclerosis were classified as showing obstructive (≥50% luminal narrowing) CAD or not. Conventional echocardiographic parameters of LV systolic and diastolic function were obtained; in addition, *(1)* global longitudinal strain (GLS) and strain rate (indices of systolic function) and *(2)* global strain rate during the isovolumic relaxation period and during early diastolic filling (indices of diastolic function) were assessed using speckle-tracking echocardiography. In addition, the pretest likelihood of obstructive CAD was assessed using the Duke Clinical Score.

Results. Based on MSCT, 32% of patients were classified as having no CAD, whereas 33% showed nonobstructive CAD and the remaining 35% had obstructive CAD. Multivariate analysis of clinical and echocardiographic characteristics showed that only high pretest likelihood of CAD (odds ratio [OR] 3.21, 95% 1.02-10.09, p = 0.046), diastolic dysfunction (OR 3.72, 95% CI 1.44-9.57, p = 0.006), and GLS (OR 1.97, 95% CI 1.43-2.71, p <0.001) were associated with obstructive CAD. A value of GLS ≥−17.4 yielded high sensitivity and specificity in identifying patients with obstructive CAD (83% and 77%, respectively), providing a significant incremental value over pretest likelihood of CAD and diastolic dysfunction.

Conclusions. The GLS impairment aids detection of patients without overt LV systolic dysfunction having obstructive CAD.

INTRODUCTION

Among patients with suspected coronary artery disease (CAD), scoring tools that take demographic and clinical characteristics into account are traditionally used to estimate the likelihood of obstructive CAD and to identify those who could benefit from further diagnostic tests.[1-3] In the diagnostic workup of these patients, the assessment of left ventricular (LV) function can provide additional information, refining the initial clinical evaluation.[4] In particular, the presence of reduced LV ejection fraction (EF) or wall motion abnormalities significantly increase the likelihood of obstructive CAD.[4,5] In addition, the presence of LV diastolic dysfunction may also be a marker of coronary atherosclerosis, even when global LV systolic function is normal.[6-8]

In patients without overt LV systolic dysfunction, the presence of subclinical reduction of myocardial function may be a marker of CAD as well.[9] For instance, the Multiethnic Study of Atherosclerosis (MESA) observed that a progressive impairment of myocardial contraction (despite normal LVEF) was associated with an increasing severity of coronary atherosclerosis (detected by multislice computed tomography [MSCT] or electron-beam computed tomography).[9]

Although LV diastolic dysfunction and subclinical LV systolic dysfunction have been shown as possible markers of CAD, it is unknown whether their detection could improve patients' stratification. Accordingly, the aim of the present evaluation was 2-fold. *First*, to explore the relation between obstructive CAD, LV diastolic dysfunction, and subclinical LV systolic dysfunction. *Second*, to assess the potential incremental value of LV diastolic dysfunction and subclinical LV systolic dysfunction over the initial estimate of pretest likelihood of obstructive CAD. The MSCT coronary angiography was performed to detect coronary atherosclerosis and obstructive CAD;[10] 2-dimensional echocardiography with speckle-tracking analysis was used to evaluate LV systolic and diastolic function.[11-13]

METHODS

Patient population

A total of 182 consecutive outpatients referred to MSCT for coronary evaluation, because of increased risk profile and/or stable chest pain, were included. Two-dimensional echocardiography with speckle-tracking analysis was performed in all patients within 1 month of MSCT coronary angiography. Both MSCT coronary angiography and extensive echocardiographic examination are part of clinical diagnostic workup of patients with known or suspected CAD.

Patients with overt LV systolic dysfunction (LVEF <50%) or with LV wall motion abnormalities were excluded. Also, patients with a history of CAD, cardiomyopathy, significant (moderate or severe) valvular heart disease, congenital heart disease, rhythm other than sinus, conduction abnormalities, technically inadequate echocardiographic studies, or contraindications to MSCT were excluded. Known CAD was defined as history of acute coronary syndrome, percutaneous or surgical coronary revascularization, and/or angiographically documented coronary stenoses ≥50% luminal diameter.[14] Contraindications for MSCT were known allergy to iodinated contrast agent, renal failure (defined as glomerular filtration rate <30 ml/min), and pregnancy.

For each patient, the presence of coronary risk factors (diabetes, systemic hypertension, hypercholesterolemia, positive family history, cigarette smoking) and the presence of chest pain were recorded. In addition, the pretest likelihood of obstructive CAD was assessed using the Duke Clinical Score,[2] which takes age, gender, coronary risk factors, and type of chest pain into account. In accordance to the Duke Clinical Score, the patient population was then categorized as having a low (≤30%), intermediate (31-70%), or high (>70%) pretest likelihood of obstructive CAD.[15]

Two-dimensional echocardiography

Echocardiography was performed using a commercially available system (Vivid 7 Dimension, GE Health care, Horten, Norway) equipped with a 3.5-MHz transducer. Standard M-mode, 2-dimensional images, and Doppler and color Doppler data were acquired from the parasternal and apical views (4, 2, and 3 chambers) and digitally stored in cine-loop format; analyses were subsequently performed off-line using EchoPAC version 7.0.0 (GE Health care, Horten, Norway).

Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were measured according to the Simpson's biplane method, and LVEF was calculated as [(EDV-ESV)/EDV] ×100. The LV mass was calculated using the formula proposed by Lang et al.[16] and Devereux and Reicheck [17] and normalized for body surface area (LV mass index, gram per square meter).

Transmitral and pulmonary vein flows were obtained by pulsed-wave Doppler tracings, obtained in accordance to the recommendations of the American Society of Echocardiography.[18] Early (E) and late (A) diastolic waves, deceleration time (DT) of E wave, and pulmonary vein systolic (PVs) and diastolic (PVd) velocities were measured. Diastolic function was then classified as follows:[19] *(1)* normal, when the E/A ratio = 0.9-1.5, DT = 160-240 milliseconds, and PVs ≥ PVd; *(2)* diastolic dysfunction grade 1 (mild), when the E/A ratio was <0.9, DT >240 milliseconds, and PVs > > PVd; *(3)* diastolic dysfunction grade 2 (moderate), when the E/A ratio = 0.9-1.5, DT = 160-240 milliseconds, and PVs < PVd; *(4)* diastolic dysfunction grade 3 (severe), when the E/A ratio >2.0, DT <160 milliseconds, and PVs > > PVd; and *(5)* diastolic dysfunction grade 4 (severe), when the E/A ratio >2.5, DT <130 milliseconds, and PVs > > PVd.

In addition, the septal mitral annulus early (E') velocity was measured by tissue Doppler imaging and the E/E' ratio was calculated, as estimate of LV filling pressures.[19,20]

Speckle-tracking analysis

Longitudinal strain analysis of the LV was performed by speckle-tracking imaging (EchoPAC version 7.0.0). Grayscale 2-dimensional apical images of the LV (4-, 2-, and 3-chamber views) were used with frame rate ranging from 80 to 100 frames/s. From an end-systolic frame, the endocardial border was manually traced, and the software traces automatically 2 more concentric regions of interest to include the entire myocardial wall. Speckle-tracking analysis detects and tracks the unique myocardial ultrasound patterns frame by frame. The in-plane frame-to-frame displacement of each pattern over time is used to derive strain. The software validates automatically the segmental tracking along the cardiac cycle and allows the operator further adjustment of the region of interest to improve the tracking quality.

As described previously,[11] mean global longitudinal strain (GLS) and strain rate (GLSR) were calculated, as indices of global LV systolic function, by averaging the global longitudinal strains and strain rates obtained automatically from each apical view (Figure 1). Similarly, the following indices of diastolic function were obtained (Figure 1):[21] *(1)* global strain rate during the isovolumic relaxation period (GSRivrt) and *(2)* global strain rate during early diastolic filling (GSRe).

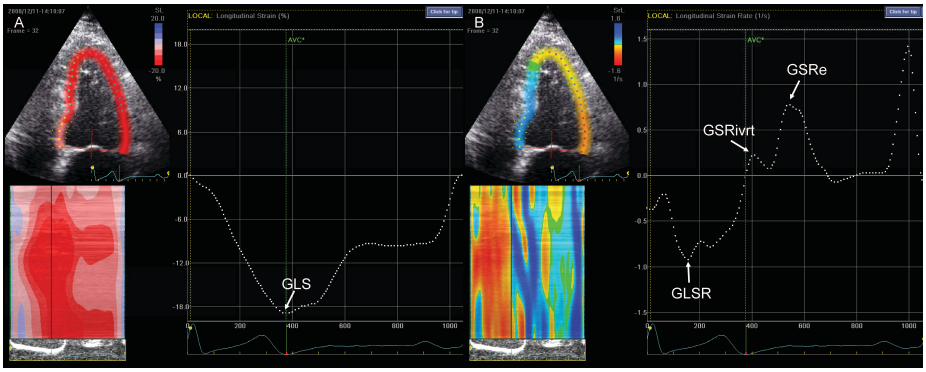

Figure 1. Global longitudinal strain and strain rate curves. Global longitudinal strain (**panel A**) and strain rate (**panel B**) curves obtained by speckle-tracking analysis from an apical 4-chamber view.

Multislice computed tomography

Data acquisition

The MSCT coronary angiography was performed with a 64-slice MSCT scanner (Aquilion 64, Toshiba Medical Systems, Tokyo, Japan). The heart rate and blood pressure were monitored before the examination in each patient. In the absence of contraindications, patients with a heart rate ≥ 65 beat/min were administered oral β-blockers (metoprolol 50 or 100 mg, single dose, 1 hour before the examination). Noninvasive MSCT coronary angiography was therefore performed according to protocols previously described.[10] Data were subsequently transferred to dedicated workstations for postprocessing and evaluation (Vitrea 2, Vital Images, Minnetonka, Minnesota, USA).

