

Tricuspid valve endocarditis

Syed T. Hussain¹, James Witten², Nabin K. Shrestha³, Eugene H. Blackstone^{1,4}, Gösta B. Pettersson¹

¹Department of Thoracic and Cardiovascular Surgery, Heart and Vascular Institute, ²Cleveland Clinic Lerner College of Medicine, ³Department of Infectious Disease, Medicine Institute, ⁴Department of Quantitative Health Sciences, Research Institute, Cleveland Clinic, Cleveland, OH, USA
Correspondence to: Gösta B. Pettersson, MD, PhD. Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, 9500 Euclid Avenue/Desk J4-1, Cleveland, OH 44195, USA. Email: petterg@ccf.org.

Right-sided infective endocarditis (RSIE) is less common than left-sided infective endocarditis (IE), encompassing only 5–10% of cases of IE. Ninety percent of RSIE involves the tricuspid valve (TV). Given the relatively small numbers of TVIE cases operated on at most institutions, the purpose of this review is to highlight and discuss the current understanding of IE involving the TV. RSIE and TVIE are strongly associated with intravenous drug use (IVDU), although pacemaker leads, defibrillator leads and vascular access for dialysis are also major risk factors. *Staphylococcus aureus* is the predominant causative organism in TVIE. Most patients with TVIE are successfully treated with antibiotics, however, 5–16% of RSIE cases eventually require surgical intervention. Indications and timing for surgery are less clear than for left-sided IE; surgery is primarily considered for failed medical therapy, large vegetations and septic pulmonary embolism, and less often for TV regurgitation and heart failure. Most patients with an infected prosthetic TV will require surgery. Concomitant left-sided IE has its own surgical indications. Earlier surgical intervention may potentially prevent further destruction of leaflet tissue and increase the likelihood of TV repair. Fortunately, TV debridement and repair can be accomplished in most cases, even those with extensive valve destruction, using a variety of techniques. Valve repair is advocated over replacement, particularly in IVDUs patients who are young, non-compliant and have a higher risk of recurrent infection and reoperation with valve replacement. Excising the valve without replacing, it is not advocated; it has been reported previously, but these patients are likely to be symptomatic, particularly in cases with septic pulmonary embolism and increased pulmonary vascular resistance. Patients with concomitant left-sided involvement have worse prognosis than those with RSIE alone, due predominantly to greater likelihood of invasion and abscess formation in left-sided IE. Patients with isolated TVIE have an operative mortality between 0–15% and excellent survival.

Keywords: Tricuspid valve (TV); infective endocarditis (IE); right-sided endocarditis



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Introduction

Infective endocarditis (IE) is associated with high morbidity/mortality and is most frequent on the left side of the heart. Right-sided IE (RSIE) is relatively rare, encompassing only 5–10% of IE cases (1,2). The vast majority of RSIE cases involve the tricuspid valve (TV), with pulmonic valve involvement accounting for less than 10% of all right-sided cases (2). Most TVIE cases are treated medically, and only 4.1% of all IE surgeries in North America are for TVIE (3). RSIE is strongly associated with intravenous

drug use (IVDU), although medical device implantation, including pacemakers and defibrillators, and vascular access for dialysis are also major risk factors, due especially to an exponential increase in their use. Patients with uncorrected congenital heart disease are also at increased risk for RSIE.

Staphylococcus aureus is the predominant causative organism in TVIE, and the rise of methicillin resistance is an increasing issue (1,2,4). Most patients with TVIE are successfully treated with antibiotics, and surgery is primarily considered only for large vegetations, recurrent septic pulmonary emboli, failure of medical therapy and

infected prosthetic valves, and less often for severe tricuspid regurgitation (TR) and heart failure. Concomitant left-sided IE has its own indications (1) and carries a worse prognosis than right-sided infection alone (5), due predominantly to its greater likelihood for invasion and abscess formation (5,6). Overall mortality for RSIE is between 5–15% (1,7).

Given that the majority of cases are managed medically and relatively small numbers of TVIE cases are operated on at each institution, there is very little literature beyond small, single-institution case series. The purpose of this review is to highlight the current understanding of TVIE and discuss clinically relevant issues.

