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Review Article

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Early Surgery in Valvular Heart Disease

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ABSTRACT

The burden of valvular heart disease (VHD) is increasing with age, and the elderly patients with moderate or severe VHD are notably common. When to operate in asymptomatic patients with VHD remains controversial. The controversy is whether early surgical intervention should be preferred, or a watchful waiting approach should be followed. The beneficial effects of early surgery should be balanced against operative mortality and long-term results. Indications of early surgery in each of the VHD will be discussed in this review on the basis of the latest American and European guidelines.

Keywords: Mitral valve insufficiency; Aortic valve stenosis; Aortic valve insufficiency; Endocarditis; Cardiac surgical procedures

INTRODUCTION

The burden of valvular heart disease (VHD) is increasing with age, and the elderly patients with moderate or severe VHD are notably common.[1] Among all cardiac operations in the United States, the proportion of surgical procedures related to VHD is 10–20%.[2] Mitral and aortic valve (AV) diseases are the most common, and mitral regurgitation (MR) and aortic stenosis (AS) are most responsible for the diagnosis.[3] It is generally accepted that preemptive treatment at early-stage of the disease can preclude morbidity and mortality. The beneficial effect of early surgery should be balanced against surgical risks and long-term results. A commonly used study method is comparing the outcomes of early surgery and watchful waiting of the patients with early stage of disease (asymptomatic). A randomized controlled trial comparing the 2 treatment strategies has rarely been conducted in this field. Therefore, care should be taken to interpret the data from observational studies. We aimed to review the benefits of early surgical intervention and optimal timing of surgery in each of the VHD entities.

EARLY SURGERY IN SEVERE MITRAL REGURGITATION

Degenerative MR is the most common cause of primary MR in developed countries including myxomatous degeneration or fibroelastic deficiency.[2] As severe MR progresses, subsequent left ventricular (LV) enlargement and dysfunction, atrial fibrillation (AF) and pulmonary

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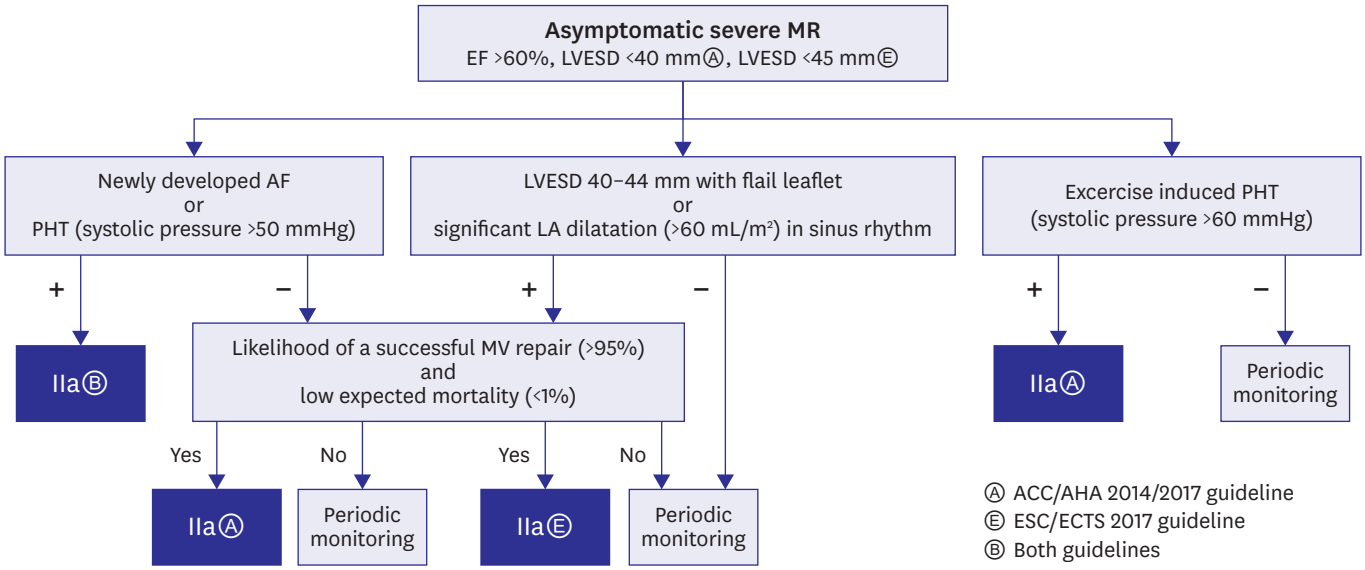

