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

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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

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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/STSTWebRiskCalc273/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 $\pm$ 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 $\geq 50\%$ 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

TABLE 1. Clinical characteristics of patients with left-sided infective endocarditis treated surgically

Characteristic	Infective endocarditis type			Invasiveness		
	NVE (n = 413)	PVE (n = 362)	P value	Noninvasive IE (n = 323)	Invasive IE (n = 452)	P value
Demographic data						
Age (y)	55 ± 14	60 ± 14	<.0001	55 ± 14	59 ± 15	<.0001
Female sex	139 (34)	91 (25)	.012	111 (35)	121 (27)	.02
Presentation						
NYHA functional class III-IV	132 (32)	99 (27)	.16	106 (33)	125 (28)	.12
Emergency or salvage	22 (5.3)	20 (5.6)	.9	14 (4.4)	27 (6.0)	.4
Previous stroke	142 (34)	126 (35)	.8	120 (37)	147 (33)	.16
Previous MI	86 (21)	103/359 (29)	.011	65/321 (20)	124/451 (27)	.02
Complete heart block or pacer	18/408 (4.4)	45 (13)	<.0001	12 (3.8)	51 (11)	.0002
Acute or chronic renal disease requiring dialysis	70 (17)	37/359 (10)	.008	38/321 (12)	69/451 (15)	.17
Preoperative length of stay (d)*	1.8, 5.8, 12	1.9, 5.9, 13	.3	1.9, 6.2, 12	1.8, 5.4, 12	.05
Cardiac morbidity						
Previous cardiac operation			<.0001			<.0001
None	343 (83)	0 (0)		202 (63)	147 (33)	
1	65 (16)	238 (66)		86 (27)	209 (46)	
2	4 (0.96)	99 (28)		27 (8.4)	76 (17)	
≥3	1 (0.24)	25 (7.0)		6 (1.8)	20 (4.5)	
Aortic valve						
Stenosis	41 (9.9)	14 (3.9)	.001	15 (4.7)	40 (8.8)	.02
Regurgitation grade 3+/4+	189 (46)	94 (26)	<.0001	132 (41)	151 (33)	.03
Mitral valve						
Stenosis	23 (5.6)	9 (2.5)	.03	16 (5.0)	16 (3.5)	.3
Regurgitation grade 3+/4+	160 (39)	62 (17)	<.0001	119 (37)	103 (23)	<.0001
Noncardiac comorbidity						
Hypertension	254 (62)	254 (70)	.009	195 (61)	313 (69)	.01
Pharmacologically treated DM	95/404 (24)	77/352 (22)	.6	58/315 (18)	114/441 (26)	.02
COPD	53 (13)	69 (19)	.02	53/321 (17)	71/451 (16)	.8
Peripheral arterial disease	57 (14)	35 (9.7)	.10	39/321 (12)	53/451 (12)	.9
Operative details†						
AV repair	17 (4.1)	3 (0.83)	—	16 (5.0)	4 (0.88)	—
AV replacement						
Mechanical	16 (3.9)	9 (2.5)	—	15 (4.6)	10 (2.2)	—
Xenograft	101 (24)	38 (11)	—	90 (28)	49 (11)	—
Allograft	111 (27)	246 (68)	—	52 (16)	305 (67)	—
MV repair	141 (34)	50 (14)	—	94 (29)	97 (21)	—
MV replacement						
Mechanical	22 (5.3)	16 (4.4)	—	23 (7.2)	15 (3.3)	—
Xenograft	114 (28)	96 (27)	—	99 (31)	111 (25)	—
CPB time (min)	129 ± 58	184 ± 68	<.0001	120 ± 50	179 ± 69	<.0001
Aortic clamp time (min)	103 ± 48	134 ± 51	<.0001	91 ± 39	135 ± 52	<.0001

Data presented as mean ± standard deviation or n (%), unless otherwise noted. NYHA, New York Heart Association; MI, myocardial infarction; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; AV, aortic valve; MV, mitral valve; CPB, cardiopulmonary bypass; IE, infective endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis. *Data presented as 15th, 50th, 85th percentiles. †Included procedures on noninfected valves.

invasive IE. Of the 238 with isolated mitral valve IE, 68 (29%) had PVE ($P < .0001$ for the difference from aortic valve IE) and 84 (35%) had invasive IE ($P < .0001$ for difference from aortic valve IE). Of the 142 with double valve IE, 11 (7%) had PVE of 1 valve and NVE of the other, 25 (18%) had PVE involving both valves, 77 (55%) had NVE of both valves, and 3 (2%) had 1 repaired native valve; 97 patients (69%) had invasive disease.

