Imaging

Cardiac Magnetic Resonance Imaging Pericardial Late Gadolinium Enhancement and Elevated Inflammatory Markers Can Predict the Reversibility of Constrictive Pericarditis After Antiinflammatory Medical Therapy
A Pilot Study
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Background—Constrictive pericarditis (CP) is a disabling disease, and usually requires pericardiectomy to relieve heart failure. Reversible CP has been described, but there is no known method to predict the reversibility. Pericardial inflammation may be a marker for reversibility. As a pilot study, we assessed whether cardiac magnetic resonance imaging pericardial late gadolinium enhancement (LGE) and inflammatory biomarkers could predict the reversibility of CP after antiinflammatory therapy.

Method and Results—Twenty-nine CP patients received antiinflammatory medications after cardiac magnetic resonance imaging. Fourteen patients had resolution of CP, whereas 15 patients had persistent CP after 13 months of follow-up. Baseline LGE pericardial thickness was greater in the group with reversible CP than in the persistent CP group (4 ± 1 mm versus 2 ± 1 mm, P = 0.001). Qualitative intensity of pericardial LGE was moderate or severe in 93% of the group with reversible CP and in 33% of the persistent CP group (P = 0.002). Cardiac magnetic resonance imaging LGE pericardial thickness ≥ 3 mm had 86% sensitivity and 80% specificity to predict CP reversibility. The group with reversible CP also had higher baseline C-reactive protein and erythrocyte sedimentation rate than the persistent CP group (59 ± 52 versus 12 ± 14 mg/L, P = 0.04 and 49 ± 25 versus 15 ± 16 mm/h, P = 0.04, respectively). Antiinflammatory therapy was associated with a reduction in C-reactive protein, erythrocyte sedimentation rate, and pericardial LGE in the group with reversible CP but not in the persistent CP group.

Conclusions—Reversible CP was associated with pericardial and systemic inflammation. Antiinflammatory therapy was associated with a reduction in pericardial and systemic inflammation and LGE pericardial thickness, with resolution of CP physiology and symptoms. Further studies in a larger number of patients are needed. (Circulation. 2011;124:1830-1837.)

Key Words: pericarditis, constrictive inflammation cardiac imaging techniques magnetic resonance imaging gadolinium

Classic constrictive pericarditis (CP) is characterized by thick pericardial fibrosis and frequent calcification that causes progressively debilitating heart failure. Pericardiectomy is usually required to definitively relieve heart failure symptoms. The mortality rate for pericardiectomy is high even in the most experienced medical centers (4% to 6%).1,2 The prognosis after pericardiectomy is variable for reasons that are not well understood.1

Clinical Perspective on p 1837

CP is traditionally presumed to be irreversible. However, a Spanish group of investigators and our center have described reversible CP,3-5 in which constrictive physiology and hemodynamics resolve without pericardiectomy. Although the reasons for this resolution are not well established, it has been postulated that inflammation and edema lead to pericardial thickening, poor compliance, and constriction.5 Antiinflammatory therapy may reduce pericardial inflammation and edema, thereby restoring pericardial compliance.

Cardiovascular magnetic resonance imaging (CMR) has been increasingly used in the diagnosis of pericardial diseases.6-9 Case reports have shown that high signal intensity on T2-weighted fast spin echo (FSE) or postgadolinium inversion-recovery gradient echo images can identify pericar-
dial inflammation. A small series also reported that CMR late gadolinium enhancement (LGE) can accurately identify pericardial inflammation. Although it has been postulated that pericardial inflammation may play a role in the pathogenesis of reversible CP, the relationship between systemic inflammation and pericardial inflammation remains unknown. Furthermore, it is uncertain whether systemic inflammatory markers and CMR pericardial LGE can predict the reversibility of CP. We herein report the results of our pilot study to answer a question that has important clinical implications in our management of patients with CP.

**Methods**

**Study Population**

The study was approved by the Mayo Institutional Review Board. We reviewed all pericardial disease cases at the Mayo Clinic in Rochester from 2002 to 2008. Patients were included in the present study if (1) they had a definite diagnosis of CP, (2) had undergone CMR with LGE before antiinflammatory therapy, and (3) received antiinflammatory medications afterward. There were 288 patients who underwent CMR for pericardial disease from 2002 to 2008. Among them, 89 patients had a definitive diagnosis of CP. Twenty-nine patients received antiinflammatory medications after CMR and were the subjects of the present study. Thirty healthy subjects were also studied as controls.

