Clinical and Functional Correlates of Myocardial Fibrosis in Dilated Cardiomyopathy

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Abstract

Background: The purpose of our study was to investigate the presence of myocardial fibrosis in patients with dilated cardiomyopathy compared to clinical and functional patterns and in comparison to a control cohort.

Methods: We examined 45 consecutive patients with dilated cardiomyopathy and no coronary artery disease (ejection fraction (EF) 38.5±8.9%). Results were compared with 46 controls similarly distributed for age with normal EF (63±5.5%). Late gadolinium enhancement sequences and functional parameters of left ventricular function were obtained.

Results: We observed a significant difference between patients and controls in late gadolinium enhancement, that is, 30 (67 %) of the patients presented subepicardial or midmyocardial lesions of enhancement, whereas only 5 (11%) of the controls did so, (p=0.0001). Stroke volume and cardiac output were significantly lower in patients with lesions, compared to patients without lesions. Patients with lesions had a higher NYHA class. There were significantly more patients than controls with enhancement of the pericardium (47% vs 15%, p =0.001).

Conclusion: In patients with dilated cardiomyopathy, the presence of myocardial lesions correlates with LV functional parameters and clinical markers of heart failure. The regional distribution pattern indicates an important role of remote myocarditis and perimyocarditis in the etiology of this disease.

Keywords: Cardiovascular magnetic resonance imaging; Cardiomyopathy; Myocarditis; Fibrosis; Late gadolinium enhancement

Abbreviations: CMR: Cardiovascular Magnetic Resonance; DCM: Dilated Cardiomyopathy; ECG: Electrocardiogram; EF: Ejection Fraction; Gd-DTPA: Gadolinium-Diethylenetriaminepentaacetate; HF: Heart Failure; LV: Left Ventricular, Left Ventricle; LGE: Late Gadolinium Enhancement

Introduction

Heart failure (HF) is a significant cause of morbidity and mortality worldwide [1]. It is estimated that around 5 million people in the United States [2] and 10 million people in the main European countries [3] suffer from HF, with increasing impact of health care systems as the average age of the population rises. Patients with dilated cardiomyopathy (DCM) have increased mortality due to progressive heart failure and sudden cardiac death [4]. Non-invasive imaging plays a central role in the diagnosis, assessment of prognosis, and monitoring of therapy. Specifically, accurate risk stratification and individualization of care according to the patient’s pathology are increasingly important factors. Of note, determining the etiology of cardiac dysfunction in patients with heart failure influences management and prognosis [5]. Despite complete evaluation including history, physical examination, blood work, echocardiography, coronary angiography, and endomyocardial biopsy, however, there is lack of good prognostic markers and in about 50% of patients with dilated cardiomyopathy, the etiology is not identified [5,6].

Cardiovascular magnetic resonance (CMR) has emerged as the most efficient tool to non-invasively characterise the phenotype of patients with HF [7-9]. It has the potential to improve diagnostic efficiency and allows for assessing cardiac morphology, function, flow, perfusion, tissue injury, and fibrosis in a single session [7,10-12]. T1-weighted images acquired 10 to 30 minutes after application of paramagnetic contrast agents ("late Gadolinium enhancement", LGE) visualize myocardial fibrosis or necrosis as bright regions due to the increased volume of distribution and delayed washout of the contrast agent [10,13]. LGE has been applied to differentiate viable from non-viable tissue [14,15] and is an accurate and robust method used in the diagnosis of fibrosis in ischemic and nonischemic cardiomyopathies, and myocarditis [10,14,16]. This is relevant for patients with ventricular dysfunction, since fibrosis is related to arrhythmia and failure to respond to treatment [17,18]. The purpose of our study was to investigate the presence of myocardial fibrosis in patients with dilated cardiomyopathy compared to clinical and functional patterns and in comparison to a control cohort.

Methods

Patients

We prospectively studied 47 consecutive patients with non-

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ischemic cardiomyopathy. These patients were compared to 46 age-matched controls with normal left ventricular function and no cardiac disease. Patients and controls were examined by experienced cardiologists. All but two patients (due to their youth: 18 and 27 years) underwent coronary angiography, and coronary artery disease was ruled out. Both patients and controls underwent 12-lead ECG and transthoracic echocardiography and in controls a non-invasive stress test (bicycle exercise and/or dynamic stress echocardiography or adenosine CMR examination) was performed.