Risk factors

Intravenous drug users

Infection resulting from IVDU constitutes approximately 30–40% of all TVIE cases (1,8,9). The IE presentation is with TV lesions in 50–65% of IVDU, and the prevalence of IE in IVDUs is about 2–5% per year (4,9,10). There is no single hypothesis to explain why IE of the right-sided valves occurs most commonly in IVDU. The various hypotheses to explain this include differences in effects of injected substances on valves and valve endothelium, differences in infecting organisms, a higher bacterial load and immunologic changes associated with IVDU. It is assumed that there is a dynamic combination of host, environmental, immunological and microbial factors acting in concert to cause predominantly RSIE in this population, with specific factors contributing relatively more or less in any individual patient (10). Once the valve has been infected and damaged or replaced, repeated episodes of IE occur ever more frequently in IVDUs, with reinfection of up to 28% (5). One study reported a long-term cumulative incidence of reoperation of 20% in IVDU, as opposed to less than 5% in non-users (9). The cumulative incidence of death was similar between the two groups at approximately 20% (9). This is echoed by other papers that found no difference in survival between users and non-users (11,12).

IVDU patients are more likely to be younger, and their very high likelihood of continued drug use is a serious clinical challenge. However, it has become clear that from a survival standpoint, IVDU itself is not a contraindication to surgery (4). A multidisciplinary approach to these patients is required, with drug rehabilitation and long-term cessation of drug use essential in preventing reinfection (1,9).

Cardiac implantable electronic device (CIED) infection

CIED lead infection is an increasingly important cause of TVIE (1,3,8). CIED infection should be considered separate from TVIE in that the majority of CIED infections are localized to the device pocket and leads and do not involve the TV. This distinction is sometimes confused in the literature (13,14). IE should be considered CIED related only if there is evidence of valve vegetations and/or tricuspid insufficiency, in concert with positive blood cultures. Lead echo-densities are very common and indistinguishable from IE vegetations, but most of the time they are not infectious vegetations (14). On the other hand, CIED-related IE should always be suspected and considered in cases of CIED infection. Principles of surgical management of CIED-related IE will be discussed below.

Indwelling lines (hemodialysis, parenteral nutrition and chemotherapy)

Chronic IV access infections account for approximately 10% of all IE, 8% of which occur in hemodialysis patients (2). This study, however, had an over-representation of North American patients, who accounted for 60% of the study cohort. A smaller North American study demonstrated that approximately 20% of hemodialysis-related IE involved the TV (15). Dialysis patients often have a greater burden of comorbidities, including diabetes, hypertension and atrial fibrillation, besides their end-stage renal disease (15). The most common microbes are *S. aureus* and *Enterococcus spp* (15). There is a lack of literature about patients with IE due to chronic IV access, especially focusing on surgical management. TVIE-specific discussion is even less common, so it is difficult to get guidance from these small sample sets besides recognizing the overall poor health of these patients.

Microbiology

S. aureus is the predominant causative microorganism for TVIE, occurring in 60–90% of cases in some studies, irrespective of associated risk factors (1,2,4,8). *Pseudomonas aeruginosa*, other gram-negative microorganisms, fungi, enterococci, streptococci and polymicrobial infections occur less frequently (1). These pathogens are rare and vary by source of infection. However, coagulase-negative staphylococci are more common and represent 25% of CIED-related infections (1,2,4).

S. aureus IE is associated with the highest morbidity/mortality, and the proportion of *S. aureus* cases with methicillin resistance is increasing (1,6). *S. aureus* is associated with a larger number of comorbid factors, including hemodialysis, IVDU and advanced age (1,6).

HIV infection is another comorbidity associated with IVDU and IE, and its prevalence varies drastically by region. However, there appears to be little impact of HIV infection on the occurrence of IE if CD4 counts are above 200 cells/ μ L (1,4). Two studies have also noted a very high prevalence of hepatitis C in patients with IVDU and right-sided IE (16,17).