Each subject’s demographic data were extracted. Clinical information was collected, including cause of CP, comorbidities; symptoms and duration; New York Heart Association (NYHA) functional class (class I—without limitations of physical activity; ordinary physical activity does not cause fatigue, palpitation, or dyspnea; class II—slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in symptoms; class III—marked limitation of physical activity; they are comfortable at rest; less than ordinary activity causes symptoms; and class IV—inability to perform any physical activity without discomfort; symptoms present even at rest); the use of antiinflammatory agents, maximal dose, and duration of use; echocardiograms; C-reactive protein (CRP); and erythrocyte sedimentation rate (ESR). Pathology of the surgically removed pericardium in patients who underwent pericardectomy was evaluated as described previously. The presence of constriction was based on clinical presentation of heart failure with documentation of constrictive physiology or hemodynamics by echocardiography or cardiac catheterization. Constrictive physiology was defined by (1) dissociation of intrathoracic and intracardiac pressure, as evidenced by characteristic respiratory variation in mitral inflow and hepatic venous flow velocities, and (2) exaggerated interventricular dependency, as evidenced by characteristic ventricular septal motion and phasic change in left ventricle (LV)/right ventricle size with respiration on echocardiography. The diagnostic cardiac catheterization findings for CP were characteristic phasic respiratory change in transmural gradient with simultaneous measurement of LV and pulmonary capillary wedge pressure, and discordant right ventricular and LV peak systolic pressure changes, as well as increased filling pressures in the LV and right ventricle. Resolution of CP is defined as a patient having an improvement of at least 1 grade in NYHA function class, which is often associated with hemodynamic resolution on echocardiography.

**Echocardiography**

From transthoracic echocardiography (TTE), data on dissociation of intrathoracic and intracardiac pressure and exaggerated interventricular dependency were collected, as described previously. In addition, LV chamber size and wall thickness, LV ejection fraction, mitral inflow Doppler E and A velocity and E/A ratio, medial mitral annulus systolic velocity, and early and late diastolic velocity on tissue Doppler (s’, e’, and a’) were measured. Cardiac output and cardiac index were also calculated.

**Cardiac Magnetic Resonance Imaging**

ECG-gated CMR was performed with a 1.5-T system (Twin Speed EXCITE, GE Healthcare). Initial scout images, 4-chamber, 3-chamber, 2-chamber, and short-axis cine steady-state free precession (SSFP) images were obtained with the following parameters: Echo time 1.7 ms, repetition time 3.4 ms, flip angle 45°, matrix 256×192, field of view 320 to 440 mm with phase field of view 0.75 to 1.0, and 8-mm slice thickness with 1-mm gap. Double and triple inversion-recovery fast spin echo (FSE) black-blood images were also obtained in axial and short-axis views with the following parameters: 6-mm slice thickness, 2-mm gap, echo time 42 ms (double inversion recovery), 85 ms (triple inversion recovery), flip angle 90°, echo train length 32, matrix 256×256, and field of view 320 to 440 mm with phase field of view 0.75 to 1.0. LGE images covering the entire heart in short-axis and 3 long-axis views were obtained between 7 and 12 minutes after intravenous injection of gadodiamide 0.2 mmol/kg with segmented inversion recovery fast gradient echo sequences (echo time 1.6 ms, repetition time 3.7 ms, flip angle 20°, matrix 256×160, field of view 320 mm with slice thickness 6–8 mm without a gap). Selection of the optimal inversion time for LGE images was accomplished by use of a multiple-inversion-time cine fast gradient echo sequence (cine-IR), which generates a series of 40 images in a single slice location with increasing inversion time. Imaging parameters for the cine-IR sequence were as follows: Matrix 224×160, echo time 2.8 ms, repetition time 5.9 ms, flip angle 12°, bandwidth 32 kHz, number of excitations 0.5, field of view 40 cm, and slice thickness 8 mm.