Inclusion criteria were left ventricular ejection fraction less than 50% and no underlying coronary heart disease or chronic disease. Patients were excluded if they had significant coronary artery disease as defined by the presence of stenosis of ≥50% of one or more coronary arteries, acute myocardial or pericardial disease, known congenital heart disease, LV hypertrophy as defined by a septal or inferior wall diameter ≥11 mm, significant valvular disease (regurgitation ≥ degree 2 on echocardiography and CMR or relevant stenosis), renal failure (creatinine ≥1.8 mg/dl), or known severe claustrophobia.

All patients and controls gave written informed consent and the study was approved by our local ethics board. One patient experienced claustrophobia during the CMR examination and in another, late enhancement image quality was insufficient. Our final cohort thus comprised 45 patients who were compared to 46 age-matched controls without structural heart disease.

Cardiovascular magnetic resonance imaging

All images were acquired on a 1.5 T magnetic resonance system (Intera CV 1.5T, Philips Medical Systems, Best, the Netherlands; software Release 11). We used a five element cardiac phased-array coil combined with a homogeneity correction algorithm (Constant Level Appearance; CLEAR). This algorithm generates sensitivity maps for each synergy coil element (relative to the body coil sensitivity) to calculate uniformity correction [19]. Data acquisition was ECG-triggered.

LGE imaging was obtained in all patients and controls ten minutes after iv. administration of 0.2mmol/kg gadolinium. We performed 3D inversion recovery turbo gradient echo sequences (2 acquisitions, field of view 330 mm, matrix size 256x256, slice thickness 5 mm, no gap, echo time 1.4 ms, TR shortest, flip angle 15 degrees, incorporated fat-saturation) with inversion times individually optimized for each measurement to maximum myocardial signal suppression. A contiguous stack of slices was obtained covering the entire left ventricle without gap during two breath holds. The ability of this inversion recovery sequence to detect midmyocardial or subepicardial LGE has been tested at the beginning of the studies and reported previously [20]. Heart rate or body surface area did not affect image quality or the presence of LGE in patients or controls. In addition, a 4-chamber long axis view was obtained.

CMR image analysis

All images were analyzed by the same investigator blinded to other data. LGE was considered present if visually apparent. Functional and morphological data were evaluated using view forum 6.5 (Philips Medical Systems, Best, the Netherlands). Regions of interest were drawn manually. To evaluate LV function and dimensions, we acquired steady-state free precession imaging (field of view 350 mm, matrix 256x256, echo time 1.6 ms, repetition time 4.0 ms, flip angle 60 degrees, slice thickness 10 mm, no gap) in 2-, 3-, and 4-chamber long-axis and 3-D short-axis views. Phase-contrast velocity images in the ascending aorta were obtained to measure stroke volume and rule out significant aortic insufficiency. Pericardial LGE was differentiated from fat by carefully excluding high signal intensity layers directly connected to perivascular fat.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology: Shewan LG and Coats AJ. Ethics in the authorship and publishing of scientific articles. Int J Cardiol 2010; 144:1-2.

Statistical analysis

Data are presented as means and standard deviation for quantitative variables and as absolute and relative frequencies for categorical variables. Variables between patients and controls were compared using t-tests for quantitative and Chi-Square-tests for categorical variables. All tests were two-sided and used a significance level of 0.05 to indicate statistical significance. Statistical analysis was performed using SAS software (Statistical Analysis System) Version 9.

Results

Patient characteristics

Patient and control baseline characteristics are shown in Table 1. Control subjects did not differ significantly regarding age. Seven patients had moderately elevated blood pressure values, with none of them however showing an increased LV mass. In 43 patients coronary artery disease was ruled out by coronary angiography, and in 2 patients and in all controls by bicycle exercise tests, stress echocardiography or adenosine stress perfusion CMR.