Data analysis

The MSCT data analysis was performed by 2 experienced observers who had no knowledge of the patient's medical history, symptom status, and echocardiographic data; disagreement was solved by consensus or evaluation by a third observer. The MSCT coronary angiograms were evaluated for the presence of obstructive CAD (≥50% luminal narrowing) on a patient level. For this purpose, both the original axial dataset as well as curved multiplanar reconstructions were used. Each coronary artery was evaluated for the presence of any atherosclerotic plaque, defined as structures >1 mm2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue, as described previously.[22] Subsequently, the coronary arteries were further classified as *(1)* completely normal, *(2)* having nonobstructive CAD when atherosclerotic lesions <50% of luminal diameter were present, or *(3)* having obstructive CAD when atherosclerotic lesions ≥50% of luminal diameter were present. The prevalence of normal coronary arteries, (any) CAD (including obstructive

and nonobstructive CAD), and obstructive CAD in the patient population was evaluated.

Statistical analysis

Continues variables are expressed as mean and SD. Categorical data are presented as absolute numbers and percentages. Differences in continuous and categorical variables between patients with normal coronary arteries, nonobstructive CAD, and obstructive CAD at MSCT coronary angiography were assessed using the 1-way analysis of variance test and the chi-square test, respectively; if the result of the analysis was significant, post hoc test with Bonferroni's correction was applied.

Univariate and multivariate logistic regression analysis (enter model) were performed to evaluate the association between the presence of obstructive CAD at MSCT coronary angiography, the traditional assessment of pretest likelihood of obstructive CAD (Duke Clinical Score), and the following echocardiographic variables: LVEF, LV mass index, presence of diastolic dysfunction, E/E' ratio, GLS, GLSR, GSRivrt, and GSRe. Only significant ($p < 0.05$) univariate predictors were entered as covariates in the multivariate model. Odds ratios and 95% CI were calculated. Model discrimination was assessed using C-statistic, and model calibration was assessed using Hosmer-Lemeshow statistic.

Receiver operator characteristic (ROC) curve analysis was performed to determine the accuracy of GLS to detect obstructive CAD, with an area under the curve value of 0.50 indicating no accuracy and a value of 1.00 indicating maximal accuracy. In addition, to determine the potential incremental value of diastolic dysfunction and GLS over the traditional assessment of pretest likelihood of obstructive CAD (Duke Clinical Score), ROC curves were constructed for 3 models: *model 1*, Duke Clinical Score alone; *model 2*, combination of Duke Clinical Score and presence of diastolic dysfunction; and *model 3*, combination of Duke Clinical Score, diastolic dysfunction, and GLS. For this purpose, the statistical significance of the difference between the areas under the ROC curves

was tested using the method proposed by Hanley and McNeil.[23] The Bayes' theorem was then applied to estimate the posttest likelihood of obstructive CAD yielded by the variables that provided incremental value over the pretest likelihood of obstructive CAD (Duke Clinical Score).

In addition, variability and reproducibility of speckle-tracking measurements were assessed. The coefficient of variation (ie, the ratio between the mean value and the SD) was computed for each parameter. Reproducibility of speckle-tracking measurements was analyzed with repeated measurements by 1 experienced observer at 2 different time points and by a second experienced observer in 20 randomly selected individuals. Intraobserver and interobserver agreements for each parameter were evaluated by Bland-Altman analysis. Furthermore, intraclass correlation coefficients were used as indicators of reproducibility.

All statistical tests were 2 sided, and a P value <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software package (SPSS 15.0; SPSS Inc, Chicago, IL).

The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper and its final contents. No extramural funding was used to support this work.

RESULTS

Clinical and echocardiographic characteristics of the patient population

Clinical and echocardiographic characteristics of the patient population are summarized in Table 1. The mean age was 54±10 years, and 108 patients (59%) were male. A total of 76 patients (42%) were asymptomatic, whereas 76 patients (42%) had history of noncardiac chest pain or atypical angina, and 30 patients (16%) had a history of typical angina. The Duke Clinical Score was low, intermediate, and high, respectively, in 88 (48%), 60 (33%), and 34 (19%) patients.

