Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–8, 2017

0301-5629/$ - see front matter

ELSEVIER

http://dx.doi.org/10.1016/j.ultrasmedbio.2017.02.014

● *Original Contribution*

CARDIAC AMYLOIDOSIS SHOWS DECREASED DIASTOLIC FUNCTION AS ASSESSED BY ECHOCARDIOGRAPHIC PARAMETERIZED DIASTOLIC FILLING

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(*Received* 13 *June* 2016; *revised* 16 *February* 2017; *in final form* 19 *February* 2017)

Abstract—Cardiac amyloidosis is a rare but serious condition with poor survival. One of the early findings by echocardiography is impaired diastolic function, even before the development of cardiac symptoms. Early diagnosis is important, permitting initiation of treatment aimed at improving survival. The parameterized diastolic filling (PDF) formalism entails describing the left ventricular filling pattern during early diastole using the mathematical equation for the motion of a damped harmonic oscillator. We hypothesized that echocardiographic PDF analysis could detect differences in diastolic function between patients with amyloidosis and controls. Pulsed-wave Doppler echocardiography of transmitral flow was measured in 13 patients with amyloid heart disease and 13 age- and gender matched controls. E- waves (2 to 3 per subject) were analyzed using in-house developed software. Nine PDF-derived parameters were obtained in addition to conventional echocardiographic parameters of diastolic function. Compared to controls, cardiac amyloidosis patients had a larger left atrial area (23.7 ± 7.5 cm^2 vs. 18.5 ± 4.8 cm^2, $p = 0.04$), greater interventricular septum wall thickness (14.4 ± 2.6 mm vs. 9.3 ± 1.3 mm, $p < 0.001$), lower e' (0.06 ± 0.02 m/s vs. 0.09 ± 0.02 m/s, $p < 0.001$) and higher E/e' (18.0 ± 12.9 vs. 7.7 ± 1.3, $p = 0.001$). The PDF parameter peak resistive force was greater in cardiac amyloidosis patients compared to controls (17.9 ± 5.7 mN vs. 13.1 ± 3.1 mN, $p = 0.03$), and other PDF parameters did not differ. PDF analysis revealed that patients with cardiac amyloidosis had a greater peak resistive force compared to controls, consistent with a greater degree of diastolic dysfunction. PDF analysis may be useful in characterizing diastolic function in amyloid heart disease. (E-mail: martin.ugander@gmail.com) © 2017 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Echocardiography, Diastology, Parameterized diastolic filling, Cardiac amyloidosis.**

INTRODUCTION

Amyloidosis is an umbrella term for rare but severe diseases involving accumulation of insoluble fibrillary amyloid proteins in the extracellular matrix in tissues and organs (Banypersad et al. 2012; Fitzgerald et al. 2011, 2013; Koyama et al. 2015). Deposition of the pathologic proteins leads to disruption of the structure and function of the tissues with a median survival of 12 months from diagnosis without treatment, which decreases to 5 months once the cardiac muscle is infiltrated (Fitzgerald et al. 2013). Early diagnosis is important, permitting initiation of treatment aimed at improving survival. There are several non-invasive ways to detect cardiac involvement, including electrocardiography (ECG), cardiac biomarkers in the blood, genetic testing and imaging using modalities such as echocardiography, cardiovascular magnetic resonance and scintigraphy (Banypersad et al. 2012; Falk and Quarta 2015; Koyama et al. 2015; Liu et al. 2011). However, these methods all have limitations. Existing methods may be inconclusive on their own or unreliable because of the influence by physiological factors including filling pressures, or limited availability in the routine clinical practice, time consuming, expensive or too invasive for the already frail patient population (Banypersad et al. 2012; Khouri et al. 2004). To date, the reference standard has required tissue biopsy when the amyloid fibril type cannot be defined with existing methods or when cardiac amyloidosis is an isolated feature (Banypersad et al. 2012; Falk and Quarta 2015).

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Currently, clinical assessment of diastolic dysfunction encompasses several echocardiographic measures and a variety of algorithms for grading of severity (Khouri et al. 2004; Nagueh et al. 2009). Unfortunately, the current algorithms are inadequate for classification of a sizable minority of patients due to divergent results.

