Surgical Management of Mitral Valve Infective Endocarditis

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Active mitral valve infective endocarditis is a challenging clinical problem with a high rate of mortality. Surgery is currently performed in more than 40% of patients, and selecting those patients who will benefit from surgical intervention and performing a technically sound operation at the proper time are keys to optimizing outcomes. Moderate-to-severe and severe mitral regurgitation, large, mobile vegetations, paravalvular abscess, embolic events, failure of antibiotic therapy, and infection with a fungal organism are indications for prompt operation. The use of computed tomography imaging is important to determine whether there are noncardiac sources of infection, and transesophageal echocardiography is essential to delineate valvular dysfunction, identify paravalvular abscesses, rule out involvement of other valves, and plan operative therapy. In most cases, surgery should not be delayed because of cerebrovascular emboli. Mitral valve repair is favored over replacement whenever possible, is associated with superior short- and long-term outcomes, and should be possible in most cases. Operative mortality is <10% and 5-year survival is >80%.

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Active mitral valve infective endocarditis (IE) is a challenging clinical problem. The in-hospital mortality from left-sided IE ranges from 26%[1] to 30%[2] and has not decreased in the past 40 years[3] despite progress in medical and surgical treatment. The incidence of IE has also remained constant over time and affects 5-15 per 100,000 people per year.[4] Although risk factors such as rheumatic heart disease have become less prevalent, intravenous drug use, degenerative valvular disease, and health care-associated infection are more common and may account for the unchanged prevalence of mitral valve IE. In North America, health care exposure, such as intravenous therapy, hemodailysis, hospitalization, or residence in a long-term care facility, accounts for 38% of all IE.[5] In a contemporary prospective international cohort study, 46.6% of patients with IE underwent operative intervention.[5] Operations for mitral valve IE are uncommon; they comprise only 5.8% of mitral valve operations in North America, and thus individual surgeon experience is limited.[6] Identifying patients who will benefit from surgery, operating at the correct time, and performing a technically sound operation are critically important to decrease the mortality and morbidity of mitral valve IE.

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PATHOPHYSIOLOGY

In left-sided native valve IE, the mitral valve is involved in 50%-56% of cases, the aortic valve in 35%-49% of cases,[2,5] and both valves in 15% of cases.[1] In contemporary series of left-sided IE, *Staphylococcus aureus* and *Streptococcal* species are the most common causative bacteria.[5] The vegetation of IE typically forms on the atrial side of the mitral valve beyond areas of high shear stress in areas of low shear stress[7] and is composed of bacteria, platelets, and fibrin.[4] Factors that favor the development of an endocarditic lesion include bacteremia, endocardial damage, unfavorable hemodynamics, virulent bacteria, and defects in host defense.[7]

The pathogenesis of vegetation formation in endocarditis depends on the interaction of host and bacterial factors. On the host side, endothelial damage (in rheumatic or degenerative disease) and dysfunction leads to exposure of the extracellular matrix, release of cytokines, expression of adhesion molecules, and increased tissue factor activity.[8] Bacteria

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Table 1. Modified Duke Criteria

Major criteria	• Two separate positive blood cultures with organisms typical for IE: Viridans Streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, community-acquired enterococci • Echocardiographic evidence of endocardial involvement: vegetation, abscess, new partial dehiscence of a prosthetic valve, new valvular regurgitation
Minor criteria	• Predisposing heart condition or intravenous drug use • Temperature >38.0°C • Vascular phenomena: arterial emboli, pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions • Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor • Microbiologic evidence that does not meet a major criterion

HACEK, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*; IE, infective endocarditis.

express microbial surface component reacting with adhesive matrix molecules, or MSCRAMMs, that bind to the extracellular matrix.[4] Endothelial damage is not a prerequisite for bacterial adhesion. *S aureus* has fibrinogen- and fibronectin-binding proteins that bind directly to fibrinogen and fibronectin on the surface of otherwise undamaged endothelial cells.[9] Bacteria are also able to bind and activate platelets.[8]

In either case, bacterial adhesion to the valve is the primary event that subsequently generates an inflammatory response.[4] Monocytes respond to cytokines and contribute to ulceration, tissue destruction and fibrotic scarring of the valve.[9] Tissue factor activates the coagulation cascade and attracts platelets, which are integral components of the vegetation.[8] As the vegetation grows, bacteria continue to bind and proliferate within it where they are relatively protected from host defenses.

