CARDIAC MAGNETIC RESONANCE IMAGING FOR THE DIAGNOSIS OF ENDOMYOCARDIAL FIBROSIS

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Abstract. Endomyocardial fibrosis (EMF) is a common cause of restrictive cardiomyopathy in the tropics and has been underdiagnosed in the past. Sometimes it is difficult to differentiate EMF from other restrictive cardiomyopathies. Currently, echocardiography is used for the initial investigations that might lead to a diagnosis of EMF. In this study, we evaluate the usefulness of cardiac magnetic resonance (CMR) imaging as an alternative noninvasive diagnostic tool. Twenty-eight patients (17 men and 11 women; aged 51.9±13.5 years), who were diagnosed as having restrictive cardiomyopathy after comprehensive echocardiography, underwent CMR imaging with the standard cardiomyopathy protocol. EMF was diagnosed in seven (25%) of these patients. Five patients with EMF had bi-ventricular involvement and one each had right and left ventricular involvement. Myocardial edema indicating acute inflammation was seen in one (14.3%) patient. Apical thrombus was seen in four (57.1%) cases. Subendocardial delayed enhancement was always present in the involved ventricles. Our results show that CMR imaging with late gadolinium enhancement can clearly detect the common hallmarks of EMF: endocardial fibrous tissue and obliteration of the involved ventricular apex.

Keywords: endomyocardial fibrosis, cardiac MRI, cardiac magnetic resonance imaging

INTRODUCTION

Endomyocardial fibrosis (EMF) is a frequent restrictive cardiomyopathy in tropical regions (Mocumbi *et al*, 2008a). It is characterized by fibrotic tissue deposition in the endocardium of the apex and subvalvular region of one or both ventricles. Morphology of the heart is usually distorted with reduced volumes of the involved ventricle, whereas atrial volumes are increased. The cause of EMF is unknown. However, early hypereosinophilia may play a role in its pathogenesis (Mocumbi *et al*, 2008a). Hypereosinophilic syndrome is defined as persistent marked eosinophilia (>1,500 eosinophils/mm^3) in the absence of a primary cause (such as parasitic or allergic disease) and in the presence of evidence-based eosinophil-mediated organ damage (Ogbogu *et al*, 2007; Sheikh and Weller, 2007). Cardiac involvement is a major cause of morbidity and death (Fauci *et al*, 1982; Sheikh and Weller, 2007). Eosinophil-mediated heart damage results from microvascular and endocardial injury, which often induces

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thrombosis (Fauci *et al*, 1982). Medication alone is often unsatisfactory, and surgical resection of the fibrous tissue is necessary for patients scored in the New York Heart Association (NYHA) functional classes III and IV (de Oliveira *et al*, 1990).

Echocardiography is a noninvasive and first-line investigative method for the diagnosis of EMF (Mocumbi *et al*, 2008a; Sliwa and Mocumbi, 2010). It permits quantification of the degree of morphological and hemodynamic compromise and is useful for follow-up after treatment (Sliwa and Mocumbi, 2010). However, echocardiography cannot characterize the myocardial fibrous tissues in detail, nor can it differentiate EMF from other left ventricular (LV) apical obliterations such as apical hypertrophic cardiomyopathy (Mocumbi *et al*, 2008b), cardiac tumors (Niino *et al*, 2002; Mocumbi *et al*, 2008b), apical thrombus and ventricular non-compaction (Salemi *et al*, 2006). For patients with predominantly right ventricular (RV) involvement, EMF should be differentiated from Ebstein's anomaly (Alipour *et al*, 1980; Mocumbi *et al*, 2008b) and constrictive pericarditis (Mocumbi *et al*, 2008b).

Conventional ventriculography was long considered the gold standard method for the diagnosis of EMF (Barretto *et al*, 1989). However, with improvements in echocardiography diagnosis, ventriculography is no longer routinely performed because of its invasiveness (Mocumbi *et al*, 2008a). Endomyocardial biopsy allows the diagnosis of EMF in only about 50% of the patients (Barretto *et al*, 1986).

Cardiac magnetic resonance (CMR) imaging provides detailed information on cardiac morphology and function, including excellent visualization of the ventricular apex. Late gadolinium enhancement (LGE) images allow us to evaluate the presence of EMF and inflammation by the relative accumulation of gadolinium as the result of slower washout kinetics and the increased extracellular volume (Kim *et al*, 2000; Mahrholdt *et al*, 2005). The aim of the present study was to evaluate the diagnostic value of CMR for EMF cases.