For patients with invasive disease, the stage of invasiveness was cellulitis in 305 (69%), abscess formation in 344 (76%), an abscess cavity in 204 (45%), and a pseudoaneurysm in 45 (9.9%; Table 2). Advanced invasiveness was more common in those with isolated aortic valve IE than in those with isolated mitral valve disease, just as was full-circumference IE. PVE was most often associated with invasive IE and NVE with noninvasive IE.

TABLE 2. Valve pathology observed at surgery for left-sided infective endocarditis

Pathologic findings	AV (n = 395)	MV (n = 238)	AV + MV (n = 142)		
			AV only	MV only	Both
Vegetations	329 (83)	224 (94)	11 (7.8)	15 (11)	111 (78)
Integrity abnormality of cusp or leaflet	123 (31)	119 (50)	21 (15)	36 (25)	36 (25)
Invasive disease*	270 (68)	84 (35)	54 (38)	7 (4.9)	37 (26)
Invasive disease stage*,†					
Cellulitis	182 (67)	67 (80)	33	6	17
Abscess	220 (82)	41 (49)	60	1	16
Abscess cavity	126 (46)	20 (24)	38	3	14
Pseudoaneurysm	32 (12)	1 (1.2)	4	2	0
Invasive disease extent (annular circumference)					
<1/3	74 (30)	38 (49)	20	5	6
1/3-1/2	96 (38)	33 (42)	29	16	8
Full circumference	80 (32)	7 (9.0)	16	0	2

Data presented as n (%). AV, Aortic valve; MV, mitral valve. *Percentage of invasive disease. †Invasive stage definitions as reported by Pettersson and colleagues.⁸

The most common causative organisms were *Staphylococcus aureus*, coagulase-negative *S enterococcus*, and *Streptococcus viridans* (Table 3). *Staphylococcus* species were most likely to be associated with invasive IE, streptococcus least likely, with the degree of invasiveness about equal for other organisms.

Hospital Outcomes

Hospital mortality was 8% overall, 7% for aortic valve IE, 6% for mitral valve IE, and 14% for combined aortic and mitral valve IE. Hospital mortality was higher (10%) for those with PVE than for those with NVE (6.3%, $P = .04$; Table 4) and was 11% among patients with invasive IE versus 4.4% among those with noninvasive disease ($P < .0001$). Renal failure was also more common after surgery for PVE and for invasive disease. Postoperative atrial fibrillation was less common after surgery for PVE. The use of an intra-aortic balloon pump was more common after surgery for aortic valve IE ($P = .005$). Postoperative sepsis occurred in 10% of patients with mitral IE and 5.1% of those with aortic valve IE ($P = .02$).

Survival

Overall unadjusted survival at 30 days, 6 months, and 1, 3, 5, and 7 years for these endocarditis patients was 92%, 84%, 81%, 72%, 66%, and 60%, respectively. The hazard function resolved to 2 phases, with an early phase lasting about 6 months and accounting for about one half of the 245 deaths, and a late declining phase thereafter. Survival was higher for those with isolated aortic valve IE than for the mitral and combined groups (73% at 5 years vs 60% and 51%, respectively; $P < .0001$; Figure E2, A).

PVE versus NVE. Survival was similar after surgery for PVE or NVE (67% vs 64% at 5 years; $P[\log\text{-rank}] = .6$; Figure E2, B) and when stratified by valve ($P = .8$ after isolated aortic valve IE surgery, $P = .3$ after isolated mitral valve IE surgery, and $P = .4$ after combined aortic and mitral valve IE surgery; Figure 1).

