EDITORIAL COMMENT

Toward Reducing Embolic Complications From Endocarditis*

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Our understanding of infectious endocarditis (IE) has grown in conjunction with some of the major advances in the history of medicine (1). One of the earliest reports of the disease comes from Lazere Riviere, who in 1646 reported on a patient who suffered from progressive shortness of breath and a palpable murmur over the heart. At autopsy, Riviere found “small round outgrowths, the largest of which blocked the aortic valve.” In 1806, Jean Nicolas Corvisart coined the term “vegetations” and suggested—as they were similar to the venereal “cauliflower”—that they may be caused by syphilis (2). Corvisart’s pupil Theophile Laennec devised the stethoscope in 1816. This enabled Corvisart to document the various murmurs that occur in IE, yet the cause and systemic complications of IE remained a mystery.

In 1852 William Senhouse Kirkes described findings due to breaking off of parts of the vegetations that subsequently became lodged in blood vessels of various organs (3). It was Rudolf Virchow who, in his Die Cellularpathologie, called this phenomenon “embolism” after seeing that the “thrombi” lodged in blood vessels bore a strong resemblance under the microscope to vegetations (4). Virchow also described “small granules” within these vegetations. These “bacteria, vibros, and micrococci,” he concluded in 1871, were “vegetal” and not “pathological” in IE (4). However, Emmanuel Winge presented a case of endocarditis in 1869 and proposed that these granules were “parasitic” organisms and had entered through the skin before becoming involved in the disease on the heart valves. This debate continued until the arrival of ideas on infection by Louis Pasteur and Robert Koch. It was Arnold Netter who in 1881 as a student described the novel practice of culturing blood from patients with endocarditis and subsequently inoculating animals with the growth of bacteria. His supervisor Joseph Grancher in 1884 coined the term “infectious” endocarditis in recognition of the fact that no single microbe was the sole cause of endocarditis.

William Osler was the first to realize that IE occurred on valves previously damaged by rheumatic fever or congenital valve disease and proposed that platelets were deposited from the bloodstream to cause vegetations (5). Osler then devised the terms “acute” and “chronic” for the two clinical extremes of IE. Osler’s ability of clinical synthesis meant that his name was posthumously awarded to many aspects of IE, such as Osler’s nodes. Emmanuel Libman went on to further classify acute IE, which was fatal within days, and “Osler’s subacute” IE, which lasted weeks to months. In 1911 in New York, Libman saw Gustav Mahler who had been diagnosed with “mitral contraction” (6). Mahler had developed a sore throat while in New York and shortly afterwards began to have fevers. Streptococcus viridans grew in his blood culture, and he died some three months later at the age of 51, never finishing the Tenth Symphony. Thus, IE remained a deadly ailment until the 1940s when the development of penicillin made IE potentially curable.

Although the incidence of IE has remained stable at 1.7 to 6.2 cases per 100,000 person-years, the clinical profile has continued to evolve (7). Thus, successive surveys of IE drawing from the same population have continued to detect changes in its clinical picture even over a period of 10 years (8). In the developed world, the chronic form of IE described by Osler has been superseded by a more rapidly diagnosed and fulminant illness. Men still outnumber women (1.7:1), but the median age has increased from 30 to 40 years in the pre-antibiotic era to 47 to 69 years recently (7). Consequently, degenerative valve disease and prosthetic valve IE have become more common rather than rheumatic heart disease. Prosthetic valve IE now accounts for 16% to 31% in some surveys (8,9). Concurrently IE has become more common in those with hemodialysis, diabetes mellitus, intravenous drug use, and nosocomial infections (7).

As the presence of vegetations is pathognomonic of the IE, it is not surprising that the sole means of visualizing them in vivo has become integral to its diagnosis. The first report of M-mode echocardiography to visualize bacterial vegetations was made in 1973 by Dillon et al. (10). Since then, technological advances, including the advent of transthoracic echocardiography, have significantly improved the ability to detect vegetations, particularly on the prosthetic valves, and to make an accurate diagnosis of abscess (11).

Cardiac and neurologic complications of IE, including septic micro-embolization, have the largest effect on long-term survival (7). Embolization occurs in approximately 11% to 25% of the patients with IE, and results in death in 24% to 50% of those who sustain an embolus (12,13). Assuming the prevalence of IE to be 5/100,000 population and the incidence of embolization conservatively to be 20%, approximately 2,800 people experience embolic events related to IE every year in the U.S. (14). Highly mobile vegetations >10 mm in size on transthoracic echocardiography have been shown to have a higher incidence of embolization (15–17). The type of organism involved may influence the likelihood of embolization with *Streptococcus viridans* (18) or *Staphylococcus aureus* (19) associated with a
higher incidence of embolization. Other studies have found that vegetations on either right-sided valves or the mitral valves are more likely to embolize (16,17,19). When present in patients with IE, anti-phospholipid antibodies and soluble adhesion molecules are more likely to lead to embolization (20,21). Conversely, patients with no discernable vegetations can still suffer from embolic events secondary to the immunologic and hematologic changes in the blood resulting from infection (22). Thus, the underlying pathogenesis of embolization has a complex etiology.

