Diastolic dysfunction revisited: A new, feasible, and unambiguous echocardiographic classification predicts major cardiovascular events

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Background Echocardiographic classification of DDF has been widely discussed. The aim of this study was to investigate the independent prognostic value of established echocardiographic measures in a community-based population and create a new classification of DDF.

Methods Within the Copenhagen City Heart Study, a prospective, community-based study, 1851 participants were examined by echocardiography including Tissue Doppler Imaging (TDI) in 2001 to 2003 and followed with regard to MACE (median, 10.9 years).

Results We found that persons with impaired myocardial relaxation as defined by low peak early diastolic mitral annular velocity *e′* by TDI had higher incidence of clinical and echocardiographic markers of cardiac dysfunction and increased risk of MACE. Among persons with impaired relaxation, only echocardiographic indices of increased filling pressures such as $LAVi \geq 34$ mL/m^2 (HR 1.97 (1.13-3.45, $P = .017$), $E/e' \geq 17$ (HR 1.89 (1.34-2.65), $P < .001$), and $E/A > 2$ (HR 5.24 (1.91-14.42), $P = .001$) provided additional and independent prognostic information on MACE. Based on these findings, we created a new classification of DDF where all grades were significant predictors of MACE independently of age, sex, and cardiac clinical risk markers (Mild DDF: HR 1.99 (1.23-3.21), $P = .005$; Moderate DDF: HR 3.11 (1.81-5.34), $P < .001$; Severe DDF: HR 4.20 (1.81-9.73), $P < .001$). Increasing severity of DDF was linearly associated with increasing plasma proBNP concentrations.

Conclusions In the general population, the presence of echocardiographic markers of elevated filling pressures in persons with impaired relaxation increased the risk of MACE significantly. Based on this, we present a new, feasible, and unambiguous classification of DDF capable of accurate risk prediction in the community. (Am Heart J 2017;188:136-46.)

Diastolic dysfunction (DDF) is established as a predictor of major adverse cardiac events (MACE) in the general population.[1-4] However, classification of DDF has been widely discussed and numerous classification methods have been proposed.[1,5-10] Many classification algorithms leave patients as indeterminate due to incongruent echocardiographic measures.[11] The recently published guideline proposes an entirely new approach.[9] However, it has yet to be validated.

A number of echocardiographic measures have been shown to reflect DDF. In this study, our focus is on the following:

- Mitral inflow measurements such as peak early filling (*E*-wave) and late diastolic filling (*A*-wave) velocities, the *E/A* ratio, and deceleration time (*DT*) of early filling velocity are regarded as the traditional diastolic echocardiographic measures representative of filling pressures at the time of measurement as they are affected by preload.[5,12]
- Tissue Doppler Imaging (TDI) is an echocardiographic technique which enables measurement of tissue velocities. Quantification of peak early diastolic

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mitral annular velocity (e') by TDI reflects myocardial relaxation and the ratio between peak early mitral inflow velocity and peak early diastolic mitral annular velocity (E/e') reflects filling pressures.[5,13]

- Left atrial volume (LAV) or left atrial volume index (*LAVi*) is thought to reflect the effects of elevated filling pressures over time.[2,5]

Studies have shown all of the measures mentioned above to correlate individually with cardiovascular prognosis and survival in both clinical and general populations.[2-4,14-25]

In most studies, DDF is classified as either mild (grade I), moderate (grade II) or severe (grade III and IV). Mild is defined as an impaired relaxation pattern without an increase in filling pressures, moderate is defined as impaired relaxation with a moderate increase in filling pressures (pseudonormal filling) and severe is characterized by a restrictive filling pattern, either reversible (grade III) or fixed (grade IV). However, cutoff values for the included echocardiographic measures vary, as do the algorithms by which the final grade is reached.[1,5-9] The classifications utilize many different echocardiographic measures; however, the only measure showing abnormality across all DDF grades seems to be e' as a measure of impaired relaxation. Impaired relaxation is widely regarded as the first step in the progression of DDF.[1,26]

This study aims to investigate the independent prognostic value of traditional echocardiographic measures and establish a new and simpler algorithm for grading DDF.

Methods

Study population

This study was performed as a substudy of the 4th Copenhagen City Heart Study,[4,27] a longitudinal cohort study of cardiovascular disease and risk factors. This study includes 2221 randomly selected men and women (age 20-93 years) who underwent echocardiographic examination including both conventional echocardiography and color TDI with measurement of septal and lateral peak early diastolic mitral annular velocities (e′). Whether a participant underwent echocardiography was completely independent of his or her health status and other risk factors. One hundred fifty-seven with atrial fibrillation and/or significant valvular disease and/or inadequate quality of the echocardiographic examination as well as 213 persons who did not have both septal and lateral color TDI measurements were excluded. After exclusion of persons with significant valvular disease, there were no persons left with significant mitral annular calcification.

All subjects gave informed consent to participate and the study was performed in accordance with the second Helsinki Declaration and approved by the regional ethics committee.

Health examination

Participants were questioned and examined at baseline. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. Diabetes mellitus was defined as plasma glucose concentration ≥11.1 mmol/L; use of insulin; or other antidiabetic medicine, self-reported disease, or hemoglobin A_{1c} level >7.0%. Ischemic heart disease was defined as a history of hospital admission for acute coronary artery occlusion, percutaneous coronary intervention or coronary artery bypass grafting, or major ischemic alterations on the electrocardiogram as defined by Minnesota codes 1.1 to 3. The plasma pro-B-type natriuretic peptide concentration was quantified with a processing-independent assay.[28]

Echocardiography

Three experienced echocardiography technicians performed all echocardiograms using GE Vingmed Ultrasound's Vivid Five with a 2.5 MHz probe (Horten, Norway). The echocardiograms were analyzed off-line with the investigator blinded to other information. LAV was measured using the biplane area-length method in the apical four- and two-chamber views.[29] Evaluation of mitral inflow velocities (early *E* and late *A*) and left ventricular (LV) dimensions/dilatation, mass index/hypertrophy, and ejection fraction were performed as previously described.[4] Color TDI loops were obtained in the apical four-chamber view at the highest possible frame rate and e' was measured within a 6 mm circular sample volume in the septal and lateral mitral annular positions and averaged. Smoothing of the curves by averaging velocities over 30 milliseconds was done by the software.

All cut-off values for echocardiographic measures were defined as suggested by the relevant guidelines.[5,9,29] Increased *LAVi* was defined as $LAVi \geq 28$ mL/m^2. Mitral inflow patterns were defined as recommended by the 2009 guideline.[5] Impaired myocardial relaxation was defined as average septal and lateral $e' < 7$ cm/s (corresponding to approximately <9 cm/s by pulsed wave TDI).[30] E/e'-ratio was calculated as a measure of left ventricular filling pressures. Normal filling pressures and elevated filling pressures were defined as $E/e' \leq 10$ and $E/e' \geq 17$, respectively (corresponding to approximately $E/e' \leq 8$ and $E/e' \geq 13$ by pulsed wave TDI).[30] Intra- and inter-observer variability of mitral annular velocities has previously been shown to be low.[31]

Outcome

Participants were followed from the examination in 2001 to 2003 until April 2013 or time of event. Median follow-up was 10.9 years. The primary end point was MACE defined as cardiovascular death or admission due to either heart failure or acute myocardial infarction. Follow-up was registry-based[32,33] and 100% complete.