Abnormal Left Ventricular Contractile Response to Exercise in the Absence of Obstructive Coronary Artery Disease Is Associated with Resting Left Ventricular Long-Axis Dysfunction

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Background: The etiology of reduced left ventricular (LV) ejection fraction after exercise, without obstructive coronary artery disease or other established causes, is unclear. The aims of this study were to determine whether patients undergoing treadmill stress echocardiography with this abnormal LV contractile response to exercise (LVCRE) without established causes have resting LV long-axis dysfunction or microvascular dysfunction and to determine associations with this abnormal LVCRE.

Methods: Of 5,275 consecutive patients undergoing treadmill stress echocardiography, 1,134 underwent cardiac computed tomography angiography or invasive angiography. Having excluded patients with obstructive coronary artery disease, hypertensive response, submaximal heart rate response, resting LV ejection fraction < 50%, and valvular disease, 110 with "abnormal LVCRE" and 212 with "normal LVCRE" were analyzed. Resting mitral annular velocities were measured to assess LV long-axis function. Myocardial blush grade and corrected Thrombolysis In Myocardial Infarction frame count were determined angiographically to assess microvascular function.

Results: Comparing normal LVCRE with abnormal LVCRE, age (mean, 59.7 ± 11.1 vs 61.4 ± 10.0 years), hypertension (53% vs 55%), diabetes (16% vs 20%), and body mass index (mean, 29.1 ± 5.4 vs 29.5 ± 6.4 kg/m^2) were similar ($P > .05$). Abnormal LVCRE had reduced resting LV long-axis function with lower septal (mean, 6.1 ± 1.9 vs 7.7 ± 2.2 cm/sec) and lateral (mean, 8.1 ± 2.9 vs 10.4 ± 3.0 cm/sec) e′ velocities ($P < .001$) and larger resting left atrial volumes (mean, 37.3 ± 10.1 vs 31.1 ± 7.2 mL/m^2, $P < .001$). On multivariate analysis, female gender (odds ratio [OR], 1.21; 95% confidence interval [CI], 1.15–1.99; $P < .001$), exaggerated chronotropic response (OR, 1.49; 95% CI, 1.09–2.05; $P < .001$), resting left atrial volume (OR, 2.38; 95% CI, 1.63–3.47; $P < .001$), and resting lateral e′ velocity (OR, 1.70; 95% CI, 1.22–2.49; $P = .003$) were associated with abnormal LVCRE, but not myocardial blush grade or corrected Thrombolysis In Myocardial Infarction frame count.

Conclusions: An abnormal LVCRE in the absence of established causes is associated with resting LV long-axis dysfunction and is usually seen in women. (J Am Soc Echocardiogr 2015;28:95-105.)

Keywords: Exercise echocardiography, Coronary angiography, Myocardial function, Microvascular dysfunction

Treadmill stress echocardiography (TME) is a robust technique that is widely used for the noninvasive diagnosis of coronary artery disease (CAD). A normal left ventricular (LV) contractile response to exercise (LVCRE) involves a reduction in LV end-systolic volume and an increase in LV ejection fraction (LVEF),[1] which excludes obstructive CAD with high diagnostic accuracy.[2] In contrast, an abnormal LVCRE is defined as an increase in LV end-systolic volume and no change or reduction in LVEF after maximal exercise. As well as CAD, other conditions associated with an abnormal LVCRE are hypertensive response to exercise,[3] failure to achieve ≥85% maximum age-predicted heart rate,[4] reduced resting LVEF,[5] hypertrophic cardiomyopathy,[6] and severe resting valvular disease.[7,8] Although current theories postulate that in the absence of these conditions, microvascular dysfunction or resting LV long-axis dysfunction may cause an abnormal LVCRE, this remains unclear. However, regardless of etiology, such patients with an abnormal LVCRE in the absence of a clear cause may not have a benign prognosis.[9]

Resting LV long-axis dysfunction may be identified on echocardiography using pulsed-wave Doppler tissue imaging by measuring long-axis tissue velocities at the septal and lateral mitral annulus.

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Abbreviations

CAD = Coronary artery disease

CI = Confidence interval

CTCA = Computed tomographic coronary angiography

CTFC = Corrected Thrombolysis In Myocardial Infarction frame count

ICA = Invasive coronary angiography

LV = Left ventricular

LVCRE = Left ventricular contractile response to exercise

LVEF = Left ventricular ejection fraction

MBG = Myocardial blush grade

OR = Odds ratio

TME = Treadmill stress echocardiography

Furthermore, myocardial blush grade (MBG) and corrected Thrombolysis In Myocardial Infarction frame count (CTFC) are sensitive measures that can be measured on invasive coronary angiography (ICA) to determine resting microvascular function. Therefore, we sought to determine whether patients with an abnormal LVCRE in the absence of CAD or other known causes have resting LV long-axis dysfunction or microvascular dysfunction and to determine associations with this response.