Disease invasiveness. Survival was worse after surgery for invasive IE than after surgery for noninvasive disease, with a 5-year survival of 62% versus 70%, respectively (Figure E2, C). However, when stratified by affected valve position, invasive mitral IE and invasive double valve IE

TABLE 3. Microbiologic etiology of infective endocarditis

Microorganism*	Noninvasive (n = 323)				Invasive (n = 452)				P value (invasive vs noninvasive)
	Overall	NVE (n = 240)	PVE (n = 83)	P value	Overall	NVE (n = 173)	PVE (n = 279)	P value	
<i>Staphylococcus aureus</i>	71 (22)	58 (24)	13 (16)	.11	122 (27)	59 (34)	63 (23)	.007	.11
Coagulase-negative <i>Staphylococcus</i>	40 (12)	25 (10)	15 (18)	.07	99 (22)	24 (14)	75 (27)	.0012	.0007
Enterococcus	42 (13)	33 (14)	9 (11)	.5	51 (11)	21 (12)	30 (11)	.6	.5
<i>Streptococcus viridans</i>	70 (22)	62 (26)	8 (10)	.002	50 (11)	26 (15)	24 (8.6)	.03	<.0001
Gram-positive cocci†	21 (6.5)	19 (7.9)	2 (2.4)	.08	25 (5.5)	17 (9.8)	8 (2.9)	.002	.6
Fungal	8 (2.5)	1 (0.42)	7 (8.4)	<.0001	11 (2.5)	2 (1.2)	9 (3.2)	.17	>.9
Polymicrobial	12 (3.7)	9 (3.8)	3 (3.6)	>.9	12 (2.7)	6 (3.5)	6 (2.2)	.4	.4
Other	23 (7.1)	11 (4.6)	12 (15)	.003	46 (10)	11 (6.4)	35 (13)	.03	.14
Not identified	36 (11)	22 (9.2)	14 (17)	.05	36 (8.0)	7 (4.1)	29 (10)	.02	.13

Data presented as n (%). NVE, Native valve endocarditis; PVE, prosthetic valve endocarditis. *Final diagnosis. †Not identified further.

TABLE 4. In-hospital complications after surgery for left-sided endocarditis

Complication	NVE (n = 413)	PVE (n = 362)	P value	Noninvasive (n = 323)	Invasive (n = 452)	P value
In-hospital death	26 (6.3)	37 (10)	.04	14 (4.4)	49 (11)	.001
Bleeding	30 (7.2)	24 (6.7)	.8	19 (5.9)	35 (7.7)	.3
Stroke	16 (3.9)	14 (3.9)	.9	12 (3.7)	18 (4)	.9
New renal failure requiring dialysis	27 (6.5)	34 (9.5)	.13	17 (5.3)	44 (9.7)	.02
Renal failure	55 (13)	80 (22)	.001	41 (13)	94 (21)	.004
Prolonged ventilation (>24 h)	145 (35)	151 (42)	.04	96 (30)	200 (44)	<.0001
Sepsis	36 (8.7)	34 (9.5)	.13	21 (6.5)	49 (11)	.04
Atrial fibrillation	110 (29)	50 (16)	<.0001	71 (24)	89 (22)	.4
Use of IABP	12 (2.9)	18 (5.0)	.13	7 (2.2)	23 (5.1)	.04
Length of stay*						
ICU (h)	25, 74, 335	27, 102, 327	.02	25, 67, 282	28, 114, 357	<.0001
Postoperative (d)	6.2, 12, 22	6.8, 12, 26	.2	6.1, 10, 23	7.0, 13, 24	.002
Hospital (d)	10, 19, 36	11, 19, 36	.2	10, 18, 34	11, 19, 37	.2

Data presented as n (%), unless otherwise noted. NVE, Native valve endocarditis; PVE, prosthetic valve endocarditis; IABP, intra-aortic balloon pumping; ICU, intensive care unit. *Data presented as 15th, 50th, 85th percentiles.

were associated with worse survival, but invasive and noninvasive aortic valve IE as well as noninvasive mitral valve IE and noninvasive double valve disease were all associated with similar and better survival than were invasive mitral and invasive double valve IE (Figure 2).

