Feasibility of Left Ventricular Global Longitudinal Strain Measurements from Contrast-Enhanced Echocardiographic Images

Diego Medvedofsky, MD, Roberto M. Lang, MD, Eric Kruse, RDCS, Brittney Guile, RDCS, Lynn Weinert, RDMS, Boguslawa Ciszek, RDCS, Zachary Jacobson, RDCS, Jacqueline Negron, RDCS, Valentina Volpato, MD, Aldo Prado, MD, Amit R. Patel, MD, and Victor Mor-Avi, PhD, *Chicago, Illinois; and Tucumán, Argentina*

Background: Although left ventricular global longitudinal strain (GLS) is an index of systolic function recommended by the guidelines, poor image quality may hamper strain measurements. While contrast agents are commonly used to improve endocardial visualization, no commercial speckle-tracking software is able to measure strain in contrast-enhanced images. This study aimed to test the accuracy of speckle-tracking software when applied to contrast-enhanced images in patients with suboptimal image quality.

Methods: We studied patients with a wide range of GLS values who underwent transthoracic echocardiography. Protocol 1 included 44 patients whose images justified use of contrast but still allowed noncontrast speckle-tracking echocardiography (STE), which was judged as accurate and used as a reference. Protocol 2 included 20 patients with poor image quality that precluded noncontrast STE; cardiac magnetic resonance- (CMR-) derived strain was used as the reference instead. Half the manufacturer recommended dose of a commercial contrast agent (Definity/Optison/Lumason) was used to provide partial contrast enhancement. Higher than normal mechanical indices (0.6-0.7) and lowest frequency range for maximal penetration settings were used for imaging. GLS was measured (Epsilon) with and without contrast-enhanced images and by CMR-derived feature tracking (TomTec). Comparisons included linear regression and Bland-Altman analyses.

Results: The contrast STE analysis failed in 4/64 patients (6%). Manual corrections were needed to optimize tracking with contrast in all patients. GLS measurements were in good agreement between contrast and noncontrast images ($r = 0.85$; mean GLS in the contrast images, −12.9% ± 4.7%; bias, 0.34% ± 2.4%). Good agreement was also noted between contrast STE- and CMR-derived strain ($r = 0.83$; mean, GLS −13.5% ± 4.0%; bias, 0.72% ± 2.5%).

Conclusions: We found that GLS measurements from contrast-enhanced images are feasible and accurate in most patients, even in those with poor image quality that precludes strain measurements without contrast enhancement. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Left ventricular function, Myocardial strain, Speckle-tracking echocardiography, Contrast-enhanced images

During the last decade, speckle-tracking echocardiography- (STE-) derived left ventricular (LV) global longitudinal strain (GLS) has been incorporated into routine clinical practice,[1] after it was demonstrated to accurately reflect LV function and independently predict morbidity and mortality.[2-7] Accordingly, GLS analysis was included in the recent chamber quantification guidelines.[8] In the United States, an estimated 15% of echocardiography studies have poor image quality and contrast agents are recommended for better visualization of endocardial borders and to allow the quantification of LV volumes and ejection fraction (EF) in these patients. GLS was shown to be more sensitive and better predict outcomes than EF.[9] Although it is possible to measure GLS in a subset of patients with suboptimal image quality,[9,10] in many patients with poor image quality, GLS measurements are not possible, resulting in a diagnostic disadvantage, which may affect clinical management.

Cardiac magnetic resonance (CMR) is the established reference standard for LV size and function quantification. In patients with poor-quality echocardiographic images, CMR is the best alternative to determine LV volumes and function. CMR-derived strain by feature tracking has been used as a reference technique in several studies[11-19] and is particularly useful in patients with echocardiographic poor-quality images. However, the availability of CMR is limited, and until recently, no commercial STE software

From the Department of Medicine, University of Chicago Medical Center, Chicago, Illinois (D.M., R.M.L., E.K., B.G., L.W., B.C., Z.J., J.N., V.V., A.R.P., V.M.-A.); and Centro Privado de Cardiologia, Yerba Buena, Tucumán, Argentina (A.P.).

Conflicts of Interest: None.

Reprint requests: Victor Mor-Avi, PhD, 5758 South Maryland Avenue, MC 9067, Room 5512, Chicago, IL 60637 (E-mail: vmoravi@bsd.uchicago.edu).

0894-7317/$36.00

https://doi.org/10.1016/j.echo.2017.10.005

Abbreviations

CMR = Cardiac magnetic resonance

EF = Ejection fraction

GLS = Global longitudinal strain

ICC = Intraclass correlation coefficient

LV = Left ventricular

LVOT = Left ventricular outflow tract

STE = Speckle-tracking echocardiography

has been able to measure strain from contrast-enhanced echocardiographic images.

In this study, to bridge this gap in the diagnostic arsenal, we tested the feasibility of using STE software (Epsilon Imaging, Ann Arbor, MI) with contrast-enhanced images. Specifically, we aimed to optimize the imaging settings to facilitate this approach and tested its accuracy against the two aforementioned reference standards, namely, noncontrast STE when possible and CMR feature tracking as an alternative in patients with poor quality of nonenhanced images, precluding STE analysis.