MATERIALS AND METHODS

We conducted a cross-sectional survey at Radiology Department, Srinagarind Hospital, Khon Kaen University using data obtained retrospectively from medical records and the picture archiving and communication system (PACS) from December 2011 to December 2013. The PACS is a medical imaging technology which provides economical storage of and convenient access to images from multiple modalities including CMR. Electronic images and reports are transmitted digitally via PACS. Inclusion criteria were: a clinical diagnosis of diastolic heart failure, defined by the typical symptoms and signs of heart failure in a patient showing preserved LV ejection fraction (LVEF) without valvular disease. Ventricles of normal size, normal to reduced systolic function, atrial dilatation, normal pericardium and the absence of septal bounce were used as the diagnostic criteria for restrictive cardiomyopathy using echocardiography (Ammash *et al*, 2000; Nihoyannopoulos, 2009). The exclusion criteria were: creatinine clearance ≤ 30ml/min, relative or absolute contra-indications to CMR imaging studies and the presence of other systemic or cardiac diseases. To evaluate the diagnostic performance of CMR imaging for EMF patients, we compared the results obtained from EMF patients with those from age- and sex-matched controls, who were seven healthy volunteers (4 men

and 3 women, mean age ± SD of 55.9±14.5 years). The present study was approved by the Ethics Committee of the Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand (HE571089).

CMR imaging protocol

CMR imaging was performed with a 1.5-T magnet (Magnetom Avanto, Siemens, Germany) using a cardiac phased-array surface coil. The cardiac images were obtained during breath-holding for 12 to 15 cardiac beats (10 to 15 seconds in average) at the end of the inspiration with electrocardiographic gating. Standard cardiomyopathy protocols with specific pulse sequences were used: steady-state free precession (SSFP), late gadolinium enhancement (LGE) and double inversion recovery fast spin echo T1 and T2 weighted images along the axial, 4-chamber, 2-chamber, 3-chamber and short axis views (Kramer *et al*, 2008). Cine images using the SSFP technique were obtained for the comprehensive evaluation of cardiac morphology and quantification of cardiac volumes and ejection fractions. Patients received an intravenous bolus of 0.2 mmol/kg of gadolinium-based contrast agent. Ten minutes after gadolinium injection, images were acquired using the LGE technique, which is a gradient-echo pulse sequence with an inversion-recovery preparatory pulse (Kim *et al*, 2000). After contrast, the inversion time was adjusted to null the signal from normal myocardium (dark myocardium) and the fibrous tissue region was clearly seen as intensely bright.

Image analysis

CMR image analysis was performed by one cardiovascular radiologist and one cardiologist with extensive experience in interpreting CMR images in several clinical situations, with a deep knowledge of the pulse sequences, its pitfalls, and artifacts (verification of CMR level 3 experience) and blinded to the clinical data and the results of CMR image data.

Statistical analysis

All data were expressed as mean ±SD and frequency (%) for discrete variables. The baseline population characteristics of the participants in the control and case groups were compared using Student's *t*-test (for continuous variables) or χ^2 test (for categoric variables). Two-sided $p<0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS software version 15 (SPSS, Chicago, IL).

RESULTS

Twenty-eight patients (17 men and 11 women; mean age ± SD of 51.9±13.5 years), who were diagnosed with restrictive cardiomyopathy after comprehensive echocardiography, underwent CMR imaging with the standard cardiomyopathy protocol. EMF was diagnosed in seven patients (25%) (3 men and 4 women, mean age ± SD of 52.6±8.9 years). Demographic data and CMR image characteristics of EMF and age-and sex-matched control groups are shown in Table 1. Mean left and right ventricular ejection fractions of EMF patients were similar to those of controls (55.9±8.0% versus 60.2±7.7%, p=0.33 and 54.2±3.4% versus 56.9±4.1%, p=0.19). Mean left and right atrial areas of EMF patients were significantly enlarged compared with the control group (39.3 ± 2.4 versus 17.5 ± 0.5 cm^2, p=0.003 and 37.2 ± 2.9 versus 17.1 ± 0.6, p=0.004). All cases of EMF showed typical findings that consisted of subendocardial delayed enhancement on LGE images, mainly in the apex and eventually in the subvalvular region of the involved ventricles, without being confined to coronary artery territory, and

Table 1
Demographic data and cardiac magnetic resonance characteristics for the EMF group and the control group.

