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● *Original Contribution*

NORMAL REFERENCE VALUES FOR ASSESSING DIASTOLIC FUNCTION USING THE PARAMETERIZED DIASTOLIC FILLING FORMALISM METHOD IN PATIENTS WITH NORMAL RESULTS OF REST AND STRESS ECHOCARDIOGRAPHY

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Abstract—The parameterized diastolic filling (PDF) method can be used to study the mechanics of early diastolic left ventricular (LV) filling. However, there are no publications describing the reference ranges of the PDF parameters. This study retrospectively recruited patients with normal results on rest and stress echocardiography and no diabetes or hypertension (n=138, 45% female). DICOM images of the resting E-wave from transmitral pulsed wave Doppler flow velocities were analyzed using freely available software. Viscoelastic energy loss (*c*) and stiffness (*k*) were higher in males compared to females ($p \leq 0.001$ for both). There were no correlations between any of the PDF parameters and age ($p > 0.05$ for all). In males, stiffness was correlated with systolic blood pressure (r=0.24, p=0.04), and load and filling energy were correlated with diastolic blood pressure (r=-0.27, p=0.02, and r=-0.29, p=0.01, respectively). Sex-specific normal 95% reference limits for PDF analysis of early LV filling are presented for clinical use. (E-mail: martin@ugander.com)

Key words: **Diastolic function, Echocardiography, Kinematic analysis, Parameterized diastolic filling, Diastolic reference limits.**

INTRODUCTION

The clinical assessment of diastolic function by echocardiography can be complex and can be performed using a number of proposed methods. These methods typically involve a phenomenological approach to interpreting echocardiographic estimates of impaired relaxation or increased filling pressures (Nagueh et al. 2016). An alternative approach is to study left ventricular (LV) filling mechanistically. It has been demonstrated that early LV filling velocities can be accurately described kinematically as a case of damped harmonic motion in a framework called the parameterized diastolic filling formalism (PDF) (Kovács et al. 1987). The PDF method involves mathematically describing the contour of the E-wave, as recorded by transmitral pulsed wave (PW) Doppler, in terms of three physical properties: stiffness or tendency to recoil (k), viscoelastic energy loss or damping (c), and load (x_0). For every E-wave these constants can be obtained by using the E-wave data as input to a curve fitting algorithm that mathematically describes the velocity profile over time in terms of these mechanical properties. An example of the curves obtained with different levels of c and k are shown in Figure 1. Furthermore, these three fundamental physical properties can be used to derive several additional parameters of potential diagnostic and pathophysiological interest. A summary of the PDF parameters is provided in Table 1. The PDF method can be applied to all patients with a clearly delineated E-wave, potentially offering new insights into cardiac function. It has been used to study prognosis in heart failure (Rich et al. 1999), and pathophysiological characteristics in diabetes (Riordan et al. 2005; Zhang et al. 2007), hypertension (Kovács et al. 1997) and amyloidosis (Salman et al. 2017). Software for clinically feasible PDF analysis of E-waves has recently been described and made freely available (Sundqvist et al. 2016). However, there are no published data regarding the normal

