Pericardial Disease in Familial Mediterranean Fever*

An Echocardiographic Study


We studied 30 randomly selected patients with familial Mediterranean fever (FMF) by M mode echocardiography to determine the frequency of pericardial involvement. There was no evidence of congestive heart failure, uremia, or any other illness known to be associated with pericardial disease in the study population. Eight of the 30 patients (27 percent) had echocardiographic evidence of pericardial disease. Two had pericardial effusions, two had pericardial thickening, and four either or both. Patients with pericardial involvement had a mean duration of FMF of 28.9 ± 12.2 (SD) years vs 18.5 ± 10.6 (SD) years for those without pericardial disease (P < .02). We concluded that pericardial involvement is common in FMF and that its occurrence as detected by echocardiography increases with duration of illness.

Familial Mediterranean fever (FMF) is an inherited disease of unknown etiology primarily found in Sephardic Jews, Armenians, and Levantine Arabs. It is characterized by recurrent, short, self-limited attacks of fever, peritonitis, pleuritis, or synovitis. In addition, in some patients systemic amyloidosis develops, with subsequent renal failure and death. Despite the recurrent inflammation of serous membranes, there have been only a few case reports of pericardial disease in nonuremic patients. Systematic echocardiographic studies to evaluate the presence of pericardial disease in symptomatic or asymptomatic patients with this entity have not been reported to our knowledge. We therefore undertook an echocardiographic study of 30 patients with FMF to assess the prevalence of pericardial disease.

Materials and Methods

Thirty patients were randomly selected from the roster of the UCLA FMF Clinic (210 total patients). All patients satisfied the criteria for diagnosis of FMF as outlined by Heller et al. There were 18 males and 12 females, with a mean age of 33 years (range, 9 to 61). The mean duration of the disease was 21.2 ± 11.8 years (SD; range, 4 to 46). All patients were interviewed and examined by a cardiologist. None of the patients had evidence of congestive heart failure, uremia, or other systemic disease known to be associated with pericardial disease.

Echocardiographic Technique

M mode echocardiograms were taken with a commercially available Smith-Kline Ekoline 20A ultrasonoscope interfaced with a Honeywell 1856 fiberoptic recorder as previously described. The damping control and a switched gain circuit were used to identify and accentuate the posterior pericardial echoes. Echocardiograms from FMF patients were reviewed independently by three observers blinded to the interpretations of one another. All three observers had to be in agreement regarding the diagnosis of pericardial effusion or thickening for the purpose of the study. A single band of moving pericardial echoes with no separation between epicardium and pericardium at low gain was considered normal. A pericardial effusion was diagnosed per the criteria of Horowitz et al when a posterior echo-free space was clearly imaged between the epicardium and pericardium in conjunction with flattening of the motion of the pericardium relative to the epicardium. Pericardial thickening was diagnosed when parallel posterior pericardial echo interfaces were imaged per the criteria of Schnitberger et al. Echocardiograms of 50 subjects randomly selected from the UCLA Normal Population Echocardiographic File (total of 300 subjects) were also reviewed independently; these subjects had otherwise normal results of echocardiograms, resting and ambulatory ECGs, treadmill tests, phonocardiograms, and normal cardiac histories and physical examination results.

A 12-lead ECG was obtained in the last 20 patients at the time of echocardiographic study to look for abnormali-
Table 1—Clinical Data from FMF Study Patients

<table>
<thead>
<tr>
<th>State at Time of Study</th>
<th>History of Chest Pain</th>
<th>Pericardial Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>PE</td>
</tr>
<tr>
<td>Acute</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>4</td>
</tr>
</tbody>
</table>

*Abbreviations: PE/PT, pericardial effusion and/or pericardial thickening; PT, pericardial thickening; and PE, pericardial effusion.

ties of the QRS-ST-T wave configuration that may be present due to superficial myocarditis.\(^{13}\) Nonsimultaneous ECGs in the first ten patients were obtained and reviewed similarly.

Student’s unpaired t test was used in comparing duration of FMF with the presence of pericardial disease. Data are expressed as mean ± 1 SD.

Results

Twenty-six of the 30 patients had experienced acute chest pain during acute attacks of FMF at some time in the past. Only four of these 26 had symptoms of chest pain at the time of this study; the other 22 patients had no complaints of chest pain at the time of examination (Table 1). Two of the four patients (50 percent) with chest pain at the time of study had echocardiographic evidence of pericardial disease—pericardial thickening in one and pericardial thickening, effusion, or both in the other. None had friction rubs. Of the 26 patients who were asymptomatic, six (23 percent) had echocardiographic evidence of pericardial disease; two of the six had pericardial effusions, one had pericardial thickening, and three had a pattern of pericardial effusion, thickening, or both (Fig 1). Four of the 30 patients had no history of chest pain and showed no ECG or echocardiographic evidence of pericardial disease.