Figure 1. Early surgical indications for asymptomatic patients with severe MR. Adapted from ACC/AHA 2014/2017 and ESC/ECTS 2017 guidelines. Following the arrows according to the decision pathways leads to a recommendation for MV surgery.
ACC/AHA = American College of Cardiology/American Heart Association; AF = atrial fibrillation; EF = ejection fraction; ESC/ECTS = European Society of Cardiology/European Credit Transfer System; LVESD = left ventricular end-systolic dimension; LA = left atrium; MR = mitral regurgitation; MV = mitral valve; PHT = pulmonary hypertension.

hypertension (PHT) can lead to death. Therefore, the patients with severe MR could be best managed by correction of regurgitation before any structural changes and functional impairment occur (**Figure 1**).

Enriquez-Sarano et al.[4] demonstrated that, in asymptomatic patients with degenerative MR, those with effective regurgitant orifice (ERO) ≥40 mm² showed a worse 5-year survival, as compared with those with ERO between 39–20 mm² and under 20 mm² (58±9% vs. 66±6% vs. 91±3%, p<0.01). This finding suggests that the subgroups which can be benefitted from early surgery may exist. We showed, in our first study,[5] a better 7-year event-free survival rate in the early surgery group (99±1% vs. 85±4%, p=0.007). In addition, cardiac mortality reduction with early surgery (5±2% vs. 1±1%, p=0.016) was demonstrated in our expanded registry.[6] In this study, the patients underwent early mitral valve (MV) repair was benefitted with better event-free survival and reduced cardiac mortality. Of note, in a younger age subgroup (<50 years old), the benefit of early surgery was not evident. Suri et al.[7] showed the patients underwent early surgery showed a better 10-year survival rate (86% vs. 69%, p<0.001) in patients with severe MR caused by flail mitral leaflet from the results of largest Mitral Regurgitation International Database (MIDA) registry.

In asymptomatic patients with preserved LV function and dimensions (left ventricular ejection fraction [LVEF] >60% and left ventricular end-systolic dimension [LVESD] <40 mm in American College of Cardiology/American Heart Association [ACC/AHA] 2014 guideline[8] and LVESD <45 mm in European Society of Cardiology/European Association for Cardio-Thoracic Surgery [ESC/EACTS] 2017 guideline[9]), early surgery should be considered (Class IIa) when new-onset AF and (or) PHT (systolic pulmonary artery pressure more than 50 mmHg at rest) develop. According to the ACC/AHA 2014 guideline,[8] exercise-induced PHT (systolic pulmonary artery pressure >60 mmHg) can be another trigger for early surgery (Class IIa indication). Regardless of new-onset AF or PHT, early surgery in patients with preserved LV function and dimensions should be considered (class IIa) in a highly-qualified center where a successful MV repair (>95%) and

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low mortality (<1%) are expected.[10] Unless 2 conditions are not guaranteed, an early MV repair cannot be justified. According to the ESC/EACTS 2017 guideline,[9] in asymptomatic patients with normal LVEF and LVESD of 40–44 mm, the early surgery is indicated when they have a significantly increased LA dilation (>60 mL/m^2) without other triggers or flail leaflet. However, early surgery should only be considered in highly qualified centers.[9][11]

Concerning the possibility of repair, 2-dimensional echocardiography including transesophageal approach can provide most of the relevant anatomic information for the repair. However, the real-time 3-dimensional transesophageal echocardiography (TEE) is needed for the accurate evaluation of the feasibility of repair in complex MV lesions.[12] Early surgery can be advocated only when MV repair is durable for a long time (reoperation-free survival rate is 90% at 10 years and 80% at 20 years), and long-term survival identical to that of the matched control and quality of life are guaranteed.