Table 1. Baseline characteristics of the patient population

Variable	n = 182
Age (years)	54±10
Male gender	108 (59%)
Family history of CAD	81 (45%)
Diabetes	42 (23%)
Hypertension	95 (52%)
Smoker	59 (32%)
Hypercholesterolemia	74 (41%)
BMI	26.9±4.5
Symptoms	
- asymptomatic	76 (42%)
- non-anginal or atypical chest pain	76 (42%)
- typical chest pain	30 (16%)
Duke Clinical Score	
- low	88 (48%)
- intermediate	60 (33%)
- high	34 (19%)
LVEDV (ml)	108±30
LVESV (ml)	41±15
LVEF (%)	62±7
LV mass index (g/m^2)	100±26
Diastolic function	
- normal	99 (55%)
- diastolic dysfunction grade 1	79 (43%)
- diastolic dysfunction grade 2	4 (2%)
E/E' ratio	10.0±4.3
GLS (%)	-17.6±2.4
GLSR (s^{-1})	-0.87±0.13
GSRivrt (s^{-1})	0.31±0.13
GSRe (s^{-1})	0.97±0.28

BMI: body mass index; CAD: coronary artery disease; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; GLS: global longitudinal strain; GLSR: global longitudinal strain rate; GSRe: global strain rate during early diastolic filling; GSRivrt: global strain rate during the isovolumic relaxation period; LV: left ventricular.

By definition, LVEF was within normal limits in all patients, whereas diastolic dysfunction was observed in 83 patients (45%). Regarding the speckle-tracking–derived parameters, GLS was −17.6±2.4%, GLSR was

-0.87 ± 0.13 s^{-1}, GSRivrt was 0.31 ± 0.13 s^{-1}, and GSRe was 0.97 ± 0.28 s^{-1}.

Coronary artery disease: correlation with clinical and echocardiographic parameters

Based on the results of MSCT coronary angiography, 59 patients (32%) were classified as having no CAD. A total of 60 patients (33%) showed nonobstructive CAD, whereas at least 1 significant (≥50% luminal narrowing) stenosis was observed in the remaining 63 patients (35%).

The clinical and echocardiographic characteristics of these 3 groups are summarized in Table 2 and Figure 2. Patients with normal coronary arteries were younger and more frequently female; in addition, they showed a lower prevalence of coronary risk factors and less often had typical angina. Consequently, the pretest likelihood of obstructive CAD, assessed using the Duke Clinical Score, was significantly lower in this group of patients as compared to those with nonobstructive CAD and obstructive CAD (analysis of variance $p < 0.001$). No significant difference in LVEF was noted among the 3 groups, whereas the patients with obstructive CAD showed a higher prevalence of diastolic dysfunction, as compared to the other 2 groups (Table 2).

A progressive impairment of the speckle-tracking parameters was observed across the 3 groups of patients (Figure 2); specifically, patients with obstructive CAD had significantly impaired GLS and GLSR, as compared to the other 2 groups (Figure 2). In addition, patients with obstructive CAD showed significantly impaired GSRivrt and GSRe, as compared to the patients with normal coronary arteries (Figure 2).

Table 2. Clinical and echocardiographic characteristics of the patient population in relation to the presence of coronary artery disease

	No CAD (n = 59)	Non-obstructive CAD (n = 60)	Obstructive CAD (n = 63)	p value
Age (years)	49±9 * †	54±9	57±10	<0.001
Male gender	26 (44%) ‡	35 (58%)	47 (75%)	0.003
Family history of CAD	29 (49%)	24 (40%)	28 (44%)	0.60
Diabetes	8 (14%)	15 (25%)	19 (30%)	0.086
Hypertension	25 (42%)	30 (50%)	40 (64%)	0.060
Smoker	13 (22%) §	19 (32%)	27 (43%)	0.048
Hypercholesterolemia	11 (19%) * †	26 (43%)	37 (59%)	<0.001
BMI	26.2±4.6	27.8±4.7	26.5±4.0	0.11
Symptoms	§			0.046
- asymptomatic	27 (46%)	27 (45%)	22 (35%)	
- non-anginal or atypical chest pain	29 (49%)	21 (35%)	26 (41%)	
- typical chest pain	3 (5%)	12 (20%)	15 (24%)	
Duke Clinical Score	† ‖			<0.001
- low	49 (83%)	25 (42%)	14 (22%)	
- intermediate	7 (12%)	25 (42%)	28 (45%)	
- high	3 (5%)	10 (16%)	21 (33%)	
LVEDV (ml)	107±32	105±30	111±29	0.51
LVESV (ml)	41±15	40±15	43±15	0.56
LVEF (%)	63±8	62±7	62±8	0.86
LV mass index (g/m^2)	92±22 ‡	99±23	109±30	0.001
Diastolic function	§	§		0.007
- normal	38 (64%)	38 (63%)	23 (37%)	
- diastolic dysfunction grade 1	21 (36%)	21 (35%)	37 (59%)	
- diastolic dysfunction grade 2	-	1 (2%)	3 (5%)	
E/E' ratio	8.7±2.7 §	10.2±3.5	10.9±5.8	0.014

* = p <0.05 vs. CAD <50%. † = p <0.001 vs. CAD ≥50%. ‡ = p <0.01 vs. CAD ≥50%. § = p <0.05 vs. CAD ≥50%. ‖ = p <0.001 vs. CAD <50%. Abbreviations as in Table 1.

