Prediction of Outcomes in Patients with Chronic Ischemic Cardiomyopathy by Layer-Specific Strain Echocardiography: A Proof of Concept

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Background: Cardiac magnetic resonance imaging (CMR) has been established as a powerful tool for predicting mortality. However, its application is limited by availability and various contraindications. The aim of this study was to evaluate the predictive value of layer-specific myocardial deformation analysis as assessed by strain echocardiography for cardiac events in patients with chronic ischemic left ventricular dysfunction in comparison with CMR.

Methods: Three hundred ninety patients (mean age, 63 ± 4 years; 69% men; mean left ventricular ejection fraction [LVEF], 41 ± 7%) with chronic ischemic cardiomyopathy were prospectively enrolled and underwent strain echocardiography and CMR within 3 ± 1 days. LVEF, wall motion score index, and circumferential strain (CS), longitudinal strain, and radial strain for total wall thickness and for three myocardial layers (endocardial, midmyocardial, and epicardial) were determined by echocardiography. The extent of total myocardial scar (TMS) was determined by CMR. Follow-up was obtained for a mean of 4.9 ± 2.2 years. Cardiac events were defined as readmission for worsening of heart failure, ventricular arrhythmias, or death of any cause. The incremental value of LVEF, strain parameters, and TMS to relevant clinical variables was determined in nested Cox models.

Results: There were 133 cardiac events (34%). Baseline clinical data associated with outcomes were age (hazard ratio [HR], 1.27; $P = .04$), diabetes mellitus (HR, 1.52; $P = .001$), and renal insufficiency (HR, 1.77; $P = .001$) by multivariate analysis. The addition of LVEF, global and endocardial strain parameters, and TMS increased the predictive power, but endocardial CS (HR, 1.52; $P < .01$) caused the greatest increment in model power ($\chi^2 = 39.2$, $P < .001$). Endocardial CS < −20% was found to be the optimal predictor of prognosis.

Conclusions: Endocardial CS is a powerful predictor of cardiac events and appears to be a better parameter than LVEF, TMS by CMR, and other strain variables by echocardiography. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Chronic ischemic cardiomyopathy, Long-term-survival, Mortality, Myocardial deformation imaging, Two-dimensional speckle-tracking echocardiography

The identification of patients with chronic ischemic cardiomyopathy (ICM) at high risk for adverse clinical events is essential to improving guidance of therapy and patient prognosis. Various traditional echocardiographic parameters have been shown to provide prognostic information in these patients, such as left ventricular (LV) volumes and LV ejection fraction (LVEF), wall motion score index (WMSI), and mitral regurgitation.[1–3] However, there are some limitations related to image quality, reproducibility, expertise, and geometric assumptions. Furthermore, quantification of total myocardial scar (TMS) assessed by CMR has been shown to be a powerful predictor of mortality.[4,5] However, there are some limitations, such as contraindications for assigned patients, restricted availability, and costs.

Recently, parameters determined from two-dimensional speckle-tracking echocardiography allow the assessment of active myocardial deformation with respect to total wall thickness as well as specific myocardial layers.[6,7] It has already been shown that the measurement of global longitudinal strain (GLS) (regarding the total myocardial wall thickness) is significantly related to long-term outcome in patients with ICM.[8–10] The aim of the present study was to evaluate the prognostic power of various parameters obtained by myocardial deformation imaging compared with CMR

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0894-7317/$36.00

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http://dx.doi.org/10.1016/j.echo.2016.02.001

Abbreviations

CMR = Cardiac magnetic resonance imaging

CS = Circumferential strain

GCS = Global circumferential strain

GLS = Global longitudinal strain

ICM = Ischemic cardiomyopathy

LS = Longitudinal strain

LV = Left ventricular

LVEF = Left ventricular ejection fraction

TMS = Total myocardial scar

WMSI = Wall motion score index

for the prediction of cardiac events. To the best of our knowledge, this is the first study to include layer-specific echocardiographic data.

METHODS

Patients

For this prospective study, we screened 437 unselected patients with known chronic ICM (defined as known coronary artery disease and LVEF ≤ 50%) who were hospitalized for heart failure and underwent echocardiography and CMR within 3 ± 1 days between 2007 and 2012 (Figure 1). All patients received optimal medical treatment for ≥3 months and coronary revascularization (all vessels were classified as open by recorded Thrombolysis In Myocardial Infarction grade 3 flow) according to current guidelines[11] before inclusion in the study. Patients with recent myocardial infarctions (<90 days), atrial fibrillation, and relevant valvular heart disease were excluded. All patients gave informed written consent. Detailed follow-up was performed using recordings in a central database (including device interrogation) and by telephone contact using a scripted interview annually.

