# Left Atrial Function in Preclinical Diastolic Dysfunction: Two-Dimensional Speckle-Tracking Echocardiography–Derived Results from the BEFRI Trial

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*Background:* Patients with preclinical left ventricular (LV) diastolic dysfunction (DD) are prone to develop heart failure with preserved ejection fraction. Although left atrial (LA) enlargement and deterioration of LA function in apparent DD and heart failure with preserved ejection fraction have been previously described, data regarding phasic LA strain (LAS) in preclinical DD are scarce.

*Methods:* In a cross-sectional trial, echocardiographic parameters of DD, LA volume index, and global LA reservoir, conduit, and pump function were prospectively analyzed in 473 women from the general population in Berlin, Germany (BErlin Female RIsk evaluation (BEFRI) study), using standard and two-dimensional speckle-tracking echocardiography.

*Results:* One hundred thirty-one women (29.7%) showed early-stage DD (impaired relaxation [DD1]) and 22 (5.0%) showed an echocardiographically more advanced stage of DD (pseudonormal filling [DD2]). Compared with women with normal diastolic function (DD0), those with DD1 displayed lower LA reservoir and conduit function (DD0, 43.2 ± 8.5% and 27.2 ± 8.0%; DD1, 33.3 ± 8.0% and 16.1 ± 7.1%; $P < .001$) but significantly higher LA pump function (DD0, 17.6 ± 5.4%; DD1, 18.9 ± 5.5%; $P < .05$). In patients with DD2, all three phases of LAS were markedly impaired compared with those with DD0 (reservoir, conduit, and pump function, 29.0 ± 6.3%, 15.1 ± 5.4% [$P < .001$], and 14.9 ± 4.1% [$P < .05$], respectively). LA reservoir and conduit function was significantly associated with DD; in receiver operating characteristic curve analysis, these parameters showed higher diagnostic accuracy in detecting early DD compared with LA volume index. In multivariate analysis, LA reservoir strain remained significantly associated with DD.

*Conclusions:* All three components of LAS showed specific alterations in different stages of DD. LA reservoir and conduit function was markedly reduced before symptoms, LA enlargement, and elevations of noninvasively estimated LV filling pressures occurred. Analysis of LA function featured higher discriminative strength in diagnosing early-stage DD compared with the well-established parameter LA volume index. Assessment of LAS allows diagnosis of impaired LA function and DD in a subclinical stage and might enable timely preventive and therapeutic interventions. (J Am Soc Echocardiogr 2016;■:■-■.)

*Keywords:* LA strain, Left atrial function, Diastolic dysfunction, Left atrial remodeling, 2D speckle tracking, Women

Preclinical diastolic dysfunction (DD) is defined as DD without signs of congestive heart failure and a normal left ventricular (LV) ejection fraction.[1] This entity has been associated with adverse outcome and identifies patients at high risk for developing heart failure with preserved ejection fraction (HFpEF).[2,3] Beyond established parameters of DD, several studies described alterations of left atrial (LA) mechanics in DD.[4-7]

LA function modulates LV filling by its reservoir (LA filling during ventricular systole), conduit (passage of blood from the left atrium and pulmonary veins to the left ventricle during early diastole), and pump (atrial contraction during late diastole) functions.[8,9] Distinct alterations of LA function and filling pressures with progressive stages of heart failure have been described using volumetric calculation

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**Abbreviations**

**BEFRI** = BErlin Female RIsk evaluation

**BNP** = Brain natriuretic peptide

**DD** = Diastolic dysfunction

**DD0** = Normal diastolic function

**DD1** = Impaired relaxation

**DD2** = Pseudonormal filling

**HFpEF** = Heart failure with preserved ejection fraction

**LA** = Left atrial

**LAS** = Left atrial strain

**LAVI** = Left atrial volume index

**LV** = Left ventricular

**ROC** = Receiver operating characteristic

**STE** = Speckle-tracking echocardiography

**2D** = Two-dimensional

methods, standard Doppler, and invasive micromanometric measurements.[10-12] These changes are crucial in maintaining optimal cardiac output also in the presence of impaired ventricular relaxation and high LV filling pressures.[8,10] In contrast to LA enlargement, which is clearly associated with DD, as well as with cardiovascular morbidity and mortality,[13,14] two-dimensional (2D) speckle-tracking echocardiography (STE)–derived data concerning changes of LA function in DD are scarce. An echocardiographic substudy of the Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction trial demonstrated a significant reduction of LA strain (LAS) affecting all three LA phases in patients with HFpEF with and without LA enlargement.[15] In this setting, however, it remains unclear whether reductions of LAS are due to severely impaired LV relaxation and elevated filling pressures or whether LV and LA remodeling develop simultaneously in evolving HFpEF.