Risk-adjusted mortality. Invasive IE involving the mitral valve was associated with much worse survival than invasive aortic valve disease (46% vs 74% at 5 years, respectively; $P < .0001$; Figure E3, A). Although the risk estimates stayed the same, this was not the case for the propensity-matched patients (55% vs 73% at 5 years; $P = .4$, Figure E3, B). This resulted from differences in the risk factors for early mortality, such as elevated bilirubin and blood urea nitrogen, peripheral arterial disease, and older age, as well as differences in risk factors for late

survival, including older age and chronic obstructive pulmonary disease (Table E2). Thus, unmatched patients with invasive mitral valve disease had particularly poor survival (Figure 3).

DISCUSSION

As a paradoxical effect of advances in medical and surgical therapy, the incidence of IE has increased during the past 30 years.¹⁵⁻¹⁹ People live longer, undergo procedures with the potential for bacteremia, and an increasing number undergo heart surgery or receive prosthetic valves, pacemakers, and defibrillators, all factors associated with an increased risk of IE.

To our knowledge, our report represents the first endocarditis study in which pathologic type has been systematically coded and staged, as described in an earlier

FIGURE 1. Survival after surgery for native or prosthetic valve left-sided valve infective endocarditis (IE). Each symbol represents a death, and vertical bars represent the 68% confidence limits, equivalent to ± 1 standard error. Solid green lines indicate native valve endocarditis; dashed orange lines, prosthetic valve endocarditis; filled circles, aortic valve IE alone; open circles, mitral valve IE alone; and triangles, aortic and mitral valve IE.

FIGURE 2. Survival after surgery for invasive versus noninvasive left-sided infective endocarditis according to valve position. Solid blue lines indicate noninvasive infective endocarditis; and dashed red lines, invasive infective endocarditis. Each symbol represents a death, and vertical bars represent the 68% confidence limits, equivalent to ± 1 standard error.

FIGURE 3. Survival after surgery for invasive infective endocarditis for propensity-matched and unmatched isolated aortic and mitral valve cases. Each symbol represents a death, and vertical bars represent the 68% confidence limits, equivalent to ± 1 standard error.

publication,⁸ with outcomes analyzed by disease invasiveness and stage. The present study also reports a contemporary surgical experience with IE at a surgically aggressive tertiary center operating on >100 patients with IE annually.

Traditionally, the general disease factors associated with worse outcomes after surgery for left-sided IE have been PVE, the presence of an abscess, and an aggressive organism (*S aureus*). In the present study, we focused, not only on these factors, but also on a direct comparison of aortic and mitral IE. This revealed several new observations of differences between them. There were almost twice as many aortic cases as mitral cases, the aortic cases had a much higher percentage of PVE, and the aortic disease was correspondingly more invasive. The characteristics of the patient population affected by mitral valve IE were very different from those of patients with aortic valve IE, with the mitral patients at greater risk (Figure E1, B). Although overall mortality was 8%, better than we have reported previously, it was still higher than that for any other surgical valve disease.¹⁵⁻¹⁸ Both mortality and survival were worse for mitral IE than for aortic IE and even worse for combined aortic and mitral IE. The characteristics and behavior of concomitant mitral and aortic valve IE were more like those of mitral valve disease. Similar outcomes for mitral IE have been reported previously.^{6,20}

In our present study, PVE, although associated with greater hospital mortality, was not associated with worse survival than NVE in any group, although the PVE patients were older and had more comorbidities. This is in contrast to previous reports. For example, David and colleagues⁴ reported much worse long-term survival for patients with PVE than for those with NVE. Leontyev and colleagues²¹ reported hospital mortality of 24% and 5-year survival of 37% in 152 PVE patients in a recent series. Worse outcomes in PVE patients have been reported by several others.²²⁻²⁸

