Blood culture-negative early prosthetic valve endocarditis: be aware of fungi!

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Prosthetic valve endocarditis (PVE) is associated with significant mortality and morbidity. Despite medical advances in surgical techniques, PVE continues to complicate cardiac valve surgery. The incidence is highest within the first 12 months following surgery and affecting 1–3% of patients. PVE may arise early or late after surgery. According to the microbiological profile, the most appropriate cut-off time to distinguish between early and late-onset PVE is 1 year. The timing of the infection reflects different pathogenic mechanisms that, in turn, influence the epidemiology, microbiology, pathology and clinical manifestations of the infection. In early-onset PVE, microorganisms can reach the valve prosthesis by direct contamination intraoperatively or via haematogenous spread during the initial days and weeks after surgery. As pointed out by Thuny et al in this issue (see page 743), different mechanisms, including iatrogenic causes and hospital-acquired infections, may contribute to the disease. In early PVE, pathogens have direct access to the prosthesis–annulus interface and to perivalvular tissue along suture pathways because the valve sewing ring, cardiac annulus and anchoring sutures are not endothelialised early after valve implantation. These structures are coated with host proteins that may favour the adherence of some microorganisms. Staphylococci are the most frequently isolated microorganisms in more than one third of cases, and most of them offer therapeutic challenges, being methicillin resistant. Unfortunately, blood cultures may be negative in a significant proportion of these patients.

What is the microbiological profile of early PVE with negative blood cultures?

Thuny et al prospectively analysed data of 31 early-onset PVE from 718 patients with blood culture-negative endocarditis (BCNE) referred to their well-reputed centre and laboratory from France and abroad over more than 7 years (June 2001 to February 2009). The laboratory adopted a multimodal strategy incorporating serological, molecular and histopathological assays from patients. Data were compared with a sample of 22 patients with early-onset PVE with positive blood cultures and 625 patients with community-acquired BCNE in the same period. Fungi were the most common pathogen identified in patients with early-onset PVE and negative blood cultures.

The study coming from a well-reputed group of international experts on infective endocarditis is welcome and timely and is the first to analyse specifically the microbiological profile of early-onset PVE with negative blood cultures.

The results of the study raise two important issues. The first issue is related to the problem of how to reduce BCNE. Cultures are negative in endocarditis for three major reasons: the previous administration of antimicrobial agents; inadequate microbiological techniques and infection with highly fastidious bacteria or non-bacterial pathogens (eg, fungi). The last two options seem particularly important in the setting of early PVE. Diagnostic tests for culture-negative endocarditis include special culturing techniques (eg, shell phial and lysis centrifugation), molecular techniques (eg, PCR and serological assays) and histopathological evaluation of valvular tissue when surgical excision is performed. Only an extensive diagnostic strategy may succeed in reducing the number of BCNE.

In the published study, a causative pathogen was identified in one third of cases. Considering that the study comes from a tertiary referral centre for BCNE, it is evident how much diagnostic capabilities need improvement in non-specialised centres, and how far we are from the solution of the problem as well as from the complete understanding of the microbiology of the disease.

The second issue is specifically related to the microbiology of early-onset PVE with negative blood cultures. Fungi were the most commonly identified pathogen (16%), followed by Streptococci (10%), Lactobacillus spp (8%) and Legionella spp (3%). Fungi are an important cause of PVE in up to 10% of cases. Nevertheless, approximately two of three are still without a definite aetiology even in a tertiary referral centre for the disease. On this basis there is a real need for more research on the topic to obtain a better understanding of the microbiology of the disease, especially in unselected cases.

Current European and American guidelines on the management of infective endocarditis recommend empiric antibiotic schemes aimed at the treatment of the most common bacterial causes (Staphylococci, Gram-negative bacilli and Enterococci) but may fail in patient subgroups with a high prevalence of fungal infections. According to the results of the study published in this issue of Heart, the authors suggest the early consideration of surgery in cases of suspected fungal infection in order to reach the diagnosis by culture and/or molecular methods, and the possible addition of empirical fungicidal therapy in cases with negative blood cultures after a first empiric antibiotic therapy.

Nevertheless, the authors acknowledged some study limitations. Either the relatively small sample size or the selection of patients referred to a tertiary referral centre for molecular and microbiological diagnosis are important potential selection biases. The reported patients with early-onset PVE and negative blood cultures may thus not be fully representative of ‘the real world’ of early-onset PVE. On this basis, there is a need for further research on this topic, possibly with larger and multicentre studies. In our view, the study has the great merit of underlining a problem, but the solution still seems far away.