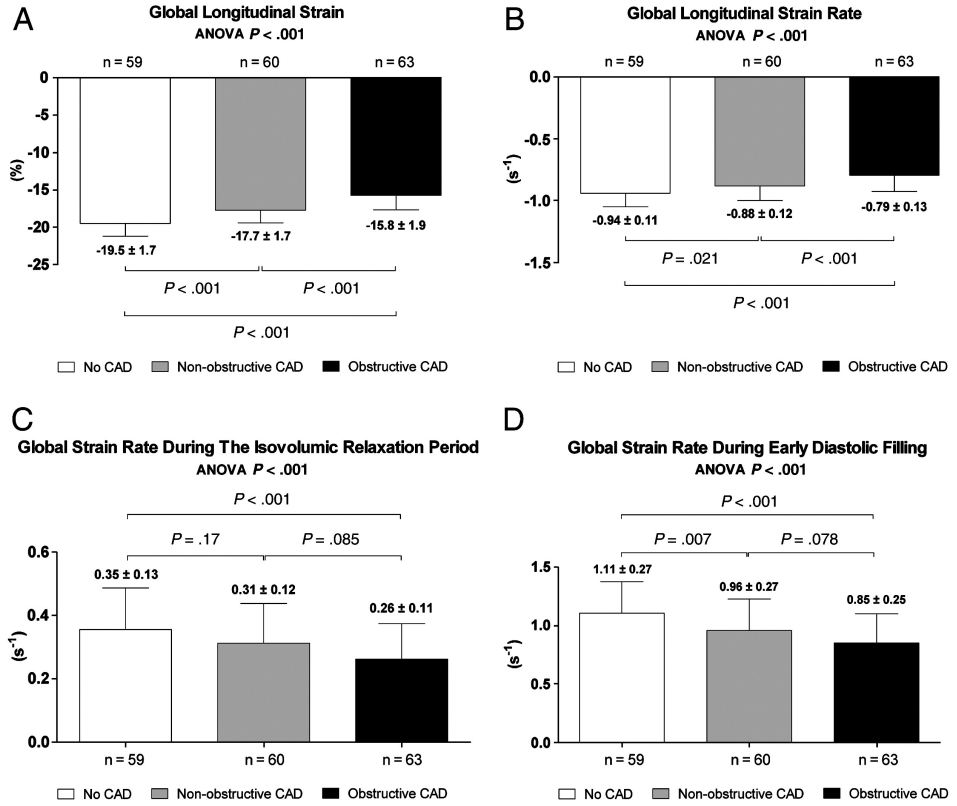

Figure 2. Progressive impairment of the speckle-tracking parameters with increasing severity of CAD. Differences in GLS (**panel A**), GLSR (**panel B**), GSRivrt (**panel C**), and GSRe (**panel D**) among patients with no CAD (white bars), nonobsructive CAD (gray bars), and obstructive CAD (black bars).

Univariate and multivariate analysis

Table 3 shows the results of the univariate and multivariate logistic regression analysis performed to determine the independent correlates of obstructive CAD. At univariate analysis, several variables were significantly related to obstructive CAD as follows: Duke Clinical Score, LV mass index, presence of diastolic dysfunction, GLS, GLSR, GSRivrt, and GSRe. However, at multivariate analysis, only high Duke Clinical Score (odds ratio [OR] 3.21, 95% CI 1.02-10.09, p = 0.046), presence of diastolic dysfunction (OR 3.72, 95% CI 1.44-9.57, p = 0.006), and GLS

(OR 1.97, 95% CI 1.43-2.71, p <0.001) were independent factors associated with obstructive CAD.

At ROC curve analysis (Figure 3), GLS ≥−17.4% had the highest sensitivity and specificity for identification of patients with obstructive CAD (83% and 77%, respectively).

Table 3. Univariate and multivariate logistic regression analyses to determine the independent correlates of obstructive coronary artery disease

	Univariate		Multivariate	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Duke Clinical Score				
- intermediate vs. low	4.63 (2.16-9.93)	<0.001	2.30 (0.87-6.04)	0.092
- high vs. low	8.54 (3.48-20.94)	<0.001	3.21 (1.02-10.09)	0.046
LVEF *	0.99 (0.95-1.03)	0.60	-	-
LV mass index *	1.02 (1.01-1.04)	0.001	1.01 (0.99-1.03)	0.33
Presence of diastolic dysfunction	3.07 (1.63-5.80)	0.001	3.72 (1.44-9.57)	0.006
E/E' ratio *	1.09 (0.99-1.19)	0.055	-	-
GLS *	2.20 (1.73-2.80)	<0.001	1.97 (1.43-2.71)	<0.001
GLSR †	2.36 (1.69-3.28)	<0.001	1.39 (0.91-2.13)	0.13
GSRivrt †	0.62 (0.48-0.82)	0.001	0.88 (0.61-1.27)	0.50
GSRe †	0.77 (0.68-0.88)	<0.001	1.17 (0.96-1.44)	0.12
			C-statistic = 0.89	

*: OR and 95% CI are intended for 1 unit increase. †: OR and 95% CI are intended for 0.1 unit increase. CI: confidence intervals; OR: odds ratio. Other abbreviations as in Table 1.

