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● *Original Contribution*

CONSISTENT REGIONAL HETEROGENEITY OF PASSIVE DIASTOLIC STRETCH AND SYSTOLIC DEFORMATION IN THE HEALTHY HEART: AGE-RELATED CHANGES IN LEFT VENTRICLE CONTRACTILITY

RUTA JASAITYTE,* JAN D'HOOGE,* LIEVEN HERBOTS,† ANA M. DARABAN,* FRANK RADEMAKERS,* and PIET CLAUS*

*Division of Cardiovascular Imaging and Dynamics, Department of Cardiovascular Sciences, Catholic University of Leuven, Leuven, Belgium; and †Heart Center Hasselt, Jessa Hospital, Hasselt, Belgium

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Abstract—The consistency of the normal spatial distribution of segmental passive stretch (PreS) and systolic strain (SS) within the left ventricle was investigated and a recently proposed echocardiographic estimate of left ventricular (LV) contractility was used to detect contractility changes with age. Hereto, in 54 healthy subjects, segmental PreS and SS were measured on tissue Doppler images of six left ventricle walls. For each subject, a linear regression line was estimated through the segmental PreS and SS values. The slopes and intercepts of this PreS-SS relationship did not differ between age groups, suggesting no changes in LV contractility with age. Moreover, a consistent regional distribution of PreS was observed, with the highest values measured in the septum, resulting in a similar distribution of SS as a direct consequence of the Frank-Starling mechanism. (E-mail: ruta.jasaityte@uzleuven.be) © **2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Left ventricular strain, Passive diastolic left ventricular stretch, Myocardial deformation imaging, Contractility.**

INTRODUCTION

The Frank-Starling law postulates that at a given contractile state, left ventricular (LV) systolic performance increases with increasing pre-load in a length-dependent manner. This remains valid on the global and regional LV myocardial levels (Glower et al. 1985). More recently, the relationship between contractile state and pre-load has been assessed non-invasively using myocardial deformation imaging techniques (Jasaityte et al. 2013). Indeed, in a healthy individual, a major part of variability in systolic deformation (strain) within the ventricle can be attributed to segmental differences in regional passive stretch during atrial contraction (Zwanenburg et al. 2005). Moreover, the slope of the resulting stretch-strain relationship is not influenced by an acute increase in pre-load and changes with changing intrinsic LV inotropic state, suggesting that it could potentially be used as a non-invasive estimate of global LV contractility (Jasaityte et al. 2013). However, before such an estimate can be used in clinical practice to detect myocardial pathology, the effect of aging on the intrinsic contractility of the healthy left ventricle should be elucidated. Whereas some studies have reported a blunted inotropic response to β-adrenergic stimulation in the elderly (Stratton et al. 1992), data regarding age-related changes in LV contractility at rest are sparse.

Additionally, little is known about the normal spatial intra-ventricular passive PreS (left ventricular stretch during atrial contraction) distribution pattern and its determinants. Even though simulation studies have clearly found that regional variance in passive stretch can result from local differences in wall curvature and thickness (Choi et al. 2010), these findings cannot directly be translated to the living heart. Besides that, *in vivo* regional differences in the timing of myocardial electrical excitation (Ramanathan et al. 2006) might play a significant role in the heterogeneity and magnitude of both passive diastolic stretch and systolic strain (SS) within the left ventricle.

The present study was therefore designed to address these two issues. First, we aimed to investigate the

Address correspondence to: Ruta Jasaityte, Division of Cardiovascular Imaging and Dynamics, Department of Cardovascular Sciences, UZ Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium. E-mail: ruta.jasaityte@uzleuven.be

uniformity of the normal PreS distribution pattern within the left ventricle and to compare it with that of SS. Second, we used the intra-ventricular stretch-strain relationship to detect how LV contractility changes with age in healthy individuals.

METHODS

Study population

Sixty-five healthy volunteers were recruited to the study by local advertising. None of the participants had symptoms, history or signs of acute or chronic cardiovascular disease (myocardial infarction, arrhythmias, LV hypertrophy, excitation and conduction disturbances on the electrocardiogram [ECG]). The baseline echocardiographic examination of these subjects revealed sinus rhythm and normal LV systolic and diastolic function appropriate to age and ruled out any structural heart disease. All participants signed an informed consent before inclusion. The study complied with the Declaration of Helsinki, and the local ethics committee approved the study protocol.

