Exercise Limitation Associated With Asymptomatic Left Ventricular Impairment

Analogy With Stage B Heart Failure

Wojciech Kosmala, MD, PhD,*† Christine L. Jellis, MD, PhD,‡ Thomas H. Marwick, MBBS, PhD, MPH†

ABSTRACT

BACKGROUND Stage B heart failure (SBHF) describes asymptomatic ventricular disease that may presage the development of heart failure (HF) symptoms. This entity has been largely defined by structural changes; the roles of sensitive indicators of nonischemic left ventricular (LV) dysfunction, such as LV strain, are undefined.

OBJECTIVES This study sought to define the association of exercise capacity with left ventricular hypertrophy (LVH) and systolic/diastolic dysfunction in asymptomatic patients with HF risk factors.

METHODS We used echocardiography to study 510 asymptomatic patients (age 58 ± 12 years) with type 2 diabetes mellitus, hypertension, or obesity. The results of cardiopulmonary exercise testing in patients with structural evidence of SBHF were compared with those in patients with subclinical dysfunction, defined by reduced LV strain ($>-18\%$) or increased LV filling pressure (E/e′ >13).

RESULTS Compared with healthy subjects, groups with LV abnormalities differed in terms of oxygen uptake (peak VO_2): 25.5 ± 8.2 versus 21.0 ± 8.2 for strain $>-18\%$ ($p < 0.001$); 26.4 ± 8.0 versus 19.0 ± 7.2 for E/e′ >13 ($p < 0.0001$); and 26.0 ± 7.7 versus 15.9 ± 6.9 ml/kg/min for LVH ($p < 0.0001$). SBHF, defined as ≥ 1 imaging variable present, was associated with lower peak VO_2 (beta $= -0.20$; $p < 0.0001$) and metabolic equivalents (beta $= -0.21$; $p < 0.0001$), independent of higher body mass index and insulin resistance, older age, male sex, and treatment with beta-blockers.

CONCLUSIONS LVH, elevated LV filling pressure, and abnormal myocardial deformation were independently associated with impaired exercise capacity. Including functional markers may improve identification of SBHF in nonischemic heart disease. (J Am Coll Cardiol 2015;65:257–66) © 2015 by the American College of Cardiology Foundation.

Despite remarkable advances, heart failure (HF) remains a major public health problem with an ongoing increase in prevalence (1-3). The progressive nature of HF is reflected in the American College of Cardiology/American Heart Association guidelines, which stratify the disease into 4 stages, differing in terms of cardiac involvement, clinical manifestations, and refractoriness to treatment (4,5). Asymptomatic patients with HF risk factors (including hypertension, type 2 diabetes mellitus [T2DM], and obesity) have stage A heart failure (SAHF). Patients with stage B heart failure (SBHF) have asymptomatic left ventricular (LV) damage, a greater likelihood for developing overt HF, and specific treatment implications. The frequency of subclinical HF may exceed 50% in community members >45 years of age (6); therefore, early recognition of SBHF offers the potential of altering disease progression therapeutically (7).

The early stages of ischemic HF are more often complicated by LV structural and functional remodeling than nonischemic etiologies, which seem to be

marked by more functional than structural changes [8-12]. The exclusive reliance on the presence of left ventricular hypertrophy (LVH) and/or reduced left ventricular ejection fraction (LVEF) to ascertain SBHF may be insufficient to detect the early stages of nonischemic HF. In this study, we compared the association of LVH and systolic/diastolic dysfunction with exercise capacity, a widely accepted prognostic correlate and marker of disease severity. Our hypothesis was that functional markers (systolic and diastolic dysfunction) would have a similar association with exercise capacity as the structural marker LVH in patients in the asymptomatic stages of HF due to T2DM, hypertension, or obesity.

METHODS

PATIENTS. We prospectively recruited 510 asymptomatic patients with T2DM, obesity, or hypertension from the hospital clinic and community of 2 tertiary medical centers (Princess Alexandra Hospital in Brisbane, Australia [n = 223] and the University Hospital in Wroclaw, Poland [n = 287]). Obesity was defined as body mass index ≥30 kg/m². Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg; diastolic BP ≥90 mm Hg in at least 2 properly measured, seated BP readings on each of ≥2 office visits; or patient on antihypertensive therapy. T2DM was diagnosed according to standard criteria (plasma glucose level, either fasting or 2-h value in 75-g oral glucose tolerance test, or glycated hemoglobin A1c [HbA₁c] value).

Participants confirmed their ability to perform physical activity without dyspnea or fatigue. We excluded patients with documented microvascular or macrovascular complications of diabetes, moderate or severe valvular heart disease, congenital heart disease, other significant comorbidities (including malignancy), renal failure, significant psychiatric illness, or absence of stable sinus rhythm. All patients underwent stress echocardiography and were excluded if they had either a history of ischemic heart disease or positive stress testing.

The study complied with the Declaration of Helsinki, and study approval was granted by the human research ethics committees at both institutions. All patients provided informed consent.

DEMOGRAPHIC, ANTHROPOMETRIC, AND METABOLIC DATA. Clinical data were collected regarding patient age, sex, and anthropometry (height, body weight, and hip and waist circumferences). Serum glucose level, insulin level, HbA₁c value, creatinine level, and lipid profile were obtained after 12-h fasting and before administration of hypoglycemic agents. Insulin resistance was determined by the homeostasis model assessment for patients not on supplemental exogenous insulin therapy, calculated as the product of fasting insulin level multiplied by fasting glucose level divided by 22.5.

HEMODYNAMIC DATA AND EXERCISE CAPACITY. Hemodynamic parameters including heart rate and systolic and diastolic BPs were measured at baseline and at peak exercise. Tonometric pulse wave velocity (SphygmoCor, AtCor Medical, Sydney, Australia) between carotid and femoral sites was used to determine aortic stiffness.

Exercise testing was performed on a treadmill using the Bruce protocol and standard cardiopulmonary stress equipment. Ventilation, oxygen uptake, and carbon dioxide production were monitored continuously, and peak oxygen uptake (peak VO₂) was calculated as the average oxygen consumption during the last 30 s of exercise. Exercise capacity was also estimated in metabolic equivalents (METs) based on peak exercise intensity.

ECHOCARDIOGRAPHY. Standard commercially available cardiac ultrasound machines (Vivid 7 and Vivid E9, General Electric Medical Systems, Milwaukee, Wisconsin) were used to perform resting echocardiograms. Images were saved in raw data format for offline analysis to assess LV wall thickness, valvular morphology, and chamber volumes. LV mass was measured using standard criteria and normalized for body size (body surface area or height to the power of 2.7) to obtain left ventricular mass index (LVMI) [13]. LVH was determined according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography [14]. The modified Simpson biplane method was used to measure LVEF.

Pulsed wave Doppler recordings of LV inflow were acquired from the apical 4-chamber view with the sample volume placed between the tips of the mitral leaflets. Peak early (E) and late diastolic flow velocities (A), ratio of peak early and late diastolic flow velocities (E/A), and deceleration time of early diastolic flow wave were assessed.

Pulsed wave tissue Doppler was performed to establish peak early diastolic mitral annular velocity (e′). The ratio of mitral inflow early diastolic velocity to the average e′ velocity obtained from the septal and lateral sides of the mitral annulus (E/e′) was calculated to estimate LV filling pressure, and a value >13 was considered to reflect LV filling pressure elevation [15]. Conventional apical views (4-chamber, 2-chamber, and long-axis) in color tissue Doppler format were