The aim of our study was therefore to assess whether phasic LAS is already altered in preclinical DD, a stage usually associated with normal LA size and filling pressures. We comprehensively analyzed echocardiographic data from a well-phenotyped cohort of women from the cross-sectional BErlin Female RIsk evaluation (BEFRI) study. By widening the understanding of mechanistic changes of LA function, the results may provide further insights into the pathophysiology of DD and HFpEF. In addition, analysis of LA function, rather than LA size, may allow earlier diagnosis of DD and timely perception of its impact on LA function.

## METHODS

### Study Population

The BEFRI trial was a cross-sectional study designed to identify predictors of incorrect subjective risk estimation in the general female urban population aged 25 to 74 years in Berlin, Germany. Details on the design of BEFRI have been published in detail previously.[16] In brief, objective cardiovascular risk and individual risk perception were investigated in 1,066 randomly selected women aged 25 to 74 years. Four women who intended to participate were excluded from analysis, three because they had reached the age of 75 years at the time of inclusion and one because of major literacy issues. We performed extensive assessment of medical history, focusing on cardiovascular diseases and thorough clinical investigation, which comprised somatometric measures, blood pressure measurement, electrocardiography, and blood samples. Women were carefully screened for atrial fibrillation by electrocardiographic analysis, on the basis of medical treatment and history. Subjective perception of absolute cardiovascular risk was then compared with the cardiovascular risk estimate according to the Framingham score for women.[16] The trial was approved by the institutional ethics committee of Charité University of Berlin, and all participants gave informed written consent. Of the 1,066 subjects of the BEFRI cohort, 473 women volunteered for echocardiographic measurements.

Baseline characteristics of the study population are depicted in Table 1. Hypertension was defined as resting systolic or diastolic blood pressure of ≥140 mm Hg or ≥90 mm Hg, respectively, or use of antihypertensive medication. Blood pressure and somatometric measurements such as waist-to-hip ratio and body mass index were measured as described in detail previously.[16] Limitations of physical activity were systematically recorded and graded according to the New York Heart Association classification.[17]

### Echocardiography

For comprehensive transthoracic echocardiographic examination, 473 women were prospectively enrolled between April 2013 and February 2014. Standard echocardiography was performed using a Vivid E9 system (GE Vingmed Ultrasound AS, Horton, Norway) with an M5S 1.5- to 4.5-MHz transducer. Two cycles were recorded for each view. LV dimensions, LV ejection fraction, and global longitudinal systolic LV strain as well as LA volume index (LAVI), assessed by the biplane disk summation technique, were analyzed in accordance with the recent recommendations of the American Society of Echocardiography.[18] Standard parameters to assess diastolic LV function comprised early (VE) and late (VA) diastolic transmitral inflow velocity, deceleration time, the average of septal and lateral early diastolic mitral annular velocity (e′) assessed by pulsed-wave tissue Doppler, and the E/e′ ratio to estimate LV filling pressures. In line with the guidelines, the classification of diastolic function was conducted according to these echocardiographic parameters, listed in Table 1. Diastolic function was graded according to the recommendations of the American Society of Echocardiography (DD1, impaired relaxation; DD2, pseudonormal filling).[19]

### Two-Dimensional Speckle-Tracking Analysis of the Left Atrium and the Left Ventricle

Standard 2D images from the apical four-chamber view were recorded during a single breath-hold. For 2D speckle-tracking analysis of LAS, focus was set on the interatrial septum, avoiding foreshortening, and a frame rate of 60 to 80 frames/sec was set during image acquisition. Two cardiac cycles were recorded and stored for offline analysis (EchoPAC PC; GE Vingmed Ultrasound AS). LAS was set to zero at the beginning of the QRS complex (QRS-triggered analysis). After manual tracing of the endocardial LA borders, the region of interest was automatically determined, and speckles were traced frame by frame. In case of insufficient tracking, manual adjustments were applied to optimize tracking quality. Phasic LAS and LAVI were calculated as the mean values from three valid measurements. Different phases of global LAS were identified from the plotted curve: peak systolic strain (LA reservoir function), LAS during passive LV filling (conduit phase), and strain during peak atrial contraction. LA reservoir function was determined by peak systolic strain, LA conduit function was calculated as LA reservoir function − LAS during passive LV filling, and LA pump function was calculated as LAS during passive LV filling − LAS during peak atrial contraction[20] (Figure 1). Global longitudinal LV strain was analyzed as previously described.[21,22]