CMR images were reviewed by 2 experienced readers (DF and JG) who were blinded to clinical and echocardiographic data. Readers evaluated images independently and then resolved discrepancies in a consensus reading. Maximal pericardial thickness was measured on SSFP, FSE, and LGE images. The site of maximal thickness was measured on either axial or short-axis images and verified if possible in 2 planes. Readers attempted to avoid obvious regions of potential volume averaging, such as pericardial reflection sites on axial images. Presence or absence of LGE in pericardium was documented and was rated qualitatively as none (no apparently visible LGE), mild (faint LGE in pericardium that has signal intensity less than the signal of the ventricular blood pool), moderate (obvious enhancement that is visually similar to the ventricular blood pool), or severe (obvious significant LGE in pericardium that has signal intensity visually greater than ventricular blood pool). The representative grading for LGE severity images is shown in Figure 1. LV and right ventricular volumes, LV mass, and ejection fraction were measured by tracing epicardial and endocardial borders on end-diastolic and end-systolic short-axis SSFP images (Mass Analysis 6+; Medis). The presence or absence of pleural effusion was also noted.

**Statistical Analysis**

Data were expressed as mean±SD for continuous variables, median (10% to 90% confidence interval) for ordinal variables, and percentages for categorical data. Fisher exact test was used to compare differences in categorical data between the 2 groups. A paired or unpaired Student *t* test was used to compare differences in continuous variables between the 2 groups for repeated measurements in the same subject (before and after therapy) or for different subject groups (reversible versus persistent CP group) when appropriate. Wilcoxon rank sum test was used to compare differences in ordinal variables between the 2 groups. Two-sided *P*=0.05 was regarded as statistically significant. A weighted *κ*-statistic was computed to assess interobserver variability and was defined as follows: Very good=0.81 to 1, good=0.61 to 0.80, moderate=0.41 to 0.60, fair=0.21 to 0.40, and poor ≤0.20.

**Results**

**Patient Characteristics**

There were 288 patients who had contrast-enhanced CMR for pericardial assessment from 2002 to 2008. Of these, 89
patients had a definitive diagnosis of CP. Twenty-nine patients received antiinflammatory medications after CMR and were the subjects of the present study. The mean age of the 29 study patients was 56±16 years, with 83% being male. The majority of the patients presented with heart failure symptoms such as edema, ascites, or dyspnea (85%), whereas the other patients presented with fatigue, anorexia, or abnormal liver function test. All patients had clinical features, physical examination, and echocardiography and/or cardiac catheterization findings consistent with CP.

There were 60 patients not included in the study group who had CP and underwent CMR but did not receive antiinflammation therapy. The clinical profile of these 60 patients was similar to the 29 study patients with regard to age, sex, the cause of the constriction, symptoms, and NYHA function class (all \( P > 0.05 \)). Thirty-nine of the 60 patients underwent pericardiectomy. Sixteen patients were considered poor surgical candidates because of significant comorbidity or poor long-term prognosis. Five patients declined surgery. Of the 21 patients who did not undergo pericardiectomy, 16 patients had follow-up. None of the 16 cases had spontaneous resolution of constriction.

Fourteen patients had resolution of CP, whereas 15 had persistent CP after medical therapy at the mean follow-up of 12±7 months and 13±7 months, respectively. Compared with the persistent CP group, the reversible CP group had more idiopathic disease and more collagen vascular disease as the cause of the CP, whereas fewer subjects had prior radiation or cardiac surgery (\( P = 0.03 \)). There were no significant differences between the 2 groups in duration of symptoms, with a trend toward shorter duration in the reversible CP group. The time from onset of symptoms to CMR was 3.4±4.1 month in the reversible CP group versus 5.9±7.8 months for the persistent CP group (\( P = 0.33 \)). The time from onset of symptoms to initiation of therapy was 3.5±4.3 months for the reversible CP group versus 6.4±8.1 months for the persistent CP group (\( P = 0.30 \)). There was also no significant difference between the 2 groups regarding the type of antiinflammatory agents received. The daily maximal dose was 53±15 mg for prednisone, 2050±412 mg for ibuprofen, and 1.1±0.3 mg for colchicine. The mean duration of medical therapy was 3.1±1.4 months. Other subject characteristics are detailed in Table 1.

Baseline TTE

There were no significant differences between the 2 groups in baseline TTE features, as shown in the Table 2. Most patients had characteristic 2-dimensional and Doppler examination findings for CP, as shown in the Table 2.