In contrast, in our study, the patients with invasive disease had distinctly worse overall outcome, mortality, and survival than those with noninvasive disease. However, when analyzed by affected valve, this was true only for invasive mitral valve IE. Although the statistical significance disappeared after propensity matching, the risk estimate remained the same. This is in agreement with our perception that we have learned to master invasive aortic IE but not invasive mitral IE. We debride the aortic root extensively without fear because we trust that reconstruction with an allograft will be easy and straightforward and produce excellent results. In contrast, mitral valve IE is invasive to the atrioventricular groove, and radical debridement, sterilization, and drainage of the infected area are much more difficult. One concern is that debridement is less controlled and suboptimal when invasion into the atrioventricular groove is deep. In addition, no replacement alternative is available for the mitral valve that is equally simple to implant and as good as the allograft is for the aortic valve; allograft mitral valve replacement is not simple and is still experimental.²⁹ Fortunately, a lower percentage of mitral valve IE is invasive, and when invasive, few cases are deep and extensive. In the published data, it is also well recognized that IE with an annular or a periannular abscess is associated with a worse prognosis, and operative mortalities as high as 31% have been reported. Differences among studies are related to multiple factors, with the experience of the surgical team an important one.^{1-6,22,30,31} However, these studies combine aortic and mitral IE and do not separate them. Also, in the published studies, it is difficult to distinguish between invasive disease and PVE. For 135 patients with a paravalvular abscess treated surgically, David and colleagues⁵ reported a mortality stratified by the involved valve of 10.9%, 11.1%, and 30%, respectively, for aortic, mitral, and combined aortic and mitral endocarditis and by NVE versus PVE of 11.6% and 19.7%, respectively.

Although the role of surgery in active IE has expanded, the indications and timing of surgery are still debated.³²⁻³⁶ With increasing experience, surgical mortality for active IE has decreased considerably,¹ and surgeons have become increasingly aggressive. We have all learned and accepted the basic principles for how to manage such disease operatively: Radical debridement of all infected tissues, generous irrigation, use of allografts for aortic root replacement when the aortic annulus is involved, use of autologous pericardium when additional tissue is needed, and avoidance of foreign material, prosthetic grafts, and glue.¹⁻³ The surgical results will depend on many variables, including patient characteristics, timing of surgery,³²⁻³⁶ whether an emergency procedure is required,^{30,37} virulence of the organism,^{1,36,38} whether the affected valve is native or prosthetic, and whether the

infection has extended into the valve annulus and surrounding tissues, causing abscesses, fistulas, and pseudoaneurysms with an increased risk of adverse outcomes, including death. Although some organisms, such as *S aureus*, are more aggressive and invasive than others, most will eventually be invasive and destructive, given enough time. That the pathologic stage is more important than whether it is NVE or PVE suggests that we should operate earlier to avoid allowing the infection to become more invasive.

Strengths and Limitations

The present study was a contemporary, but retrospective, study from a busy tertiary referral center with long-standing interest in the surgical treatment of endocarditis. Coding of the pathologic entity was based on all available information and was done by a single surgeon, not the operating surgeon in most cases. Survival bias has been brought up as a factor unfairly favoring surgery³⁹; however, we can operate only on patients who are still alive and operable when we first see them.

CONCLUSIONS

Hospital mortality for surgically treated left-sided IE has decreased, and the added risk of PVE has been neutralized. We attribute this to our aggressive team approach and treatment strategies, including early surgery. However, the outcomes are still worse for mitral valve IE. The residual obstacles are related to the patient, the inherent mitral valve anatomy in patients with invasive disease, and the lack of an alternative mitral valve prosthesis optimal for IE.

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APPENDIX E1. VARIABLES CONSIDERED IN MULTIVARIABLE ANALYSES**Demographic Data**

Age (years), sex, race (black, white, other), height (cm), weight (kg), body surface area (m^2), body mass index (kg/m^2)

Presentation

New York Heart Association functional class (I-IV), emergency or salvage operation, complete heart block, previous stroke, previous myocardial infarction

Cardiac Comorbidity

Preoperative atrial fibrillation, systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), number of previous cardiac operations, heart failure

Noncardiac Comorbidity

Pharmacologically treated diabetes (insulin and noninsulin dependent), hypertension, peripheral arterial disease, history of smoking, chronic obstructive pulmonary disease, renal failure requiring dialysis, blood urea nitrogen (mg/dL), creatinine (mg/dL), bilirubin (mg/dL), cholesterol (mg/dL) (total, high-density lipoprotein, low-density lipoprotein), triglycerides (mg/dL), hematocrit (%)