In conclusion, on the basis of the present study, until we have further data, it is important to have a high degree of suspicion of fungal infections in the presence of early-onset PVE with negative blood cultures, remembering that most cases still do not have a specific microbiological diagnosis and are not, reasonably, fungal, thus the choice of empiric antifungal therapies should be carefully weighed in the single patient as well as the need for ‘diagnostic’ surgery. At the same time the number of negative blood cultures should be reduced as much as possible with the aid of a multimodal diagnostic strategy, incorporating serological, molecular and histopathological assays from patients.

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Recurrent pericarditis: an autoimmune disease?

Noel R Rose

Recurrent pericarditis, like chronic myocarditis, is often considered to be an autoimmune consequence of a prior viral infection. Both the pericardium and the heart develop from the mesoderm, but embryologically the two organs are quite distinct. The embryonic heart enters and invaginates the pericardial sac giving rise to the visceral pericardium or epicardium on the heart surface, and to the parietal peritoneum. They are separated by the pericardial cavity which normally contains 15–50 ml of straw-coloured fluid.

The diagnosis of acute pericarditis is usually based on severe chest pain, diminished heart sounds, sometimes with an audible pericardial friction rub, and typical electrocardiographic changes. A long list of aetiologies has been associated with pericarditis, including infectious and non-infectious causes. Infectious agents include viral, bacterial and mycotic agents. The viruses implicated in pericarditis include Coxackievirus B, adenovirus, rhinovirus, echovirus, influenza, cytomegalovirus, herpesvirus and human immunodeficiency virus (HIV). Polymerase chain reaction (PCR) and in situ hybridisation, together with the presence of antibody, are used to identify the most common infectious agents.

Although the diagnosis of pericarditis is relatively straightforward, the aetiology and pathogenesis of the disease remain biological enigmas. Many of the problems linked to understanding of the pathogenesis of pericarditis are reflected in other inflammatory diseases that reputedly follow a viral infection. How much of the disease can be attributed to the infectious process itself and how much to a host generated immune response? The issue is not one of purely academic interest. It relates importantly to the approach to treatment. Often acute pericarditis seems to resolve spontaneously. Sometimes, however, one or more recurrences take place and the disease may progress to a constrictive pericarditis resulting in heart failure. Cases of acute pericarditis are often successfully treated with analgesics alone or with anti-inflammatory drugs. Colchicine may be added to the regimen. Steroids are employed in more difficult cases, but sometimes steroids appear to exacerbate the disease. The results are reminiscent of immunosuppressive trials of myocarditis, another inflammatory heart disease with a possible viral aetiology. On average, immunosuppression does not significantly benefit the population of patients with myocarditis. Some individuals, however, improve with the treatment, whereas others appear to worsen. One can conjecture that the patients who improve with immunosuppression have a predominantly immune-mediated disease, whereas those who worsen are suffering from an infectious process. Perhaps many patients have both processes going on and show neither great benefit nor harm.

A number of years ago we offered some commonsense suggestions for deciding whether a human disease is caused by (or significantly enhanced by) autoimmunity. Direct evidence comes from transfer of the disease from an affected subject to a naive individual. In humans, transfer at this time can be accomplished only with antibody-mediated diseases—for example, when maternal to fetal transfer occurs. More often the investigator must rely on indirect evidence based on a model in an experimental animal. If the requisite antigen can be identified, the disease can sometimes be reproduced by immunising a susceptible experimental animal with the counterpart antigen. In other instances, nature provides the investigator with a spontaneous disease in animals that is a fair approximation of the human disorder. These days investigators frequently intervene to manipulate the immune response by altering the cytokine balance, thereby reducing the natural homeostasis of the immune system. At the present time, most of our understanding of the pathogenic mechanisms of autoimmune disease has come from studies of such experimental models. When neither direct nor indirect evidence can be attained, investigators turn to circumstantial evidence. How do these steps apply to pericarditis?

There is a body of circumstantial evidence that links of pericarditis to an autoimmune process. An increased number of pro-inflammatory cells and cytokines have been described in the pericardial tissues and fluid. (ii) Antibodies against pericardial tissue are reported in serum and pericardial fluid of many patients. (iii) The presence of an infectious

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