Functional parameters

The values are listed in Table 2. Compared to controls patients had significantly lower LV ejection fraction. LV end-diastolic and end-systolic volumes and LV end-diastolic diameters were greater in patients than in controls. Stroke volume and cardiac output were lower in patients compared to controls.

Table 1: Clinical Characteristics of the Patients and Controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=45)</th>
<th>Controls (n=46)</th>
<th>p</th>
<th>Variable</th>
<th>Patients (n=45)</th>
<th>Controls (n=46)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>59.0 (11.5)</td>
<td>54.0 (15.5)</td>
<td>0.09</td>
<td>Heart rate</td>
<td>73.5±15.5</td>
<td>71.6±11.1</td>
<td>0.62</td>
</tr>
<tr>
<td>Female (%)</td>
<td>8 (13)</td>
<td>13 (28)</td>
<td>0.05</td>
<td>LV ejection fraction</td>
<td>38.5±8.9</td>
<td>63.0±5.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height, cm (SD)</td>
<td>172.5 (5.0)</td>
<td>176 (10.3)</td>
<td>0.15</td>
<td>LV stroke volume</td>
<td>87.0±20.9</td>
<td>96.6±9.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Weight, kg (SD)</td>
<td>78.3 (14.3)</td>
<td>80.4 (15.6)</td>
<td>0.65</td>
<td>LV end-diastolic volume, ml</td>
<td>229.6±88.7</td>
<td>155.6±40.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (SD)</td>
<td>26.2 (3.9)</td>
<td>25.8 (3.6)</td>
<td>0.75</td>
<td>LV end-diastolic volume, ml</td>
<td>144.2±62.7</td>
<td>60.3±25.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>133.6 (18.9)</td>
<td>128.1 (14.9)</td>
<td>0.25</td>
<td>LV end-diastolic diameter, mm</td>
<td>82.9±6.3</td>
<td>52.1±3.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>78.0 (13.1)</td>
<td>74.6 (7.9)</td>
<td>0.27</td>
<td>Cardiac output, L/min</td>
<td>6.1±1.6</td>
<td>6.9±1.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

LV indicates left ventricular. Values are expressed as mean ± standard deviation.
Assessment of myocardial lesions

Contrast enhancement of the myocardium (late gadolinium enhancement, LGE) was observed in 30/45 patients but only 5/46 controls (p<0.0001). Regions of contrast enhancement usually revealed a patchy distribution originating primarily from the epicardial quartile or midmyocardial wall location, with one or several foci within the myocardium and were predominantly located in the septum (51% of the patients with enhancement) and lateral free wall (26%), less often in the inferior (18%) or anterior (5%) areas (Figure 1 and 2). Ten of the 30 patients (26%) had foci in more than one wall area, predominately septal and lateral (7 patients). We never observed contrast enhancement originating from the subendocardial portion of the wall, as would be typical for myocardial infarction.

Patients with intramyocardial lesions were older and had a higher NYHA classification (Table 3). Stroke volume and cardiac output were significantly lower, and LV ejection fraction was modestly reduced compared to patients without lesions.

Assessment of pericardial pathology

Twenty-one (47%) of the patients had a mild-to-moderate contrast enhancement of the pericardium, for the most patients locally distributed in the lateral or anterolateral part of the pericardium, compared to 7 (15%) of the controls, p=0.001 (Figure 1 and 2). Thirteen patients (29%) and 7 controls (15%), p=0.11 presented locally-thickened pericardium (≥4 mm), primarily in the lateral or anterolateral parts of the pericardium (Figure 1). Small pericardial effusions were apparent in nine patients and no controls (p=0.001)

Discussion

We observed that a significant proportion of patients with dilated cardiomyopathy and no coronary artery disease show midwall or subepicardial lesions and alteration of the pericardium. We also demonstrated that myocardial fibrosis was associated with NYHA class, as well as stroke volume and cardiac output, which were significantly lower in patients with lesions compared to those without intramyocardial enhancement. This is important additional information on myocardial structure improving accuracy for better management of patients with heart failure.

