Preclinical Systolic and Diastolic Dysfunction Assessed by Tissue Doppler Imaging is Associated With Elevated Plasma Pro-B-type Natriuretic Peptide Concentrations

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ABSTRACT

Background: Heart failure is a major public health problem. To improve its grave prognosis, early identification of cardiac dysfunction is mandatory. Conventional echocardiography is not suitable for this. Tissue Doppler imaging (TDI), however, could be so.

Methods and Results: Within a large community-based population-study (n = 1012), cardiac function was evaluated by conventional echocardiography (left ventricular hypertrophy, dilatation, systolic, and severe diastolic dysfunction), TDI, and plasma proBNP. Averages of peak systolic (s′), early diastolic (e′), and late diastolic (a′) velocities from 6 mitral annular sites were used. TDI was furthermore quantified by a combined index (eas-index) of diastolic and systolic performance: e′/(a′ × s′). Compared with controls, persons with elevated plasma proBNP concentrations (n = 100) displayed lower systolic and diastolic performance by TDI, in terms of lower s′ ($P = 0.017$) and a′ ($P < .001$), and higher e′/a′ ($P = .002$) and eas-index ($P < .001$). This pattern remained significant after multivariable adjustment for age, sex, body mass index, heart rate, estimated glomerular filtration rate, hypertension, diabetes, ischemic heart disease, and conventional echocardiography. Furthermore, TDI provided incremental information over conventional echocardiography in predicting elevated plasma proBNP concentrations.

Conclusions: Preclinical systolic and diastolic dysfunction by TDI is associated with elevated plasma proBNP levels, even when conventional echocardiography is normal. (*J Cardiac Fail 2009;15:489–495*)

Key Words: Heart failure, population, diagnosis, echocardiography, ProBNP.

Adults at age 40 years have a lifetime risk of >20% of developing heart failure,[1] a severe condition with a long-term prognosis as grave as the most frequent types of cancers.[2] To improve this dismal picture, early identification of persons with initial cardiac dysfunction is necessary for prompt intervention. Heart failure is a progressive disease and most of the patients referred to hospital have already long passed the initial phases. Thus, population-based studies are essential when investigating initial cardiac dysfunction.

Conventional echocardiography is the key examination in the hospital setting of patients suspected of heart failure.[3,4] However, because many persons in the community with heart failure have neither systolic nor definite diastolic dysfunction as assessed by conventional echocardiographic measures,[5] it is mandatory to evaluate the potential of other diagnostic tools. Tissue Doppler imaging (TDI), a recent echocardiographic technique, is able to evaluate longitudinal myocardial function, which is suggested to be affected early in many cardiac conditions.[6,7] Furthermore TDI has been shown to provide diagnostic and prognostic information incremental to conventional echocardiography in patients with heart failure.[8–12] The potential of TDI in detecting preclinical cardiac dysfunction, however, still remains to be tested. Because the natriuretic peptides have

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shown to predict future events of heart failure and cardiovascular death in apparently asymptomatic persons in the community,[13] we aimed to evaluate the association between plasma pro-B-type natriuretic peptide (proBNP) and cardiac function, as assessed both by conventional echocardiography and TDI in a large, population-based study.

Methods

Study Population

This study was performed as a substudy of the 4th Copenhagen City Heart Study, a longitudinal cohort study of cardiovascular disease and risk factors.[14,15] At the first examination from 1976 to 1978, a random sample of 19,329 predominantly Caucasian citizens living within a well-defined area of the inner Copenhagen City boundary was drawn from the Central Office of Civil Registration and invited to take part in the study. At the fourth examination from 2001 to 2003, 12,600 persons were invited in a random order. This study population consisted of participants from the previous examinations (n = 11,600), supplemented by a random sample of persons from the younger age strata (n = 1000). Out of these, 6238 (49.5%) participated. The present article includes 1012 randomly selected men and women (20 to 93 years) who underwent an echocardiographic examination including color TDI and measurement of plasma proBNP concentration. Whether or not a participant underwent echocardiography was completely independent of his or her health status and other risk factors. Persons with known heart failure, atrial fibrillation, significant valvular stenosis, or regurgitation were excluded.

All subjects gave written informed consent to participate, and the study was performed in accordance with the 2nd Helsinki Declaration and approved by the regional ethics committee.

