Preliminary Observations of Prognostic Value of Left Atrial Functional Reserve during Dobutamine Infusion in Patients with Dilated Cardiomyopathy

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Background: The importance of left atrial (LA) functional reserve in patients with depressed left ventricular function remains unclear. Thus, the aim of this study was to test the hypothesis that diminished augmentation of LA function during dobutamine stress might be associated with cardiovascular events in patients with dilated cardiomyopathy.

Methods: Eighty-four patients with dilated cardiomyopathy with a mean ejection fraction of 34 ± 9% were retrospectively recruited, and LA strain was determined as the averaged global speckle-tracking longitudinal strain from apical four-chamber and two-chamber views during dobutamine stress (20 μg/kg/min). The systolic component of LA strain was considered to reflect reservoir function, whereas the passive and active emptying components were considered to reflect passive and active emptying function, respectively. Event-free survival was tracked for 17 months.

Results: Multivariate Cox proportional-hazards analysis identified LA volume index (hazard ratio [HR], 1.060; $P < .001$) and β-blocker use (HR, 0.048; $P < .05$) as the independent variables associated with cardiovascular events among the baseline parameters and changes in systolic LA strain (HR, 0.971; $P = .02$), in passive emptying LA strain (HR, 0.942; $P < .001$), and in left ventricular early diastolic strain rate (HR, 0.986; $P = .03$) under dobutamine as the variables among the functional reserve parameters. In sequential Cox models, a model based on clinical variables ($\chi^2 = 9.3$) was improved by conventional echocardiographic parameters ($\chi^2 = 19.2$, $P = .012$) and LA strain parameters at rest ($\chi^2 = 40.1$, $P = .005$) and further improved by the addition of changes in LA strain parameters under dobutamine ($\chi^2 = 61.6$, $P < .001$).

Conclusions: The assessment of LA reservoir and passive emptying function during dobutamine stress provides important incremental prognostic value in patients with dilated cardiomyopathy. (J Am Soc Echocardiogr 2014;27:430-9.)

Keywords: Dobutamine stress echocardiography, Left atrial function, Speckle-tracking strain, Idiopathic dilated cardiomyopathy, Left atrial reserve

The principal role of the left atrium (LA) is to modulate left ventricular (LV) diastolic filling and cardiac performance through reservoir, conduit, and booster pump functions,[1] without an elevation in mean left atrial pressure, and it is particularly important when LV relaxation is impaired and LV compliance reduced.[2] During hemodynamic stress or exertion, LA reservoir, conduit, and active emptying functions increase to maintain LV filling at an optimal level during hemodynamic alterations.[3] However, in patients with heart failure (HF), compensatory augmentation of LA function is impaired as a result of both increased workload imposed on the LA myocardium and intrinsic LA myocardial dysfunction.[4] Consequently, the increase in LA pressure during hemodynamic stress is more significant in the presence of combined atrial and ventricular dysfunction.[5] In patients with LA failure, such an increase in LA pressure may lead to pulmonary venous hypertension, an increase in pulmonary wedge pressure, and subsequent pulmonary congestion and dyspnea.[6,7]

Although LA structural and functional remodeling has been proposed as a predictor of cardiovascular outcomes,[8-10] the potential impact of LA functional reserve on cardiovascular outcomes during stress testing remains unclear. We hypothesized that diminished augmentation of LA function during dobutamine stress may be associated with cardiovascular events in patients with depressed LV function.

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Abbreviations

AUC = Area under the curve

CI = Confidence interval

DCM = Dilated cardiomyopathy

GLS = Global longitudinal strain

HF = Heart failure

HR = Hazard ratio

LA = Left atrial

LV = Left ventricular

LVEF = Left ventricular ejection fraction

S-LAa = Active left atrial strain

S-LApass = Passive left atrial strain

S-LAs = Systolic left atrial strain

SR-LVe = Peak left ventricular global longitudinal early diastolic strain rate

METHODS

Study Population

Ninety-six consecutive patients with compensated HF due to idiopathic dilated cardiomyopathy (DCM) were retrospectively recruited for this study. Six of the recruited patients (6%) were excluded from all subsequent analyses because of suboptimal quality of images, as were six patients (6%) with atrial fibrillation. Exclusion criteria also included a history of electrocardiographically confirmed atrial fibrillation or atrial flutter or the presence of other major cardiac arrhythmia, more than mild mitral valve disease, previous valve surgery, and DCM of ischemic etiology by coronary angiography. The final study population thus comprised 84 patients. The diagnosis of idiopathic DCM was established according to the following criteria: (1) presence of LV dilation (LV end-diastolic diameter ≥ 55 mm); (2) reduced LV ejection fraction (LVEF) (all <45%); (3) coronary angiographic evidence of absence of coronary artery disease, defined as >50% stenosis of a major epicardial vessel or a history of myocardial infarction or previous coronary revascularization; and (4) absence of cardiac muscle disease secondary to any known systemic diseases. At the time of enrollment, all patients were in clinically stable condition and receiving optimal and maximally tolerated pharmacologic therapy. This study was approved by the local ethics committee of our institution, and written informed consent was obtained from all patients.