Preoperative Echocardiographic Data

Aortic valve regurgitation grade, mitral valve regurgitation grade, tricuspid valve regurgitation grade, aortic valve stenosis, mitral valve stenosis, left ventricular (LV) ejection fraction (%), LV internal diastolic diameter (cm), LV internal systolic diameter (cm), LV end-diastolic volume (mL), LV end-systolic volume (mL), LV mass (g), left atrial diameter (cm), left atrial volume (mL)

Procedural

Type of aortic or mitral valve surgery (repair; replacement with mechanical valve, xenograft, or allograft; native or prosthetic), concomitant tricuspid valve surgery, coronary artery bypass grafting, use of internal thoracic artery, incision (full sternotomy or less invasive), cardiopulmonary bypass time (min), aortic clamp time (min), surgeon

Endocarditis Details

Prosthetic or native valve, invasive disease, micro-organism pathology, Duke criteria

Experience

Date of operation (days from January 1, 2002, to surgery)

FIGURE E1. Results of propensity matching for various isolated invasive mitral valve infective endocarditis and isolated invasive aortic valve disease. A, Mirrored histogram of propensity score distribution. *Darkened bars* represent matched patients. B, Covariable balance before and after matching. Values on the horizontal axis represent the percentage standardized difference* between mitral valve and aortic valve IE groups. C, Standardized differences* between matched and unmatched cases. *PVE*, prosthetic valve endocarditis; *CoNS*, coagulase-negative staphylococci; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricular ejection fraction; *Afib*, atrial fibrillation; *NYHA*, New York Heart Association; *GP*, gram-positive; *BUN*, blood urea nitrogen; *Preop*, preoperative; *DM*, diabetes mellitus; *LA*, left atrial; *AV*, aortic valve; *MV*, mitral valve. *Austin PC, Mamdani MM. A comparison of propensity score methods; a case study estimating the effectiveness of post-MI statin use. *Stat Med.* 2006;25:2084-106.

FIGURE E2. Survival after surgery for left-sided infective endocarditis (IE). Each symbol represents a death, and vertical bars represent the 68% confidence limits, equivalent to ± 1 standard error. A, Stratified by involved valve. Filled circles indicate aortic valve IE alone; open circles, mitral valve IE alone; and triangles, aortic and mitral valve IE. B, Stratified by native (solid green line and open circles) versus prosthetic (dashed orange line and filled circles) valve endocarditis. C, Invasive (dashed red line and filled circles) versus noninvasive (solid blue line and open circles) disease.

FIGURE E3. Survival after surgery for invasive aortic valve infective endocarditis (IE) versus mitral disease. Each symbol represents a death, and vertical bars represent the 68% confidence limits, equivalent to ± 1 standard error. Solid lines indicate parametric estimates enclosed within a 68% confidence band. Orange solid line and filled circles indicate aortic valve IE; and purple solid line and open circles, mitral valve IE. A, Unadjusted survival. B, Propensity-matched patients.

TABLE E1. Preoperative patient characteristics associated with invasive isolated mitral valve infective endocarditis (vs invasive isolated aortic disease)

Factor	Coefficient ± SE	P value	Reliability (%)*
NVE	2.2 ± 0.34	<.0001	95
Previous stroke	0.78 ± 0.33	.02	30
Preoperative dialysis	0.88 ± 0.39	.02	30
Larger LA volume	0.044 ± 0.0078	<.0001	84
Female sex	1.5 ± 0.33	<.0001	69
Intercept	−5.4 ± 0.59	<.0001	—

C-statistic = 0.85. SE, Standard error; NVE, native valve endocarditis; LA, left atrial.

*Percentage of times factor appeared in 1000 bootstrap models.