DIAGNOSIS

The diagnosis of IE is based on the Duke Criteria.[10] The diagnosis of IE depends on the presence of 2 major, 1 major and 3 minor, or 5 minor criteria (Table 1). In clinical practice, the large majority of patients with mitral valve IE present with positive blood cultures and echocardiographic evidence of valvular involvement. Active endocarditis is defined as ongoing infection in a patient who has not yet completed a full course of intravenous antibiotics. The diagnosis of mitral valve IE is usually established by the time surgical evaluation is requested. Delayed diagnosis of IE is common.

BENEFIT OF OPERATION IN ACTIVE ENDOCARDITIS

There have been no randomized controlled trials in which investigators address the benefits, indications, timing, and technique of operation for IE. All available evidence is retrospective and observational; thus, it is subject to selection bias and survivor selection treatment bias.[11]

Numerous studies have reported both short-[12-14] and long-term[15-17] survival benefit of operation for patients with active IE. In one study in which the authors used propensity matching to compare 218 matched patients from a cohort of 513, 230 of whom underwent operation and 283 of whom received medical therapy alone, operative intervention was associated with significantly lower 6-month mortality (15% vs 28%, hazard ratio = 0.45), with the greatest survival benefit found in patients with moderate-to-severe congestive heart failure (6-month mortality = 14% vs 51%, hazard ratio = 0.22).[12] In another study in which the authors used propensity matching to compare 720 patients who received early surgery with 832 patients who received medical therapy alone, early surgery was associated with significantly lower in-hospital mortality (unadjusted mortality 12.1% vs 20.7%). The mortality benefit of surgery was demonstrated in multivariable and propensity-matching analyses, with a demonstrated absolute mortality risk reduction of 5.9% in both cases.[14]

There is some controversy over the benefit of early surgery for native valve IE. The authors of one retrospective study of 546 patients with left-sided endocarditis concluded that surgery for IE was not associated with a survival benefit.[18] Key limitations of this report included a high operative mortality (27%) and a noncontemporary series (1980-1998). The large majority of contemporary series demonstrate the benefit of early surgery for left-sided endocarditis.

Current single-institution[19-21] and national series[6] of patients undergoing surgery for mitral valve IE have reported mortality rates of less than 10% compared to the overall 30% mortality rates reported for all patients diagnosed with left-sided IE. There are 2 randomized controlled trials underway to examine the benefit of early vs delayed surgery in IE,[22,23] although both suffer from important design and methodological issues, including the inclusion of patients with prosthetic and native valve endocarditis and exclusion of patients with a history of stroke. The decision of on whom to operate and when is difficult and should be approached on a case-by-case basis and in consultation with a team, including an infectious disease specialist and a cardiologist.

INDICATIONS FOR SURGERY

The surgeon should offer early operative intervention to patients with active mitral valve IE with any of the following:

- moderate-to-severe or severe mitral regurgitation, with or without heart failure
- vegetation size ≥10 mm
- mobile vegetation
- paravalvular abscess
- evidence of a single embolic event, including stroke
- failure of antibiotic therapy
- infection with a fungal organism

Heart failure is the most important risk factor for mortality in IE. Mitral insufficiency precedes and leads to the development of heart failure. Therefore, a key indication for operation in mitral valve IE is severe or moderate-to-severe mitral valve insufficiency. The presence of congestive heart failure is not required to proceed to operation, because the goal of operation in the setting of mitral insufficiency is to prevent the development of heart failure. Antibiotic therapy alone will not lead to a decrease in the severity of mitral regurgitation.

