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Active aortic endocarditis in young adults: long-term results of the Ross procedure

Short Title: The Ross procedure in endocarditis

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Abstract

Background. The best valvular substitute remains controversial in young adults with active aortic valve endocarditis. Ross procedure has gained interest because of its theoretical resistance to infection. We aimed to report our long-term outcomes of the Ross procedure in this indication.

Methods. Between March 1992 and January 2019, 511 patients underwent a Ross procedure in our institution. Among them, we included 38 patients who suffered from an active aortic valve infective endocarditis. The mean age was 33.9 ± 8.1 years. Six patients had emergent procedures, 17 patients had perivalvular involvement. Pulmonary autograft was implanted using the full root technique in 78.9% of patients. Median follow-up was 12 years (IQR [1.75 - 16.25]).

Results. The hospital mortality rate was 5.3%. Estimated overall survival was $84.2 \pm 6.6\%$ at 10 years. There were two cases of recurrent endocarditis, both requiring reoperation. Six other patients required reoperation on autograft and/or homograft. Estimated freedom from recurrent endocarditis or reoperation was $89.4 \pm 5.9\%$ at 10 years.

Conclusions. In experienced centers, Ross procedure is a reliable alternative to prosthetic or homograft valve replacement in young adults suffering from active aortic valve endocarditis, with a low operative risk and good long-term results.

Abstract word count: 195

Infective endocarditis is a rare and serious condition, associated with high morbidity and mortality^{1,2}. Aortic valve (AV) is involved in 40 to 67% of cases³⁻⁵. Surgical treatment is indicated in the active phase in case of uncontrolled infection, perivalvular involvement, heart failure, or to prevent emboli from large or mobile vegetation⁶. AV repair is restricted to highly selected patients^{5,7}. Thus, prosthetic valve replacement is currently performed in the majority of patients.

Guidelines do not favor any particular valvular substitute, but recommend a tailored approach for each situation⁶. In young adults, the choice between AV substitutes remains controversial⁸. Homografts have been suggested by some authors as the best substitute⁹⁻¹³, but their scarce availability and the concern for their durability in young adults have limited their use. Besides, mechanical valves are associated with a risk of bleeding complications between 0.5 and 2% per patient-years¹⁴⁻¹⁷, whereas bioprostheses expose young adults to a high risk of early structural valve deterioration and to several reoperations^{18,19}.

The Ross procedure allows for the implantation of an autologous AV substitute, offering excellent hemodynamic performances and long-term durability²⁰. However, this operation is rarely performed in the context of infective endocarditis²¹⁻²⁷.

The aim of this study was to review our 27 year-experience of the Ross procedure, in the setting of active aortic valve infective endocarditis (AIE).

Patients and Methods

Study population

Between March 1992 and January 2019, 511 patients underwent a Ross procedure in our institution. Among them, we included 38 patients who suffered from an active AIE, operated before the end of the antibiotic treatment as defined by the 2015 ESC Guidelines⁶. The mean age was 33.9 ± 8.1 years (range 18 to 53 years). The diagnosis of AIE was made according to the modified Duke criteria²⁸, including clinical, echocardiographic and microbiological evaluations²⁹. Preoperative patients' characteristics and echocardiographic data are detailed

in Table 1. Six patients were operated emergently, including four patients with cardiogenic shock and two patients with septic shock.

Microbiological data are detailed in Table 2. A causative microorganism was identified in 31 patients (81.6%). The portal of entry of the microorganisms was known in 24 patients (63.2%). The median time between antibiotic therapy and surgery was 9 days [2.0 – 20.25].

Surgical technique

The procedures were performed through a median sternotomy under normothermic cardiopulmonary bypass. Myocardial protection was achieved with intermittent antegrade infusions of cold blood cardioplegia.

To ensure removal of all infected tissues, the surgeon carefully inspected all valves, and debrided all abscesses and necrotic tissues.

During the first part of our experience, pulmonary autograft was implanted using the subcoronary technique³⁰ in 3 patients (7.9%) or the full root replacement technique³¹ in 30 patients (78.9%). In 2003, we introduced a modified root replacement technique³², with an inclusion of the autograft in a Valsalva Dacron graft (Vascutek Gelweave Valsalva; Terumo Aortic, Glasgow, UK). This modified technique was used in 5 selected patients (13.2%), in case of good infection control without any perivalvular involvement.

The right ventricular outflow tract was reconstructed in 21 patients (55.3%) using a cryopreserved pulmonary homograft when available (European Homograft Bank, Clinique Saint Jean, Brussels, Belgium), or with a stentless porcine root otherwise³³. Perioperative data are summarized in Table 3.

Follow up

Follow-up was closed on June 2019 and was 97% complete. One patient was lost to follow-up because he moved away from France. Clinical data were collected by phone contact with the patient or the referring physician. Echocardiographic evaluations were performed and prospectively collected before discharge and annually afterwards.

Morbidity and mortality were reported according to the 2008 guidelines³⁴. The median clinical follow up was 12 years [1.75 - 16.25], ranging from 0 to 24 years. Cumulative follow-up was 456 patients-years.

The Ethics committee approved this retrospective study and patient consent was waived.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 20.0 (SPSS Inc. Chicago, USA). Continuous variables are expressed as means \pm standard deviations in case of normal distribution, or median [quartiles] otherwise. Categorical variables are expressed as absolute numbers (proportions). Cumulative survival probability and freedom from reoperation or recurrent endocarditis were estimated using the Kaplan-Meier method.

