A Model of Myocarditis in Humans

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In this issue of Circulation, Midei and colleagues from The Johns Hopkins University report a high incidence of myocarditis in women with postpartum congestive heart failure. Myocarditis was first convincingly documented to be a cause of peripartum cardiomyopathy in 1982 by Melvin et al at King's College Hospital in London through use of perimortem transvenous endomyocardial biopsy. Since then, two other groups have reported larger series of 113 and 144 subjects in whom endomyocardial biopsy revealed incidences of myocarditis of 45% and 29%, respectively. The 78% incidence in the Johns Hopkins study is the highest rate reported in a series of this size.

The Hopkins study may be atypical in other respects. Most investigators have noted a marked preponderance of women over 30 years of age (only half of the patients were over 30 years of age in the Hopkins study) and of multipara (only 60% in the Hopkins study). There is a known predilection of this disease for black women; only half of the patients in the study by Midei and coworkers were black. Finally, the incidence of improvement in this study is considerably higher than that previously reported. The investigators believe that therapy explains this difference.

Although this series may be somewhat atypical of the US and worldwide experience with peripartum cardiomyopathy, it provides a unique model through which to examine myocarditis in humans. This group of patients with dilated cardiomyopathy is homogeneous, and the time of onset of disease is accurately defined. This is not the case in most other series in which the disease may have been present for years before endomyocardial biopsy is performed. This series further qualifies as a useful model because of its uniform diagnostic criteria for myocarditis and its completeness and thoroughness of follow-up.

We have learned three lessons by study of this model of myocarditis in humans. First, in living patients with relatively recent onset of disease, the sampling error of endomyocardial biopsy in detecting myocarditis is not a significant problem. Seventy-eight percent of this group had biopsy results that were positive. Thus, the maximum error rate was 22%, and the real rate was probably less because some of the subjects with negative biopsy results probably did not have myocarditis. Four samples of myocardium were obtained at each biopsy procedure. This appears to be a sufficient number to allow accurate detection of myocarditis in humans. This figure agrees with the estimates of 98%5 and 99%6 for sensitivity for detection of cardiac transplant rejection, to which myocarditis is histologically similar, and this figure disagrees strongly with Chow et al,7 who predicted a substantial sampling error for detection of myocarditis even when as many as 15 samples were obtained. The latter study was flawed by its inclusion of few typical cases of myocarditis and by its dependence on autopsy tissue, which is obtained at an unequivocally different stage of disease than is an endomyocardial biopsy.

The second lesson provided by the Hopkins series concerns the relation between chronicity of myocarditis and the probability of positive biopsy results. Here, we take advantage of knowing when the disease actually began: in close proximity to the time of parturition. Positive biopsy results were obtained in 10 of 13 (77%) subjects between 0 and 3 months of delivery and in four of five (80%) subjects between 3 and 6 months. These data show that in this human model the inflammatory process may frequently persist for several months and that endomyocardial biopsy as long as 6 months after disease onset may yield accurate detection. However, the data cannot be construed to support a strategy of delaying the biopsy procedure in patients having symptoms, because all patients in the Hopkins study underwent biopsy shortly after presentation.

The third lesson from this model is a confirmation of a clinical impression that we and others have held. That is, myocarditis presents either as a disease of acute onset or of relatively insidious onset. In the Hopkins study, five patients were admitted with rapidly progressing disease within 3 weeks (average, 10 days) of delivery. The other patients were admitted considerably later and were believed by the investigators to have had a gradual onset of symptoms. We have the additional clinical impression

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(which is not reflected in the Hopkins series) that the acute presentation of myocarditis is characterized by a relatively rapid outcome, that is, either prompt resolution or prompt deterioration.

