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Review Article

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Right Sided Endocarditis

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Abstract

With the rising prevalence of drug abuse, increasing placement of intravascular catheters and use of implantable cardiac devices, the epidemiology and nature of right sided endocarditis (RSE) has changed over the course of years. RSE due to intravenous drug abuse (IVDU) is an important public health issue and can cause significant economic burden on healthcare facilities. It poses its own unique challenges due to the demographic of the population it affects. Late and varied presentations, lack of access to healthcare and support systems, non-compliance, and ongoing use of drugs, requires a superior logistical and coordinated approach unique to this subset of population to attain good outcomes. While not a novel disease, longstanding controversies with regards to antibiotic regimens, timing of as well as the type of surgery remain. There is paucity of data around outcomes with different treatment modalities. Optimal guidelines for RSE among IVDU are yet to defined. We will examine the predictors of high mortality, with a focus on identifying early, patients that will benefit from surgical management. We will review the available evidence on the outcomes data and efficacy of various surgical interventions that have been described.

Keywords: Right sided endocarditis; Intravenous drug abuse; Infective endocarditis; Tricuspid valve; Tricuspid valve endocarditis

Abbreviations: RSE: Right Sided Endocarditis; IVDU: Intravenous Drug Abuse; IE: Infective Endocarditis; LSE: Left Sided Endocarditis; RSLE: Right And Left Sided Endocarditis; IDUs: IV Drug Users; TV: Tricuspid Valve; TVE: Tricuspid Valve Endocarditis; VS: Vegetation Size; RHF: Right Heart Failure; TR: Tricuspid Regurgitation; MTV: Mechanical Tricuspid Valves; BTV: Bioprosthetic Tricuspid Valve

Introduction

Historically, infective endocarditis (IE) has been a disease predominantly of patients with pre-existing valve disease and community-acquired bacteria. With the emergence of new predisposing factors such as intravenous drug abuse (IVDA), cardiac device and intravascular access device implantations, the epidemiology of IE has changed substantially over the past few years. The microbiological profile is changing with an increase in incidence of S. aureus and Group D streptococci and the rates of S. viridians seem to decrease. There has been increase in rates of early surgical intervention in first three months from about 30% to 50% and decrease in-hospital mortality rate from about 20% to 16% [1-4,11]. Right sided endocarditis (RSE) constitutes 5-10% of all IE with majority of them affecting the tricuspid valve (TV) [2]. IVDA, implanted foreign material such as pacemaker device and unrepaired congenital heart disease have been implicated as the three most common predisposing factors, in that order, for RSE [5]. Up to 86% of IE in IDUs is exclusively right sided with tricuspid valve being the most common culprit [6]. In a prospective study of IE among IV drug users (IDUs), higher rates of IE were found in HIV seropositive IDUs than HIV seronegative IDUs with inverse association between IE rates and CD4 count [9]. S. aureus is the most common infecting organism in RSE, followed by S. viridans and enterococci [5,7,8].

Prognostic Indicators

Presence of concomitant left sided endocarditis (LSE) with RSE has been shown to be a statistically significant independent

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predictor of operative mortality [10]. Patients with isolated RSE have more favorable clinical outcomes with lower early (<30 days) and late mortality (at 1, 5, 10 and 20 years). In the study by Musci, et al. of 20 year single center experience, there were significant differences in survival rates between RSE and RSLE (right and left sided endocarditis) group- the 30 day, 1-, 5-, 10- and 20 year survival rate after RSE operation was 96.2%, 88.4%, 73.5%, 70.4% and 70.4%, respectively, compared to 72%, 67.8%, 50.8%, 35.6% and 35.6% after operation for RSLE (p = 0.0093). This could be explained by greater likelihood of emergency operations, more aggressive nature of disease, high dose inotropic support requirement and higher incidence of intracardiac abscess in RSLE group [11]. Vegetation size (VS) >2.0cm, fungal etiology and age >40 have also been shown to be important predictors of worse outcomes with increase in mortality [7,11,12]. Hecht, et al. retrospectively reviewed 132 episodes of RSE and found that VS > 2.0 cm was associated with higher mortality when compared with vegetations of 2.0 cm or less (33% compared with 1.3%, p < 0.001)

