EDITORIAL COMMENT

Echocardiography Predicts Embolic Events in Infective Endocarditis*

Shelley Shapiro, MD, PhD, FACC*
Leon Iri Kupferwasser, MD†
Los Angeles, California and Mainz, Germany

Infective endocarditis can be a devastating disease. Embolic events, particularly strokes, are dreaded complications that often leave persistent disability after the infection is successfully treated. Despite advances in surgical techniques and antibiotic therapy, the incidence of embolism remains about 30% to 40% and has been unchanged over the last 10 to 20 years. Consequently, clinicians are often faced with the dilemma of whether to try to avoid embolic complications by intervening surgically or to treat medically and wait. To date there are no clear answers, as established criteria for surgery are based on heart failure, unresolving infection and recurrent emboli. Interventions are often too late to prevent the destructive effects of the first major embolic event. Researchers have tried to identify factors that predispose to embolic events, with the hope of using these predictors to select patients for early intervention and reduce the incidence of severe embolic episodes.

The article by Di Salvo et al. (1) in this issue of the Journal examines the echocardiographic predictors of embolic events in infective endocarditis. The study population at this tertiary care center consisted of 178 consecutive patients with definite endocarditis as established by the Duke criteria. The patients were evaluated with multiplane transesophageal echocardiograms to accurately assess the echocardiographic characteristic of the vegetations. The patients underwent prospective screening for emboli using computed tomography (CT) scans of the abdomen, thorax and head. The echocardiographic features of the lesions, including size, location and mobility, the demographic features of the patients and the bacteriological features of the infection were all compared using univariate and multivariate analyses to determine the relationship among these features and the occurrence of embolic events. The study concludes that both the size of the vegetations and their mobility were related to the incidence of embolic events. Patients with vegetations >10 mm had a 60% incidence of emboli. Patients with severely mobile vegetations >15 mm had an 83% incidence and were at the greatest risk. This observation held up in multivariate analysis. The investigators conclude that the morphologic characteristics of the vegetations may predict an embolic event and that early preventive surgery might be warranted in these patients. The large number of patients and the use of transesophageal echocardiograms increase the importance of the findings.

However, there are problems and provisos, many of which the investigators themselves point out. Although some studies supported the findings of Di Salvo et al. (1) and reported a significant association between the morphological characteristics of the vegetative lesion and the probability of an embolic event (2–4), others did not find such a relationship (5). To some extent the controversy might be due to selection bias or the different design of the studies. However, Di Salvo et al. (1) themselves demonstrated that factors independent of the echocardiographic appearance of the vegetation might be associated with the occurrence of an embolic event—for example, the infecting organism (Staphylococcus aureus). Many of the patients underwent valve replacement or repair early in their hospital course and, therefore, the effect of treatment in altering outcome cannot be assessed.

The timing of the occurrence of the emboli is also unclear. Moreover, 14 of the 66 emboli were asymptomatic, limiting the role of any preventive measures. At what time point in the course of the disease were the emboli present—before initiation of therapy or after antibiotic treatment? The CT evaluations for emboli were not repeated during the course of treatment. Thus, only a snapshot was obtained of the clinical events. This has implications for designing treatment strategies. The right-sided emboli (9 of 66 overall embolic events) were not assessed by spiral CT angiogram or pulmonary angiogram but rather by chest CT. This raises questions about the interpretation of the pulmonary findings. Differentiating between emboli and metastatic infections in the lung is difficult. Of concern, a significant number of patients without vegetations had evidence of emboli. Embolic events occurred in 20% of the patients in whom vegetations could not be detected by echocardiography. These occurrences might be a result of embolization of the macroscopic portion of the vegetation or due to vegetations adherent to nonvalvular cardiac structures.

However, this finding suggests that embolic events might occur independently of vegetation size and mobility in a substantial number of patients. This phenomenon has also been reported in other studies and has occurred in patients who suffered strokes after the echocardiographic investigation. It also suggests that other factors impact the occurrence of emboli and that the appearance or size and mobility alone is not enough. Are there biological factors that might...
be related to the occurrence of emboli and, when used in conjunction with echocardiographic features, might increase predictive power? Do therapies that reduce vegetation size decrease the incidence of emboli?

