Residual patient, anatomic, and surgical obstacles in treating active left-sided infective endocarditis

Syed T. Hussain, MD,[a] Nabin K. Shrestha, MD,[b] Steven M. Gordon, MD,[b] Penny L. Houghtaling, MS,[c] Eugene H. Blackstone, MD,[a,c] and Gösta B. Pettersson, MD, PhD[a]

Objectives: To identify and understand residual patient, anatomic, and surgical obstacles in treating active left-sided infective endocarditis (IE), we categorized the intraoperative pathologic entities in patients with left-sided IE and correlated the pathology (noninvasive vs invasive) and organism with IE context (affected valve, native vs prosthetic [PVE]) and surgical results.

Methods: From January 2002 to January 2011, 775 patients underwent surgery for active left-sided IE. Registries were queried, and endocarditis-related pathology was based on the echocardiographic findings and operative notes. Propensity adjustment and matching (55 pairs) were used for risk-adjusted outcome comparisons between the invasive aortic and mitral cases.

Results: A total of 395 patients had isolated aortic (PVE 59%, invasive 68%), 238 isolated mitral (PVE 29%, invasive 35%), and 142 combined aortic and mitral (PVE 44%, invasive 69%) IE. The 30-day survival was 92% and was similar for native valve endocarditis and PVE in all 3 valve combinations. Invasive versus noninvasive IE was associated with greater hospital mortality (11% vs 4.4%, $P = .001$). Patients with invasive IE had worse intermediate-term survival than those with noninvasive IE for mitral ($P = .001$) and aortic plus mitral ($P = .02$) IE but not for isolated aortic IE. This difference persisted in the matched patients.

Conclusions: During the past decade, we have had low hospital mortality for surgically treated left-sided IE and have neutralized the added risk of PVE. However, outcomes remain worse for mitral versus aortic valve IE, with residual obstacles related to patient factors, inherent mitral valve anatomy in patients with invasive disease, and lack of an alternative mitral valve prosthesis optimal for IE. (J Thorac Cardiovasc Surg 2014;148:981-8)

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The objectives of surgery for infective endocarditis (IE) are to debride and remove infected tissue and foreign material, prevent embolic events, and restore cardiac integrity and functional valves. Despite the reduction of operative mortality and risk of subsequent prosthetic valve endocarditis (PVE) by a strategy that includes early radical surgery, the risks remain greater than those of operations for any other valve disease.[1-6] These risks are related not only to the surgical challenges of treating IE but also to patient comorbidities and the local and systemic consequences of the IE: Local effects manifested by pathology stage related to the involved valve, and systemic effects by embolic events and dissemination and toxicity of the infection, both organism and time related. Traditionally, aortic and mitral valve endocarditis results are presented together or separately, and the outcomes have been related to general disease factors such as PVE, the presence of abscesses, or an aggressive organism. This has prevented the identification of both commonalities and contrasts of pathologic features and outcomes across the spectrum of left-sided IE.

Thus, the primary objectives of the present study were to identify and understand the residual patient, anatomic, and surgical obstacles to reducing the risk of surgical treatment of active left-sided IE. To accomplish this, we categorized the spectrum of intraoperative pathologic features in patients with active left-sided IE, correlated the pathology stage (noninvasive vs invasive IE) and organism with the IE context (affected valve, native valve endocarditis

From the Department of Thoracic and Cardiovascular Surgery,[a] Heart and Vascular Institute, Department of Infectious Disease,[b] Medicine Institute, and Department of Quantitative Health Sciences,[c] Research Institute, Cleveland Clinic, Cleveland, Ohio.

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Address for reprints: Gösta B. Pettersson, MD, PhD, Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, 9500 Euclid Ave, Desk J4-1, Cleveland, OH 44195 (E-mail: petterg@ccf.org).

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Abbreviations and Acronyms
IE = infective endocarditis
NVE = native valve endocarditis
PVE = prosthetic valve endocarditis

[NVE] vs PVE) and surgical results, and compared the outcomes after accounting for patient morbidities.

METHODS

Patients

From January 1, 2002, to January 1, 2011, 963 left-sided IE cases were identified from the existing infectious disease and cardiac surgery registries, the medical records were reviewed, and the patients were classified using modified Duke criteria.[7] Only cases meeting criteria for active aortic or mitral IE were included in the study[1,8]; healed and remote endocarditis (188 cases, 20% of left-sided IE) were excluded, leaving a study population of 775 cases. Of these, 395 patients (51%) had isolated aortic valve IE, 238 (31%) isolated mitral valve IE, and 142 (18%) combined aortic and mitral valve IE. Patient characteristics, operative procedure details, and hospital outcomes were extracted from a prospective registry of all cardiac operations, and the microbiologic laboratory results and infectious disease serology were retrieved from the infectious disease registry. The Cleveland Clinic institutional review board approved the use of data extracted from all registries and a de novo review of the medical records for use in research, with patient consent waived.