S. aureus has not only emerged as a dominant cause of IE but also an independent predictor of mortality. S. aureus infections are often complicated with large vegetations, more aggressive valve destruction and embolic phenomena resulting in an increased risk of mortality. In the study of 329 IE patients by Cabell, et al. patients with S. aureus IE had a trend towards higher mortality at 30 days compared to the non S. aureus IE group (18.9% vs 14.7%; p=0.31) and a significantly higher 1 year mortality rate (43.9% vs 32.5%; p=0.04) [1,5,13-15]. S aureus prosthetic IE is a very high-risk subgroup with an increase in in-hospital mortality (p<0.01) [13]. In analyses by John, et al. and Chirouze, et al. S. aureus prosthetic IE was associated with increased mortality, as high as 40% and 47.5%, respectively [29,30].

In a prospective study of 116 patients of S. aureus IE, including 30 patients with isolated RSE, Remadi, et al. identified, on multivariate analyses, comorbidity index, congestive heart failure, severe sepsis, prosthetic valve infective endocarditis, and major neurologic events as predictors of in-hospital mortality. Severe sepsis, early surgery and comorbidity index were associated predictors of overall mortality; and the comorbidity index >2 as the only predictor of late mortality.

Management of Right Sided Endocarditis

There are significant differences in treatments of RSE and LSE. Successful management of RSE requires a multispeciality team of cardiology, infectious disease, and cardiovascular surgery as well when indicated.

Prognosis of RSE is relatively good with in-hospital mortality rates of <10% [16,17]. Fortunately most cases of isolated RSE have a favorable prognosis with low in-hospital mortality rate and respond well to medical therapy [7,21]. In the study of 132 episodes of right sided endocarditis by Hecht, et al. of the 102 episodes with known end-point, 92 responded to medical management alone [7]. Current guidelines on the prevention, diagnosis, and treatment of infective endocarditis by the European society of cardiology also suggest a conservative approach over surgery for uncomplicated RSE [27]. RSE is termed as uncomplicated in the absence of intracardiac and extracardiac complications, significant hemodynamic compromise, or persistent infection with highly virulent organisms. The role of early surgical intervention in LSE has been well established. However the indications for surgery and the type of surgery for RSE have been a matter of much debate. This is due to the relatively rare incidence of RSE and with most cases being managed medically, it hard to accumulate enough surgical cases to perform a large-scale analysis.

Commonly cited indications for surgery have been large size vegetation, persistent sepsis, severe right heart failure, fungal etiology, annular abscesses, concomitant LSE and recurrent pulmonary emboli. European Society of Cardiology published guidelines for indications for surgery that include microorganisms difficult to eradicate (e.g. persistent fungi) or bacteremia >7 days (S. aureus, Pseudomonas) despite adequate antimicrobial therapy, persistent TV vegetations >20mm after recurrent pulmonary emboli with or without concomitant right heart failure (RHF), and RHF secondary to severe tricuspid regurgitation (TR) refractory to medical therapy [27]. Some authors suggest that intractable right heart failure and severe sepsis despite antibiotic treatment are the most important indicators for surgery [18]. Leitman, et al. observed that the combination of staphylococcal endocarditis with large vegetations in the older patients was associated with mortality risk of 50%, P= 0.02. The authors concluded that MRSA is the strongest independent predictor of mortality and vegetation size >1.0cm in context of MRSA infection or older age (>60 years) should be considered for early surgical intervention [19].