The mean duration of illness in those patients with pericardial disease was 28.9 ± 12.2 years (N = 8), while those without evidence of pericardial disease had a mean duration of illness of 18.5 ± 10.6 years (N = 22). This was a significant difference (P < .02).

Electrocardiograms were performed immediately after the echocardiograms in 20 subjects: 13 were normal, five showed ST segment elevation, and two showed nonspecific ST-T changes. In the five patients with ST elevation, the pattern was more consistent with early repolarization\(^{13-16}\) because of an upward concave elevation of the RS-T segment with distinct J points with the RS-T elevation most distinct in the midprecordial leads and no T wave abnormalities; however, an epicardial injury pat-

Figure 1. Echocardiograms in FMF. (A) Pericardial effusion in a 52-year-old woman with 30-year history of FMF. (B) Pericardial thickening and/or effusion in a 51-year-old man with FMF for 44 years. (C) Pericardial thickening in a 25-year-old woman with 22-year history of FMF. C = chord; EN = endocardium; IVS = interventricular septum; LV = left ventricle; PP = parietal pericardium; RV = right ventricle; VP = visceral pericardium. 1 cm and 1/4 sec calibration marks shown.
ECCGs were remote from echocardiographic study; one revealed nonspecific ST-T abnormalities and the rest were normal. None of the 50 subjects from the normal population file was thought to have a pattern of pericardial effusion or thickening.

**Discussion**

Although familial Mediterranean fever is a disease characterized by recurrent polyserositis, there is little documentation of pericardial disease. Sohar et al\(^1\) in a study of 470 patients did not observe a single case of pericarditis and concluded that pericardial involvement must be extremely rare. Six cases of pericarditis associated with FMF have been previously described (Table 2).\(^5\) Some of these, however, may have represented pericardial disease unrelated to FMF; certainly in three patients (3,5,7) pericardial involvement may have been due to intercurrent disease. However, studies by Eliakim et al\(^8\) and Siguier et al\(^2\) suggest that pericarditis may be an occasional feature of FMF.

To our knowledge, there has been no systematic study to evaluate the likelihood of pericardial involvement in FMF. M mode echocardiography is highly effective in evaluating pericardial effusions and thickening.\(^11,12\) Previous studies have used only electrocardiography in their evaluation of pericardial involvement in FMF. The ECG can be quite useful in the diagnosis of acute pericarditis, particularly when ST segment and T wave changes are seen to evolve in serial tracings.\(^14\) However, in acute, subacute, or chronic pericardial disease, the ECG may show only nonspecific changes or may be within normal limits,\(^15\) and therefore cannot be used to exclude pericarditis. In the subset of patients having both ECG and M mode echocardiographic studies, the echocardiogram clearly documented pericardial involvement in 8/20 (40 percent), whereas the ECG failed to predict pericardial abnormalities in any patient.

We obtained echocardiographic evidence of pericardial disease in eight of 30 patients (27 percent) with FMF. The mean duration of disease, 28.9 ± 12.2 years in the patients with pericardial disease vs 18.5 ± 10.6 years in those without (P < .02), implies that the frequency of pericardial disease increases with the duration of illness. We can speculate that recurrent episodes of pericardial inflammation might be necessary before echocardiographic detection of pericardial thickening is possible. The presence of pericardial thickening as well as effusion, as seen in many of our patients, may be of clinical importance. A small effusion developing rapidly within a thickened pericardium could lead to cardiac tamponade.\(^18\) In such cases more frequent follow-up may be indicated. All patients with pericardial disease (8/20) by echocardiography also had experienced chest pain during their FMF attacks; however, a high proportion of patients (18/20) who experienced chest pain did not have echocardiographic evidence of pericardial disease. Therefore, a history of pleuritic chest pain did not strictly correlate with presence of echocardiographic pericardial disease. Clearly, when acute pericarditis consists of a fibrinous reaction without effusion, the echocardiogram can be normal. Thus, our patients with chest pain and normal echocardiograms may still have had pericardial disease. The echocardiographic evidence of pericardial disease in eight of 30 patients (27 percent) with FMF. The mean duration of disease, 28.9 ± 12.2 years in the patients with pericardial disease vs 18.5 ± 10.6 years in those without (P < .02), implies that the frequency of pericardial disease increases with the duration of illness. 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Thus, our patients with chest pain and normal echocardiograms may still have had pericardial disease. The echocardiographic
gram may only be abnormal when pericardial effusion occurs or when repeated acute episodes result in pericardial thickening. It should be noted that echocardiographic evidence of pericardial disease was relatively frequent in asymptomatic patients, and therefore its detection during an episode of chest pain does not necessarily indicate that the chest pain is due to pericarditis.

ACKNOWLEDGMENT: The authors wish to thank Stephanie Thessomboon, R.D.M.S., and Maureen Hiss, R.D.M.S., for their technical assistance.

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