Diagnosis

The usual manifestations of TVIE are persistent fever and bacteremia. Multiple septic pulmonary emboli cause chest pain, cough and occasionally hemoptysis (1). Systemic emboli are rare manifestations of TVIE and, when noted, should be considered evidence of either left-sided involvement or paradoxical embolism (1). Right heart failure is rare and caused by increased pulmonary pressure combined with severe TR or TV obstruction from huge vegetations. Pulmonary septic emboli cause pulmonary infarcts and pulmonary abscesses, and may be complicated by pneumothorax and empyema.

The gold standard for diagnosing IE is the modified Duke Criteria (18). However, these criteria may be difficult to determine in TVIE: first, the right heart has many echocardiographically anomalous anatomic features that may be difficult to distinguish from vegetations; second, septic emboli are pulmonary, as opposed to systemic, and clinically less obvious until they cause pulmonary infarcts and abscesses; third, early pulmonary radiographic findings may be mistaken for pneumonia (1).

Treatment

As mentioned earlier, prognosis of RSIE is relatively good. Non-operative management of TVIE with antibiotics alone clears the bacteremia in 70–85% of cases and is associated with 7–11% in-hospital mortality. Between 5–16% of RSIE cases eventually require surgical intervention, with reported operative mortality between 0–15% for patients with isolated TVIE (1,3,5,7,9).

Medical management

The choice of initial, empiric antimicrobial therapy depends

on the suspected microorganism (1). Being the most likely causative organism, *S. aureus* must always be covered, particularly in IVDUs and catheter related infections (1). In IVDUs with underlying valve lesions and/or left-sided involvement, coverage for streptococci and enterococci should be included (1). Therapy should be adjusted once the causative microorganism has been identified and its sensitivity determined. The appropriate choice and duration of antibiotic therapy should be guided by an infectious disease expert (1).

Surgery

Indications for and timing of surgery

The indications for surgery in RSIE are not well defined, but should be considered in the presence of any of the following (1,19):

- (I) TV vegetations >20 mm and recurrent septic pulmonary emboli with or without concomitant right heart failure;
- (II) IE caused by microorganisms that are difficult to eradicate (e.g., fungi) or bacteremia for at least 7 days (e.g., *S. aureus*, *P. aeruginosa*) despite adequate antimicrobial therapy; and
- (III) Right heart failure secondary to severe TR with poor response to diuretic therapy.

With increasing experience in treating TVIE, surgical intervention has in-hospital mortality similar to or lower than antibiotic therapy alone (1,7). Timing of surgery in RSIE is less clear than in left-sided IE. Earlier intervention prevents further septic pulmonary embolism and further destruction of TV leaflet tissue, increasing the likelihood of good repair. Early operation for TVIE should be considered in the presence of any of the following: concomitant left-sided IE, atrial septal defect, infected indwelling catheters or pacing leads and prosthetic valve endocarditis (7). Patients with RSIE have often suffered from septic pulmonary emboli, multiple pulmonary infarcts and abscesses, resulting in elevated pulmonary pressure and increased vascular resistance. This reduces their tolerance to severe TR. Although pulmonary issues may be an argument to postpone operating, large or huge vegetations that increase the risk of additional emboli make the argument for surgical intervention more compelling—the decision regarding when to operate must be based on clinical judgment.

Principles of surgery

The principles of surgery for TVIE include radical

debridement of vegetations/infected tissue and valve repair whenever possible. If the valve is largely destroyed and non-repairable, and if the pulmonary pressures and vascular resistance are elevated, replacement is necessary (1,5,7). If pulmonary vascular resistance is low-normal, excising the valve without replacement may work as a temporary solution (1,3). In IVDUs patients, who are most likely young and non-compliant, valve replacement is associated with a higher risk of recurrent infection and reoperation (7).

Tricuspid valve repair

Fortunately, TV repair can be accomplished in most cases, even those with extensive valve destruction, using a variety of techniques (7,17,20-22). These include autologous pericardial patch augmentation of the destroyed leaflets, implantation of an annuloplasty ring and expanded polytetrafluoroethylene neo-chords, used as necessary. Contrary to the assumption that implantation of prosthetic annuloplasty rings should be avoided in IE, especially in IVDU patients, risk of reinfection with their use is very low. Dawood *et al.* reported no reinfection in the repair group using an annuloplasty ring, despite high prevalence of IVDUs patients in their population, whereas 21% of patients with TV replacement required late re-operation for prosthetic valve IE (7). Suture annuloplasty to avoid a ring can be expected to result in a higher recurrence of TR and annulus dilatation.