Thus, the potential limitations of predicting embolic events by the sole use of echocardiographic parameters led us to consider or try to identify these other factors. Importantly, the study by Di Salvo et al. (1) provided a parameter that is independent of the vegetations' morphological characteristics but significantly impacts the frequency of embolic events (S. aureus as the causative micro-organism). Perhaps distinct bacterial characteristics and virulence mechanisms (e.g., binding of the organism to the component constituents of the vegetation, exotoxin production, etc.) might impact the frequency of embolic events. Bacterial–platelet interactions or bacterial–endothelium interactions might play a key role in this respect. Several studies have shown that the capacity of selected endocarditis pathogens to initiate platelet aggregation in vitro parallel their propensity to induce endocarditis in vivo (6,7). Other studies reported that the staphylococcal in vitro susceptibility to small, cationic, endogenous peptides with potent microbicidal activity, termed platelet microbicidal proteins, are significantly associated with embolic events and bacterial hematogenous dissemination in experimental S. aureus endocarditis (8,9). Whether these endogenous peptides have a clinical role remains to be shown.

Other cellular factors not addressed in the current study may also need to be considered. Several investigations have demonstrated that systemic bacterial infections, even in the absence of cardiac involvement, represent an independent risk factor for an embolic event (10,11). Inflammation–induced procoagulant changes and endothelial cell activation appear to play a major role in this setting. Antiphospholipid antibodies may have an impact on the occurrence of embolic events in infection–related events (12). In this context, infective endocarditis differs from other infectious diseases due to the presence of cardiac vegetations as an additional independent risk factor for an embolic event. Antiphospholipid antibodies, coagulation parameters, and endothelial cell activation have recently been reported to be substantially associated with the risk for an embolic event in infective endocarditis (12,13). The limitation in predicting embolic events by transesophageal echocardiography was demonstrated in a subgroup of patients lacking such antiphospholipid antibodies who demonstrated larger vegetations but did not show an elevated risk for embolic events.

To take the question of biological factors further, are there opportunities to intervene therapeutically using our knowledge that some of these cell-mediated factors in endocarditis influence the biology of the embolic process? A potential therapeutic approach in patients with infective endocarditis and vegetative lesions might be the use of aspirin. Platelets are a key component of vegetations. Therefore, platelet inhibition might diminish vegetation evolution and embolic frequency in infective endocarditis.

In several studies using animal models mirroring clinical S. aureus endocarditis, aspirin was shown to significantly reduce vegetation size (14), vegetation bacterial density (15) and the incidence of embolization (16). However, it remains to be shown whether these effects can only be found in S. aureus endocarditis or whether they exist in endocarditis caused by different pathogens.

Moreover, whether aspirin has a prophylactic role in the prevention of endocarditis–induced embolic events is an open question. Good clinical data on this issue are scarce. An initial observational study indicated a trend toward a salutary influence of aspirin in endocarditis (17), whereas a recent prospective Canadian trial showed no favorable effects but an increase in bleeding events in patients who received 325 mg per day of aspirin (18). Thus, the therapeutic benefit of altering the biological processes that affect vegetation size and fragility may have untoward consequences (e.g., bleeding). Identifying factors that affect the incidence of emboli may not help in identifying the type of therapeutic intervention that would best be undertaken to avoid emboli. Removing a vegetation based on echocardiographic appearance may not be beneficial. Even if chemical or biological features of the vegetation are as important as size in determining propensity to embolize, knowing how to utilize these insights is unclear.

Di Salvo et al. (1) have given support to the ocular reflex—large vegetations that look bad are bad. It still remains to be determined whether early surgical intervention will prevent emboli and improve outcomes. It also remains to be determined how to combine the findings of Di Salvo et al. with the cell biology.

Therefore, it seems important to develop cooperative multicenter studies designed to link morphology and biology to answer questions relating these factors to therapy.

Reprint requests and correspondence: Dr. Shelley Shapiro, USC Keck School of Medicine, Cardiology Division AHC117, 1355 San Pablo Street, Los Angeles, California 90033.

REFERENCES

7. Scheld WM, Valone JA, Sande MA. Bacterial adherence in the