There is strong evidence that the likelihood of vegetation embolization is directly related to vegetation size. In one study, 70% of patients with vegetations ≥15 mm in length had evidence of embolic phenomena compared with 27% of patients with vegetations <15 mm.[24] In another study, the presence of a vegetation >10 mm in length had the greatest predictive value for new embolic phenomena.[25] Patients with vegetations >15 mm in length had greater predicted 1-year mortality than those with vegetations <15 mm (RR = 1.8).[25] In both studies, patients with moderately (pedunculated, remains in the same chamber during the cardiac cycle) or severely (prolapsing, crosses the coaptation plane of the valve leaflets) mobile vegetations had more new embolic events than patients with absent (fixed without detectable motion) or low (fixed base and a mobile free edge) mobility vegetations (62% vs 18%[24]; adjusted odds ratio = 2.4[25]).

Although rare, IE as the result of fungal organisms responds poorly to medical therapy and carries a reported mortality rate of 37%-72% and the presence of fungal mitral valve infective endocarditis should trigger surgery.[26,27] A paravalvular abscess in mitral valve endocarditis can progress to fistula, psuedoaneurysm, or extracardiac rupture[28] with devastating consequences: surgery is mandatory.

Studies have shown that one or more embolic events are predictive of future embolization (relative risk = 1.73, 95% confidence interval = 1.02-2.93).[29] Surgery is indicated if there is clinical or radiographic evidence of a single embolic event (including stroke) to prevent further embolization.

Cerebral injury is common in patients with active left-sided IE; its prevalence is related to the sensitivity of the test used to look for it. Clinical stroke is diagnosed in 25%-29% of patients with left-sided endocarditis.[30,31] In patients undergoing computed tomography (CT) before mitral valve operation, there is evidence of acute brain embolism in 40%-50% of patients.[18,32] Magnetic resonance imaging (MRI) is the most sensitive neurological imaging modality, and evidence of cerebral embolism is seen on brain MRI in as many as 80% of patients with left-sided IE,[30] which is similar to autopsy series.[33] These findings imply that many patients are undergoing successful operation with undetected cerebral embolism.

If hemorrhage is present on head CT, a CT angiogram should be performed to rule out the presence of a mycotic aneurysm. If an unruptured aneurysm is detected, the preferred treatment is usually antibiotic therapy and delayed valve operation, along with neurosurgical consultation.[34] A ruptured aneurysm requires endocasvular or operative intervention, and here valve operation must be delayed as well. If an aneurysm is not detected on CT angiography but clinical suspicion is high, a conventional four-vessel cerebral angiogram should be performed.

Splenic infarction is a common finding (40%) in patients with left-sided IE and should not delay operation. Splenic abscess is less common (3%-5%) but should be addressed before heart valve operation with splenectomy or percutaneous drainage. On CT, splenic infarctions classically appear as multiple, well-defined low-density wedge-shaped lesions. They are seen at the periphery of the spleen and their apices point toward the hilum. Splenic abscesses are usually solitary, ill-defined, hypodense asymmetric rim-enhancing lesions found in the middle of the spleen.[35] Operations for endocarditis in the presence