IE Characteristics

The etiology of IE was determined by review of the microbiologic laboratory results and infectious disease serology. The surgical pathologic type was coded and stored in a Research Electronic Data Capture database, as previously described.[8] Coding was determined from reviews of patient records, operative reports, and pre- and intraoperative transesophageal echocardiograms. IE was defined as noninvasive if it was confined to the cusps and leaflets and invasive if the infectious process extended beyond the cusp or leaflets into the annulus and surrounding structures. All pathologic findings were coded by the same surgeon (S.T.H.) retrospectively until 2008 and prospectively from January 2009 onward (in close collaboration with G.B.P.).

IE Management

At Cleveland Clinic, patients presenting with IE are treated by a multispecialty team. Surgery is advocated as soon as an indication has been established; we do not wait for heart failure to develop. However, many patients are already in heart failure when referred. All patients undergo brain imaging preoperatively to exclude hemorrhagic stroke. Having effective antibiotics on board at surgery is important, because we have seen persistent IE when this was not the case. When a patient is stable and without an elevated risk of embolic events, waiting for cultures and the sensitivity pattern may be justified. At surgery, radical debridement of all infected tissues and foreign material is followed by generous irrigation. Local antiseptics and antibiotics are used sparingly.

Allografts are preferred for aortic root reconstruction in patients with annulus destruction and invasive disease. When the annulus can be preserved, the choice of valve will not differ from that for other patients with valve disease. Mitral valve repair is preferred, and replacements are performed with chordal sparing when possible; autologous pericardium is the preferred material when needed for additional reconstructions.[1]

Outcomes

Postoperative complications were defined according to The Society of Thoracic Surgeons Adult Cardiac Surgery database (available at: http://riskcalc.sts.org/STSWebRiskCalc273/About%20the%20STS%20Risk%20Calculator%20v2.73.pdf).

Follow-up of all patients who have undergone a heart valve operation is performed at 2 and 5 years and at 5-year intervals thereafter. This active follow-up protocol was supplemented with Social Security Death Master File information,[9,10] with a closing date of April 27, 2011, 6 months after the query on October 27, 2011. A total of 2465 patient-years of follow-up data were available for analysis. Among the survivors, the median follow-up was 3.5 years, with 25% followed up >6 years and 10% >7.5 years.

Data Analysis

Continuous variables are summarized as the mean ± standard deviation or as the 15th, 50th (median), and 85th percentiles when the distribution was skewed. Comparisons were made using the Wilcoxon rank-sum test. Categorical data are summarized using frequencies and percentages. Comparisons were made using the chi-square test or Fisher's exact test when the frequency was <5. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Inc, Cary, NC). Uncertainty is expressed by 68% confidence limits equivalent to ±1 standard error. In all analyses, repaired native valves were included in the NVE group.

Risk factors for mortality. Survival was studied overall, by affected valve, by NVE versus PVE, and by noninvasive versus invasive disease, overall and, again, by affected valve. Nonparametric survival estimates were obtained using the Kaplan-Meier method, and a parametric method was used to resolve the number of phases of an instantaneous risk of death (hazard function) and to estimate its shaping parameters.[11] Thereafter, multivariable analyses were performed in the hazard function domain. Initially, separate models were developed for the aortic and mitral groups to uncover any possible interactions (varying effects of risk factors for each valve). Next, variable selection (Appendix E1 lists the candidate variables) was performed using bagging, with retention of variables with at least a 50% chance of $P < .05$. For this, stepwise regression was performed on 500 bootstrap data sets. Using the median rule, the variables that appeared in ≥50% of the bootstrap models were retained in the final model.[12,13]

Risk adjustment using propensity method. Risk adjustment focused on invasive disease in the isolated aortic and isolated mitral valve IE groups. Initially, a parsimonious model was developed to understand the important differences between these 2 groups (Table E1). Multivariable logistic regression analysis was used with preoperative (only) candidate variables (Appendix E1). Variable selection used bagging and 1000 bootstrap samples, as described. Compared with invasive isolated aortic valve IE, invasive isolated mitral valve IE was associated with NVE, previous stroke, preoperative dialysis (acute or chronic), larger left atrial size, and female sex (Table E2).

Thereafter, we augmented the parsimonious model with 17 other variables representing preoperative patient demographic data, symptoms, and cardiac and noncardiac comorbidities that might be related to unrecorded selection factors (semisaturated model). A propensity score was calculated for each patient by solving the propensity model for the probability of being in the mitral valve IE group (compared with aortic).[14] Next, using only the propensity score, patients with mitral IE were matched to patients with aortic IE using a greedy matching strategy. Patients whose propensity scores deviated >0.15 were considered unmatched. This yielded 55 well-matched patient pairs (Figure E1), 65% of the possible matches.

RESULTS

Pathologic Characteristics

Of the 775 patients, 395 had aortic valve IE, 238 had mitral valve IE, and 142 had combined aortic and mitral valve IE (Table E3); 362 (47%) had PVE and 452 (58%) had invasive IE (Table 1). Of the 395 patients with isolated aortic valve IE, 232 (59%) had PVE and 270 (68%) had