Incremental value of GLS to predict obstructive CAD

The ROC curves were generated to determine the predictive value of Duke Clinical Score alone (model 1), Duke Clinical Score combined with the presence of diastolic dysfunction (model 2), and Duke Clinical Score combined with the presence of diastolic dysfunction and GLS (model 3), with respect to obstructive CAD. As shown in Figure 4, the presence of diastolic dysfunction did not provide any incremental value over the Duke Clinical Score (p = .25 for model 2 vs model 1). In contrast, by adding GLS (with ≥−17.4% used as cutoff value) (model 3), the ability to detect

obstructive CAD was significantly improved (area under the curve 0.83, 95% CI 0.77-0.88, p <0.001 vs model 1 and model 2).

The diagnostic impact of GLS on the estimated pretest likelihood of obstructive CAD is shown in Figure 5.

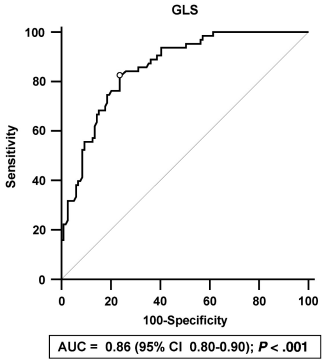

Figure 3. Accuracy of GLS to detect obstructive CAD. Receiver-operator characteristic curve, testing the accuracy of GLS to detect obstructive CAD. GLS ≥−17.4% provided the highest sensitivity (83%) and specificity (77%) for identification of patients with obstructive CAD (positive likelihood ratio 3.51, negative likelihood ratio 0.23). AUC indicates area under the curve.

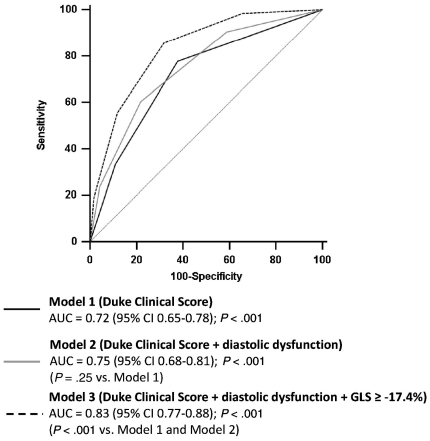

Figure 4. Incremental value of GLS. Receiver-operator characteristic curves testing the potential incremental value of diastolic dysfunction and GLS ≥−17.4% over the Duke Clinical Score to detect obstructive CAD. AUC indicates area under the curve.

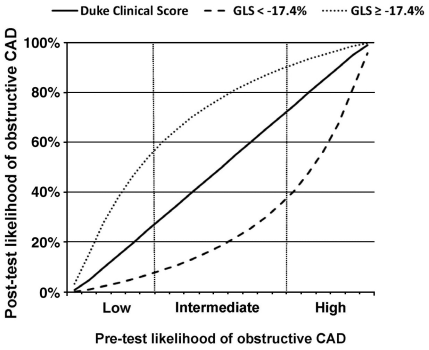

Figure 5. Effect of GLS on probability of obstructive CAD as a function of pretest likelihood. Estimated posttest likelihood of obstructive CAD yielded by the GLS compared to the pretest likelihood of obstructive CAD estimated using the Duke Clinical Score. The positive and negative likelihood ratios provided in the legend of Figure 3 were used to calculate the estimated posttest likelihood of obstructive CAD.

Variability and reproducibility of speckle-tracking parameters

Variability and reproducibility of speckle-tracking measurements are shown in Table 4. The assessment of GLS had lower variability and higher reproducibility, as compared to the assessment of strain rate parameters.

Table 4. Variability and reproducibility of speckle-tracking measurements

	Variability	Intraobserver agreement		Interobserver agreement	
	CV	Mean±2SD	ICC	Mean±2SD	ICC
GLS	0.14	-0.20±0.53%	99%	-0.25±1.37%	97%
GLSR	0.15	-0.02±0.07s^{-1}	97%	-0.03±0.10s^{-1}	93%
GSRivrt	0.42	–0.01±0.10s^{-1}	95%	0.01±0.13s^{-1}	91%
GSRe	0.29	0.03±0.14s^{-1}	97%	-0.02±0.21s^{-1}	95%

CV: coefficient of variation; ICC: intraclass correlation coefficient; SD: standard deviation. Other abbreviations as in Table 1.

