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● *Original Contribution*

PROMINENT PAPILLARY MUSCLES IN FABRY DISEASE: A DIAGNOSTIC MARKER?

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Abstract—Fabry disease is often linked with a prominent papillary muscle. It remains unknown whether this sign could be used as a diagnostic marker to screen for Fabry patients. Standard echo was performed in 101 consecutive patients with concentric left ventricular (LV) hypertrophy (28 Fabry, 30 Friedreich, 34 isolated arterial hypertension, 9 amyloidosis) and 50 healthy controls. In addition, the areas of both papillary muscles, as well as the LV endocardial circumference, were manually traced in short axis views. A ratio of papillary muscle size to LV circumference was calculated (PM_LV_ratio). The papillary muscle area was positively correlated to LV wall thickness in this cohort ($p < 0.0001$; $r = 0.58$). In all patient subgroups, the absolute papillary muscle area was significantly enlarged and the PM_LV_ratio was significantly higher when compared with controls. However, Fabry patients showed a significantly larger absolute papillary muscle area than Friedreich and amyloidosis patients and a higher PM_LV_ratio than hypertensive and amyloidosis patients. Enlarged absolute papillary muscle area was evidenced in 21 (75%), and increased PM_LV_ratio was found in 22 (78%) of 28 Fabry patients. Combining these two parameters yields a sensitivity of 75% and specificity of 86% for diagnosing Fabry disease with LV hypertrophy. Only 10 of 73 non-Fabry patients (14%) (4 Friedreich, 1 amyloidosis, 5 hypertensive) showed an increased absolute papillary muscle area and PM_LV_ratio. In conclusion, this study confirmed the assumption that the prominent papillary muscle could be an echocardiographic marker for detection of Fabry patients with concentric LV hypertrophy. (E-mail: Weidemann_F@medizin.uni-wuerzburg.de) © **2011 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Fabry, Papillary muscle, Echocardiography, Cardiomyopathy.**

INTRODUCTION

The papillary muscle of the left ventricle (LV) is important for the functionality of the mitral valve apparatus and can be involved in many pathologies, *e.g.*, myocardial infarction or LV outflow tract obstruction (Abouliatim et al. 2009; Austin et al. 2009; Bolman 2009; Delgado et al. 2009; He and Bhattacharya 2008; Rama et al. 2008; Rankin et al. 2008). Moreover, the papillary muscle is a leading visual landmark in standard echocardiography. So far, imaging studies have focused mainly on the position of the papillary muscle in the LV or its regional function (*via* strain rate imaging) (Dagdelen et al. 2003; Harrigan et al. 2008; Karvounis et al. 2006). In contrast, little is known about the echocardiographic quantification of the papillary muscle size itself.

Fabry disease (FD) is an X-chromosomal–linked lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (Desnick et al. 1995). The lack of this enzyme leads to a typical cardiomyopathy characterized by concentric LV hypertrophy, which can exceed a wall thickness of 20 mm (Hoigne et al. 2006; Linhart et al. 2001; Strotmann et al. 2005; Takenaka et al. 2008; Weidemann et al. 2005; Weidemann et al. 2008). From autopsy studies, it is known that the papillary muscle hypertrophies as well (Ueno et al. 1991), and thus it was speculated in case reports and review articles that a prominent papillary muscle is a typical Fabry feature and might be of diagnostic use (Fig. 1) (Linhart et al. 2001; Strotmann et al. 2005; Weidemann et al. 2008). Moreover, it is possible that other cardiac pathologies with concentric LV

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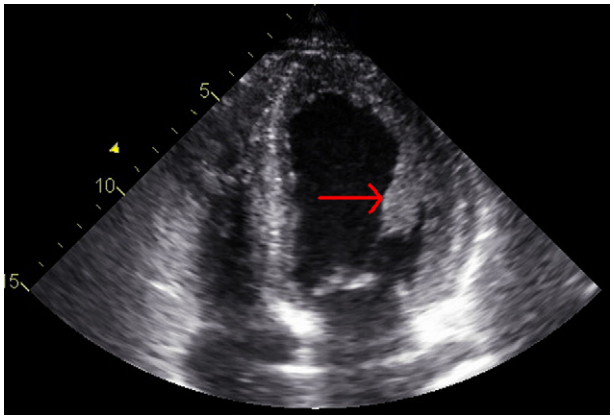

Fig. 1. A four-chamber view of a patient with a typical Fabry cardiomyopathy. Note the prominent papillary muscle arising from the LV lateral wall.

hypertrophy like hypertension and Friedreich ataxia could also lead to a prominent papillary muscle.