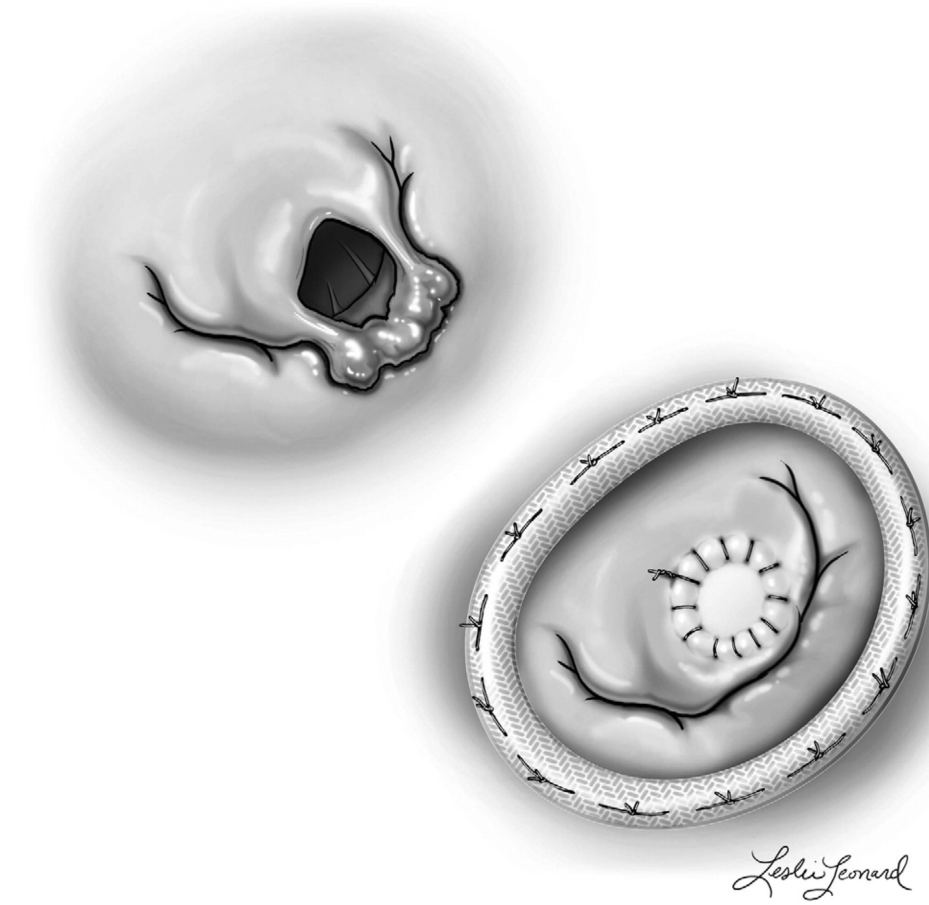

Figure 1. Top left, a lenticuloform vegetation with perforation of the anterior leaflet. Bottom right, repair with a pericardial patch and an annuloplasty ring.

of a splenic abscess historically carry a 100% mortality rate because of infection of the new valve.[36] It is our approach to perform staged splenectomy (usually laparoscopic) followed by mitral valve operation if a splenic abscess is present. Paravertebral abscess or other primary sources of infection should be similarly addressed before operation.

Preoperative Workup

Before surgery, workup should include the following:

1. A CT scan of the head, chest, abdomen, and pelvis (with intravenous contrast if renal function is normal) to determine whether embolism has occurred, with particular attention paid to cerebral emboli and splenic abscess as discussed above and to rule out other primary sites of infection.
2. Preoperative transesophageal echocardiography; it has a greater sensitivity than transthoracic echocardiography and is better suited for visualizing the valve, characterizing the vegetation, detecting paravalvular abscess, and identifying lesions on other valves.[37]
3. Left heart catheterization, if indicated.
4. Oral and maxiofacial surgery consultation to evaluate and treat periodontal disease
5. Infectious disease consultation

Timing of Operation

We favor early operation for active mitral valve IE with any of the aforementioned indications, ideally within days of hospital admission or consultation. Operation should be scheduled as soon as a comprehensive work-up is completed. Advantages of early operation include prevention of additional thromboembolic events, minimization of ongoing valvular destruction with an increased likelihood of heart valve repair compared with replacement, shortened hospitalization, and earlier relief of hemodynamic compromise caused by valvular regurgitation. There are no data that demonstrate a benefit to waiting a