Health Examination

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication.[16] Diabetes mellitus was defined as plasma glucose concentration ≥11.1 mmol/L, use of insulin or other antidiabetic medicine, self-reported disease, or HbA_{1c} level >7.0%.[17,18] Ischemic heart disease was defined as either a history of hospital admission from acute coronary artery occlusion, percutaneous coronary intervention or coronary artery bypass grafting, or major ischemic alterations on the electrocardiogram as defined by the Minnesota codes 1.1-3. Estimated glomerular filtration rate (GFR) was calculated by Cockcroft-Gault formula.

$$[140 - \text{age (years)}] \times [\text{weight (kg)}] \times [1.23 \text{ if male; if female}] / [\text{serum creatinine } (\mu\text{mol/L})].$$

Plasma proBNP Measurement

The plasma proBNP concentration was quantified using a processing-independent assay.[19] The analytical validation of this assay has been reported elsewhere.[20,21] The results from this assay compares well with the commercially available Modular NT-proBNP assay by Roche. In a separate patient cohort study, measurement with 2 assays correlated well on regression analysis (n = 370, $r^2 = 0.91$; $P < .001$; Goetze et al, unpublished data, 2008). The study population was divided into persons with normal or elevated plasma proBNP concentrations: individuals with plasma proBNP concentrations ≥90th percentile of the expected value according to age and sex, were defined as having elevated concentrations of plasma proBNP; whereas the normal proBNP group consisted of individuals with plasma proBNP concentrations <90th percentile of the expected plasma proBNP concentration according to age and sex.

Echocardiography

Three experienced echo technicians using GE Vingmed Ultrasound's Vivid Five with a 2.5 MHz probe (Horten, Norway) performed all echocardiograms. All subjects were examined with color TDI, 2-dimensional and M-mode echocardiography, and conventional spectral Doppler in the left lateral decubitus position. All images were recorded using second harmonic imaging at the time of end-expiration. The collected data were stored on magneto-optical discs and an external FireWire hard drive (LaCie, France) and analyzed offline with commercially available software (EchoPac, GE Medical, Horten, Norway) with the investigator being blinded to other information.

Conventional Echocardiography

The 16 standard segments model, as suggested by the American Society of Echocardiography,[22] was used for evaluation of regional function. Left ventricular systolic dysfunction was defined as left ventricular ejection fraction <50%.

One loop was recorded of the parasternal long axis and 1 M-mode still frame between the tips of the mitral leaflets and the tips of the papillary muscles. If the correct 90° angle to the long-axis of the ventricle could not be obtained, 2-dimensional images were used instead to quantify the myocardial thickness and the dimensions of the left ventricle. Left ventricular mass index was calculated as the anatomic mass[23] divided by body surface area.[24] Left ventricular hypertrophy was defined as left ventricular mass index ≥104 g/m^2 for women and ≥116 g/m^2 for men.[25] Left ventricular dilation was considered present if the diameter of the left ventricle at end-diastole (cm) divided by height (m) ≥ 3.3 cm/m.[22]

Pulsed wave Doppler at the apical position was used to record mitral inflow between the tips of the mitral leaflets. Peak velocities of early (E) and atrial (A) diastolic filling and deceleration time of the E-wave were measured and the E/A ratio was calculated. Severe diastolic dysfunction was defined as deceleration time of the E-wave <140 ms and $E/A_{<50\ years} > 2.5$, $E/A_{50\text{-}70\ years} > 2$, or $E/A_{>70\ years} > 1.5$, respectively.[26]

A normal conventional echocardiographic examination identified subjects without left ventricular hypertrophy, dilation, systolic dysfunction, or severe diastolic dysfunction.

Color TDI

Color TDI loops were obtained in the apical 4-chamber, 2-chamber, and apical long-axis views at the highest possible frame rate. Peak systolic (s′), early diastolic (e′), and late diastolic (a′) velocities were measured within a 6-mm circular sample volume as shown in Fig. 1. Smoothing of the curves by averaging velocities over 30 ms was done by the software. Left ventricular longitudinal function was assessed by averaging myocardial velocities in the septal, lateral, inferior, anterior, posterior, and anteroseptal mitral annular positions. Ratios of E/e′, e'/a′, and e′/(a′ × s′) (eas-index) were calculated, as measures of left ventricular filling pressure, diastolic performance, and combined systolic and diastolic performance, respectively.