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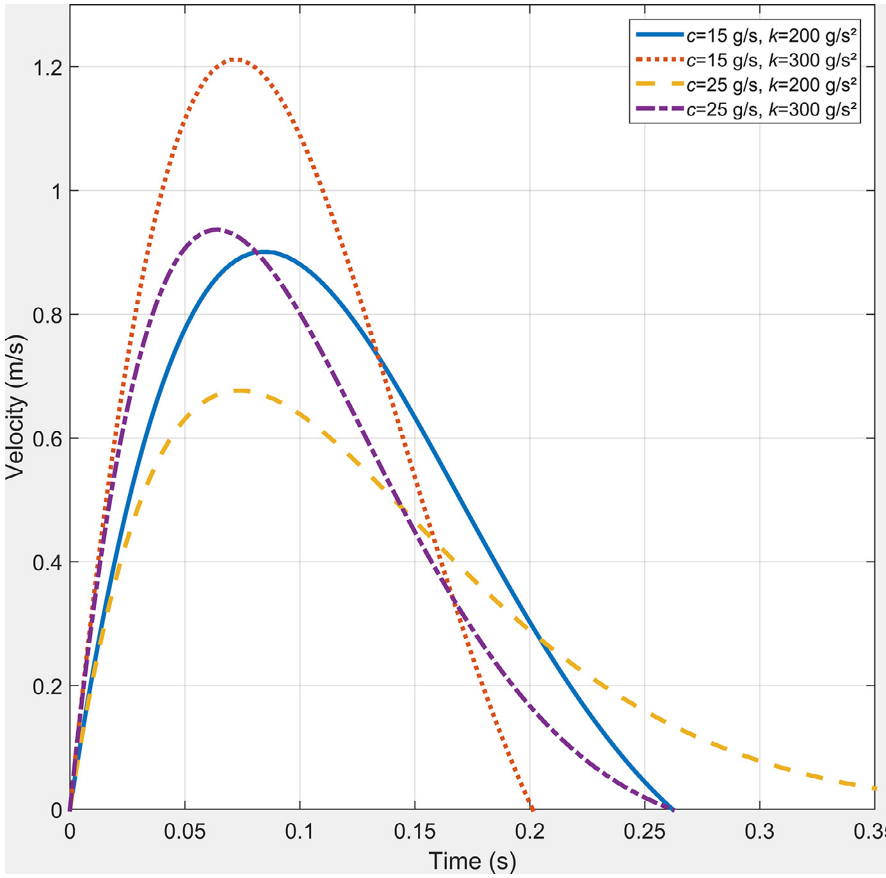

Fig. 1. **Illustration of the PDF method.** PDF curves as obtained with different combinations of the stiffness parameter k and the viscoelastic energy-loss parameter c. Blue solid line: $c = 15$ g/s, $k = 200$ g/s^2. Orange dotted line: $c = 15$ g/s, k increased to 300 g/s^2. Yellow dashed line: c increased to 25 g/s, $k = 200$ g/s^2. Purple dash-dotted line: c increased to 25 g/s, k increased 300 g/s^2. A change in x_0 would change the amplitude of the curve without changing the acceleration or deceleration times.

reference limits of the PDF measures in a healthy population. The aim of this study was to provide such reference limits in order to facilitate the use of the PDF method in clinical research.

MATERIALS AND METHODS

Study population

A normal population of patients undergoing echocardiography between July 29, 2015 and December 31, 2015 was identified at the out-patient echocardiography lab at the National Heart Centre Singapore (NHCS) by retrospectively screening patients attending for stress echocardiography, using data available in an existing clinical echocardiographic database. The present study made use of the baseline echocardiogram recorded shortly before the patients underwent stress echocardiography. This design was chosen pre-hoc as a robust way to ascertain that patients were indeed normal for the following reasons: (i) stress echocardiography patients at NHCS are rigorously characterized in terms of cardiovascular comorbidities using a dedicated clerking proforma which is completed by the attending doctor supervising the test, (ii) all patients undergo 12-lead ECG with electronic documentation made of cardiac rhythm and ECG morphology in each case, (iii) coronary insufficiency, which may be subclinical and yet exert strong influence on cardiac diastology, is unlikely to remain undetected during stress echocardiography. Exclusion criteria were a history of diabetes mellitus, hypertension, or atrial fibrillation, and echocardiography findings including an inducible wall motion abnormality at stress, resting LV ejection fraction (LVEF) <55 %, left atrial or LV dilation, septal hypertrophy, or more than mild valvular disease. Limits of normality for these measures were defined according to the 2015 echocardiography guidelines (Lang et al. 2015). Finally, additional exclusion criteria included patients with suboptimal transmitral PW Doppler recordings due to unevaluable image quality, or fusion of the E- and A-wave involving more