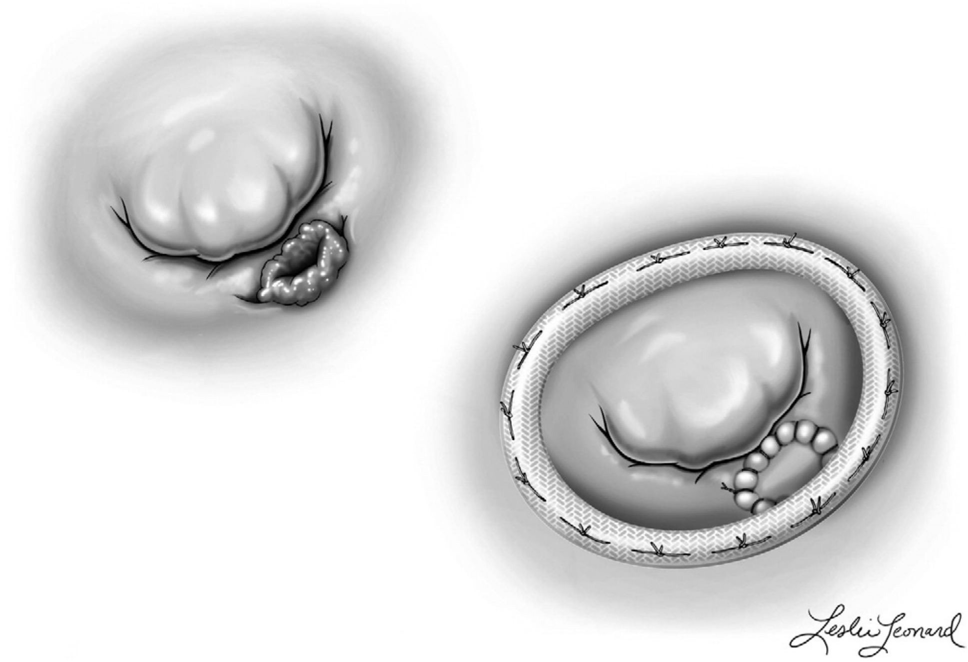

Figure 2. Top left, a vegetation with perforation of the posterior leaflet. Bottom right, Repair with a pericardial patch and an annuloplasty ring.

prescribed period after the initiation of antibiotics before proceeding to surgery. If feasible, delay of operation is recommended for patients with evidence of septic shock as cardiopulmonary bypass predictably leads to profound and sometimes refractory vasodilatation. In general, because operation is associated with improved outcomes, the only reason to delay operation for a clear indication is to address a condition that would otherwise increase operative mortality.[7]

Timing of Operation in the Presence of Cerebral Embolic Lesions

The presence of stroke or radiographic evidence of cerebral embolism in patients with IE presents a challenge. Traditional recommendations to delay operation for 2-3 weeks of antibiotic therapy[38] were based on a series of 34 patients who were operated on an average of 3 weeks after stroke onset with new/worsened stroke in 2 patients (6%). There is strong accumulating evidence that early surgery is safe and preferred in this situation. In one recent series, 58 patients with active mitral valve IE (half of whom had evidence of cerebral embolism on brain imaging) underwent surgery at a median of 4 days after hospital admission, with only one (1.7%) perioperative stroke that occurred in a patient with a normal preoperative head CT scan.[18] In another series the authors reported no new strokes among 25 patients (16 with acute cerebral embolization on MRI, 7 of whom had preexisting clinical stroke) with operation at a median of four days after admission for left-sided endocarditis.[30] No patients in any of the aforementioned series had a hemorrhagic conversion during or after operation. On the basis of these data, evidence of brain embolism, clinical or radiographic, does not provide sufficient cause to delay surgery. Delay of operation should be considered for large volumes of intracranial blood (greater than 2 cm in diameter).

Principles of Surgery

All existing intravascular lines should be removed in the operating room. The standard approach is median sternotomy with combined antegrade and retrograde cardioplegia. It is desirable to avoid excess cardiac manipulation during cannulation to avoid embolization. We use a standard interatrial groove incision to access the left atrium. It is essential to invest adequate time to allow careful valve inspection and assessment. All infected material should be removed and inflamed tissue sharply resected. Although aggressive debridement is important, Frater[7] has correctly pointed out that absolute microbiologic sterility of remaining tissue is not essential because IE without vegetations will predictably heal without surgery. Our “limits of resection” are generally to debride back to tissue that will reliably hold sutures.