TABLE E2. Incremental risk factors for death after surgery for left-sided infective endocarditis

Factor	Coefficient ± SE	P value
Early phase		
Older age*	0.27 ± 0.14	.05
Higher bilirubin†	0.74 ± 0.15	<.0001
Higher blood urea nitrogen†	0.91 ± 0.17	<.0001
Peripheral arterial disease	1.2 ± 0.24	<.0001
Concomitant CABG	0.72 ± 0.24	.003
MV only group‡	−0.031 ± 0.38	.9
Combined AV and MV group‡	0.52 ± 0.29	.08
Invasive disease in AV IE	0.040 ± 0.34	.9
Invasive disease in MV IE	0.30 ± 0.30	.3
PVE	0.33 ± 0.26	.2
Late phase		
Older age*	0.40 ± 0.108	.0002
Lower hematocrit†	−1.6 ± 0.44	.003
COPD	0.59 ± 0.21	.005
Preoperative dialysis	1.9 ± 0.21	<.0001
Left atrial diameter > 6 cm	1.14 ± 0.39	.004
Lower cholesterol§	0.073 ± 0.024	.003
MV affected	0.65 ± 0.23	.005
Invasive disease in aortic IE	0.081 ± 0.21	.7
Invasive disease in mitral IE	−0.18 ± 0.26	.5

SE, Standard error; CABG, coronary artery bypass grafting; MV, mitral valve; AV, aortic valve; IE, infective endocarditis; PVE, prosthetic valve endocarditis; COPD, chronic obstructive pulmonary disease. *Exp(age/50), exponential transformation. †Logarithmic transformation. ‡Compared with AV group. §(200/cholesterol)², inverse squared transformation. ||MV group and combined AV and MV group compared with AV group.

TABLE E3. Clinical and management characteristics of patients treated surgically for left-sided infective endocarditis

Characteristic	AV (n = 395)	MV (n = 238)	AV and MV (n = 142)
Demographic data			
Age (y)	58 ± 15	57 ± 14	55 ± 15
Female sex	92 (23)	102 (43)	38 (27)
Presentation			
NYHA functional class III-IV	108 (27)	76 (32)	48 (34)
Emergency or salvage	18 (4.6)	15 (6.3)	9 (6.4)
Previous stroke	120 (30)	100 (42)	47 (33)
Previous MI	105 (27)	55 (23)	29 (21)
Complete heart block or pacer	35 (9.0)	12 (5.2)	16 (12)
Acute or chronic renal disease requiring DM	43 (11)	42 (18)	22 (16)
Preoperative length of stay (d)*	1.9, 5.4, 11	1.8, 6.6, 13	1.9, 5.9, 13
Cardiac morbidity			
Previous cardiac operation			
None	147 (37)	134 (56)	68 (48)
1	176 (45)	70 (30)	49 (35)
2	60 (15)	23 (9.7)	20 (14)
≥3	12 (3.0)	10 (4.2)	4 (2.8)
AV			
Stenosis	32 (8.1)	9 (3.8)	14 (9.9)
Regurgitation grade 3+/4+	214 (56)	2 (0.96)	68 (50)
MV			
Stenosis	1 (0.25)	24 (10)	7 (5.0)
Regurgitation grade 3+/4+	41 (11)	125 (55)	56 (42)
Noncardiac comorbidity			
Hypertension	269 (68)	158 (67)	82 (58)
Pharmacologically treated DM	82 (21)	65 (28)	25 (18)
COPD	66 (17)	33 (14)	25 (18)
Peripheral arterial disease	46 (12)	32 (14)	14 (9.9)
Operative management			
AV repair	9 (2.3)	4 (1.7)	7 (4.9)
AV replacement			
Mechanical	14 (3.5)	0 (0)	11 (7/8)
Xenograft	78 (20)	10 (4.2)	51 (36)
Allograft	287 (73)	2 (0.84)	68 (48)
MV repair	57 (14)	67 (28)	67 (47)
MV replacement			
Mechanical	0 (0)	29 (12)	10 (7.0)
Xenograft	5 (1.3)	142 (60)	63 (44)
CPB time (min)	160 ± 66	121 ± 47	193 ± 79
Aortic clamp time (min)	120 ± 44	91 ± 39	154 ± 63

Data presented as mean ± standard deviation or n (%), unless otherwise noted. AV, Aortic valve; MV, mitral valve; NYHA, New York Heart Association; MI, myocardial infarction; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass. *Data presented as 15th, 50th, 85th percentiles.