Tricuspid valve replacement

Whilst the choice of prosthesis for TV replacement remains controversial, long-term survival is similar regardless of prosthesis type used in many series (23,24). However, if valve replacement becomes necessary in TVIE, a bioprosthesis is preferable to a mechanical valve, which requires life-long anticoagulation in patients in whom IVDU is predominant and non-compliance is a major issue (1,3,7,17,20-22). If a mechanical valve is implanted, access to the right ventricle for pacemaker leads and pulmonary catheters is also lost.

Tricuspid valve excision

Complete excision of the TV without prosthetic replacement was first described by Arbulu *et al.* (25). They reported 64% survival among 53 IVDUs patients, 22 years after valvectomy (25). However, in up to a third of patients it will cause ascites, peripheral edema and low cardiac output due to right ventricular dysfunction within 6–9 months. Surprisingly, valvectomy accounted for 7.2% of

operations performed for TVIE in North America (3). TV excision for IE should be limited to extreme cases only, and only if pulmonary artery pressure and vascular resistance are not elevated (1). Subsequent valve replacement should be considered once the infection is resolved.

Tricuspid valve surgery and conduction system injury

Injury to the conduction system is a major concern with TV surgery, and the risk is greater in replacement *vs.* repair patients (3,7). TV replacement resulted in significantly more heart block (16%) than did repair (3%, $P < 0.0001$) in 910 operations reported in North America for TVIE from the Society of Thoracic Surgeons database (3). This prevalence of heart block may be higher than it need be: the atrio-ventricular node is localized between the coronary sinus and the membranous septum, and the bundle dives down under the atrial portion of membranous septum in the corner between the membranous septum and the tricuspid annulus where deep suture bites will cause heart block.

Placement of a CIED may be necessary after surgery due to previous or new heart block, but a CIED is an important additional risk factor for reinfection. There is no clear recommendation concerning the optimal timing of CIED implantation/reimplantation. Factors such as persistent bacteremia and pacemaker/CIED dependency should be considered, with the decision individualized to each patient (1,13,14,19). Placement of permanent endocardial leads across a bioprosthesis may result in regurgitation, and is likely to reduce prosthesis durability by causing leaflet fibrosis and retraction. Epicardial leads placed at the time of surgery may prevent these issues and may also have a lower risk of becoming infected. Epicardial lead placement at the time of surgery should be considered when there is heart block that is not resolved in the operating room, or high suspicion of damage to the conduction system and likely need for permanent pacing. Epicardial leads have a higher threshold and drain pacemaker batteries faster.

Management of cardiac implantable electronic device lead infection

CIED lead infections resulting in IE should be evaluated for the possibility of percutaneous removal. Management usually involves CIED, and lead removal and antibiotic therapy. Conservative management of CIED infection with antibiotics alone usually fails and carries increased mortality (13,14). Percutaneous extraction of trans-venous leads is preferable and usually possible. Surgical removal should be performed for patients with TV involvement, or when

the leads are old and seem tethered to the TV. If there is evidence of TVIE on trans-esophageal echocardiography (TEE), the device and leads should be removed (19). If there is a lead mass without a valve lesion, device removal has been advocated by some, based on “lead endocarditis”. However, as mentioned earlier, likelihood of non-infected thrombi or “vegetations” on leads in patients undergoing TEE is very high (1–50%) (19).

Post-operative outcomes

Medical therapy remains the primary treatment and is effective, with surgery reserved for a minority of cases (1,4,19). TVIE has an in-hospital mortality of <10% and long-term mortality of <15% (1,2,19). Continuing IVDU is a significant risk factor for IE recurrence and death. *S. aureus* infection is another independent predictor of poor outcomes (1,5,22), as is hemodialysis (15), valve replacement (*vs.* repair) (7), vegetation >20 mm, fungal etiology and HIV infection with a CD4 count below 200 cells/ μ L (1).