Vegetations should be sent for gram stain and culture. Underlying mitral valve pathology (ie, degenerative disease, rheumatic disease) should be identified.

The surgeon must determine the feasibility of valve repair because there is strong evidence that mitral valve repair is superior to replacement in the setting of IE. In a national series, repair rates were lower for patients with active IE (16%) than for those with treated IE (41%), and overall repair rates were lower in IE (30%) than they were in other types of mitral valve disease.[6] Despite the advantages of repair, reported repair rates are highly variable in mitral valve IE, ranging from 5% to 80%, suggesting room for improvement. Patients with mitral valve IE are often young, and mitral repair compared with replacement confers a long-term survival advantage. In a systematic review of mitral valve repair and replacement in IE, repair was associated with substantially lower rates of repaired/prosthetic valve endocarditis and stroke. Reoperation rates were also lower after repair than after replacement.[39] Although there is an understandable urgency to limit the duration of an operation in the setting of mitral valve IE, time invested in performing a repair is worthwhile.

There are common patterns of infection observed on the mitral valve. In our experience, the most common pattern is a perforation of the anterior leaflet with a surrounding lenticuloform or wind sock vegetation (Fig. 1). Although these perforations are often large and sometimes involve more than 50% of the anterior leaflet, they are frequently amenable to repair. We have reconstructed the anterior leaflet with a fresh autologous pericardial patch,[40] whereas others have reported success using 0.625% glutaraldehye-treated autologous pericardium as patch material.[41] Running 5-0 monofilament suture is used to secure the patch. Patching of an anterior leaflet perforation is almost always possible unless there is significant destruction of the leading free edge (ie, the most ventricular aspect of the coaptation surface). It is sometimes necessary to re-suspend the reconstructed anterior leaflet with polytetrafluoroethylene neochords.

Posterior leaflet destruction can usually be treated with a resectional approach but will also occasionally require patch augmentation (Fig. 2). Commissural involvement presents a challenge. Repair can be accomplished by resection of the involved segments, with wide mobilization of the base of the posterior leaflet and advancement of the posterior leaflet into the commissure (Fig. 3).[42] Underlying degenerative disease should be treated by the use of standard techniques.

