Stress-induced alteration of left ventricular eccentricity: An additional marker of multivessel CAD

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Background. **Abnormal left ventricular (LV) eccentricity index (EI) is a marker of adverse cardiac remodeling. However, the interaction between stress-induced alterations of EI and major cardiac parameters has not been explored. We sought to evaluate the relationship between LV EI and coronary artery disease (CAD) burden in patients submitted to myocardial perfusion imaging (MPI).**

Methods and results. **Three-hundred and forty-three patients underwent MPI and coronary angiography. LV ejection fraction (EF) and EI were computed from gated stress images as measures of stress-induced functional impairment.**

One-hundred and thirty-six (40%), 122 (35%), and 85 (25%) patients had normal coronary arteries, single-vessel CAD, and multivessel CAD, respectively. Post-stress EI was lower in patients with multivessel CAD than in those with normal coronary arteries and single-vessel CAD ($P = 0.001$). This relationship was confirmed only in patients undergoing exercise stress test, where a lower post-stress EI predicted the presence of multivessel CAD ($P = 0.039$).

Conclusions. **Post-stress alterations of LV EI on MPI may unmask the presence of multivessel CAD. (J Nucl Cardiol 2019;26:227–32.)**

Key Words: Left ventricular remodeling • eccentricity index • gated SPECT • CZT • ejection fraction

Abbreviations

CZT	Cadmium-zinc-telluride
SPECT	Single-photon emission computed tomography
EI	Eccentricity index
MPI	Myocardial perfusion imaging

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INTRODUCTION

Myocardial perfusion imaging (MPI) on single-photon emission computed tomography (SPECT) represents a reference standard for the evaluation of myocardial ischemia. However, in patients with multivessel coronary artery disease (CAD), the accuracy of MPI can be diminished.[1] Additional left ventricular

(LV) functional parameters, such as stress-induced LV dilatation and systolic dysfunction, have been suggested as valuable tools for the identification of patients with multivessel CAD.[2] Interestingly, apart from perfusion and functional data, MPI on SPECT may also give information on LV three-dimensional structure, by the quantification of the LV eccentricity index (EI).[3] A lower EI, representing a more spherical LV, has been associated with the presence of CAD, ultimately predicting adverse patients prognosis.[3,4] However, since the role of an impaired LV EI has been studied mostly in patients with depressed systolic function,[4] the possible clinical impact of abnormal values of LV EI in patients with preserved LV systolic function has not been yet fully evaluated.

We aimed at evaluating the possible clinical value of the assessment of LV EI in patients with preserved LV systolic function submitted to MPI, and its ability in unmasking the presence of multivessel CAD.

MATERIALS AND METHODS

Patient Population

Between June 2014 and December 2016, 2745 patients underwent stress/rest MPI on a dedicated cadmium-zinc-telluride (CZT) cardiac camera (Discovery NM 530c; GE Healthcare; Haifa, Israel) in our laboratory. Of those, 343 consecutive patients with chest pain and normal LV systolic function [ejection fraction (EF) >50%] underwent MPI followed by coronary angiography within 3 months. The study was approved by the Local Ethical Committee and conformed to the Declaration of Helsinki on human research. Written informed consent was obtained from every patient.

Imaging Protocol

Two-hundred and thirty-seven (69%) underwent exercise, while 104 patients (31%) dipyridamole (0.56 mg/kg IV over 4 minutes) stress testing. Of the patients undergoing exercise stress test, 165 (49%) reached >85% of the age-predicted maximum heart rate or a rate pressure product (RPP) >26000, while in 102 (30%) the test was ended because of stress-induced severe chest pain and/or significant ST-segment depression. In every patient, the ratio between stress and rest RPP values was calculated as measure of stress-related cardiac workload. CZT imaging was performed with a single-day protocol (185-222 MBq of ^{99m}Tc-tetrofosmin during stress and 370-444 MBq at rest). Stress-CZT was performed 10-15 minutes after radiopharmaceutical injection with an acquisition time of 7 minutes. Patients were injected at rest 30 minutes after the end of the first acquisition and then, after an interval of 30-45 minutes, a second acquisition was carried out for 6 minutes.[5,6] List mode files were acquired and stored. Images were reconstructed on a standard workstation (Xeleris II; GE Healthcare, Haifa, Israel) using a dedicated iterative algorithm without resolution recovery or attenuation correction.