Echocardiography

Echocardiography was performed with a Vivid 7 and E9 system (GE Vingmed Ultrasound AS, Horten, Norway) equipped with a 2.5-MHz transducer. The frame rate for these studies was between 56 and 92 frames/sec, using tissue harmonic imaging. Three LV parasternal short-axis views at the basal, midventricular, and apical levels and three views from an apical window (two-chamber, four-chamber, and long-axis views) were acquired. An 18-segment model[12] was used to divide the left ventricle. Wall motion was assessed by visual interpretation for each LV segment as normokinetic, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic. WMSI was calculated for each patient as the average of the analyzed segmental values. LVEF was assessed using the biplane Simpson method using manual tracing of digital images.

Myocardial Deformation Imaging

Analysis was performed offline with the aid of a commercially available software package (EchoPAC 113 1.0; GE Vingmed Ultrasound AS). It allows calculation of mean strain values for total wall thickness and additionally for each of three myocardial layers (endocardial, midmyocardial, and epicardial), as described previously,[6,7] within a few minutes (Figure 2). Circumferential strain (CS), longitudinal strain (LS), and radial strain myocardial deformation parameters were determined for each myocardial segment and averaged considering all 18 segments to obtain one summarized data point. Following actual echocardiographic definitions, the label "global" was used only for strain data regarding the total myocardial wall thickness. All echocardiographic data were analyzed by two blinded experienced cardiologist.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) was performed on a 1.5-T whole-body magnetic resonance scanner (Achieva; Philips Medical Systems, Best, the Netherlands), as described previously,[13] within 3 ± 1 days after echocardiography. Each myocardial segment was evaluated for the presence of hyperenhancement, defined as an area of signal enhancement ≥2 SDs of the signal intensity of nonenhanced myocardium. The total myocardial area and the contrast-enhanced area of each segment were traced manually. TMS was calculated, defined as the percentage contrast-enhanced area of the total myocardial area ($area_{hyperenhancement}/area_{myocardium} \times 100$). All CMR data were analyzed by two blinded, experienced cardiologists.

Clinical Follow-Up

Clinical follow-up was performed annually by telephone contact and a centrally recorded database (including reports of implantable cardioverter-defibrillator device interrogation). All verification of database recordings and interviews were performed by an experienced nurse or physician. During the interview, the patient or a family member was queried for the occurrence of cardiac events, defined as readmission for worsening of heart failure, ventricular arrhythmias, or death of any cause. If such an event was identified, the referring general practitioner was contacted for detailed information. Ventricular arrhythmias were ranked as clinical events only if documented by device interrogation or definite electrocardiography.

Statistical Analysis

Clinical characteristics of the study population are presented as frequencies or as mean ± SD. Continuous variables were compared using Student's t test, the Wilcoxon test, or analysis of variance as appropriate. We used the χ^2 test or Fisher exact test to test the null hypothesis that two dichotomous variables were independent.

To define intraobserver and interobserver variability, the same observer and a second independent observer repeated the analysis in 40 randomly selected patients using the same two-dimensional echocardiographic or CMR loop. Intraclass coefficients were calculated.

Univariate analysis was performed to establish the relationship between baseline clinical data and cardiac events. Cox proportional hazards analysis was used to determine significant predictors for cardiac events. Variables with univariate significance of <0.1 were selected for inclusion in the multivariate model. A series of nested models with the separate addition of all myocardial deformation parameters, LVEF, and TMS were undertaken. The ability of myocardial deformation parameters as well as TMS to predict cardiac events was explored with a random-effects model to address the issue of repeated observations (data on multiple segments per patient used in the analysis). The output of a generalized estimating equation approach with a binomial distribution, a logit link, and a working correlation matrix with exchangeable correlation assumption allowed the derivation of receiver operating characteristic curves, which were used to designate cutoffs. Using these cutoffs, we compared the sensitivity and specificity of all parameters for the prediction of cardiac events according to the McNemar test.

To express uncertainty concerning the true parameters, 95% CIs were calculated using 1,000 bootstrap samples from the original data, with sample size equal to that of the study presented here. These bootstrap CIs allowed a formal statistical comparison of areas under the curve.

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