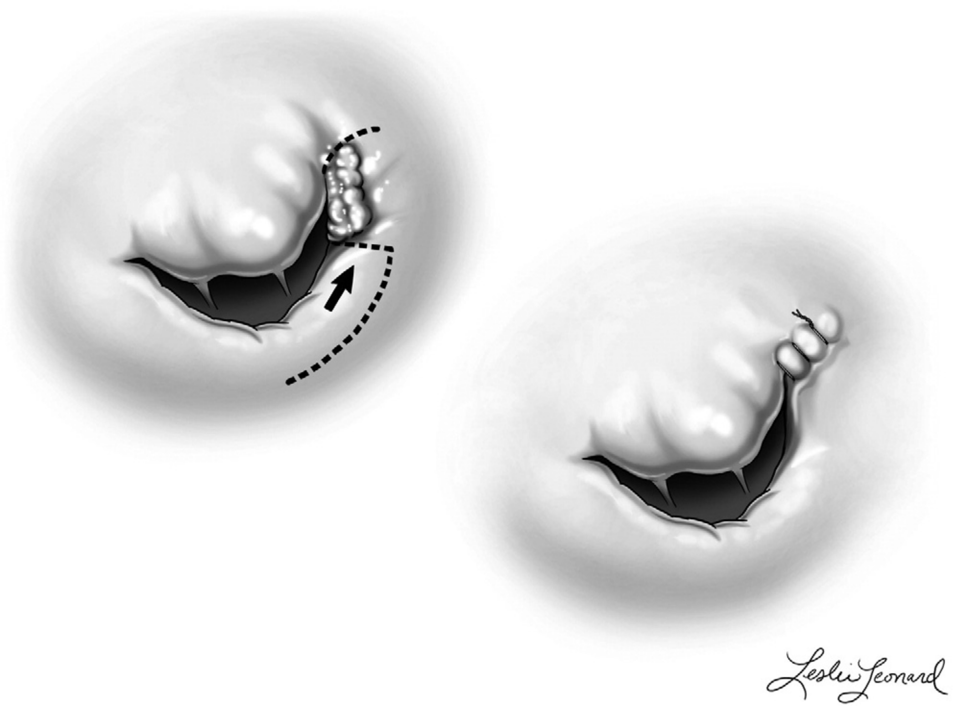

Figure 3. Top left, IE with a vegetation involving the posteromedial commissure. Bottom right, repair after resection of the involved segments, wide mobilization of the base of the posterior leaflet, and advancement of the posterior leaflet into the commissure.

Table 2. Series of Mitral Valve Surgery in Active Infective Endocarditis

Author, Year	n	% Active	% Repair	% Operative Mortality	Follow-Up, Years	% Survival, Years	% Redo/ Recurrence	% Stroke
Dreyfus[46] 1990	40 (32 MV)	100	100	2.5	2.5	95 (2.5)	0/0	—
Podesser[47] 2000	22	100	100	9.1	3.8	87 (5)	13.6/0	—
Sternik[48] 2002	44	100	36	13.6	3.3	74 (5) replace	13.6/11.4	—
Mihaljevic[49] 2004	53	100	40	7.5	4	79 (5)	9.4/5.7	9.4 (early)
Ruttmann[50] 2005	68	100	50	11.8	2.7	85 (5) repair 82.7 (5) replace	7.4/7.3	—
Zegdi[51] 2005	37	100	100	2.7	11.7	89 (5) 80 (10)	13.5/5.6	0
de Kerchove[52] 2007	81	100	78	17.5	5	73 (5) 69 (10)	9.9/1.2	2.5
Sheikh[20] 2009	104	100	15	8.7	5.6	73 (5)	10.6/8.7	6.7
Musci[53] 2010	280	100	22	19.3	—	—	11.4/5.7	1.8 (early)
Jung[21] 2011	102	100	40	2.9	4.7	97.5 (5) repair 85.8 (5) replace	4.9/2.9	2.9

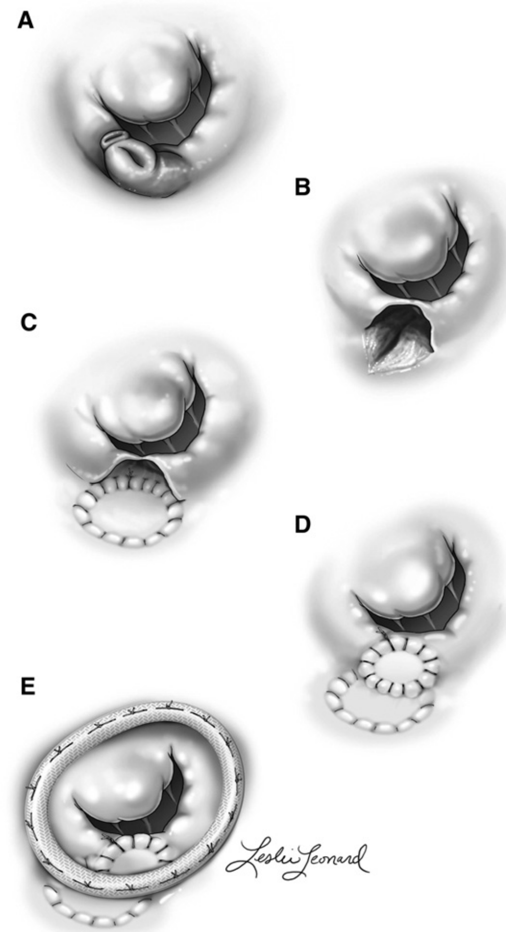

Figure 4. (A) Posterior annular abscess. (B) Appearance of the mitral valve after debridement of the abscess and the AV groove. (C) An oval patch of bovine pericardium covers the defect in the AV groove and extends onto the free wall of the ventricular myocardium as well as onto the posterior left atrial wall. (D) An autologous pericardial patch is used to repair the defect in the posterior annulus. (E) The final repair, including an annuloplasty ring.