Higher priority of surgery (emergency *vs.* urgent *vs.* elective) could be pointed to as an independent risk factor for early mortality as well (5).

Tricuspid valve infective endocarditis with concomitant left-sided infective endocarditis

RSIE differs from left-sided IE in many ways (3,21,26). RSIE is a more indolent disease and unlike left-sided IE, medical therapy is more effective (1). Reported in-hospital mortality for left-sided IE approached more than 20%, whereas the in-hospital mortality for RSIE is less than 10% (1-3,5,7). Patients with concomitant left-side involvement also are sicker at the time of surgery and have significantly worse clinical outcomes than those with isolated RSIE (5). Musci *et al.* performed 84 operations in 79 patients—for isolated RSIE in 57 and combined right- and left-sided IE in 27 (5). There was a highly significant difference in survival of patients operated on for RSIE compared with those having combined right- and left-sided IE: 30-day, 1-, 5-, 10- and 20-year survival after isolated RSIE operation was 96.2%, 88.4%, 73.5%, 70.4% and 70.4%, respectively, compared with 72.0%, 67.8%, 50.8%, 35.6% and 35.6% after concomitant right- and left-sided IE operation ($P=0.0093$).

Valve repair versus replacement in TVIE

Comparison of valve repair and replacement is challenging

due to a lack of large surgical series for TVIE and lack of data on operation for active *vs.* healed IE. In the STS database study by Gaca *et al.*, patients classified as having healed IE had better 30-day outcomes than those with active IE (3). TV repair was not seen to improve outcomes demonstrably over valve replacement or valvectomy. However, their study was limited by a lack of outcomes beyond the 30-day perioperative period and lack of information about the microbiology or duration of antibiotic therapy, all of which have significant effects on surgical outcomes. Gottardi *et al.* had no perioperative deaths in 22 patients undergoing surgery for active TVIE (17). Late mortality was 0% after repair and 25% after replacement at 53 ± 18 months. Dawood *et al.* found that repair was strongly protective against recurrent TVIE ($P<0.01$), with 21% (5 of 24) recurrent TVIE in the replacement group *vs.* 0% (0 of 32) in the repair group (7). Musci *et al.* reported 20-years experience of surgical treatment of RSIE, and although they did not find a significant difference in survival between the repair and replacement patients, they did show a tendency towards better survival following TV repair (5). There is an increased rate of heart block with TV replacement compared with repair (3,7).

Intravenous drug users

There is often a reluctance to operate on patients with TVIE due to IVDU, and a conservative approach is recommended by many, including current guidelines (1,19). But recurrence is not universal, and reasonable early and mid-term survival can be achieved in this group (7,9,22). Surgical treatment of RSIE, with or without involvement of the left side, can be performed with low risk and good early, mid-term and long-term results (4,5). Isolated TVIE has a similar operative mortality to left-sided IE operations (3), and experienced groups now report even 0% operative mortality for isolated TVIE (7). Similar excellent early and mid-term outcomes have been reported by others (5,17). Such improved survival may reflect earlier diagnosis, better medical management and recognition of specific bacteriologic, anatomic and clinical indications for earlier surgical intervention.

Shrestha *et al.* recently reported a 10-fold higher hazard of death or re-operation between post-operative days 90 and 180 in patients with IVDU compared with non-IVDU patients, driven mainly by operations for recurrence of IE (9). Among patients with IVDU who required re-operation, the majority (63%) were documented to have continued injecting drugs after surgery. Patients with

IVDU who survive the high-risk period appear to have a subsequent hazard of death or re-operation comparable to patients who do not inject drugs. Because IVDU is a major cause of TVIE, the implication of this and other studies is that potential long-term benefits of the treatment of IE will not be realized without more successful treatment of the underlying addiction (9).

Conclusions

When needed, TVIE operations can be performed with low operative mortality and excellent survival. Large vegetations, septic pulmonary embolism and failed medical therapies are more important reasons to operate than severe TV regurgitation. Earlier surgical intervention will prevent further embolism and destruction of TV leaflet tissue, in addition to increasing the likelihood of TV repair.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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