Subsequently, for descriptive purposes, the study population was divided into five age groups by decade: group I = 21 to 30 y, group II = 31 to 40 y, group III = 41 to 50 y, group IV = 51 to 60 y and group V = 61 to 70 y.

Study protocol

Data acquisition and analysis. An echocardiographic examination was performed with a GE Vingmed Vivid 7 scanner (GE Vingmed Ultrasound, Horten, Norway), equipped with a 2.5-MHz M3 S transducer. ECGs with clearly detectable P wave, QRS complex and T wave were simultaneously recorded during the exam. B-Mode acquisitions of four- and two-chamber views and pulsed wave Doppler recordings of the LV outflow tract and mitral valve inflow were acquired. In addition, sector size was reduced to obtain narrow-sector tissue Doppler imaging (TDI) acquisitions of properly aligned LV walls (infero-septal, antero-lateral, anterior, inferior, infero-lateral and antero-septal) and to obtain a high frame rate (180–210 Hz). Peripheral brachial artery blood pressure was measured before the examination using an electronic sphygmomanometer.

Conventional echocardiographic data were analyzed using commercially available software (Echopac Version 110.1.2, GE Vingmed). LV end-diastolic (LV EDV) and end-systolic (LV ESV) volumes were measured from apical four- and two-chamber views using Simpson's biplane method and corrected for body surface area (BSA).

The global end-diastolic LV sphericity index (SI ED) was calculated with the formula SI ED = LV EDV/(4/3 $\times$ π $\times$ ((ED LV long-axis diameter)/2)^3). The end-systolic LV SI (SI ES) was calculated with the same formula, but substituting end-diastolic by end-systolic LV volume and long-axis diameter values. Global LV end-systolic wall stress (WS) was calculated with the formula WS = $(p \times r)/2h$, where p is peripheral systolic blood pressure, r is the effective radius of the left ventricle (calculated as $3\sqrt{(3/4\,\text{LV ESV} \times \pi)}$) and h is the thickness of the LV septum measured from para-sternal long-axis images.

P wave duration, PR interval, QT interval and QRS width were measured from simultaneous ECG recordings stored together with the echocardiographic images.

Myocardial deformation analysis was performed using software in-house developed (SPEQLE, KU Leuven, Belgium). We used a previously described adapted technique to extract the segmental myocardial deformation curves to be able to measure passive diastolic stretch of the left ventricle directly (Jasaityte et al. 2013). Hereto, the P wave on the ECG, indicating the beginning of atrial contraction, instead of the start of the QRS complex, was chosen as the zero reference point for deformation. Timing of mitral valve closure, aortic valve opening, aortic valve closure and mitral valve opening were determined from the time-aligned Doppler recordings. Three samples (12 $\times$ 6 mm) were distributed equally from the base to the apex of each LV wall and manually tracked through the cardiac cycle to ensure their positions within the myocardial segment. Segments of insufficient image quality were excluded from analysis. The segmental myocardial deformation curves obtained were averaged over three consecutive heart cycles to improve signal-to-noise ratio. Longitudinal lengthening or stretch (PreS) of the left ventricle during atrial contraction was measured as the peak positive strain during atrial contraction. The total longitudinal systolic strain (SS) was defined as the total shortening of the segment (*i.e.,* strain difference between peak late diastolic strain and end-systolic strain values) (Fig. 1).

Individual stretch-strain relationship. As previously described (Jasaityte et al. 2013), for every subject included, we obtained an individual stretch-strain relationship. Hereto, in every left ventricle, separate segmental PreS and SS values were pooled and a linear regression line was estimated. For descriptive purposes, the intercepts and slopes obtained were also averaged per age group to represent the mean relationship.

To test the reproducibility of PreS, SS and the regression equations, 10 randomly chosen studies were re-analyzed by the same observer as well as by another observer. Both were blinded to the initial results. For estimation of the inter-study variability in 10 subjects, additional TDI recordings of each LV wall were acquired