Standard Echocardiographic Examination

Standard echocardiography was performed using a commercially available ultrasound system (Aplio Artida; Toshiba Medical Systems, Tochigi, Japan) equipped with a 3.0-MHz transducer, with the patient in the left lateral decubitus position. Standard LV measurements were obtained from the parasternal long-axis view in accordance with the current guidelines of the American Society of Echocardiography.[11] LV volumes and LVEF were calculated using the biplane Simpson's method, and all volumes and LV mass measurements were then normalized to body surface area. LV stroke volume was determined in terms of the velocity-time integral, assessed by means of pulsed-wave Doppler positioned at the LV outflow tract. Cardiac output was then calculated as the product of stroke volume and heart rate. The pulsed-wave Doppler–derived transmitral flow velocity, pulmonary venous flow velocity, and tissue Doppler–derived mitral annular velocity were obtained from the apical four-chamber view and used for the assessment of diastolic function.[12] Early diastolic (E′) and late diastolic (A′) mitral annular velocities were measured using spectral Doppler tissue imaging, and the E/E′ ratio was calculated to estimate LV filling pressure.[13]

Speckle-Tracking Strain Analysis

Speckle-tracking analyses of both the left ventricle and the left atrium were performed using dedicated software (Ultra Extend; Toshiba Medical Systems). Analysis of LV strain was performed for the apical four-chamber, two-chamber, and long-axis views, as previously described.[14] LV longitudinal systolic strain, systolic strain rate, and early and late diastolic strain rates were measured, followed by calculations of the averaged values of peak global longitudinal strain (GLS), peak LV global systolic strain rate, peak LV global longitudinal early diastolic strain rate (SR-LVe), and peak LV global late diastolic strain rate from three apical views.

Similarly, for speckle-tracking analysis of LA myocardial function, apical four-chamber and two-chamber images were obtained during breath hold by means of conventional two-dimensional grayscale echocardiography with stable electrocardiographic recording. Care was taken to optimize visualization of the LA cavity and to maximize LA area in apical views, avoiding foreshortening of the left atrium. Offline analyses were then performed as previously described.[15,16] Briefly, the LA endocardial border was manually traced at end-diastole using the point-and-click approach for both apical views. After adjustment of the width and shape of the region of interest, the software divided the region of interest into six segments. A total of 12 segments from subjects with satisfactory image quality were analyzed (Figure 1). Because strain at LV end-diastole (the onset of the QRS complex) is set at zero, the LA strain curve is composed of a predominantly positive wave that peaks at end-systole (systolic LA strain [S-LAs]), followed by two distinct descending phases in the early diastole (passive LA strain [S-LApass]) and late diastole (active LA strain [S-LAa]). S-LAs was considered to reflect LA reservoir function and the early diastolic (S-LApass) and late diastolic (S-LAa) components to reflect passive and active emptying function, respectively.[15,17] These strain values were calculated by averaging values obtained from all LA segments and by separately averaging values obtained from four-chamber and two-chamber views.

The use of LA strain combined with LA pressures for the assessment of LA stiffness has been reported.[18] Global S-LAs represents positive strain corresponding to the rise in LA pressure from the minimum to the maximum during LV systole. We therefore used the E/E′ ratio as a noninvasive surrogate for LA pressure, and the LA stiffness index, as a noninvasively estimated dimensionless index, was calculated as E/E′ divided by S-LAs, as previously reported.[7,19]

Dobutamine Stress Testing

All patients underwent dobutamine stress echocardiography in incremental stages lasting 5 min each. The initial dose was 5 μg/kg/min and was increased first to 10 μg/kg/min and finally to the maximal dose of 20 μg/kg/min.[19] Electrocardiograms, blood pressure, and heart rate were recorded during the entire procedure. LV contractile reserve was defined as the relative changes between baseline GLS, LVEF, and wall motion score index and their values obtained at peak stress (ΔGLS, ΔLVEF, and Δ wall motion score index, respectively), whereas diastolic reserve was defined as the relative change in SR-LVe from rest to peak stress (ΔSR-LVe). Similarly, LA "reservoir reserve," "passive emptying reserve," and "active emptying reserve" were defined as the relative changes in S-LAs (ΔS-LAs), S-LApass (ΔS-LApass), and S-LAa (ΔS-LAa), respectively.

Long-Term Follow-Up Analysis

Long-term unfavorable cardiovascular events were prespecified as primary end points of death from or hospitalization for deteriorating