Journal of Cardiac Failure Vol. ■■ No. ■■ 2016

Clinical Investigation

Left Ventricular Deformation and Myocardial Fibrosis in Patients With Advanced Heart Failure Requiring Transplantation

MATTEO CAMELI, MD,[1,2] SERGIO MONDILLO, MD,[2] FRANCESCA MARIA RIGHINI, MD,[2] MATTEO LISI, MD,[2] ALEKSANDER DOKOLLARI, MD,[3] PER LINDQVIST, PhD,[1] MASSIMO MACCHERINI, MD,[3] AND MICHAEL HENEIN, MSc, PhD[1]

Umeå, Sweden; and Siena, Italy

ABSTRACT

Purpose: To evaluate potential relationships between different components of left ventricular (LV) function and histopathological evidence for myocardial fibrosis in patients undergoing heart transplantation.
Methods: The study population included patients with advanced heart failure, referred for an echocardiographic examination before heart transplantation. Traditional LV function measurements and global longitudinal strain (GLS) by speckle tracking echocardiography, averaging all LV segments in 4-, 2-, and 3-chamber views were obtained in all subjects. LV tissue samples were obtained from all patients who underwent heart transplantation. Myocardial fibrosis was assessed using Masson's staining.
Results: Of 106 patients referred for cardiac transplantation, 47 underwent cardiac transplantation and were enrolled in the study. LV myocardial fibrosis and its grade strongly correlated with GLS (r = 0.75, $P = .0001$), modestly with global circumferential strain and LV torsion (r = 0.61, $P = .001$ and r = 0.52, $P = .01$, respectively) and weakly with mitral S′ wave (r = −0.41; $P = .01$) and mitral annular plane systolic excursion (r = −0.35; $P = .05$) but did not correlate with LV ejection fraction (r = −0.12; P = NS). GLS had the strongest accuracy for detecting LV fibrosis (area under the curve, 0.92). None of the echo parameters correlated with patient's exercise capacity.
Conclusion: Global longitudinal strain is the most accurate LV global function measure that correlates with the extent of myocardial fibrosis in patients with advanced systolic HF requiring heart transplantation.
(*J Cardiac Fail 2016;■■:■■–■■*)
Key Words: Advanced cardiac failure, heart transplantation, LV fibrosis, echocardiography, speckle tracking, LV strain.

Background

The role of myocardial fibrosis in the development and progression of cardiac failure has recently been highlighted[1,2] and shown to worsen ventricular function, particularly diastolic, contribute to cavity remodelling and increase stiffness and overall pump failure.[3–5] Patients with advanced heart failure (HF) have been shown to have extensive myocardial fibrosis irrespective of the etiology of cardiomyopathy.[6–8]

In vivo assessment of myocardial fibrosis is difficult to achieve. However, cardiac magnetic resonance (CMR), using late-enhancement technique has proven to be the gold standard for assessment of the presence and extent of myocardial fibrosis. However, monitoring its mechanism of contribution to systolic dysfunction remains challenging.[9] On the other hand, echocardiography based assessment of myocardial fibrosis in the form of "tissue characterization" has previously been studied but proved unsatisfactory. Recently developed 2-dimensional speckle-tracking echocardiography (STE) has proved superior in assessing regional myocardial function, being widely available, highly reproducible, and easily applicable, and thus potentially overcoming known CMR limitations.[10] In addition, the technique allows excellent assessment of the left ventricular (LV) deformation profile during the entire cardiac cycle[11] and has been recently

From the [1]Department of Public Health and Clinical Medicine, Heart Centre, Umeå University, Umeå, Sweden; [2]Department of Cardiovascular Diseases, University of Siena, Siena, Italy and [3]Department of Cardiac Surgery, University of Siena, Siena, Italy.

Reprint requests: Matteo Cameli, MD, Department of Cardiovascular Diseases, University of Siena, Italy. Tel: +390577585377; Fax: +390577585377. E-mail: cameli@cheapnet.it.

Manuscript received August 2, 2015; revised manuscript received February 23, 2016; revised manuscript accepted February 29, 2016.

See page ■■ for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2016.02.012

demonstrated to correlate with myocardial fibrosis in other clinical settings, such as hypertrophic cardiomyopathy.[12]

The aim of this study was to investigate the impact of myocardial fibrosis on regional myocardial deformation in a cohort of patients with advanced systolic HF requiring heart transplantation, hypothesizing that STE can indirectly assess function disturbances related to myocardial fibrosis.

Methods

A total of 106 consecutive patients with advanced systolic HF requiring heart transplantation were followed up by the Department of Cardiovascular Diseases of the University of Siena from March 2008 to May 2014.