EARLY SURGERY IN AORTIC STENOSIS

Severe AS is currently defined as an aortic valve area (AVA) <1.0 cm^2 and/or mean trans-aortic pressure gradient (PG) >40 mmHg and/or peak aortic jet velocity (Vmax) >4 m/s.[8] In symptomatic patients with severe AS or LVEF <50%, aortic valve replacement (AVR) is recommended as Class I indication.[8][9] The outcome of patients with severe AS who did not undergo AVR is extremely poor once symptoms develop after a long latent period (a mortality rate as high as 50% at 2 years and 80% at 5 years).[13] In contrast, in asymptomatic patients, the annual sudden cardiac death rate is expected to be around 1% per year.[14] This low mortality rate must be balanced against the surgical risk of AVR (1–3% of operative mortality (aged <70 years) and 3–8% in patients older than 70 years)[15] and prosthetic valve-related problems (thromboembolism, endocarditis and reoperation, at least 2–3% per year) (**Figure 2**).[8]

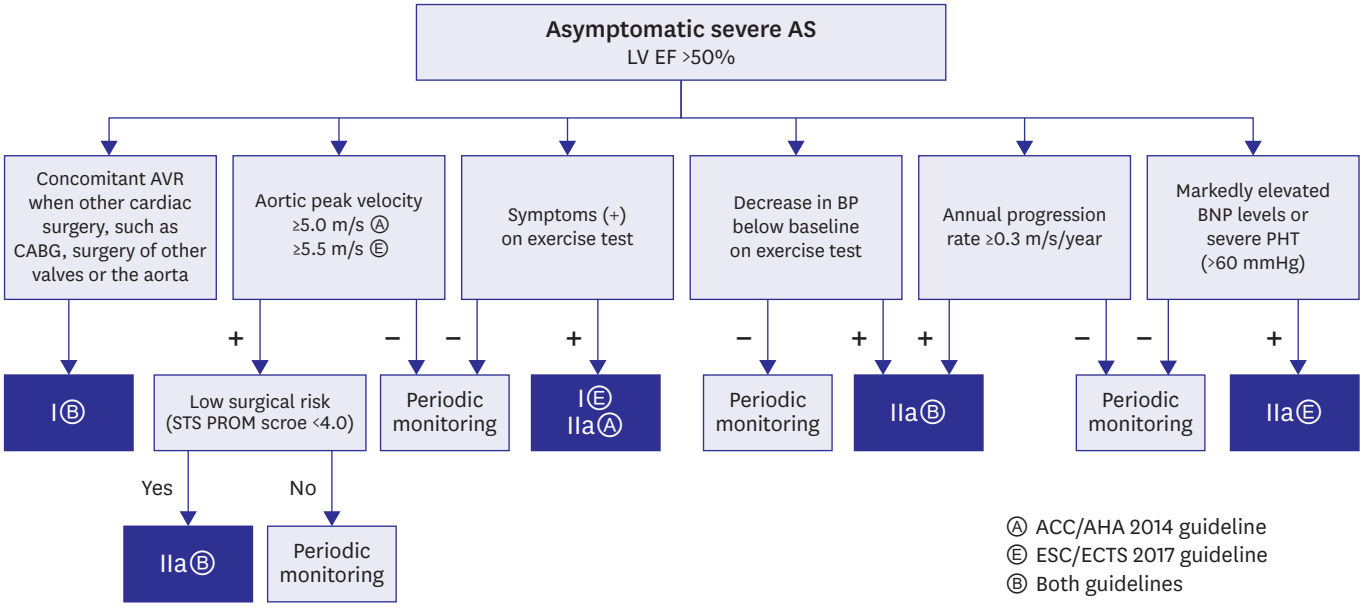

Figure 2. Indications for early surgery in patients with asymptomatic severe AS. Adapted from ACC/AHA 2014/2017 and ESC/ECTS 2017 guidelines.
ACC/AHA = American College of Cardiology/American Heart Association; AS = aortic stenosis; AVR = aortic valve replacement; BP = blood pressure; BNP = brain natriuretic peptide; CABG = coronary artery bypass graft; ESC/ECTS = European Society of Cardiology/European Credit Transfer System; LVEF = left ventricular ejection fraction; STS PROM = society of thoracic surgery predicted risk of mortality; PHT = pulmonary hypertension.