The presence of an annular abscess or significant destruction of the posterior annulus mandates careful debridement and reconstruction of the atrioventricular (AV) groove with a patch. We prefer either bovine pericardium or fresh autologous pericardium. An oval patch is fashioned that is larger than the defect in the AV groove such that it extends onto the free wall of the ventricular myocardium as well as onto the posterior left atrial wall. Running 4-0 monofilament suture is used to anchor the patch into the myocardium using closely spaced bites. This suture line then extends across the AV groove and similarly anchors the patch to the posterior left atrium.

Ventricular (and atrial) pressure apposes the patch to the atrial and ventricular walls and promotes integrity of the patch. Once the AV groove patch has been implanted, it is used to anchor pledgeted sutures for replacement or less commonly annuloplasty sutures (Fig. 4).

Although it is tempting to avoid an annuloplasty ring when fixing limited leaflet destruction from mitral valve IE, we have found that implantation of a ring is generally helpful in assuring a competent valve during long-term follow-up. Our approach is to use a rigid or semirigid complete annuloplasty ring that is "true sized" to the anterior leaflet. Some advocate avoiding a prosthetic annuloplasty ring in the setting of IE to avoid annuloplasty infection. There is no evidence to support this assertion. Repaired mitral valve IE is exceptionally uncommon after the insertion of a prosthetic annuloplasty ring. One series reports 22 cases of repaired mitral valve endocarditis over 14 years, which averages 1.6 cases/year in a very busy clinical mitral practice.[43] At our institution, there have only been 2 cases of repaired mitral valve endocarditis after more than 1000 mitral valve repairs. Failure to implant an annuloplasty ring exposes the patient to an increased risk of repair failure.

If repair is not possible and replacement is necessary, the choice between mechanical and bioprosthetic valves should be made on the basis of the usual considerations. In one study in which the authors examined outcomes of 306 patients with left-sided endocarditis, operative mortality was the same (17% vs 19%) as was 10-year survival (50% vs 51%) among those who received mechanical or bioprosthetic valves, respectively. The rate of recurrent IE was similar for patients with mechanical (2.1% per patient-year) and bioprosthetic (2.3% per patient-year) valves.[44] After operative intervention for mitral valve endocarditis, intravenous antibiotics should be continued for the total length of time specified by current recommendations, generally 4-6 weeks.[45]

Contemporary Outcomes for Active Mitral Valve IE

The results of several series of surgical mitral valve endocarditis are presented in Table 2.[20,21,46-53] In series that report repair and replacement, repair rates range widely from 15% to 78%. Operative mortality ranges from 2.5% to 19.3%, with most series reporting rates of <10%. In a review of 6627 mitral valve endocarditis operations in North America from 1994 to 2003, the overall operative mortality rate was 8.7% and the overall incidence of perioperative stroke was 3.5%. Operative mortality was higher in the active endocarditis subgroup than the treated subgroup (10.6% vs 1.8%), as was stroke (6.4% vs 1.9%).[6]

In single-institution series, 5-year estimated survival is most commonly reported, and ranges from 65% to 97.5%. The rate of stroke is 0%-2.4% per year. Recurrence of endocarditis is between 0% and 3.5% per year. Reoperation is required in 1.0%-4.1% of patients per year. In series that compare repair and replacement, repair is universally associated with more favorable short- and long-term outcomes. In a systematic review of series of mitral valve endocarditis, mitral valve repair was associated with lower mortality, fewer reoperations, fewer late recurrences of endocarditis, and fewer strokes.[39]

CONCLUSIONS: KEY PRINCIPLES

Mitral valve IE is a challenging clinical problem with high in-hospital mortality, but outcomes can be improved with well-timed, technically sound operations in patients with appropriate indications. Surgery should be performed early to reduce the risk of valve destruction and embolization. Mitral valve repair should be performed whenever possible.

Acknowledgments

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