We observed myocardial lesions in two thirds of the patients. The regions of contrast enhancement showed a pattern typical of non-ischemic injury with subepicardial or midmyocardial distribution, in one or several areas. The predominately involved regions were the septum and lateral wall.

The regional distribution patterns we observed are consistent with those reported in prior pathologic studies of non-ischemic cardiomyopathy [21,22]. Studies examining myocardial tissue samples obtained at the time of autopsy or cardiac transplantation have shown a pattern of increasing fibrosis from the epicardium to endocardium with both septal and LV free wall involvement [22-24]. The localization and incidence of irreversible injury is in agreement with previous CMR data [25,26], but higher than in a study by Assomull et al. [9]. This may be due to different patient characteristics and the higher spatial resolution we applied. Our results are also consistent with histological findings of extensive areas of interstitial and perivascular fibrosis, particularly involving the left ventricle [22,27,28]. We did not observe contrast enhancement involving the subendocardial layers, as would be typical for myocardial infarction, supporting the notion of a chronic degenerative or inflammatory process as a cause of the contrast enhancement.

In patients with dilated cardiomyopathy (DCM) and symptomatic HF, a pattern of midwall fibrosis was associated with a high rate of all-cause mortality, hospitalization [9], and cardiac death [26]. In this study, we could show that fibrosis not only correlates with parameters of systolic function but also with clinical markers for heart failure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with lesions</th>
<th>no lesions</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.4±8.8</td>
<td>54.3±14.8</td>
<td>0.051</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.2±0.8</td>
<td>1.6±0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>36.8±4.9</td>
<td>41.9±7.1</td>
<td>0.07</td>
</tr>
<tr>
<td>LV end-diastolic volume, ml</td>
<td>245.9±59</td>
<td>221.4±72</td>
<td>0.26</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>82.8±5.7</td>
<td>63.0±6.8</td>
<td>0.93</td>
</tr>
<tr>
<td>LV stroke volume</td>
<td>79.5±19.2</td>
<td>99.9±19.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.8±1.6</td>
<td>6.8±1.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

LV indicates left ventricular. Values are expressed as mean± standard deviation

Table 3: Magnetic Resonance Functional Measurements in Patients with Intramyocardial Lesions (n=30) compared to Individuals without Lesions (n=15).
Histopathological evidence of myocardial fibrosis has been associated with worsening of cardiac function [29]. Our data indicate that in such patients, the presence and regional distribution of fibrosis as determined by CMR not only helps identifying etiology of the disease but may be also useful for individual patient management by a better understanding of systolic dysfunction, its severity, reversibility and amenableity to therapeutic options.

Interestingly, 10% of our controls also had evidence for remote myocarditis. Albeit surprising on first glance, this finding is consistent with the observed high frequency in non-selective autopsy series [30].

The regional distribution of fibrosis indicates a non-ischemic etiology, specifically remote myocarditis. It is known that about 20% of acute myocarditis cases progress to dilated cardiomyopathy [31,32] and that a substantial portion of patients with myocarditis and DCM represent different stages of an organ-specific autoimmune disease in genetically predisposed individuals [33,34]. The regional distribution of lesions after acute myocarditis resembles our observation [10,35-38] and is consistent with previous reports in patients with DCM [9,35,36]. This finding supports the notion that previous myocarditis may be the underlying cause of LV dysfunction in a proportion of patients with DCM. In addition, about a third of our patients presented pericardial alterations such as enhancement and focal thickening, findings typical in perimyocarditis [39]. This is a novel observation and indicates a role of perimyocarditis in certain patients with DCM.

In a novel study Assomull et al. [40] examined patients with new-onset heart failure of unknown etiology. They examined the diagnostic accuracy of LGE to determine the etiology of heart failure in this patient collective. This approach was compared to the results of a standard consensus group determining the cause of heart failure including conventional coronary angiography. They found a very good sensitivity, specificity, and diagnostic accuracy for LGE compared to the conventional approach. This study showed that LGE is a safe, clinically effective, and potentially economical gatekeeper in patients to the conventional approach. This study showed that LGE is a safe, clinically effective, and potentially economical gatekeeper in patients with chronic heart failure – COMET. Am Heart J 149: 370-376.


References


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