Baseline Magnetic Resonance Imaging Features

There were no statistical differences in CMR findings between the 2 groups for most parameters listed in Table 3, including maximal pericardial thickness measured by FSE and SSFP sequences. However, the maximal pericardial thickness on LGE images was greater in the reversible CP than in the persistent CP group (4.1±1 versus 2.1±1 mm, \( P = 0.001 \)). In addition, more patients were qualitatively rated as having moderate or severe pericardial LGE in the reversible CP group than in the persistent CP group (93% versus

Table 1. Baseline Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Reversible CP (n=14)</th>
<th>Persistent CP (n=15)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±17</td>
<td>59±16</td>
<td>0.46</td>
</tr>
<tr>
<td>Males, %</td>
<td>79</td>
<td>87</td>
<td>0.65</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.0±1.6</td>
<td>27.8±1.5</td>
<td>0.60</td>
</tr>
<tr>
<td>CHF, %</td>
<td>79</td>
<td>93</td>
<td>0.36</td>
</tr>
<tr>
<td>NYHA class, median (10% to 90% CI)</td>
<td>3.0 (1–4)</td>
<td>3.0 (1–4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Origin of CP, %</td>
<td>7</td>
<td>53</td>
<td>0.03</td>
</tr>
<tr>
<td>Surgery</td>
<td>7</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>0</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>57</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>History of recurrent pericarditis, %</td>
<td>14</td>
<td>7</td>
<td>0.50</td>
</tr>
<tr>
<td>History of acute pericarditis, %</td>
<td>21</td>
<td>7</td>
<td>0.28</td>
</tr>
<tr>
<td>Steroid therapy, %</td>
<td>71</td>
<td>53</td>
<td>0.32</td>
</tr>
<tr>
<td>NSAID therapy, %</td>
<td>29</td>
<td>27</td>
<td>1.00</td>
</tr>
<tr>
<td>Colchicine therapy, %</td>
<td>21</td>
<td>40</td>
<td>0.28</td>
</tr>
<tr>
<td>Other, %</td>
<td>14</td>
<td>0</td>
<td>0.13</td>
</tr>
</tbody>
</table>

\( CP \) indicates constrictive pericarditis; BMI, body mass index; CHF, congestive heart failure; NYHA, New York Heart Association; CI, confidence interval; and NSAID, nonsteroidal antiinflammatory drug.

*Comparison between the reversible and nonreversible CP groups by unpaired test.
LGE pericardial thickness and PW thickness, mm 9.5 ± 1.7 10 ± 1.3 0.45 9.8 ± 1.4 10.1 ± 1.4 0.57 0.27

Abnormal septal motion, % 85 21 0.005 73 80 1.00 0.69
E, m/s 0.83 ± 0.21 0.79 ± 0.24 0.67 0.93 ± 0.53 0.85 ± 0.35 0.64 0.56
A, m/s 0.56 ± 0.14 0.67 ± 0.21 0.15 0.56 ± 0.18 0.50 ± 0.18 0.45 0.45
E/A 1.4 ± 0.5 1.2 ± 0.5 0.39 1.7 ± 0.8 1.6 ± 0.4 0.64 0.81
\( e' \), cm/s 11 ± 3 9 ± 4 0.33 11 ± 3 13 ± 4 0.35 0.49
\( a' \), cm/s 10 ± 4 10 ± 3 0.99 11 ± 5 9 ± 2 0.38 0.56
\( s' \), cm/s 8 ± 1 7 ± 1 0.18 7 ± 2 7 ± 2 0.55 0.64
E/\( e' \) 8.6 ± 2.9 11.3 ± 8.2 0.30 7.4 ± 4.5 6.7 ± 3.9 0.70 0.98
E variation, %‡ 93 7 <0.001 67 73 1.0 0.17
Hepatic V reverse, %§ 79 7 <0.001 67 87 0.32 0.17
Cardiac index, L \cdot min^{-1} \cdot m^{-2} 2.1 ± 0.3 2.7 ± 0.4 0.004 2.2 ± 0.4 2.1 ± 0.3 0.91 0.01

TTE indicates transthoracic echocardiography; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVEDS, left ventricular end-systolic dimension; and PW, posterior wall.

*Comparison between baseline and follow-up in the same group by paired test.
†Comparison between baseline in the reversible and nonreversible CP groups by unpaired test.
‡Respiratory mitral inflow E velocity variation = (E velocity of expiration – E velocity of inspiration)/E velocity of inspiration. Normal is < 25%.
§Hepatic venous expiratory reversal.