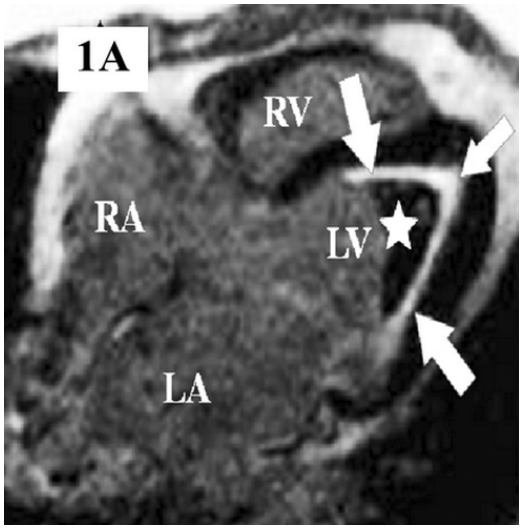
Characteristic	EMF group (n=7)	Control group (n=7)	p-value
Age (years)	52.6 ± 8.9	55.9 ± 14.5	0.65
Female/Male (Female %)	4/3 (57.1%)	3/4 (42.8%)	0.63
Height (cm)	165.7 ± 6.1	164.9 ± 9.2	0.18
Weight (kg)	61.4 ± 7.9	54.9 ± 9.3	0.85
BMI (kg/m^2)	22.3 ± 1.6	20.1 ± 2.6	0.09
LVEF (%)	55.9 ± 8.0	60.2 ± 7.7	0.33
RVEF (%)	54.2 ± 3.4	56.9 ± 4.1	0.19
LA area (cm^2)	39.3 ± 2.4	17.5 ± 0.5	0.003*
RA area (cm^2)	37.2 ± 2.9	17.1 ± 0.6	0.004*
Obliteration of ventricular apex	7 (100%)	0 (0%)	<0.0001*
Subendocardial delayed enhancement on LGE images	7 (100%)	0 (0%)	<0.0001*

Data are expressed as mean ± SD (standard deviation) or n (%) for discrete variables.
*p-value <0.05.
EMF, endomyocardial fibrosis; BMI, body mass index; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; LA, left atrium; RA, right atrium; LGE, late gadolinium enhancement.

obliteration of the involved ventricular apex (Fig 1). On the other hand, abnormal myocardial delayed enhancement or abnormal cardiac morphological changes were not seen in the seven individuals of the age-and sex-matched control group. Of the seven EMF patients, five had bi-ventricular involvement (71.4%), and one each had right- and left-ventricular involvement (14.3%). Myocardial edema indicating acute inflammation was seen in one case (14.3%). Apical thrombus was seen in four cases (57.1%) (Fig 1), all of whom had bi-ventricular involvement. In one case of bi-ventricular involvement, apical thrombus was seen only in echocardiography. Retrospective analysis revealed that the first echocardiogram of five of the seven EMF cases produced findings that did not suggest the final diagnosis of EMF. The initial diagnoses were apical hypertrophic cardiomyopathy (n=3) and cardiac amyloidosis (n=2). Pericardial effusion was observed in five cases (71.4%). Eosinophil counts were normal except for one case (14.3%) with >1,500/mm^3 eosinophils. Three cases (42.9%) underwent surgical resection of the fibrous tissue with histopathological confirmation of EMF (Fig 1). In CMR images, the ventricular architecture and the pattern of enhancement of EMF patients (Fig 2) differed from those with other major cardiomyopathies such as ventricular non-compaction, apical hypertrophic cardiomyopathy and infiltrative myocardial diseases.

DISCUSSION

EMF is one of the common causes of restrictive cardiomyopathy. In this study,



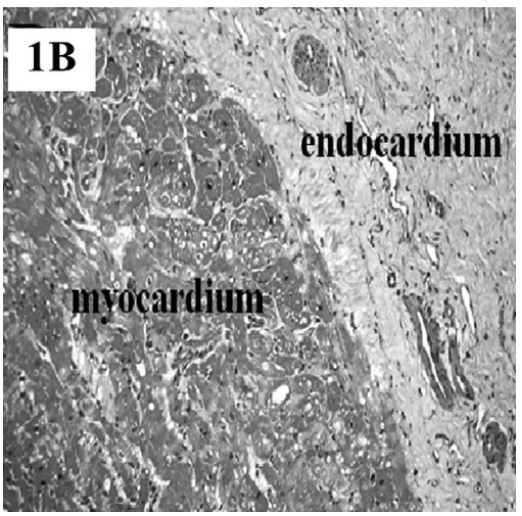
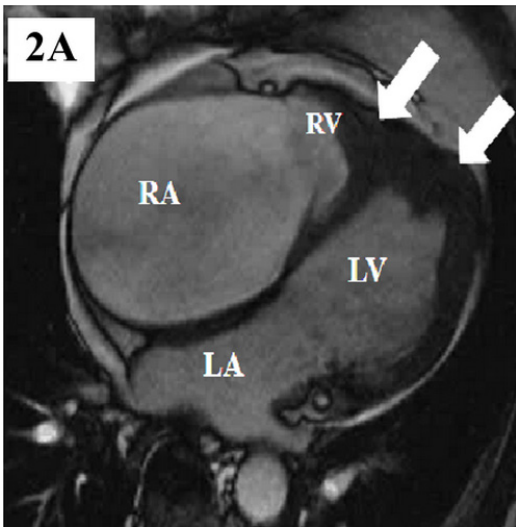


