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Research Article

Epidemiologic observations guiding clinical application of a urinary peptidomic marker of diastolic left ventricular dysfunction

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Abstract

Hypertension, obesity, and old age are major risk factors for left ventricular (LV) diastolic dysfunction (LVDD), but easily applicable screening tools for people at risk are lacking. We investigated whether HF1, a urinary biomarker consisting of 85 peptides, can predict over a 5-year time span mildly impaired diastolic LV function as assessed by echocardiography. In 645 white Flemish (50.5% women; 50.9 years [mean]), we measured HF1 by capillary electrophoresis coupled with mass spectrometry in 2005–2010. We measured early (E) and late (A) peak velocities of the transmitral blood flow and early (e') and late (a') mitral annular peak velocities and their ratios in 2009–2013. In multivariable-adjusted analyses, per 1-standard deviation increment in HF1, e' was −0.193 cm/s lower (95% confidence interval: −0.352 to −0.033; $P = .018$) and E/e' 0.174 units higher (0.005–0.342; $P = .043$). Of 645 participants, 179 (27.8%) had LVDD at follow-up, based on impaired relaxation

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in 69 patients (38.5%) or an elevated filling pressure in the presence of a normal (74 [43.8%]) or low (36 [20.1%]) age-specific E/A ratio. For a 1-standard deviation increment in HF1, the adjusted odds ratio was 1.37 (confidence interval, 1.07–1.76; $P = .013$). The integrated discrimination (+1.14%) and net reclassification (+31.7%) improvement of the optimized HF1 threshold (−0.350) in discriminating normal from abnormal diastolic LV function at follow-up over and beyond other risk factors was significant ($P \leq .024$). In conclusion, HF1 may allow screening for LVDD over a 5-year horizon in asymptomatic people. J Am Soc Hypertens 2018;■(■):1–10.

Keywords: Diastolic left ventricular function; population science; screening; urinary proteomics.

Introduction

Diastolic heart failure (DHF) represents half of all heart failure cases[1] and has a 30% death rate within 1 year of the first hospital admission.[2] Subclinical left ventricular (LV) diastolic dysfunction (LVDD) has 25% prevalence in the general population.[3,4] Hypertension, obesity, old age, and insulin resistance are among the major risk factors.[3,4] LVDD is an insidious condition evolving to DHF.[5] Screening for LVDD at the point of entry in health care is extremely challenging because it requires awareness of predisposing risk factors, clinical interpretation of vague symptoms and signs, and LV imaging demonstrating functional or structural LV changes. The observation that natriuretic peptide levels in LVDD patients are often within normal limits[3,4,6] complicates the matters further and justifies the quest for novel biomarkers specific for LVDD at an early stage long before it progresses to DHF.

Capillary electrophoresis coupled with high-resolution mass spectrometry (CE-MS) enables detection of over 5000 distinct peptides in urine samples.[7,8] We previously identified a multidimensional urinary classifier, HF1, mainly consisting of dysregulated collagen fragments,[9–11] which in case-control studies[9] and in the general population[10,11] was reproducibly associated with subclinical LVDD. In patients progressing from LVDD to DHF, the LV wall undergoes fibrosis characterized by increased interstitial deposition[12] and cross-linking of collagen I at the detriment of collagen III.[13,14] We hypothesized that urinary markers of collagen turnover, and circulating serum markers of collagen degradation might predict LVDD[3,4] over and beyond known risk factors and might therefore represent easily applicable screening tools in primary care. We tested our hypothesis in participants enrolled in the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO[9–11]), in whom we related the echocardiographically assessed diastolic LV function (2009–2013) to HF1, and the serum markers of collagen degradation measured approximately 5 years earlier (2005–2010).

Methods

Study Participants

FLEMENGHO is a family-based population study,[15,16] which complies with the Helsinki declaration[17] and received ethical approval from the Ethics Committee of the University Hospitals Leuven (approval number B32220083510). For the current analysis, we selected 655 people, whose urinary proteome had been measured in 2005–2010 (baseline) and who had undergone echocardiography in 2009–2013 (follow-up). The participation rate at echocardiography was 80.0%. We excluded 10 participants, whose diastolic LV function at follow-up could not be reliably assessed, because of atrial fibrillation (N = 6) or paced heart rhythm (N = 4). Thus, the number of participants statistically analyzed totaled 645.

Clinical Measurements

Body mass index (BMI) was weight in kilogram divided by height in meters squared. Waist circumference was determined using a measuring tape. Abdominal obesity was a waist circumference of ≥88 cm in women and ≥102 cm in men.[18] Blood pressure was the average of five consecutive auscultatory readings. Hypertension was a blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or use of antihypertensive drugs. Estimated glomerular filtration rate (eGFR) was derived from serum creatinine (Crt) by the chronic kidney disease epidemiology collaboration equation.[19] Diabetes mellitus was a self-reported diagnosis, a fasting plasma glucose (Glyc) ≥7 mmol/L, or use of antidiabetic agents.[20] Using validate questionnaires[21] and published tables,[22] we computed the energy spent in physical activity from body weight, time devoted to work, walking, sports and leisure time activities, and type of physical activity.

Echocardiography

Detailed information on the acquisition and offline analysis of the echocardiographic images is available in previous publications.[9,10] In short, echocardiographic measurements, obtained with a Vivid7 Pro device (GE Vingmed, Horten, Norway) interfaced with a 2.5–3.5-MHz phased-array probe, were averaged over three heart cycles. Diastolic LV function was assessed by the EchoPac software, version 4.0.4 (GE Vingmed, Horten, Norway). In keeping with guidelines,[23] we determined peak early (E) and late (A) diastolic velocities of the transmitral blood