Table 2. TTE Features in Reversible and Persistent Constriction at Baseline and Follow-Up

Inflammation and Reversible CP

Baseline CRP and ESR were higher in the reversible CP group than in the persistent CP group (59 ± 52 versus 12 ± 14 mg/L, \( P = 0.04 \); and 49 ± 25 versus 33 ± 5 mm/h, \( P = 0.04 \), respectively). There was a positive correlation between white blood cell count and LGE pericardial thickness at baseline (\( R = 0.55, P = 0.01 \)). There was also a trend for a correlation between ESR and LGE pericardial thickness (\( R = 0.43, P = 0.08 \)). After antiinflammation therapy, CRP, ESR, and total white blood cell count were all reduced in the reversible CP group (59 ± 52 to 2 ± 1 mg/L, \( P = 0.002 \), for CRP; 49 ± 25 to 5 ± 2 mm/h, \( P = 0.004 \), for ESR; 11.0 ± 3.3 \times 10^{10}/L to 6.5 ± 1.9 \times 10^{10}/L, \( P = 0.01 \), for white blood cell count), whereas there were no significant changes in the persistent CP group (12 ± 14 versus 13 ± 10 mg/L, \( P = 0.82 \); 33 ± 5 versus 15 ± 16 mm/h, \( P = 0.22 \); and 8.6 ± 3.1 \times 10^{10}/L versus 7.2 ± 1.1 \times 10^{10}/L, \( P = 0.33 \), respectively). Using receiver operating characteristic analysis, a CRP cutoff value of 21 mg/L
Table 3. Baseline CMR Features in Reversible and Persistent Constriction

<table>
<thead>
<tr>
<th></th>
<th>Reversible CP (n=14)</th>
<th>Persistent CP (n=15)</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>56±3</td>
<td>56±3</td>
<td>0.94</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>49±2</td>
<td>46±2</td>
<td>0.45</td>
</tr>
<tr>
<td>Abnormal septal motion, %</td>
<td>71</td>
<td>93</td>
<td>0.12</td>
</tr>
<tr>
<td>Septal flattening, %</td>
<td>71</td>
<td>73</td>
<td>0.91</td>
</tr>
<tr>
<td>RV and/or LV deformation, %</td>
<td>21</td>
<td>13</td>
<td>0.79</td>
</tr>
<tr>
<td>Focal compression, %</td>
<td>14</td>
<td>7</td>
<td>0.50</td>
</tr>
<tr>
<td>Myocardial LGE, %</td>
<td>7</td>
<td>7</td>
<td>1.0</td>
</tr>
<tr>
<td>IVC dilatation, %</td>
<td>50</td>
<td>73</td>
<td>0.20</td>
</tr>
<tr>
<td>Pericardial effusion, %</td>
<td>64</td>
<td>53</td>
<td>0.40</td>
</tr>
<tr>
<td>Complex pericardial effusion, %</td>
<td>29</td>
<td>20</td>
<td>0.79</td>
</tr>
<tr>
<td>Pleural effusion, %</td>
<td>64</td>
<td>60</td>
<td>0.81</td>
</tr>
<tr>
<td>Thick pericardium, %</td>
<td>71</td>
<td>73</td>
<td>1.0</td>
</tr>
<tr>
<td>Pericardial thickness by SSFP, mm</td>
<td>4±1</td>
<td>3±1</td>
<td>0.21</td>
</tr>
<tr>
<td>Pericardial thickness by FSE, mm</td>
<td>4±1</td>
<td>4±1</td>
<td>0.76</td>
</tr>
<tr>
<td>Pericardial LGE thickness, mm</td>
<td>4±1</td>
<td>2±1</td>
<td>0.001</td>
</tr>
<tr>
<td>No pericardial LGE, %</td>
<td>0</td>
<td>27 (n=4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mild pericardial LGE, %</td>
<td>7 (n=1)</td>
<td>40 (n=6)</td>
<td></td>
</tr>
<tr>
<td>Moderate pericardial LGE, %</td>
<td>43 (n=6)</td>
<td>33 (n=5)</td>
<td></td>
</tr>
<tr>
<td>Severe pericardial LGE, %</td>
<td>50 (n=7)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

CMR indicates cardiac magnetic resonance imaging; CP, constrictive pericarditis; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; RV, right ventricular; LV, left ventricular; LGE, late gadolinium enhancement; IVC, inferior vena cava; SSFP, steady-state free precession; and FSE, fast spin echo.