Most of the patients with less acute symptoms received immunosuppressive therapy. It is unknown what their outcomes might have been without treatment. Our clinical impression is that such patients have a bimodal outcome, some improving and some not, but that their outcomes are less dramatic, characterized either by incomplete recovery of left ventricular function or by slow, modest worsening of cardiac performance. The acute and subacute or chronic presentations of myocarditis may be a result of different disease mechanisms.

The immunologic milieu of the maternal-fetal relation may predispose to immune-mediated cardiac injury. Midei and colleagues' propose an interesting pathophysiologic explanation for peripartum myocarditis by focusing on the exposure of the maternal immune system to myometrial, placental, or fetal antigens with subsequent formation of an antibody that cross reacts with myocardial antigens. If this speculation were correct, one might expect a much higher incidence of peripartum myocarditis, because all parturient women are exposed to trophoblastic antigens. Also, their theory would have to be extended to account for the failure of most pregnant women to develop a cross-reacting antibody. As evidence that the immune-mediated injury is pregnancy specific, these investigators cited the lack of other immunologic disorders or the lack of relapse of myocarditis after treatment. Yet, these conditions only rarely develop after myocarditis in subjects who have never been pregnant. An alternative, but also unproven, explanation is the chance occurrence of a myocardial viral infection at a time when T helper cells are decreased. Even if the virus is ultimately cleared, the enhanced antigenic load may stimulate an exaggerated immune response. Further virologic and immunologic studies of peripartum myocarditis will be necessary to elucidate its mechanism.

Certain conclusions of the Hopkins group merit comment. They rather forcefully support the use of immunosuppressive therapy of peripartum myocarditis. We consider the evidence in this study too weak to justify a strong recommendation for routine antinflammatory treatment with corticosteroids. Randomized allocation of patients to treatment without immunosuppression was not performed. Previous studies have shown frequent, spontaneous resolution of parturitional congestive heart failure,1,4,8 Although there was a higher-than-usual incidence of improvement in the Hopkins series, this incidence cannot be ascribed unequivocally to the use of immunosuppression. In fact, five of eight patients (63%) who did not receive immunosuppression experienced complete recovery to congestive heart failure class 0. This was true in only 50% of treated patients. Those in the immunosuppressed group who did improve might have recovered spontaneously without treatment. The investigators proposed that the relative chronicity of symptoms in the treated patients predicted a low likelihood of natural improvement. However, spontaneous, complete recovery has been documented even after 15 months of congestive heart failure.9 In addition, the duration of follow-up in this study may have been insufficient to accurately gauge the effects of therapy. Previous investigators have observed severe cardiac failure and death as a late complication. For example, in the study by Demakis et al,8 those patients who died had survived an average of 4.7 years after delivery. The average duration of follow-up was not stated by Midei and coworkers,1 but the minimum duration of follow-up was only 6 months after the onset of symptoms. A lengthier follow-up may show that some patients later deteriorate after initially improving.

Midei and colleagues1 underemphasize the potential for adverse effects of immunosuppression. Although few were encountered in the present series, the well-known risks of corticosteroids, aza-thioprine, and other immunosuppressives certainly apply to postpartal women, especially those debilitated by significant congestive heart failure. The risk of exposure of the newborn to immunosuppressive drugs in breast milk is an additional factor to consider.

We believe that the following responses by the clinician to the study by Midei and associates1 are appropriate. First, patients who develop peripartum congestive heart failure should be treated conventionally. Second, these patients should be considered likely to have myocarditis but should not automatically be given corticosteroids and azathioprine. The evidence that this or most other forms of myocarditis improve with immunosuppression is simply insufficient at this time. Third, especially in patients in whom prompt improvement does not occur, consideration should be given to obtaining an endomyocardial biopsy. We would recommend entry of those with positive biopsy results in an ongoing international randomized trial to evaluate efficacy of immunosuppressive therapy.10

References


*(Circulation 1990;81:1154–1156)*
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Circulation. 1990;81:1154-1156
doi: 10.1161/01.CIR.81.3.1154

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/81/3/1154.citation