METHODS

Population and Study Design

We prospectively studied patients with a wide range of GLS (age 67 ± 16 years, 58% men, body surface area 2.0 ± 0.26; 73% cardiomyopathy or heart failure, 43% systemic hypertension, 23% pulmonary arterial hypertension, 27% coronary artery disease, 7% simple congenital heart disease, and 7% end-stage renal disease). The study was approved by the Institutional Review Board, and informed consent was obtained from each patient.

Protocol 1 included 44 patients referred for clinically indicated transthoracic echocardiography who qualified for contrast echocardiographic studies (two nonvisualized contiguous segments in the apical four-chamber view), in whom noncontrast STE was still possible, despite suboptimal image quality. In this protocol, GLS was measured in the contrast-enhanced as well as nonenhanced images, and the latter measurements were used as the reference for comparisons. Protocol 2 included 20 patients referred to CMR for clinical reasons who agreed to have an echocardiogram, which was performed immediately after the CMR study. These patients had poor quality of noncontrast echocardiographic images (defined as poor endocardial visualization in two or more contiguous segments in the apical four-chamber view). In this protocol, GLS was measured in the contrast-enhanced echocardiographic images and compared against CMR feature tracking-derived strain. Exclusion criteria were complex congenital heart disease, arrhythmia during acquisition, pacemaker, or defibrillator leads (in protocol 2 only).

Echocardiographic Imaging and Analysis

Transthoracic imaging was performed in the apical four-chamber view with the patient in the left lateral decubitus position (IE33 or EPIQ systems, Philips Healthcare, Andover, MA) with an X5-1 transducer. Before each acquisition, images were optimized for endocardial visualization by adjusting the gain, compress, and time-gain compensation controls.

Acquisition settings for echocardiographic contrast-enhanced imaging were optimized in a series of preliminary tests and included (1) approximately half of the manufacturer-recommended dose of a commercial contrast agent randomly assigned to each patient (Definity by Lantheus [North Billerica, MA], Optison by GE Healthcare [Marlborough, MA], and Lumason by Bracco [Monroe Township, NJ]; 1-2 mL diluted in 3 mL saline) and used to provide partial contrast enhancement with lower bubble density than that typically used for LV opacification, resulting in a certain degree of visible swirling; (2) higher than usual mechanical indices (0.6-0.7); (3) focus set at the level of the mitral valve annulus to facilitate accurate tracking of the speckles in the far field; and (4) lowest frequency range for maximal penetration. Every effort was made to avoid throughout the cardiac cycle the inclusion of any portion of the LV outflow tract (LVOT) in the image sector.

Images were stored digitally and used for offline analysis, with the readers blinded to all prior measurements. Both contrast-enhanced and nonenhanced echocardiographic images were analyzed using STE software to measure GLS (EchoInsight, Epsilon Imaging, Ann Arbor MI), which allows myocardial deformation measurements with contrast enhancement from images acquired using the above scheme and tracking within an approximately 5 mm wide region of interest, which is thinner than the default. LV boundaries were initialized in a midsystolic frame and then automatically tracked throughout the cardiac cycle. In both techniques, manual corrections were performed as needed to optimize boundary tracking throughout the cardiac cycle (Figure 1).

CMR Imaging and Analysis

CMR imaging was performed on a 1.5 T scanner (Philips, Best, Netherlands) with a five-channel cardiac coil. Steady-state free-precision dynamic gradient-echo sequence was used to obtain cine loops, during approximately 5-second breath holds (repetition time 2.9 ms, echo time 1.5 ms, flip angle 60°, and temporal resolution ~30-40 ms). Images were analyzed offline using commercial software (2D CPA MR, a module of TomTec-Arena, TomTec Imaging Systems, Unterschleissheim, Germany). Similar to echocardiographic GLS analysis, manual tracing in a midsystolic frame allowed feature tracking initialization, performed by an investigator trained in CMR-based chamber quantification (SCMR level III training) who was blinded to echocardiographic data (Figure 2).

Statistics

Echocardiographic GLS measurements with contrast enhancement were compared with those without contrast enhancement (protocol 1) and with CMR feature tracking-derived GLS (protocol 2). Comparisons included linear regression with Pearson correlation coefficients. These comparisons also included paired *t*-tests, and values of $P < .05$ were considered significant. In addition, Bland-Altman analysis was performed to assess the bias and limits of agreement between the echocardiographic GLS measurement with contrast enhancement and the corresponding reference in each protocol.

Reproducibility Assessment

The reproducibility of echocardiographic GLS measurements with and without contrast enhancement was tested using repeated measurements in 30 patients randomly selected from the group enrolled in protocol 1 and in all of the 20 patients enrolled in protocol 2. These repeated measurements were performed on the same image loops by investigators blinded to all prior measurements. To determine the intraobserver variability, images were reanalyzed one month later by the same investigator, while interobserver variability was assessed by comparing these measurements with those performed by a second independent reader. Both intra- and interobserver variability were quantified by calculating intraclass correlation coefficients (ICCs), as well as the absolute difference between the corresponding pair of repeated