*Comparison between reversible and nonreversible CP groups with unpaired \(t\)-test.

had 70% sensitivity and 72% specificity to predict reversible CP, with an area under the curve of 0.72. ESR of 41 mm/h had 70% sensitivity and 72% specificity to predict reversible CP, with an area under the curve of 0.71.

Clinical and TTE Follow-Up

The mean follow-up time was 12±7 months in the reversible CP group versus 13±7 months in the persistent CP group (\(P=0.53\)). The majority of patients in the reversible CP group had normal NYHA functional class (79%) during follow-up (versus 21% at baseline). Furthermore, diastolic blood pressure increased and jugular venous distension resolved after therapy. No similar changes occurred in the persistent CP group. At the last follow-up visit, only 2 patients in the reversible CP group were still taking medication, 1 taking colchicine and another for whom prednisone had been tapered down to 5 mg/d. One patient had recurrent CP symptoms concurrent with a rheumatoid arthritis flare-up but resolved after methotrexate.

Compared with baseline TTE, there was significant resolution of abnormal septal motion, respiratory mitral inflow E velocity variation, and expiratory hepatic venous diastolic reversal in the reversible CP group (all \(P<0.001\); Table 2). Cardiac index also increased significantly in the reversible CP group. E velocity and e’ also tended to be lower. No trends or significant changes in these TTE features were found in the persistent CP group before pericardiectomy.

There were 13 patients in the persistent CP group who underwent pericardiectomy, with a mean time from starting medical therapy to surgery of 9.3 months (2–48 months). Pathological specimens were available from 12 patients; all pericardial specimens were fibrotic. Ten patient samples had thickened pericardium (>2 mm), whereas 2 had normal pericardial thickness but were fibrotic microscopically. Calcification and granulomas were present in 5 and 2 cases, respectively. Mild chronic inflammation evidenced by mild lymphocyte infiltrate was found in 5 patients, whereas no patient had acute inflammation or significant chronic inflammation.

There was good reproducibility between the 2 magnetic resonance angiography readers, with a concordance rate of 93% in grading pericardial LGE. A weighted \(k\)-statistic was computed of \(k=0.85\).

Discussion

The present study suggests that the baseline severity of pericardial LGE in patients with CP was associated with reversibility of CP. Furthermore, patients with reversible CP had increased inflammatory biomarkers that indicated significant systemic inflammation. Antiinflammatory therapy reduced systemic inflammation, as evidenced by lowered white blood cell count, CRP, and ESR. In addition, antiinflammatory therapy was associated with a reduction in pericardial LGE severity and pericardial thickness on LGE, SSFP, and FSE images. Clinical resolution of constriction after antiinflammatory therapy was observed in 14 of the 29 CP patients. Clinical improvement was often accompanied by hemodynamic resolution of constriction on echocardiography.

CP often masquerades as other cardiovascular or noncardiovascular diseases and often poses diagnostic and therapeutic dilemmas for physicians. The correct diagnosis and appropriate therapy are frequently delayed. Although thickened pericardium has been considered as an essential diagnostic feature of CP, it has been observed that 10% to 20% of CP patients have a normal-thickness pericardium.7,13 Pericardiectomy is usually required to relieve progressively debilitating heart failure. The prognosis in CP patients after pericardiectomy is variable.1 Although some patients enjoy long-term relief of symptoms and have significant clinical improvement, others have persistent symptoms and may die prematurely.1,19

Advanced age, higher NYHA class, and a history of chest radiation were found to predict a poor outcome.1

Although surgery traditionally has been considered the only definitive treatment for CP, transient or reversible-form CP has been described that resolves without surgical intervention.3–5 It has been postulated that inflammation and edema lead to pericardial thickening, poor compliance of the pericardium, and consequently, constrictive pathophysiology.5 Our group reported that increased pericardial thickness of reversible CP was normalized with antiinflammatory therapy.3 However, systematic study has not yet been performed to address which clinical and laboratory features predict reversibility of CP with antiinflammatory medical therapy.
We made several clinically important observations in the present pilot study. First, maximal pericardial thickness measured on LGE was significantly greater in the reversible CP than in the persistent CP group. An LGE pericardial thickness of 3 mm or moderate-severe pericardial LGE on qualification had a reasonable sensitivity and specificity to predict reversible CP. Second, patients with reversible CP had more baseline systemic inflammation, as evidenced by higher baseline CRP and ESR levels, than patients with persistent CP. Third, there was a correlation between systemic inflammatory markers and the severity of pericardial LGE. Finally, antiinflammatory therapy was associated with a significant reduction in CRP, ESR, white blood cell count, and pericardial thickness determined by CMR LGE, SSFP and FSE imaging with clinical and echocardiographic evidence of resolution of constrictive hemodynamic in the reversible group but not in the persistent CP group. For echocardiographic resolution of constrictive physiology, mitral E velocity and hepatic vein variations resolved in most patients in the reversible CP group, whereas tissue Doppler parameters such as e' only showed a nonsignificant trend. This is most likely due to our small sample size with a large standard deviation, as well as the observation that e' velocity may not decrease after resolution of constriction, especially in young patients.