The main reason for unclassifiable patients depends on the definition and algorithm used while grading the diastolic function. Kuwaki et al. (2014) found 318 unclassified patients in a total of 1362 enrolled patients This was due to the inability of the diastolic dysfunction grading algorithm to accommodate classification of phenomenologically divergent results. In 2016, new updated recommendations for left ventricular (LV) diastolic function were introduced by the American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) (Nagueh et al. 2016). However, even those criteria may classify findings as indeterminate, and this is a major challenge for the field. This leads to uncertainty in clinical assessment. Even though newer echocardiography techniques that seem promising have been developed such as tissue Doppler, LV longitudinal strain assessed by color tissue Doppler, speckle tracking echocardiography and myocardial scintigraphy, their role in prognosis and management is still unclear and there is inconsistency in the literature regarding both the diagnosis and the prognosis of cardiac amyloidosis (Al-Zahrani et al. 2009; Klein et al. 1991; Koyama et al. 2002, 2015). Thus, it is desirable to develop improved methods for evaluating diastolic dysfunction, to improve diagnosis and prognosis not only in cardiac amyloidosis patients, but also in patients with diastolic dysfunction regardless of underlying etiology.

The parameterized diastolic filling (PDF) formalism is an echocardiographic method for evaluating diastolic function (Kovacs et al. 1987). PDF analysis entails describing LV filling using the same laws of physics that govern the recoil of a spring. Notably, the PDF method has been used to describe differences in diastolic function between healthy individuals and patients with diseases such as diabetes (Riordan et al. 2005) and hypertension (Kovacs et al. 1997). However, it is not known how PDF measures of diastolic function differ between cardiac amyloidosis patients and controls. Therefore, the aim of the present study was to compare PDF measures of diastolic function between cardiac amyloidosis patients and controls. We hypothesized that echocardiographic PDF analysis could detect differences in diastolic function between these two groups.

METHODS

This single-center, cross-sectional retrospective study use data from patients that had been referred for echocardiographic assessment at Heart Care Partners, Wesley Hospital, Brisbane, Australia, during the period 1998–2014. The local human subject research ethics board approved this retrospective study with a waiver of individual informed consent.

Study Population

Thirty-three patients with cardiac amyloidosis were identified. All patients had been diagnosed with amyloidosis or multiple myeloma by bone marrow biopsy and a characteristic appearance conventional echocardiography such as speckled appearance due to the high echogenicity of the amyloid fibrils, preserved LV ejection fraction, increased LV wall thickness, abnormal filling pattern, atrial thrombi, small pericardial effusion, elevated LV filling pressures and/or progressive left atrial (LA) enlargement in the setting of a normal-size ventricle. Some patients also had additional confirmation by biopsy of the skin, gut or kidney. While patients with myeloma and AL amyloidosis have different underlying etiologies, the infiltrative process upon the myocardium is similar with regards to myocardial deposition of amyloid protein. All patients had undergone stem cell transplantation. As most of the patients had undergone several echocardiographic studies before transplantation, the study with acceptable image quality closest in time before the transplantation was chosen. Echocardiographic acquisition at a heart rate (HR) >90 bpm and/or with fusion of the peak early diastolic transmitral flow velocity (E) and peak late diastolic transmitral flow velocity (A) wave that included more than two-thirds of the height of the E-wave were excluded. Patients with images of poor quality were also excluded. The resulting patient population consisted of 13 patients with echocardiographic images acquired during the period 2005–2014. The hospital database was used to identify controls with normal echocardiographic studies, no previous cardiovascular or respiratory diseases and no cardiovascular risk factors. The study population was then gender and age matched, and the same exclusion criteria regarding image quality and HR were applied. Studies of controls with an E/A ratio <1 were excluded, with the exception of controls >70 y of age (1 subject). Normally $E > A$, but with aging and increasing stiffness of the left ventricle, relaxation is impaired, resulting in a decrease in E and increase in A. Hence, an E/A ratio in the range 0.75 to 1.5 is considered normal (Nagueh et al. 2009). To ensure the included controls were in the normal range of diastolic function, we set $E/A > 1$ as an additional inclusion criterion for the controls. Medical records and clinical echocardiography reports were used to collect baseline data including age, gender, medical history, weight, height, body mass index (BMI), body surface area (BSA) and conventional echocardiographic