DISCUSSION

The results of the present evaluation can be summarized as follows: *(1)* both LV diastolic dysfunction and subclinical LV systolic dysfunction are independently related to obstructive CAD and *(2)* only the presence of subclinical LV systolic dysfunction provides significant incremental value over the Duke Clinical Score for the identification of patients having obstructive CAD.

Relation between CAD and LV diastolic dysfunction

Coronary artery disease is considered one of the potential causes of LV diastolic dysfunction.[24] Previous studies indeed showed a high prevalence of global and regional LV diastolic dysfunction in patients with CAD and normal LV systolic function.[6-8] Moreover, a progressive impairment of LV relaxation has been observed in relation to the severity of coronary atherosclerosis and the number of diseased vessels,[6,25] and a reversal of these abnormalities has been described after percutaneous coronary intervention.[26,27] Several mechanisms have been proposed to explain this association. In particular, it has been postulated that repetitive episodes of subclinical ischemia may impair LV relaxation, which is an active, energy-dependent process.[28] In addition, the presence of severely reduced coronary flow may induce structural remodeling of the myocardium (ie, myocardial fibrosis and hypertrophy and glycogen accumulation), leading to LV diastolic dysfunction.[6]

Confirming these previous observations, an independent relation between LV diastolic dysfunction and obstructive CAD was observed in the present evaluation. However, the clinical use of this relation appeared to be limited because the presence of LV diastolic dysfunction did not provide any incremental value over the traditional assessment of pretest likelihood of obstructive CAD (Duke Clinical Score). Indeed, other factors (ie, diabetes mellitus, hypertension) also can play a role in determining LV

diastolic dysfunction,[29,30] potentially reducing its accuracy in identifying patients with obstructive CAD.

Relation between CAD and subclinical LV systolic dysfunction

Few previous studies addressed the issue of subclinical LV systolic dysfunction in relation to CAD, providing contradictory results. For instance, Bolognesi et al.[31] observed an impairment of LV longitudinal shortening (assessed by tissue-Doppler and long-axis M-mode echocardiography), despite normal LVEF, among patients with obstructive CAD. Conversely, Yuda et al.[6] did not observe any difference in systolic myocardial velocity and strain rate (assessed by tissue-Doppler echocardiography) between LV segments subtended by vessels with and without obstructive CAD. More recently, Edvardsen et al.[9] evaluated the relation between myocardial systolic strain and strain rate (assessed by tagged magnetic resonance imaging) and CAD (expressed as calcium score by MSCT or electron-beam computed tomography) in a large cohort of patients without history of CAD and with normal LVEF. An impairment of regional LV systolic function was observed in relation to the presence of coronary atherosclerosis.

In the present evaluation, speckle-tracking echocardiography and MSCT coronary angiography were used to evaluate the presence of subclinical LV systolic dysfunction and CAD, respectively, in a cohort of patients with increased risk profile and/or stable chest pain and normal LVEF. Speckle-tracking echocardiography (used to assess strain and strain rate) provides a direct measure of myocardial deformation and can therefore be used to detect subtle abnormalities in LV systolic function.[13] The MSCT coronary angiography provides direct noninvasive visualization of the coronary arteries, allowing evaluation of CAD at an early stage.[10]

Interestingly, a progressive impairment of GLS and GLSR was observed with increasing severity of CAD; in addition, an independent relation between GLS and obstructive CAD was found. These data support the hypothesis that subclinical myocardial damage may be a marker of

coronary atherosclerosis even in the absence of myocardial infarction, mainly because of small-vessel microembolization, endothelial dysfunction, or chronic ischemia.[9]

Clinical implications

Besides demonstrating a strong independent relation between subclinical LV systolic dysfunction and obstructive CAD, the present evaluation showed a significant incremental value of GLS over the Duke Clinical Score for identification of patients with obstructive CAD. Especially among the patients with low or intermediate Duke Clinical Score, the presence of subclinical LV systolic dysfunction significantly increased the likelihood of having obstructive CAD. Importantly, the assessment of GLS had lower variability and higher reproducibility, as compared to the assessment of strain rate parameters; these data further confirm the clinical use of GLS and may partially explain why strain rate parameters were not independently related to obstructive CAD.

Accordingly, routine screening for subclinical LV systolic dysfunction among patients with coronary risk factors and/or stable chest pain may possibly refine the traditional clinical assessment and may be useful for selection of further diagnostic tests.

CONCLUSIONS

The LV diastolic dysfunction and subclinical systolic dysfunction are independently related to the presence of obstructive CAD. In particular, subclinical LV systolic dysfunction provides significant incremental value over the Duke Clinical Score for the identification of patients having obstructive CAD.