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However, the widely various clinical outcomes even in asymptomatic patients,[16] and reduced operative mortality (around 1%) at high-volume centers[8][14] suggest that some high-risk groups can be benefitted from preemptive early surgery. Among several observational studies showing the outcome of asymptomatic AS,[14][16-19] 2 studies[18][19] have suggested the gain of early surgery in asymptomatic patients. We demonstrated the advantage of early surgery in asymptomatic patients with very severe AS (AVA <0.75 cm^2 accompanied by a peak aortic jet velocity ≥4.5 m/s or a mean trans-aortic PG ≥50 mmHg).[18] The early surgery was associated with significantly lower 6-year all-cause and cardiac mortality rates (2±1% and 0% vs. 32±6% and 24±5%, respectively, p<0.001). In addition, in 57 propensity score-matched pairs, the early surgery remained significantly associated with lower all-cause mortality (hazard ratio [HR], 0.135; p=0.008). Taniguchi et al.[19] showed the benefit of early surgery in patients with severe AS (peak aortic jet velocity >4.0 m/s, or mean aortic PG >40 mmHg, or AVA <1.0 cm^2) using a total of 3,815 patients from the large multicenter registry. They found that the patients underwent early surgery had a lower 5-year all-cause mortality than that in the conservatively managed group (15.4% vs. 26.4%, p=0.009). Recent meta-analysis confirmed these findings.[20] In Généreux et al.'s meta-analysis[20] including 4 observational studies,[6][17][19][21] they found that the all-cause mortality of early surgery group was significantly lower (pooled adjusted HR, 0.27; 95% CI, 0.09–0.77; p=0.01). In contrast, in the meta-analysis of Lim et al.,[22] no significant all-cause mortality difference was observed between the 2-treatment strategies. The discordant results from these 2 meta-analyses clearly demonstrate the limitations; hypothesis generating role of meta-analysis. For that reason, we are waiting for the results of prospective randomized controlled trials comparing AVR to conservative treatment. The eaRly surgEry versus COnventional treatment in VERY severe aortic stenosis (RECOVERY)[23] and Aortic Valve replAcemenT versus conservative treatment in Asymptomatic seveRe aortic stenosis (AVATAR)[24] trials are ongoing.

According to the latest guidelines,[8][9] asymptomatic patients with severe AS who undergo other cardiac surgery, such as coronary artery bypass grafting, surgery of other valves or the aorta should have concomitant AVR (class I indication). Early surgery should be considered in asymptomatic patients with very severe AS (peak aortic velocity ≥5.0 m/s in ACC/AHA 2014 guideline, ≥5.5 m/s in ESC/EACTS 2017 guideline) and low surgical risk (society of thoracic surgery predicted risk of mortality score <4.0 without other comorbidities or advanced frailty). For patients with severe AS showing an abnormal exercise test, AVR is recommended. If symptoms (angina, severe dyspnea at the early stage of exercise, dizziness or syncope) are developed by exercise testing, AVR is indicated (class IIa indication in AHA/ACC 2014 guideline, class I indication in ESC/EACTS 2017 guideline). Early surgery is also indicated in patients showing abnormal blood pressure (BP) rise during exercise test (a decrease in BP below baseline is indicated as class IIa in both guideline.[8][9] In addition, early surgery is recommended (class IIa indication in ESC/EACTS 2017 guideline) in patients with rapid progressive stenosis (increase in aortic peak velocity ≥0.3 m/s/yr), elevated BNP levels (greater than 3 times the upper limit of normal range corrected by age and gender) or severe PHT (invasively measured systolic pulmonary artery pressure at rest >60 mmHg).[9]

EARLY SURGERY IN AORTIC REGURGITATION

Patients with chronic severe aortic regurgitation (AR) generally tolerate well volume overload of the LV and remain asymptomatic for a long time. Once symptoms develop, the mortality rate increases remarkably up to 10–20% per year in the absence of AVR.[25]