Robbins, et al. evaluated the prognosis of 23 episodes of RSE with echocardiographic ally predetermined VS. They found that none of the patients with VS <1.0cm required surgery, whereas 4 out of 11 patients (36%) required surgery for persistent pyrexia (p<0.005). The authors suggested that VS >1.0cm in the context of persistent fever identifies patients that will require surgery [20]. Treatment of a fungal case of endocarditis is often delayed due to recurrent negative blood cultures and anti-fungals are often unsuccessful resulting in a need for surgery in many patients. Martin-Davila et al. retrospectively studied 493 cases of RSE. On univariate analysis, it was identified that VS > 2.0cm and fungal etiology are associated with in-hospital mortality. In multivariate analysis, VS >2.0cm (P = .014, OR 10.2, 95% CI 1.6-78.0) and fungal etiology (P = .009, OR 46.2, 95% CI 2.4-1100.9) were also associated with increased mortality and the authors proposed reevaluation of the role of early surgery in such cases [12].

Bayer, et al. noted that the demonstration of tricuspid valve vegetation does identify the subset of patients that are likely

to exhibit longer time to effervescence despite appropriate antimicrobial treatment (12.3 days vs 6.8 days; p<0.005) and are likely to have higher frequency of increased RV end-diastolic (RVED) dimension (>3.0cm)(66% vs 13%; p<0.01). Only patients with increased RVED (20%) required tricuspid valve surgery either for progressive right heart failure or persistent pyrexia. However, vast majority of patients with tricuspid valve endocarditis (TVE) due to S. aureus were cured medically, regardless of the presence of vegetations. Thus, they concluded that although the presence of S. aureus tricuspid valve endocarditis with vegetations (VS>10mm) alone should not dictate early empiric valvular surgery, this subset of patients do require clinical and echocardiographic follow-up for possible short-term and long-term complications [28].

Some studies have revealed reduced mortality rates associated with surgery. Wang, et al. analyzed 35 patients admitted to Auckland City Hospital between 2005-2010 and found that surgical intervention was independently associated with reduced long-term mortality (0.078; 95% CI 0.010-0.609; p=0.015). The in-hospital mortality in the study was 11.4% (n=4), all of which occurred in the medically treated group10. In another study by Remadi, et al. the overall survival for 116 cases of S. aureus IE in the medical group was significantly lower compared with the early surgical group (39% vs. 77% survival at 36 months for a p=0.001). The in-hospital mortality was also lower in early surgery group than the medical one (16% versus 34%; p = 0.034) [13].

While most cases can be cured with medical management alone, the clinical variability, presence of poor prognostic factors and comorbid conditions must also be taken into account. It is important to identify early, the patients that will benefit from surgery, as the prognosis is better before the cardiac function deteriorates [31]. Early surgery has been independently associated with reduced hospital and overall mortality compared with nonsurgical therapy and should be considered in selected cases to improve the outcome. Remadi, et al. suggested, based on their study, the optimal timing for surgery is within 15 days of diagnosis of infective endocarditis [13].

Surgical Outcomes

The surgical management for RSE remains a matter of debate. Surgical options range from total excision of the valve without replacement to valve reconstruction to valve replacement. Vulvectomy without simultaneous prosthetic replacement as first proposed by Arbulu, et al. in 1971 is an aggressive procedure and it allows for complete excision of infected tissue. It may seem reasonable that since the presence of a previously damaged valve with IE may be a favorable predisposing risk factor for recurrent IE with ongoing drug use, absence of valve would eliminate the risk of future infections and re-operation. In the initial series of 53 patients by Arbulu, et al. who underwent tricuspid valvulotomy over the period of 25 years, 49% (24) patients returned to their drug addiction, and 18% (10) died between 6 months to 13 years, of which, 9 deaths were related to continued drug addiction, reflecting the burden associated with relapse to drug abuse. In this series, only 11% (6) patients required prosthetic valve replacement due to medically refractory right heart failure. Of the 39 patients that were alive, 37 had not required prosthetic valve insertion. Actuarial survival at 22 years was 64% and the authors concluded that among IDUs with intractable RSE, tricuspid vulvectomy or tricuspid and pulmonary valvotomy without replacement is the surgery of choice [22]. The consequent tricuspid regurgitation is usually well tolerated by patients, especially if the pulmonary artery pressure is normal [22].