We speculate that significant pericardial and/or systemic inflammation leads to cytokine release, which stimulates CRP production in the liver and produces other systemic inflammatory responses, such as increased ESR and elevated white blood cell counts in reversible CP patients. The cause of the reversible CP is more often secondary to autoimmune disorders or is an idiopathic process. Although a few patients with a history of prior cardiac surgery had reversible disease, it was more common for these patients to have persistent CP. Because cardiac surgery is now one of most common causes of CP, it is important to identify patients in this group with potentially reversible disease. In the present study, none of the patients with reversible CP had a history of chest radiation, which confirmed prior observations.

Antiinflammatory medications reduced systemic and pericardial inflammation and restored normal pericardial compliance in the patients with reversible CP. In contrast, the persistent CP group had much less inflammation within the pericardium, as suggested by much less severe pericardial LGE and less systemic inflammation than seen in the patients with reversible CP. Not surprisingly, antiinflammatory medications neither significantly changed pericardial thickness nor reduced CRP or ESR in these patients.

Interestingly, the percentage of patients positive for pericardial LGE, defined as mild or more LGE in the pericardium, was not significantly different between the 2 groups. For patients who had a thickened pericardium but no inflammation, the vascular density is low, and gadolinium distribution may be limited even though the extracellular space is increased with significant fibrosis. These patients have either no or minimal LGE, which is different from myocardium scar or fibrosis. In contrast, patients with a thickened and inflamed pericardium have hyperemia and increased vascular density, likely resulting in a significant LGE. Thus, our observations suggest that the severity of LGE is more informative than the mere presence of LGE in differentiating pericardial inflammation and the reversibility of CP.
Study Limitations

There are several limitations of the present pilot study. First, antiinflammatory therapy was not standardized and was at the individual physician’s discretion. Second, the measured differences in pericardial thickness between reversible and nonreversible patients, while significant and reproducible by both observers, are quite small, particularly in light of the 1- to 2-mm in-plane resolution of the LGE images. Adding to the difficulty of obtaining accurate pericardial measurements is the problem of volume averaging, that is, obtaining a true orthogonal view of a thin 3-dimensional structure of pericardium with relatively thick (6–8 mm) 2-dimensional images is problematic. The thickness can be overestimated if the orientation of the pericardium changes across the imaging slice. All of this suggests the importance of obtaining LGE images with higher spatial resolution, ideally 3-dimensional acquisitions. Moreover, it is also unclear why differences in pericardial thickness between patients with reversible and nonreversible CP were only significant when measured on LGE images. It is possible that the relatively intense enhancement of the pericardium on these images allowed better delineation of the pericardial borders, or perhaps alternatively, this could have led to slight overestimation of pericardial thickness on the LGE images. Nevertheless, there was good reproducibility between the 2 CMR readers, with a concordance rate of 93% in grading pericardial LGE (κ=0.85). Third, we do not have pathological data for the patients with reversible CP because they did not undergo pericardiectomy. However, Taylor et al12 reported good correlation between pericardial inflammation on pathology and LGE pericardium on CMR. Fourth, this is a retrospective observational study, and the follow-up duration was relatively short (2–25 months). It remains unknown whether these reversible CP patients will have a durable long-term resolution. Furthermore, classification of resolution was based on subjective improvement of NYHA functional class, although most patients who had clinical resolution also had hemodynamic resolution as evidenced by repeat echocardiography study (detailed in Table 2). Reanalysis of data by use of hemodynamic criteria for CP resolution showed similar results (data not shown). Finally, our sample size is small because of the relatively rarity of the disease studied, although the study patients came from a 6-year clinical experience at a tertiary medical center with an established pericardial clinic. With a small number of patients, we could not perform meaningful multivariate analysis to evaluate the incremental value of CMR GLE to the inflammation biomarkers. To confirm the present findings, we need to study prospectively a larger number of patients with CP and parameters that we have identified to be associated with reversibility. Ideally, a multicenter randomized clinical trial needs to be performed with pericardiectomy patients as the control group. However, it may be difficult for us to submit a CP patient with evidence of potential reversibility to pericardiectomy knowing the present study results. A large multicenter CP registry to validate our findings appears more realistic.