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Therefore, AV surgery is recommended in patients with symptomatic patients regardless of systolic function.[8][9] Both guidelines have been hesitant to recommend an early surgery for asymptomatic patients with severe AR. The consensus of guidelines suggests that most of the asymptomatic patients should be proposed a conservative watchful waiting strategy until symptoms, LV dysfunction, or severe LV dilatation develop. With regard to severe LV dilation in patients with preserved LVEF (≥50%), the cut-off value of LVESD for AV surgery is 50 mm both in ACC/AHA 2014 guideline[8] and ESC/EACTS 2017 guideline[9] (class II indication). For left ventricular end-diastolic dimension (LVEDD), the cut-off value is 70 mm (class IIa in 2017 ESC/EACTS guideline and class IIb in ACC/AHA 2014 guideline).

There is a paucity of data regarding the benefit of surgery in asymptomatic patients in the absence of any class I or class IIa indications. de Meester et al.[26] compared the outcomes of early surgery (not indicated as class I or IIa indication: no symptoms, normal LVEF and not much dilated LV) and the conventional treatment group. In this study, they did not show the benefit of early surgery in asymptomatic patients with AR.

EARLY SURGERY IN INFECTIVE ENDOCARDITIS

Although almost half of the patients with infective endocarditis (IE) undergo surgical treatment,[27] the optimal timing of surgical intervention remains elusive. The definition of early surgery in IE includes all surgical procedure before completion of an antibiotics therapy.[28] The purpose of early surgery in patients receiving antibiotic treatment (active phase) is to prevent progressive heart failure (HF), irreversible structural destruction and systemic embolism.[8][29-31] However, ethical concerns about delaying surgery in control patients make it difficult to perform randomized controlled trials supporting early surgery. Moreover, the comparison between surgically and medically treated groups in the