Analysis of CZT Images

The summed difference score (SDS) was calculated and graded as follows: mild ischemia ($3 < \text{SDS} \leq 7$) and significant ischemia ($\text{SDS} > 7$).[7]

LV function analysis was performed on 16-frame reformatted images. End-diastolic volume (EDV), and EF were calculated.[8] LV eccentricity was evaluated using a dedicated software (QGS/QPS; Cedars-Sinai Medical Center, CA, USA).[3] Any gated short-axis datasets with associated LV contours have the eccentricity of its mid-myocardial wall automatically computed for each interval, and expressed as an EI. Eccentricity is a measure of elongation of the LV, and varies from 0 (sphere) to 1 (line). It is calculated from the major axis R_z and the minor axes R_x and R_y of the ellipsoid that best fits the mid-myocardial surface of the LV, according to the following formula: $\text{EI} = [1-(R_xR_y/R_z^2)]^{0.5}$

Coronary Angiography

Coronary stenoses with diameter reduction >50% in the left main stem and >70% in any other vessel were considered significant.

Statistical Analysis

Groups were compared for categorical data using Fisher's exact test and for continuous variables using the analysis of variance followed by the Fisher's protected least significant difference for multiple comparisons. Appropriate non-parametric tests were used in case of non-normally distributed variables. Logistic regression analysis was used to identify the predictors of the presence of multivessel CAD among patients clinical and cardiac functional, and perfusion variables (Suppl. Table 1). Only significant variables at univariate analyses were entered in the multivariate model. All tests were 2-sided; a $P < 0.05$ was considered to be significant. Analyses were performed using JMP statistical software (SAS Institute Inc, version 4.0.0) and Stata software (Stata Statistical Software: Release 10, StataCorp. 2007, College Station, TX).

RESULTS

The clinical and CZT data of the patients population are reported in Table 1. On coronary angiography, 136/343 (40%), 122 (35%), and 85 (25%) patients had normal coronary arteries, single-vessel, and multivessel CAD, respectively.

Relationships Between CAD Burden and LV Perfusion and Functional Parameters

The presence of significant CAD was associated with more impaired LV functional and structural parameters, both at rest and after stress (Table 1).

Table 1. Clinical characteristics according to CAD extent

Parameter	Normal coronary arteries (n = 136)	Single-vessel disease (n = 122)	Multivessel disease (n = 85)	P value
Demographics				
Age, years	68 ± 11	70 ± 10	71 ± 9	**0.036**
Male gender, n (%)	86 (63)	94 (77)	64 (75)	**0.032**
Cardiovascular risk factors				
Family history of CAD, n (%)	43 (32)	24 (20)	31 (36)	**0.017**
Diabetes, n (%)	31 (23)	29 (24)	39 (46)	**<0.001**
Hypercholesterolemia, n (%)	59 (43)	48 (39)	39 (46)	0.625
Hypertension, n (%)	80 (60)	65 (53)	55 (65)	0.256
Smoking, n (%)	8 (6)	13 (11)	11 (13)	0.135
MPI protocol				0.351
Exercise stress test, n (%)	91 (67)	82 (67)	64 (75)	
Pharmacologic stress test, n (%)	45 (33)	40 (33)	21 (25)	
Perfusion data				
Summed rest score	0.5 ± 1.3	3.1 ± 3.8**	4.8 ± 6.1**,##	**<0.001**
Summed stress score	3.8 ± 3.4	9.4 ± 5.6**	13.4 ± 7.2**,##	**<0.001**
Reversible ischemia				**<0.001**
Mild ($3 < SDS \leq 7$)	45 (33)	56 (46)	31 (36)	
Significant ($SDS > 7$)	9 (7)	38 (31)**	47 (55)**,#	
LV structure and function at rest				
End-diastolic volume (mL)	86 ± 20	92 ± 23*	91 ± 23	0.084
Ejection fraction (%)	65 ± 7	62 ± 8**	63 ± 6*	**0.002**
Eccentricity index	0.89 ± 0.03	0.88 ± 0.03*	0.87 ± 0.03**	**0.001**
LV structure and function after exercise stress test				
End-diastolic volume (mL)	85 ± 20	90 ± 22	92 ± 19*	0.102
Ejection fraction (%)	64 ± 8	63 ± 8	60 ± 8**	**0.020**
Eccentricity index	0.88 ± 0.04	0.87 ± 0.04	0.85 ± 0.04**,#	**0.003**
LV structure and function after vasodilator stress test				
End-diastolic volume (mL)	87 ± 23	91 ± 28	95 ± 30	0.468
Ejection fraction (%)	64 ± 9	62 ± 10	62 ± 10	0.609
Eccentricity index	0.87 ± 0.04	0.87 ± 0.04	0.86 ± 0.05	0.350