Future Directions

More accurate quantification of pericardial LGE is desirable. Two-dimensional LGE images with higher in-plane resolution and thinner section thickness can be obtained, but at a cost in signal-to-noise ratio, which at some point will limit assessment of pericardial thickness and LGE. Similarly, 3-dimensional LGE pulse sequences are attractive because they provide intrinsically higher signal-to-noise ratios and can be obtained with higher spatial resolution than 2-dimensional LGE images. Fat-suppressed LGE pulse sequences may also be useful to improve the conspicuity of enhancing pericardium surrounded by epicardial fat. The role of proinflammatory cytokines and systemic inflammatory markers and their predictive values should be investigated, which could potentially save the expense of the CMR study. Autopsy studies have shown that myocardial atrophy and fibrosis are present in CP,21,22 which may partly explain the poor outcome in some patients after pericardiectomy.1 The prognostic value of LGE in myocardium after pericardiectomy, which reflects myocardium scar/fibrosis due to radiation or other insult to myocardium, needs to be investigated further. Finally, cardiac computed tomography can more accurately measure pericardial thickness because of its higher spatial resolution compared with CMR. In addition, cardiac computed tomography is much more sensitive than CMR for detection of pericardial calcification, which has been strongly associated with CP and may also indicate nonreversibility. However, it is also likely that the sensitivity of computed tomography for detection of pericardial enhancement is significantly lower than CMR. In addition, computed tomography entails radiation exposure for the patient, which is increased if delayed images are obtained to assess pericardial enhancement. The potential role of cardiac computed tomography in assessing patients with potentially reversible CP clearly needs further study.

Conclusions

CP is reversible in some patients and may be cured by antiinflammatory therapy in a subset of patients. Reversible CP is associated with significant pericardial and systemic inflammation. Antiinflammatory therapy was associated with a reduction in pericardial and systemic inflammation, with resolution of CP. Because this is a pilot study in a small number of patients, further studies in a larger number of patients are needed to confirm these observations. If confirmed, patients with CP and the above evidence of pericardial and systemic inflammation should be treated with antiinflammatory medical therapy before consideration of pericardiectomy.

Disclosures

None.

References

Constrictive pericarditis (CP) is a disabling disease and usually requires pericardiectomy to relieve heart failure symptoms. Reversible cases of CP after antiinflammatory therapy have been described, but there is no known method to predict the reversibility. We report our pilot study to assess whether cardiac magnetic resonance imaging (CMR) pericardial late gadolinium enhancement (LGE) can predict the reversibility of CP after a course of antiinflammatory therapy. Twenty-nine patients received antiinflammatory medications after CMR. Fourteen patients had resolution of CP, whereas 15 had persistent constrictive physiology. Baseline LGE pericardial thickness was greater in the reversible CP group than in the persistent CP group. Qualitatively rated severity of pericardial LGE was moderate or severe in 93% of the reversible CP group but not in the persistent CP group. CMR LGE pericardial thickness 3 mm had 86% sensitivity and 80% specificity to predict reversibility. The reversible CP group also had a higher baseline C-reactive protein and erythrocyte sedimentation rate level than the persistent CP group. Antiinflammatory therapy was associated with a reduction in pericardial LGE, C-reactive protein, and erythrocyte sedimentation rate in the reversible CP group but not in the persistent CP group. Our findings in this pilot observation suggest that reversible CP is associated with pericardial and systemic inflammation. Furthermore, antiinflammatory therapy is associated with a reduction of pericardial and systemic inflammation, as well as pericardial thickness on CMR LGE imaging, with resolution of constrictive physiology and symptoms. Antiinflammatory therapy should be considered in CP patients with these features before pericardiectomy. Our findings need to be validated by further studies in a larger number of patients.
Cardiac Magnetic Resonance Imaging Pericardial Late Gadolinium Enhancement and Elevated Inflammatory Markers Can Predict the Reversibility of Constrictive Pericarditis After Antiinflammatory Medical Therapy: A Pilot Study
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