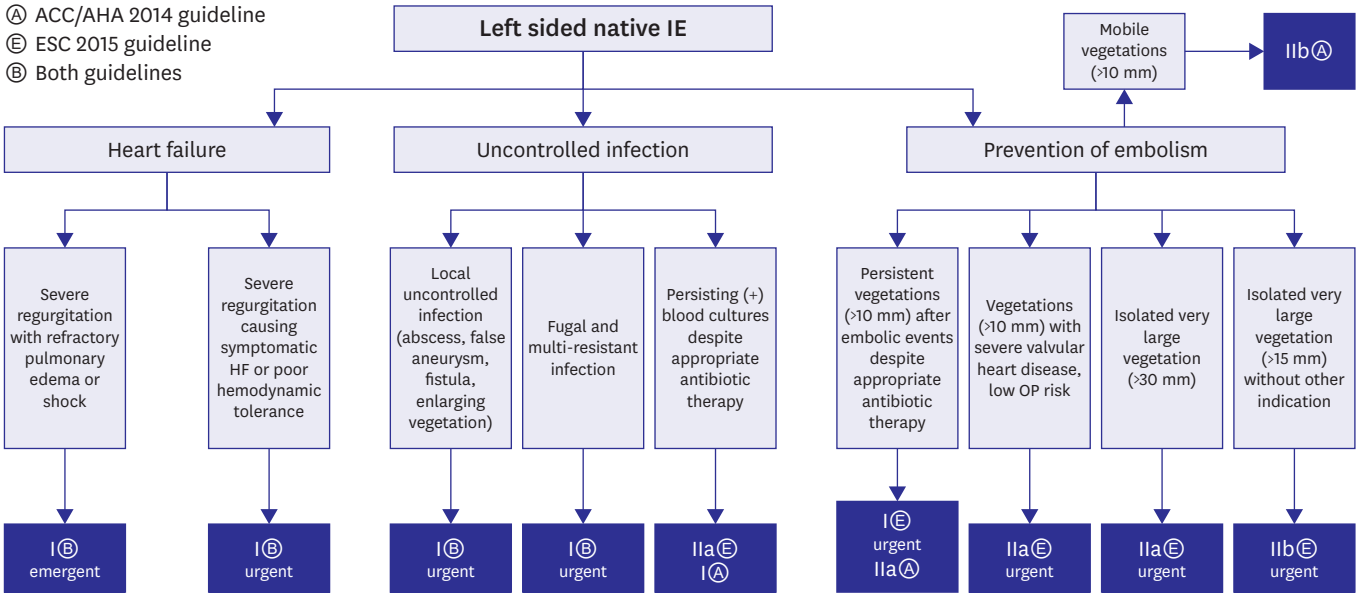

Figure 3. Indications for early surgery in patients with left-sided IE. Early surgery is performed during initial hospitalization before completion of a full therapeutic course of antibiotics. Adapted from ACC/AHA 2014 and ESC 2015 guidelines.
ACC/AHA = American College of Cardiology/American Heart Association; ESC = European Society of Cardiology; HF = heart failure; IE = infective endocarditis; OP = operative.

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observational study without randomization (inherent baseline difference exists) complicates the assessment of the surgical impact on outcomes.[28] To overcome this limitation, several observational studies calculated propensity score to calculate the effect of receiving treatment and paired treatment and control group with the similar propensity score value (propensity score matching) (**Figure 3**).[32]

The early surgery of IE is mainly recommended in patients with HF related to the valvular dysfunction, uncontrolled infection and for the prevention of embolism.[31] Vikram et al.[33] showed the mortality reduction was achieved with early surgery. Moreover, patients with moderate to severe HF were benefitted greatest in 218 propensity-matched patients with IE pairs. In a larger analysis of 1,359 IE patients with HF, the patients underwent early surgery showed lower in-hospital and 1-year mortality rates (21% vs. 45% and 29% vs. 58%, respectively) and the greater benefit of surgery in patients with moderate to severe HF was confirmed again.[34] Therefore, the early surgery can clearly be recommended for the patients with moderate to severe HF (class I indication in both guidelines).[8][31] In patients with mild HF symptom (compensated for the valvular regurgitation), initial medical management is preferred under careful and periodic observation.[30]

Surgical indications in the presence of uncontrolled infection are a persistent infection, locally uncontrolled infection or infection caused by microorganisms not easily cured by antimicrobial therapy. Uncontrolled infection in patients with IE is the second most frequent surgical indication.[29] Persistent infection indicates the blood cultures remain positive for more than 7–10 days despite appropriate antibiotics. Extracardiac abscess formation in spleen, vertebrae, brain or kidney and non-infectious fever (such as drug fever) should be excluded. Persisting blood cultures positivity 48–72 hours after initiation of antibiotics was independently associated with hospital mortality.[35] Urgent surgery should be considered (class IIa indication) if there is a persisting blood cultures positivity even after 3 days of appropriate antibiotic therapy.[31][35] In ACC/AHA 2014 guideline,[8] patients with persistent bacteremia or fevers lasting longer than 5 to 7 days after onset of appropriate antibiotics are recommended early surgery (class I indication). Locally uncontrolled infection implies a perivalvular extension of IE including abscess formation, pseudoaneurysm, fistulae, ventricular septal defect, third-degree atrioventricular block and acute coronary syndrome, and is the most frequent cause of uncontrolled infection.[31]. It also includes increasing vegetation size despite using appropriate antibiotics. The abscess formation is more common in AV (frequently in the mitral-aortic intervalvular fibrosa) than MV.[36] Although 87% of patients with these complications undergo surgery, in hospital-mortality remains still high (around 40%).[37] Patients showing the sign or evidence of locally uncontrolled infection was recommended for early surgery (class I indication in both guidelines). Multimodality imaging using TEE, multi-detector computed tomography and positron emission tomography/computed tomography are beneficial for the diagnosis of the perivalvular extension of inflammation.[31] Early surgery is recommended in uncontrolled IE caused by fungal infection, multi-resistant organisms or Gram-negative bacteria (class I indication in both guidelines).[31]

Systemic embolism, from which one-third of patients with IE suffer, is the second most common cause of mortality, after HF.[38] Embolisms can always occur before and after the diagnosis of IE and during the antibiotic treatment period. To prevent systemic embolism of IE, early diagnosis and immediate initiation of antibiotic treatment are very important. Although the chance of embolic events remarkably decreases after the initiation of proper antibiotics therapy,[39][40] surgical removal of vegetation can prevent the occurrence of embolic