METHODS

Study Population

We conducted a case-control study to evaluate 5,275 consecutive patients who underwent first-time TME at our urban tertiary hospital (Monash Medical Centre, Melbourne, Australia) between January 2009 and June 2012 for the investigation of suspected CAD. Of these, 1,134 underwent clinically indicated computed tomographic coronary angiography (CTCA) or ICA within 90 days of TME. Patients were excluded if they had known etiologies of abnormal LVCRE, namely, obstructive CAD (>50% luminal stenosis in any coronary artery) on CTCA or ICA (622 patients), a hypertensive response (defined as >210/105 mm Hg in men and >190/105 mm Hg in women) (68 patients), failure to achieve >85% of maximum age-predicted ([220 − age] × 0.85) heart rate (45 patients), moderate or greater severity valvular heart disease (18 patients), resting LVEF < 50% (15 patients), or hypertrophic cardiomyopathy (12 patients). The 354 remaining patients were divided into three groups on the basis of LVCRE: (1) 32 patients had LV regional hypokinesis with normal overall LVCRE (>5% increase in postexercise LVEF compared with rest), representing a likely false-positive result for obstructive CAD, and were therefore excluded from further analysis; (2) 110 patients had an abnormal global LVCRE, defined as either a fall or no significant (<5%) increase in postexercise LVEF compared with rest; and (3) 212 patients demonstrated a normal LVCRE, defined as a >5% increase in postexercise LVEF compared with rest (Figure 1). Our institutional ethics committee approved the study, and all patients gave informed consent.

Baseline Rest and TME

All patients underwent symptom-limited treadmill exercise testing using the Bruce protocol. Symptoms and electrocardiography were monitored continuously during exercise. Blood pressure was measured noninvasively at rest and every 3 min during exercise. All patients underwent digital two-dimensional echocardiographic examinations in the left lateral decubitus position at rest and immediately after exercise using one of two commercially available systems: Vivid 7 (GE Healthcare, Australia) or iE33 (Philips Medical Systems, Australia). Postexercise imaging was completed within 60 sec of the termination of exercise in all patients. Images were acquired using a 3.5-MHz transducer in standard parasternal and apical two-, three-, and four-chamber views and viewed on a quad screen in cine-loop format. An echocardiologist, blinded to clinical and exercise data, traced LV endocardial borders on optimal nonforeshortened apical two- and four-chamber views and subsequently derived LV volumes and LVEF using the biplane method of disks on both rest and immediate postexercise images. At rest, a separate blinded analysis was performed to assess LV long-axis function by measuring mitral annular velocities with pulsed-wave Doppler tissue imaging according to American Society of Echocardiography recommendations[10] in the apical four-chamber view at the septal and lateral mitral annulus, with measurements averaged over three consecutive cardiac cycles. The following were also measured at rest according to American Society of Echocardiography recommendations[10,11]: LV end-diastolic dimension, interventricular septal and posterior wall thickness, left atrial volume, mitral inflow velocities and deceleration time, and right ventricular systolic pressure. Also, mitral leaflets were assessed for billowing or prolapse. Effective arterial elastance index, a measure of noninvasive arterial load imposed on the heart, was calculated as end-systolic pressure divided by stroke volume index. End-systolic pressure was noninvasively approximated by multiplying the systolic blood pressure by 0.9.[12] Stroke volume was calculated by subtracting the end-systolic volume from the end-diastolic volume.

Coronary Angiography

CTCA. All studies were performed on a 320–detector row system (AquilionOne Dynamic Volume CT; Toshiba Medical, Tokyo, Japan). A bolus of 75 mL of iopromide (Ultravist 370; Bayer HealthCare) was injected into an antecubital vein at a flow rate of 5 to 6 mL/sec. An axial scanning technique was used, with slice collimation of 0.5 mm and gantry rotation time of 350 msec. Exposure parameters included an x-ray tube potential of 100 to 135 kVp and effective tube current of 400 to 580 mA, based on vendor specifications and determined by patient body mass index. Scans were performed with prospective electrocardiographic triggering using a 70% to 80% phase window. Computed tomographic coronary angiographic data sets were analyzed by a cardiologist, blinded to clinical and echocardiographic data, for the presence of coronary plaque and to verify absence of >50% luminal stenosis in any coronary segment.

ICA. ICA was performed with a 5- or 6-Fr catheter according to standard techniques via the femoral or radial approach. Two interventional cardiologists, blinded to clinical and echocardiographic data, visually evaluated images by consensus to verify absence of >50% luminal stenosis in any coronary segment and performed MBG and CTFC analyses using standard methodology[13,14] to determine resting microvascular function. In brief, duration of cine filming exceeded three cardiac cycles in the washout phase to assess the washout of myocardial blush. MBG was identified for each coronary artery according to a dye density score (0 = no myocardial blush or contrast density, 1 = minimal blush, 2 = moderate blush, and 3 = normal blush).[13] CTFC was determined according to the number of cine frames required for dye to reach standardized distal landmarks, as previously described.[14] Because the left anterior descending coronary artery is longer, the frame counts were corrected by dividing by 1.7.[15]

Reproducibility. To define the reproducibility of the resting mitral annular velocities as well as rest and poststress LVEF measurements, 20 patients across both groups were randomly selected and measured