REFERENCES

1. Diamond GA, Forrester, JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med. 1979; 300: 1350–1358
2. Pryor DB, Harrell FE Jr., Lee KL, et al. Estimating the likelihood of significant coronary artery disease. Am J Med. 1983; 75: 771–780
3. Morise AP, Haddad WJ, Beckner, D. Development and validation of a clinical score to estimate the probability of coronary artery disease in men and women presenting with suspected coronary disease. Am J Med. 1997; 102: 350–356
4. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Coll Cardiol. 2003; 42: 954–970
5. Chen YZ, Sherrid MV, Dwyer, EM Jr. Value of two-dimensional echocardiography in evaluating coronary artery disease: a randomized blinded analysis. J Am Coll Cardiol. 1985; 5: 911–917
6. Yuda S, Fang ZY, Marwick, TH. Association of severe coronary stenosis with subclinical left ventricular dysfunction in the absence of infarction. J Am Soc Echocardiogr. 2003; 16: 1163–1170
7. Lee KW, Blann AD, Lip, GY. Impaired tissue Doppler diastolic function in patients with coronary artery disease: relationship to endothelial damage/dysfunction and platelet activation. Am Heart J. 2005; 150: 756–766
8. Liang HY, Cauduro S, Pellikka P, et al. Usefulness of two-dimensional speckle strain for evaluation of left ventricular diastolic deformation in patients with coronary artery disease. Am J Cardiol. 2006; 98: 1581–1586
9. Edvardsen T, Detrano R, Rosen BD, et al. Coronary artery atherosclerosis is related to reduced regional left ventricular function in individuals without history of clinical cardiovascular disease: the Multiethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2006; 26: 206–211
10. Schuijf JD, Pundziute G, Jukema JW, et al. Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease. Am J Cardiol. 2006; 98: 145–148

11. Reisner SA, Lysyansky P, Agmon Y, et al. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr. 2004; 17: 630–633
12. Amundsen BH, Helle-Valle T, Edvardsen T, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol. 2006; 47: 789–793
13. Delgado V, Mollema SA, Ypenburg C, et al. Relation between global left ventricular longitudinal strain assessed with novel automated function imaging and biplane left ventricular ejection fraction in patients with coronary artery disease. J Am Soc Echocardiogr. 2008; 21: 1244–1250
14. Schuijf JD, Wijns W, Jukema JW, et al. Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. J Am Coll Cardiol. 2006; 48: 2508–2514
15. Meijboom WB, van Mieghem CA, Mollet NR, et al. 64-slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. J Am Coll Cardiol. 2007; 50: 1469–1475
16. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18: 1440–1463
17. Devereux RB, Reichek, N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation. 1977; 55: 613–618
18. Quinones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr. 2002; 15: 167–184
19. Lester SJ, Tajik AJ, Nishimura RA, et al. Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. J Am Coll Cardiol. 2008; 51: 679–689

20. Nagueh SF, Middleton KJ, Kopelen HA, et al. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol. 1997; 30: 1527–1533
21. Wang J, Khoury DS, Thohan V, et al. Global diastolic strain rate for the assessment of left ventricular relaxation and filling pressures. Circulation. 2007; 115: 1376–1383
22. Leber AW, Knez A, Becker A, et al. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. J Am Coll Cardiol. 2004; 43: 1241–1247
23. Hanley JA, McNeil, BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology. 1983; 148: 839–843
24. Fischer M, Baessler A, Hense HW, et al. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J. 2003; 24: 320–328
25. Rydberg E, Willenheimer R, Erhardt, L. The prevalence of impaired left ventricular diastolic filling is related to the extent of coronary atherosclerosis in patients with stable coronary artery disease. Coron Artery Dis. 2002; 13: 1–7
26. Bonow RO, Kent KM, Rosing DR, et al. Improved left ventricular diastolic filling in patients with coronary artery disease after percutaneous transluminal coronary angioplasty. Circulation. 1982; 66: 1159–1167
27. Tanaka H, Kawai H, Tatsumi K, et al. Improved regional myocardial diastolic function assessed by strain rate imaging in patients with coronary artery disease undergoing percutaneous coronary intervention. J Am Soc Echocardiogr. 2006; 19: 756–762
28. Reduto LA, Wickemeyer WJ, Young JB, et al. Left ventricular diastolic performance at rest and during exercise in patients with coronary artery disease. Assessment with first-pass radionuclide angiography. Circulation. 1981; 63: 1228–1237
29. Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. J Am Coll Cardiol. 2006; 48: 1548–1551
30. Slama M, Susic D, Varagic J, et al. Diastolic dysfunction in hypertension. Curr Opin Cardiol. 2002; 17: 368–373
31. Bolognesi R, Tsialtas D, Barilli AL, et al. Detection of early abnormalities of left ventricular function by hemodynamic, echo-tissue Doppler imaging, and mitral

Doppler flow techniques in patients with coronary artery disease and normal ejection fraction. J Am Soc Echocardiogr. 2001; 14: 764–772