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events, indeed. However, the concerns that such surgery in the presence of fragile tissue due to active inflammation may be more technically difficult to perform, which results in a high risk of postoperative complications, make it a dilemma to perform a surgery.[41] The development of imaging modality, which allows early detection of patients at high risk of embolism, surgical technique, and low operative mortality have settled a dispute for early surgery.[30] In our observational study,[42] early surgery, which was performed due to an only embolic indication within 7 days of diagnosis was associated with higher-event free survival (93±3% vs. 73±5%, p=0.0016). The benefit of early surgery remained significant in 44 propensity score-matched pairs (HR, 0.18; p=0.007). The Early Surgery versus Conventional Treatment in Infective Endocarditis (EASE) trial[43] was a prospective, randomized controlled trial comparing between early surgery within 48 hours after diagnosis and conventional-treatment strategy. In this trial, the early surgery performed in patients with large vegetation (≥10 mm), not having other indication for surgery, reduced the composite outcomes (in-hospital mortality and systemic embolism that occurred within 6 weeks after randomization, HR, 0.08; p=0.02). Long-term results of the EASE trial showed that the composite end-point (all-cause mortality, embolic events or recurrence of IE) at 4 years was significantly lower in the early surgery group (HR, 0.22; p=0.02).[44]

According to the ESC 2015 guideline,[31] urgent surgery is indicated in patients with left-sided IE and large persistent vegetations >10 mm after one or more clinical or silent embolic events despite appropriate antibiotic treatment (class I indication). In patients with large vegetation >10 mm, associated with severe VHD and low operational risk, the early surgery should be considered (class IIa indication). Early surgery should be considered in patients with isolated very large vegetation (>30 mm, class IIa indication). Surgery may be considered in patients with isolated vegetation (>15 mm) on the aortic or MV without other indication for surgery (class IIb indication). In ACC/AHA 2014 guideline,[8] early surgery may be considered (class IIb indication) in patients with large mobile vegetations (>10 mm) regardless of clinical evidence of embolic phenomenon.

EARLY SURGERY IN FUNCTIONAL TRICUSPID REGURGITATION

Functional tricuspid regurgitation (FTR) is a secondary tricuspid abnormality (no primary pathology on the tricuspid valve [TV] leaflet) by annular dilation. Annular dilation can be caused by the right ventricle dilation or isolated annular dilation by AF. Severe FTR is associated with poor functional capacity and survival if untreated.[45] Interestingly, the progression of mild or moderate degrees of FTR, uncorrected at the time of MV surgery, can be observed in approximately 25% of patients. Late progression of FTR in these patients group is associated with reduced survival,[46] which raises the concerns about the early intervention of the TV in concomitance with MV surgery.

Concomitant TV repair is recommended for patients with severe tricuspid regurgitation undergoing left-sided valve surgery (class I indication in both guideline).[8][9] TV repair should be considered (class IIa indication both in ACC/AHA[8] and ESC/EACTS guideline[9]) in patients with mild, moderate, or greater FTR at the time of left-sided valve surgery with dilated tricuspid annulus (greater than 40 mm or 21 mm/m^2 diastolic diameter on transthoracic echocardiography) or prior evidence of right HF. TV surgery may be considered in patients undergoing left-sided valve surgery with mild or moderate FTR even in the absence of annular

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dilatation when previous recent right HF (class IIb indication in ESC/EACTS 2017 guideline)[9] or PHT (class IIb indication in ACC/AHA 2014 guideline)[8] have been documented.

CONCLUSION

According to the development of surgical technique and growing evidence supporting the benefit of the early surgical intervention, the indications for early surgery in patients with VHD becomes more and more extensive. However, the optimal timing of surgery is still controversial. The choice between early surgery and conservative treatment should be tailored based on the calculation of individualized risk-benefit ratio. The early surgery can be strongly proposed only if its benefits outweigh operative risks. Especially in asymptomatic patients with severe MR (or AS), the early surgery should be preferred in the highly-qualified center where the low operative mortality, successful and durable MV repairs are certified.

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