Fig 1–Four-chamber late gadolinium enhancement CMR image (A) shows apical obliteration of left ventricle with thrombus (star). Subendocardial delayed enhancement along left ventricular endocardium represents fibrotic tissue (white arrows). Histopathologic analysis of the resected endomyocardium from the same patient (B) shows extensive fibrous thickening of the endocardium that penetrates the subendocardial myocardium with few eosinophils and inflammatory cells in the endocardium. (RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle).



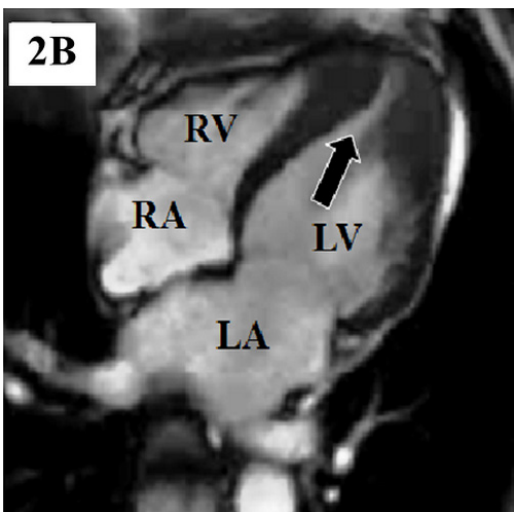


Fig 2–Four-chamber SSFP sequence CMR image of a patient with endomyocardial fibrosis shows biventricular apical obliteration (A) (white arrows) compared with the CMR image of a patient with apical hypertrophic cardiomyopathy (B) showing the classic spade-shaped left ventricular cavity (black arrow). (RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle).

EMF cases were found to constitute 25% (7/28) of restrictive cardiomyopathy cases. Five (71.4%) of these seven EMF patients were first diagnosed by echocardiography with diseases other than EMF. Our results strongly suggest that suspected EMF cases among restrictive cardiomyopathies should be investigated further using CMR imaging to reach a correct diagnosis.

In the present study, CMR images could distinguish EMF from other restrictive cardiomyopathies by the presence of typical abnormal subendocardial fibrosis and apical obliteration. CMR imaging can also demonstrate the presence of apical thrombus, which is an additional advantage of CMR for the diagnosis and management of EMF compared with echocardiography. In fact, in this study, apical thrombus was seen in four cases using CMR imaging, but was seen in only one case by echocardiography. Again, we recommend CMR imaging diagnosis for cases where electrocardiography (ECG) and echocardiography data are discordant.

CMR imaging allows noninvasive quantification of cardiac volumes and cardiac systolic function, which are shown as the left and right ventricular ejection fractions (LVEF and RVEF). In the present study, significant biatrial enlargement with preserved LVEF and RVEF, which is an atypical sign of restrictive cardiomyopathy, was seen in the EMF group but not in the control group (Table 1).

Hypereosinophilia may be found in the initial stages of the disease (Mocumbi *et al*, 2008a). All but one EMF patients (85.7%) in the present study had normal eosinophil counts, probably because they were in the late fibrotic phase of disease. In fact, histopathological findings showed few eosinophils and inflammatory cells (Fig 1).

Ventricular endomyocardial biopsy can provide definite diagnosis of several restrictive cardiomyopathies. However, its diagnostic value for EMF was only 50% (Barretto *et al*, 1986). The present results suggest that endomyocardial biopsy may not be necessary for the diagnosis of EMF if CMR images provide reliable evidence for EMF as mentioned above.

The present study was retrospective, using a small number of EMF patients. A larger scale multi-center study should be done in future to confirm the value of CMR imaging for diagnosis and the assessment of prognosis of EMF patients.

In conclusion, the present results show that CMR imaging is useful in the diagnosis of EMF by providing a clear demonstration of subendocardial fibrosis and obliteration of the involved ventricular apex, which are the hallmarks of the disease. Typical cardiac morphological changes and the pattern of enhancement seen in CMR images leads to a confident diagnosis of EMF and its application is recommended for suspected EMF cases among restrictive cardiomyopathies.

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