Bold values are statistically significant ($P < 0.05$)
* and ** $P < 0.05$ and $P < 0.01$ vs "Normal coronary arteries"; # and ## $P < 0.05$ and $P < 0.01$ vs "Single-vessel CAD"

However, these interactions were confirmed only in patients submitted to exercise stress test, with significantly lower values of post-stress EF, EDV, and EI in patients with multivessel CAD than in subjects with normal coronary arteries or single-vessel CAD (Table 1).

In fact, a significant interaction between stress test category (exercise vs vasodilator) and post-stress LV functional parameters was revealed. The correlation between increasing CAD burden and post-stress LV functional and structural impairment was confirmed only in patients submitted to exercise stress test, while disappeared in those undergoing vasodilator stress test (Table 1; Fig. 1). Weaker correlations were revealed among CAD burden and resting LV functional parameters (Suppl. Fig. 1), where neither EI nor EF values

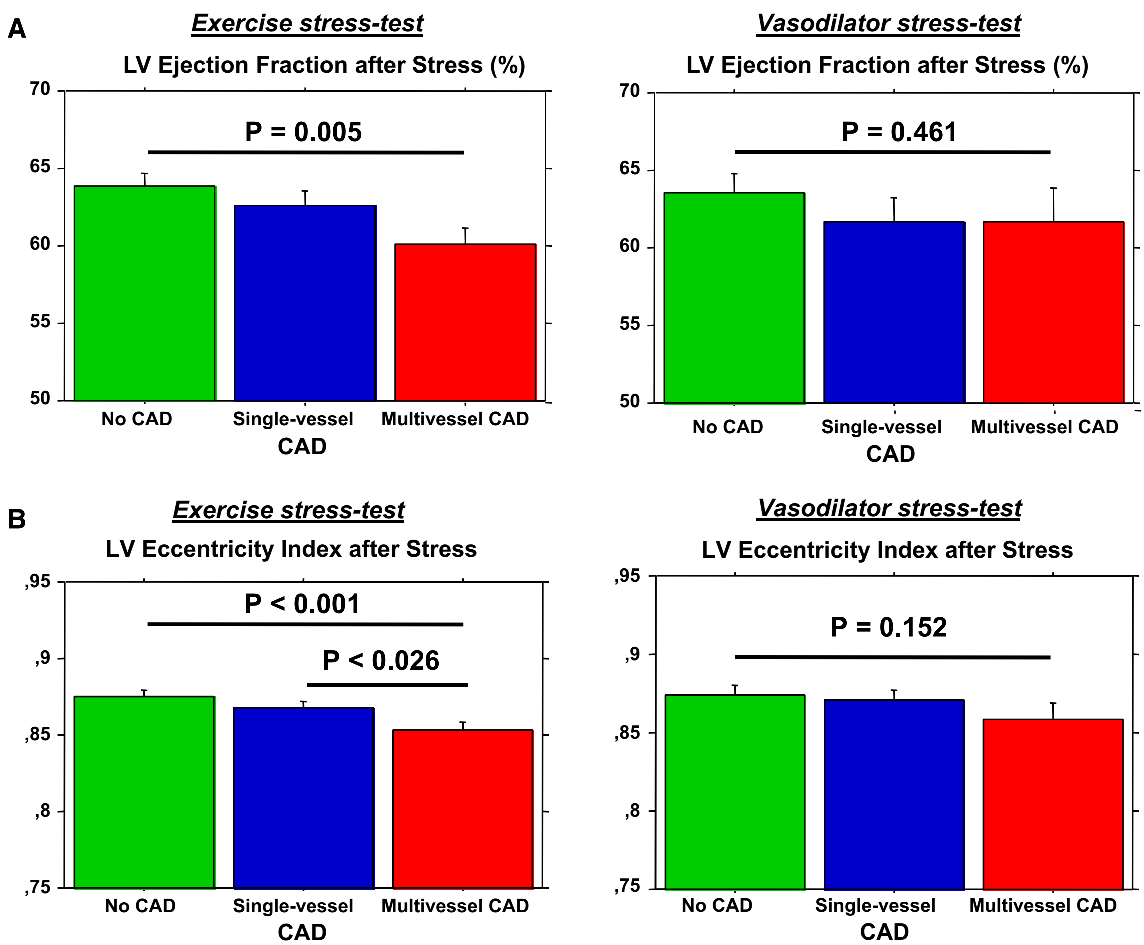

Figure 1. Relationships between CAD burden and (**A**) functional (EF) and (**B**) structural (EI) signs of stress-induced LV impairment on either exercise (*left*) or vasodilator (*right*) stress test.

could discriminate between patients with single-vessel and multivessel CAD. In this respect, modest albeit significant relationships were revealed between increasing values of stress/rest RPP-ratio, measure of stress-related cardiac workload, and more abnormal values of post-stress EI ($r = -0.11$ and $P = 0.04$).

Predictors of Multivessel CAD

In patients submitted to exercise stress test, the presence of myocardial ischemia on MPI and of abnormal values of post-stress LV eccentricity index were independent predictors of the presence of multivessel CAD (Suppl. Table 1).

On the contrary, when the analysis was limited to patients submitted to vasodilator stress test, the occurrence of myocardial ischemia on MPI remained the only predictor of multivessel CAD ($P = 0.022$ for mild ischemia and $P = 0.003$ for severe ischemia), overwhelming LV functional parameters.