Echocardiography

All patients underwent serial cardiological assessments including echocardiographic examinations. Patients who subsequently underwent cardiac transplantation were enrolled in this study and those who underwent cardiac transplantation more than 1 month after the last cardiology visit had an echocardiogram just a few hours before surgery. Patients were excluded if they had unsatisfactory imaging quality of the LV endocardial border.

All subjects gave written informed consent to participate in the study, which complied with the declaration of Helsinki, and was approved by the local ethics committee.

Echocardiographic studies were performed using a high-quality echocardiograph (Vivid e9, GE), equipped with a 3.0-MHz transducer, with the subject in the left lateral recumbent position. Measurements of LV and left atrial dimensions, LV ejection fraction, and diastolic filling velocities were made in accordance with the current recommendations of the American Society of Echocardiography and European Association of Echocardiography.[13] LV ejection fraction, measured by Simpson's method, was used as a standard index of global systolic function. The ratio between peak early (E) and late (A) diastolic LV filling velocities was used as standard index of LV diastolic function.[14] Left atrial volumes were measured using the area-length method from the apical 4- and 2-chamber views. Left atrial volumes were subsequently indexed to body surface area. The time interval between the onset of the QRS on the electrocardiogram and the aortic and mitral valve opening and closure were measured using pulsed-wave Doppler from the LV outflow and inflow, respectively.

LV longitudinal function was studied using pulsed tissue Doppler imaging by placing the sample volume at the level of lateral mitral annulus angle from the apical 4-chamber view.[15] Peak systolic (S′), early diastolic (E′), and late diastolic (A′) annular velocities were measured. S′ was considered as a relatively load-independent index of LV longitudinal systolic function. E′ and E′/A′ ratio were used as load-independent markers of myocardial relaxation.[16] The E/E′ ratio was also calculated and used as a reliable index of LV filling pressures.[17] M-mode measurements of mitral annular plane systolic excursion (MAPSE) were performed by placing the cursor perpendicular to the lateral site of the annulus.[18]

Longitudinal LV cavity dyssynchrony was quantified using pulsed tissue Doppler imaging. In 4- and 2-chamber apical views, the tissue Doppler sample was positioned in the middle of the basal segment of each of the 4 walls septal, lateral, inferior, and anterior of the left ventricle. In each of the walls, the interval between the beginning of the QRS complex on the surface electrocardiogram and the beginning of the systolic wave (S′) on the pulsed wave Doppler signal was measured. This interval corresponds to the electromechanical delay, and the mean of 3 separate measurements in consecutive cardiac cycles was used for the analysis. The difference between the maximum and minimum interval measured in the 4 walls of the left ventricle was used to quantify the degree of left intraventricular dyssynchrony (Q-S′ index).[19]

A longitudinal tissue Doppler dyssynchrony of ≥32 ms was considered significant.[20]

Myocardial speckle-tracking analysis was made from the apical 4-chamber, 2-chamber, apical long-axis, and apical and basal short-axis view images using conventional 2-dimensional grayscale echocardiography, during a brief breath-hold and with a stable electrocardiogram recording. Care was taken to obtain true apical images using standard anatomic landmarks in each view without foreshortening the left ventricle, allowing a more reliable delineation of the endocardial border. Three consecutive heart cycles were recorded and averaged. The frame rate was set between 60 and 80 frames per second.

The analysis of the recorded images was performed off-line by a single, experienced, and independent echocardiographer, who was not directly involved in the image acquisition and had no knowledge of the histopathological findings, using a commercially available, semiautomated, 2-dimensional strain software (EchoPac, GE, Milwaukee, WI). As previously described,[11] LV endocardial border was manually traced in 4-chamber, 2-chamber, and apical long-axis views, thus delineating a region of interest, composed of 6 segments. After segmental tracking, quality analysis and manual adjustment of the region of interest, the longitudinal strain (LS) curves were generated by the software for each LV segment. As shown in Fig. 1, peak LV LS, measured at the end of systole, was calculated by averaging values obtained from all LV segments in the 17-LV-segment model (global LS [GLS]) and by separately averaging values obtained in the 4-chamber, 2- chamber, and apical long-axis views (4-chamber, 2-chamber, and apical long axis, average LS, respectively). The time to peak LS (TPLS) was also measured as the average of all 18 segments (global TPLS) and by separately averaging values obtained from the 3 apical views. In patients in whom some segments were excluded because of the difficulty in achieving adequate myocardial tracking, GLS and TPLS were calculated by averaging values measured in the remaining segments. Global circumferential strain, obtained by averaging basal and apical circumferential strain values, and LV torsion were also measured as previously