Several case reports have been published since then, where in, this operation has been performed with good early success to control active IE in IVDUs in whom the valve has been destroyed supporting Arbela's study [23-25]. Eventually, 25% of these patients will require valve replacement at a future date due to intractable right heart failure [18,47]. Thus, although tricuspid valve excision may be the procedure of choice in case of extensive valve destruction with severe ongoing sepsis, especially in an IDU patient, a second stage operation with tricuspid valve replacement should be considered, few months to years later depending on the patient's hemodynamic stability and history of continuing drug abuse.

Tricuspid vulvectomy, however, still remains an infrequently performed procedure. In a recent data analysis from 2008 to 2013 of RSE cases by Shi-Min Yuan, valve replacement was the most commonly performed procedure followed by repair and valve debridement5. Another recent study by Gaca, et al. analyzed the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) database between 2002 to 2009 for TV IE operations. A total of 910 procedures were performed, of which, there were 490 TV replacements, 354 TV repairs, and 66 vulvectomy procedures during the study period. Notably, there were no significant different among these groups in operative mortality, complications, and length of stay. The in-hospital mortality for the replacement was 5.71%, for the repair group was 7.06% and for the vulvectomy group was 12.12% (p=0.34). The replacement group (16.33%), however, had significantly higher incidence of heart blocks compared to repair (3.11%) and vulvectomy (0.0%; p<0.0001)) groups [26].

Singh, et al. analyzed the data of 250 patients that underwent surgery for organic TV disease; 178 patients (71%) underwent TV repair and 72 (29%) received TV replacement (54 bioprosthetic, 18mechanical). Perioperative and midterm mortality were higher (both p < 0.001) and event free survival was lower (0.02) in the replacement group [49]. Gottardi, et al. reported excellent midterm results with regard to freedom of recurrence of endocarditis and valvular competence using complex reconstructive techniques in 18 cases of TV endocarditis [53]. Musci, et al. performed 20 TV replacement (17 bioprosthetic and 3 mechanical) and 30 TV reconstruction operations in patients with TV IE. In the

reconstruction group, aggressive debridement of infection was followed by annuloplasty with the use of autologous or homologous pericardium to ensure leaflet coaptation. The authors reported good early, mid- and late-term results. Although there was no significant difference between the 30-day, 1-, 5-, 10- and 20-year survival rates in the two groups (p = 0.43), the survival curves showed a tendency towards better survival following tricuspid valve reconstruction in comparison to the tricuspid valve replacement group in which there is a sudden drop in the survival curve between 7 and 10 years (p=0.48) [12]. Valve repair should be performed whenever possible. In lesions involving more than one leaflet or extensive endocarditic destruction, tricuspid valve reconstruction may be difficult to perform and replacement may be necessary.

In data analysis of 1144 Carbamides mechanical valve implantations, mechanical valves at tricuspid position were found to have a higher chance of thrombosis than those at aortic or mitral position ($p < 0.001$), and thus, at higher risk for re-operation. This might also necessitate higher levels of anticoagulation that may increase the risk of hemorrhagic events. Also, the early and late mortality rate of TV replacement group was significantly higher than that of the aortic valve replacement and mitral valve replacement groups ($p<0.05$) [51]. Tricuspid valve replacement has also always posed challenging questions. Due to the high rate of relapse in IDUs, there is increased risk of re-infection of implanted prosthesis and hence, re-operation. Also, compliance to long-term anticoagulation in this patient population is variable. Complete A-V block is another complication associated with the procedure. In one series of 45 patients with tricuspid valve replacement, 22% (10) required permanent pacing with epicardial (5) or endocardial (5) leads [33].