As surgical techniques have improved, earlier intervention has improved overall survival rates (23). The strongest indications for surgery are congestive heart failure due to damaged valves, uncontrolled infection including abscess formation, and relapse after appropriate medical therapy (7). As most embolization occurs before antibiotic treatment, the role for surgery in preventing this complication is undefined. As such, the mainstay of current treatment of IE is an accurate antibiotic therapy, with possible surgical intervention. The addition of antiplatelet agents or anticoagulants to this regimen is aimed to potentially reduce the risk of embolization further.

Initial formation of vegetation is thought to result from adhesion of platelets to the collagen-rich subendothelial stroma exposed by superficial damage to the valve surface (24). Subsequent propagation of a vegetation relies on continued fibrin deposition and platelet aggregation (25). Thus, antiplatelet agents may reduce the risk of embolization, especially as aspirin has been shown to protect other vascular events. Indeed, in experimental models of IE, aspirin reduced bacterial titers as well as vegetation size and in some but not all studies reduced the risk of embolization (26–28). Other antiplatelet agents such as sulphinpyrazone (29), and ticlopidine with or without aspirin (28) showed promising results in animal models. An early clinical study, although only containing nine subjects, suggested a possible protective role for aspirin in IE (30). Warfarin, on the other hand, has not been shown in experimental studies to reduce vegetation size (31,32). Several non-randomized studies suggested that warfarin may in fact increase the rate of cerebral hemorrhage especially in those with Staphylococcus species IE (13,33,34).

With this as a backdrop, the study by Chan et al. (35) reported in this issue of the Journal addresses the efficacy of aspirin in reducing the rate of embolic events in a rigorous fashion. A total of 115 patients with documented IE from 19 centers in Canada and the U.S. were double-blindly assigned to receive aspirin or placebo. Patients were followed for the primary outcome of clinical embolism, and secondary outcome of computed tomography (CT) detected subclinical stroke, death, and hemorrhage. After four weeks of follow-up, the rate of clinical embolization was 28.3% in the aspirin group compared with 20% in the placebo group without a significant difference. Although not reaching statistical significance, the rate of combined major and minor hemorrhage tended to be higher in the aspirin group (28.8%) compared with the placebo group (14.5%). At the end of the study, 70% of the patients underwent head CT demonstrating significant lesions in 39.5% of the patients on aspirin compared with 29.3% in the placebo group. In 42% of the patients undergoing transesophageal echocardiography at the onset and end of the study, vegetation size decreased to a similar extent between the two arms, and there was no significant difference in the degree of valvular regurgitation. This study thus demonstrates that despite promising experimental data aspirin does not benefit patients with IE.

However, readers are cautioned that notwithstanding this study, aspirin may still be beneficial for the subset of patients with IE. There may be a differential benefit of aspirin, depending on the site of vegetation, the size of the vegetation, or the valve type. The type of offending organism may be an important factor, because much of the preliminary experimental data originated from the use of Staphylococcus species which may have different properties compared with other pathogens (32). Unfortunately, the number of patients with different types of infection in the Chan et al. (35) series is too small for analysis. As the authors correctly point out, another potential problem is the dose of aspirin used. The dose may not have reflected that used in the experimental studies, some of which used the intravenous route. Also, the experimental studies used aspirin at the outset of the infection, but the use of aspirin in the clinical setting is understandably delayed until diagnosis, which in a large fraction of cases occurs weeks from the symptom onset. Another limitation of the study is the difficulty in using echocardiography to assess vegetation size, which has a significant variability.

The neurologic consequences of embolization are devastating. Therefore, the development of treatment strategies to prevent this complication in IE should remain at the forefront of future research. What is currently lacking is a comprehensive approach to prevent embolism in patients with IE that takes into account echocardiographic findings, the site and the type of valve involved, the offending organism, as well as the role of serum markers such as anti-phospholipid antibody and adhesion molecules. The risk of embolization may eventually be assessed from the combination of factors and from the efficacy of therapeutic modalities considered. Future studies as part of the International Collaboration on Endocarditis may demonstrate a role for aspirin in a specific subgroup with IE (14). Meanwhile, the study by Chan et al. (35) shows that blanket therapy with aspirin is not warranted at this time. Our knowledge of IE evolves with time, and it is with carefully performed studies such as this that we will have information to benefit our patients.

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