Recent Advances and Remaining Questions

Ralph Shabetai, MD

Recurrence is a serious complication of acute pericarditis, characterized by a return of pericardial pain after recovery from an attack of typical acute pericarditis. Some patients experience only a single recurrence, but in many less fortunate, pericardial pain returns unexpectedly at variable intervals during a period that may extend over many years. The pain and any associated fever and leukocytosis disappear within a day or so of high-dose corticosteroid administration (eg, 1 to 1.5 mg/kg per day prednisone in most cases), only to return during tapering to a low dose. Thereafter, the high dose is reinstituted and then maintained for 1 month or 6 weeks, after which prednisone is again slowly tapered during the next several months. This sequence may need to be repeated frequently before it becomes possible to wean the patient from steroidal therapy. This is one of the reasons recurrent pericarditis is so troublesome to patients and treating physicians alike.

Until recently, patients in whom recurrences were frequent and extended for many years often received a massive total dose of a steroid, usually prednisone or prednisolone, with a consequently unacceptable incidence of gastric hemorrhage, aseptic necrosis of the femoral head, and osteoporosis with spinal compression fracture. Seeking a less toxic treatment, physicians began to avoid corticosteroids or limited their use and treated the patients instead with nonsteroidal anti-inflammatory drugs (NSAIDs). The change often was not accomplished easily because patients, and sometimes referring physicians, had been so pleased with the prompt response to high-dose steroid administration. Good progress is being made in this regard and will continue with further education of patients about their disease and its treatment.

In the last decade of the 20th century, a number of investigators published enthusiastic reports of the efficacy of colchicine as adjuvant treatment of acute pericarditis. Not surprisingly, because recurrence is the most common major complication of acute pericarditis, subsequent papers suggested that colchicine should also be used as part of the treatment regimen for recurrences. Most of these reports were not based on large randomized trials; furthermore, when colchicine was added to the treatment regimen for recurrent pericarditis, this was done only after a corticosteroid or an NSAID failed to influence the frequency, severity, and duration of recurrence.

The COlchicine for acute PEricarditis (COPE) trial published in this issue of Circulation is the first large randomized prospective trial of colchicine added to standard treatment of acute pericarditis. Wisely, the authors selected as the primary end point the ability of colchicine to prevent recurrence and improve the clinical course of every recurrence that developed during their study. The secondary end point was the effect of this treatment regimen on the duration of pain after a first attack of acute pericarditis. The design was not double-blind placebo-controlled because colchicine is far from being a new drug, and consequently the study could not be funded by a pharmaceutical company, again exemplifying the influence of the pharmaceutical industry on medical education and publication. The authors did take all necessary steps to ensure the validity of the results in the absence of double blinding. Prednisone was reserved for patients in whom NSAID therapy was either contraindicated or poorly tolerated.

In the 120 patients studied at 2 centers, the addition of colchicine reduced the recurrence rate at 18 months from 32.3% to 10.7%, a remarkable two thirds reduction. The secondary end point, persistence of symptoms at 72 hours after the onset of acute pericarditis, was also significantly reduced by two thirds. Thus, the addition of colchicine to standard treatment for acute pericarditis has been placed on firm footing. As noted by the authors, although it promptly relieves symptoms, corticosteroid therapy is thought to promote recurrence.

The results of the COPE trial are welcome, coming as they do in a climate of considerable skepticism regarding the benefit of colchicine for recurrent pericarditis, fostered by disappointing experiences in pericarditis with colchicine noted by many physicians who have included colchicine in their treatment regimen for recurrent pericarditis. The results of COPE convincingly correct this anecdotal view of colchicine for enhancing the treatment of recurrent pericarditis.

A common misconception among physicians and fear among patients is that repeated pericardial inflammation may lead to constrictive pericarditis or cardiomyopathy but, in the 120 patients in the COPE trial, not a single case of constrictive pericarditis or cardiomyopathy was reported. This confirms that we have solid evidence to back the assurance we give to patients that, although recurrent pericarditis may
sometimes seem to be an endless problem, chronic constrictive pericarditis is a rare sequel, and myocardial damage does not ensue. Cardiac tamponade is an uncommon complication that was not seen even once in the COPE trial and would be promptly recognized in patients being studied for recurrent pericarditis.