Since 2001, a specific therapy for Fabry disease, called enzyme replacement therapy, has been available (Eng et al. 2001, 2006; Schiffmann et al. 2001; Weidemann et al. 2003). Thus, early diagnosis of this disease is important to slow the disease progression (Pieroni et al. 2003; Weidemann et al. 2005). In the past, Fabry disease was screened (using alpha-galactosidase A measurements) in cohorts with unclear concentric LV hypertrophy (Monserrat et al. 2007; Nakao et al. 1995; Sachdev et al. 2002). However, the prevalence in those cohorts was only about 1–3% in the general echocardiographic laboratories using this screening approach (Linthorst et al. 2009). Thus, finding more specific markers (for example, comparable with the sparkling texture in cardiac amyloidosis) for the cardiac involvement in Fabry disease would be desirable to preselect patients. So far, there is no systematic echocardiographic study on the quantification of the papillary muscle size, and data on the papillary muscle as a specific diagnostic marker for Fabry disease are lacking.

Thus, the aims of this study were: (i) To establish a method to quantify the papillary muscle size by echocardiography, (ii) to evaluate whether the papillary muscle is enlarged in Fabry disease and (iii) whether a prominent papillary muscle in Fabry disease is of diagnostic use to distinguish Fabry patients from patients with other concentric LV hypertrophy diseases.

METHODS

Study population

Between November 2008 and September 2009, 197 consecutive patients with the diagnosis of Fabry disease (n = 63), Friedreich ataxia (n = 71), cardiac amyloidosis (n = 10) and isolated arterial hypertension (n = 53) presenting in our echo-lab were screened for this prospective study. (The University Hospital Wuerzburg acts as a reference center for patients with Fabry disease and Friedreich ataxia. Currently, a cohort of 146 Fabry and 122 Friedreich patients are followed prospectively with echocardiography. During the observation time slot, 63 of the 146 Fabry patients presented at our center and all were included in the study). Finally, only the 101 hypertrophic patients (defined as a septal or posterior wall thickness ≥12 mm) were included in the study for further analysis.

Hypertension was defined by a repeatedly measured systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg, or if the subject was receiving antihypertensive pharmacotherapy. In all patients with essential hypertension, coronary artery disease was excluded according to negative history, normal treadmill exercise test and normal coronary angiograms. Further exclusion criteria were: moderate and severe valvular heart diseases, diabetes mellitus and other endocrine or systemic diseases. The patient data were compared with those from 50 healthy controls that were acquired from the hospital staff and their relatives. Ten of the 28 Fabry patients showed mild hypertension, which agrees with latest findings that hypertension is common (as high as 50%) in patients with Fabry disease (Kleinert et al. 2006) and therefore we did not exclude these patients from further analysis. Hypertension in these patients was easy to control with mainly one and never more than two antihypertensive drugs, and all patients were normotensive at study entry.

The study conformed to the principles outlined in the Declaration of Helsinki, and the locally appointed ethics committee approved the research protocol; informed consent was obtained from all patients.

Standard echocardiographic measurements

Left ventricular end-diastolic (LVEDD) and end-systolic dimensions (LVESD) as well as end-diastolic thickness of the posterior wall (LVPWD) and the septum (IVSD) were measured using standard M-mode echocardiographic methods and parasternal LV long-axis images (GE Vingmed Vivid 7, Horten, Norway; 3.5 MHz). Ejection fraction (EF) was calculated using the modified Simpson method. Blood pool pulsed Doppler of the mitral valve inflow was used to extract the ratio of early to late diastolic flow velocity (E/A) and the deceleration time (DT).

Evaluation of the papillary muscle

In an initial study of 60 screened subjects (20 controls and 10 patients of each patient group), the ability to see both papillary muscles in one end-diastolic image