DISCUSSION

In patients with preserved LV systolic function, the presence of multivessel CAD associates with significantly more impaired values of post-stress LV eccentricity, suggesting an interaction between diffuse myocardial ischemia and stress-induced LV remodeling.

Evaluation of Diffuse CAD on MPI: The Role of "Non-perfusion" Variables

While SPECT is considered a reference methods for the diagnosis of myocardial ischemia, there might be some categories of patients in whom the diagnostic power of MPI can be diminished.[1] To overcome this limitation, the evaluation of regional myocardial perfusion is generally coupled with the assessment of different functional or anatomical measures, i.e., transient ischemic dilatation, systolic or diastolic stunning, which may suggest the presence of diffuse CAD.[6,8] However, the accuracy of those measures is frequently insufficient in detecting significant CAD and may be influenced by the specific stress protocol employed.[9]

Our data show that, in patients with normal LV systolic function, there is a significant relationship between increasing CAD burden and stress-induced LV structural and functional abnormalities. In particular, patients with multivessel CAD tended to show signs of post-stress LV stunning and dilatation, with a significant increase of LV sphericity. Interestingly, those alterations were limited to patients undergoing exercise stress test, while disappeared in those submitted to vasodilator stress. While the impact of the specific stress protocol on the development of ischemia-induced LV functional abnormalities is still debated,[9] our data seem to suggest that an exercise stress test is probably needed to induce the sufficient amount of ischemia that may cause transient LV structural remodeling and dysfunction.