The toxic effects of oral steroid administration are significantly lessened by injecting a nonabsorbable preparation intrapericardially, as was recommended for pericardial effusion in patients with late-stage renal disease.1 Intrapericardial administration of triamcinolone is, by the same token, a good option for recurrent pericarditis and has the added advantage that the steroid is delivered where it contacts the 2 pericardial surfaces.4 Using a flexible pericardioscope, the medication can be delivered into the pericardial space, even in the absence of effusion.5 Pericardioscopy and the PerDUCER,6 an instrument developed to invade the pericardium when effusion is not present, are not available in most major medical centers; although it would be advantageous to establish at least one center in the United States where one of these techniques or a comparable technique would be used in clinical practice. At present, for most of us, pericardioscopy is still an investigational tool.

The cause of acute pericardial disease was investigated in 2 series from Spain, 1 with 231 consecutive patients7 and the other having 100 consecutive patients,8 with prospective protocols to determine the cause of pericarditis. The conclusion from these studies was that “diagnostic” pericardial tap and biopsy seldom yield the cause, whereas paradoxically, when these procedures were performed for conditions such as tamponade and suspected purulent infection or neoplastic disease, the diagnostic yield was much improved. These important studies have strongly influenced clinical practice by sharply decreasing the frequency of invasive investigation and hospitalization for uncomplicated acute pericarditis. When it appears doubtful that a patient has viral (or idiopathic) pericarditis, or has a complication such as cardiac tamponade, or fails to respond to standard anti-inflammatory treatment, hospitalization for treatment such as pericardiocentesis, and comprehensive investigation of causation are mandatory.9 For the COPE trial, Imazio et al selected high-dose aspirin as the NSAID, as they had in their earlier study of the management of acute pericarditis in which colchicine was not included, and found it safe and effective; thus, it is appropriate to use aspirin before moving to an expensive NSAID. Viral or idiopathic pericarditis is a benign, short-lived condition requiring simple treatment, usually without hospital admission. When patients present with chest pain but no risk factors or good evidence for coronary disease, careful clinical and laboratory evidence of acute pericarditis should be undertaken before embarking on comprehensive evaluation for myocardial ischemia or infarction. Markers of myocardial damage are often slightly elevated, but not to the threshold for myocardial infarction.10 The mildly elevated markers have no influence on the outcome of acute pericarditis.

A significant proportion of cases are caused by an autoimmune reaction to an initial episode of pericarditis, itself frequently caused by a virus; it is a mistake to consider all recurrence as autoimmune, and definite evidence of autoimmune pericarditis is necessary to justify this conclusion.11 Specifically, antisarcolemmal antibodies should be present, polymerase chain reaction for cardiotropic viruses and other infectious agents should be negative, and immunoglobulin M against these agents should not be detectable. In addition, tissue should be examined after immunocytochemical and immunohistochemical staining.4,5 For an initial episode of acute pericarditis and for a first or infrequent recurrence, because of their high cost and the inevitable invasion of the pericardium, those studies are difficult to justify, but they certainly deserve a place for acute pericarditis that fails to respond to NSAID therapy and frequent recurrence.

Many patients ask why the problem cannot be solved by simply removing the offending pericardium. In the series of patients studied for an average of 10 years by Fowler and Harbin,12 22 were followed for ≥5 years and 10 for ≥8 years. The importance of this study is the duration appropriate for a condition that may persist for years, occasionally even for decades. Nine had undergone pericardiectomy, but clear improvement resulted in only 2 patients. This unsatisfactory outcome differed from an earlier enthusiastic recommendation that recurrent pericarditis should be treated by pericardiectomy. Tuna and Danielson13 reported much better results that they attributed to virtually complete pericardiectomy.

Although progress has been made in the treatment of acute and recurrent pericarditis, but in recurrent pericarditis many issues require investigation. We need to find reliable noninvasive methods that will distinguish autoimmune cases from those caused by reinfection or new infection, and trials of treatment based on cause. If we can learn how to predict the outcome of pericardiectomy, then that would be a notable advance. The riddle of recurrent pain without evident pericarditis remains to be solved, and therefore the place in it for anti-inflammatory treatment is uncertain. The exact mechanism of the action of colchicines in recurrent pericarditis is in need of clarification. We lack an animal model of recurrent pericarditis. Research will include basic and clinical immunology as well as virology and a search for still more effective drugs.

Successful management requires a lot of patience on the part of physicians and patients. Patients must be informed about what is known about the condition and the merits and problems associated with the various therapeutic options, including pericardiectomy.

References
5. Maisch B, Ristic AD, Seferovic PM, Spodick DH. Intrapericardial treatment of autoimmune myocarditis with triamcinolone. Successful


Key Words: Editorials || pericarditis || colchicine
Recurrent Pericarditis: Recent Advances and Remaining Questions
Ralph Shabetai

Circulation. 2005;112:1921-1923
doi: 10.1161/CIRCULATIONAHA.105.569244

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/112/13/1921

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/