The choice of the type prosthetic valve also remains a matter of debate. Although bioprosthetic valves in tricuspid position may have better durability than their systemic counterparts, there still remains concerns over their use in young patient population [34]. After the advent of bileaflet mechanical tricuspid valves (MTV), which have lower thrombotic risk compared to the older caged-ball and tilting disk mechanical valves, the prognosis of patients with valve replacement has improved [39]. In the detailed analysis of the effect on survival of the type of prosthetic valve by Van Nooten, et al, there was a significant difference between the bioprosthetic tricuspid valve (BTV) and some older mechanical prostheses ($p = 0.04$) but not between the BTV and the bileaflet mechanical valves ($p = 0.15$).However, when the follow-up period was stratified into less than 7 years and greater than 7 years; in the long-term, the new mechanical prostheses did better than the bioprostheses ($p = 0.05$), suggesting a degradation of the valvular bioprostheses after 7 years [35]. On the contrary, in the meta-analysis of 1,160 prostheses and 6,046 follow-up years by Rizzouli, et al. no significant differences in survival and freedom from re-operation were noted. There was a large heterogeneity in the 11 studies analyzed in the meta-analysis, however, the pooled results showed identical risk for both prosthetic valve types [36]. Anselmi, et al. and Hwang, et al. identified in their respective retrospective analysis that while there was no statistically significant difference in overall survival between the two groups, the MTV group had lower freedom from thromboembolic events than BTV group [37,38].

The higher risk of thromboembolic events by MTV may be offset by the risk of valvular degradation of the bioprostheses. Many authors have favored bileaflet mechanical over bioprosthetic valves, especially, in younger patient population due to longer durability and better hemodynamic characteristics of low-profile bileaflet valves [35,39,40,50]. Also presence of mechanical left-sided valve favors the placement of the mechanical valve on the right side39. On the other hand, limited life expectancy as suggested by the severity of the clinical condition may favor the use of bioprosthetic valve over mechanical valves as pointed out by Carrier, et al. and Moon, et al. [41,50].

No study has definitively demonstrated superiority of one type over the other and the choice of prosthesis is left up to the surgeon's clinical judgment [36,42-44]. The operative and overall mortality of TVR remains high [42,45]. In any case, the pros and cons must be weighed, and the patient profile and preference must be taken into account. Unpredictable compliance to long-term anticoagulation and relapse to drug use are the most serious concerns in IDU patient population. As far as the risk of early or late postoperative prosthetic valve endocarditis is concerned, Grover, et al. have reported no difference in patients receiving the mechanical valve versus those receiving the bioprosthetic valve [46]. In most cases, young IDU patients tend to opt for mechanical valves over bioprosthetic ones due to durability concerns with the bioprostheses and need for re-operation [52]. Vegectomy and tricuspid valve repair offers the benefit of complete eradication of infected tissue, restoration of valvular anatomy, hemodynamic correction, and avoidance of prosthetic material [48]. Several repair techniques have been advocated that are beyond the scope of this review.

Conclusion

Presence of concomitant left sided endocarditis, S. aureus infection, fungal etiology, vegetation size >2.0 cm, age >40 and presence of comorbid conditions are predictors of higher mortality. It is important to recognize early, candidates that will require and will benefit from surgery. The surgical approach and the choice of prostheses are tailored on an individual basis and are left up to the cardiac surgeon's decision. Successful surgical treatment should include radical debridement of infected tissue, closure of defects that have developed and restoration of valve function by repair using homologous or autologous pericardium, or reconstruction annuloplasty. If repair is not possible, then generous valve excision is required followed by concomitant or staged prosthetic valve replacement. The clinical heterogeneity and complexity of IE makes standardization and comparison of

patients difficult and necessitates individualized, patient-tailored assessment and therapy. Successful management of RSE calls for a multidisciplinary approach, especially in the context of drug abuse, poor postoperative compliance, and related comorbidities.

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Conflict of Interest

No conflict of interest.

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