LV Remodeling on MPI: Determinants of Abnormal Cardiac Eccentricity

While abnormal LV eccentricity has been typically described in patients with depressed systolic function,[4] the value of abnormal measure of adverse LV remodeling in patients with preserved EF needs to be fully characterized. MPI on SPECT has been recently shown to allow assessing LV eccentricity with high reproducibility and low inter-observer variability (i.e., intraclass correlation coefficients $\geq$0.98).[3] In this respect, an abnormal LV EI at rest typically clusters with impaired measures of cardiac structure (i.e., LV dilatation) and function (i.e., depressed systolic and diastolic functions) and with the presence of CAD.[3] However, the possible role of stress-induced alterations of LV EI in patients with suspected CAD needs to be still evaluated.

Present data suggest that the occurrence of post-stress abnormalities of LV EI after exercise stress, identifying patients showing a transient increase of LV sphericity, could specifically predict the presence of multivessel CAD, independently from major LV functional and perfusion data. Patients with multivessel CAD also presented a significant post-stress drop of LV EF associated with dilatation, suggesting the presence of ischemia-related LV functional stunning. Moreover, despite the obvious relationship between LV EI and other major LV functional and structural parameters, only a marginal fraction of the variability of post-stress LV EI could be explained by alterations of either EF or EDV (Suppl. Fig. 2), confirming the possible value of this novel parameter of adverse remodeling.

Nevertheless, changes of LV EI might be the result of relative sub-endocardial hypo-perfusion due to increased LV intra-cavitary pressure rather than cardiac dilatation.[9] Accordingly, the administration of a vasodilator could have improved sub-epicardial perfusion through LV unloading. However, the fact that patients with multivessel CAD submitted to exercise stress test also presented a significant drop of LV EF plays against this possibility, pointing to the presence of diffuse LV ischemia as possible determinant of EI abnormalities.

LIMITATIONS

The consecutive nature of the enrolment prevented the selection of a homogeneous population of patients. While the present population may partially overlap with the population of patients of a previous report,[3] the great differences in terms of number of patients as well as study variables and end-points between the present and previous reports ensure the originality of the data. Considering the limited patients population, patients with two- and three-vessels disease were grouped together. Nevertheless, those two categories of patients behaved similarly regarding values of SDS and of post-stress LV structural and functional impairment ($P > 0.05$ for all). The inclusion of some patients with scintigraphic evidence of previous myocardial infarction could have limited the effectiveness of LV functional evaluation at gated CZT. However, the correlation between post-stress LV EI and multivessel CAD was confirmed even after excluding patients with a previous myocardial infarction (Suppl. Table 2). Nevertheless, like in the case of other LV functional measures (i.e., EF), the impact of variability in image reconstruction on EI (i.e., LV axis and wall constraints) quantification cannot be excluded. However, manual editing of CZT images was carefully limited. Moreover, the individualized dose of ^{99m}Tc-Tetrofosmin administered to our patients has been already reported to allow an excellent count statistics with limited radiation exposure.[10] Finally, no definitive information on stress effectiveness can be drawn from patients submitted to vasodilator stress test. However, of the patients undergoing pharmacologic test, 51 (48%) presented significant ST-segment depression or angina, while 50 (47%) patients had a >25% increase in RPP following vasodilator infusion, as a possible additional sign of stress effectiveness.

CONCLUSIONS

In patients with normal LV systolic function, the extent of CAD burden correlates with the development of significant stress-induced LV functional and structural abnormalities. In particular, the occurrence of post-stress alterations of LV eccentricity index may indicate the presence of multivessel CAD, independently of major perfusion and LV functional parameters.

NEW KNOWLEDGE GAINED

MPI offers the opportunity to quantify key LV functional and structural parameters and to assess the integrated effects of myocardial ischemia on cardiac mechanics. In patients with normal LV systolic function submitted to exercise stress-MPI, the development of stress-induced alterations of LV eccentricity may associate with the presence of multivessel CAD.

Disclosure

The authors have no conflicts of interest to disclose.

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