Results

Postoperative course and early mortality

One patient required a postoperative extracorporeal life support during three days, because of a low cardiac output; he was operated emergently because of a septic shock. One patient had a chest exploration for bleeding, and one patient needed a permanent pacemaker implantation for a new onset complete atrioventricular block.

All cause early mortality rate (before 30 days) was 5.3% (2 patients). The first patient died on day 0 after surgery from multiorgan failure; he suffered from a double valve endocarditis with coronary emboli and was operated emergently because of a cardiogenic shock. The second patient died on day 5 from ventricular fibrillation; he had a preoperative dilated cardiomyopathy with poor systolic left ventricular function.

Late mortality

There were five late deaths during follow up. Two patients died from lung cancer, one patient from cirrhosis, one patient from meningeal hemorrhage and one patient from unknown origin 8 years after surgery. Estimated overall survival was $84.2 \pm 6.6\%$ at 10 years and $72.9 \pm 9.5\%$ at 20 years (Figure 1).

Late echocardiographic follow up

Freedom from moderate to severe aortic regurgitation was $89.6 \pm 5.7\%$ at 5, 10 and 15 years. Freedom from severe pulmonary structural valve dysfunction was $80.0 \pm 12.6\%$ at 15 years. Freedom from autograft dilation as defined by an autograft diameter > 50 mm at 10 and 15 years were $88.1 \pm 7.9\%$ and $78.4 \pm 11.6\%$ respectively.

Recurrent endocarditis

Two patients (5.3%) developed recurrent endocarditis. The two cases presented a severe aortic regurgitation that necessitated an urgent reoperation. The first patient underwent a mechanical aortic valve replacement 7 months after initial surgery. The second patient had a reinfection on the two sides (autograft and homograft) 6 years after initial surgery, which required a mechanical Bentall on the left side and a homograft replacement by a valved graft on the right side. Both patients are alive at last follow-up and have not showed recurrent endocarditis.

Reoperations

Six other patients underwent late reoperations, detailed in Table 4. Postoperative course after those reoperations was uneventful. Every patients reoperated on the autograft previously underwent a full root replacement. Estimated freedom from recurrent endocarditis or reoperation was $89.4 \pm 5.9\%$ at 10 years and $83.0 \pm 8.2\%$ at 15 years (Figure 2).

Comment

In the setting of AIE in young adults, the choice of the optimal valve substitute remains controversial. In case of infection limited to leaflets, bioprosthesis or mechanical AV replacement can be safely performed. However, the management of a lifelong anticoagulation associated with mechanical prostheses may be challenging in this population, because of their potential comorbidities (intravenous drug user, social issues) or because of endocarditis-related neurological complications. On the other hand, early bioprosthetic valve structural deterioration is a serious concern in young adults. In a recent meta-analysis, Takkenberg et al³⁵ included 2696 patients aged less than 55 years who

received an aortic bioprosthesis and reported a pooled structural valve deterioration rate of 1.59%/year.

When perivalvular structures are involved, left ventricular outflow tract can be reconstructed using an aortic homograft, with good early results and a low risk of recurrent endocarditis. Nevertheless, homografts have a limited durability and their wall calcification over time may complicate redo surgeries. El Khoury et al ¹¹ recently reported a rate of 5.3% recurrent endocarditis and a freedom from deterioration or reoperation of 47.3% at 15 years, after aortic homograft implantation for active infective endocarditis in 112 patients.

In young adults, the Ross procedure provides an autologous tissue valve with good hemodynamic performances and high resistance to infection. In case of perivalvular involvement, it allows a reconstruction of the left ventricular outflow tract without needing any prosthetic or pericardial patch. Despite the complexity of the procedure, operative mortality is low in experienced centers, and long-term survival is comparable to the general population³⁶⁻³⁸.

Only a few series specifically reported results of Ross Procedure in active endocarditis. In our study, hospital mortality was low (5.3%) compared to high estimated surgical risk (median Euroscore II of 8.5%). This high mortality rate for Ross procedure in endocarditis patients was also reported by Stelzer et al. ³⁹. Indeed, in this series of 530 Ross procedures, hospital mortality occurred only in patients with endocarditis. Infective endocarditis was found to be a strong independent predictor of mortality with an Odds Ratio of 5.2.

In our series, the hospital mortality could have probably been reduced with a more drastic selection of patients; the two patients who died postoperatively suffered either from uncontrolled septic shock or from dilated cardiomyopathy, and a salvage prosthetic AV replacement may have been more relevant. Actually, we reserve the Ross procedure to young patients without septic choc, multi-organ failure, poor LVEF or significant comorbidities. In our opinion, intravenous drug use is not considered as a contraindication to the Ross Procedure since we have not observed any recurrence in this subgroup of patients. Despite the severe infective parameters in our series (active infective endocarditis in all

patients, 44.7% of perivalvular involvement), we only recorded two cases (5.3%) of recurrent endocarditis, which emphasizes an excellent resistance of the autograft to infections.

Our results are comparable with those published by Ratschiller et al ²⁴, who included 19 patients with an active infective endocarditis. They reported an operative mortality of 5.3%, no case of recurrent endocarditis and a freedom from reoperation of 87.4% at 10 years.

The main issue of the Ross procedure is the risk of reoperation on autograft, estimated at 0,78% per patient-year ³⁸. Reoperations are mostly due to a neoartical root dilatation, especially in the freestanding root technique. With the recent modified aorta or Valsalva graft reinforcement techniques, this progressive autograft dilatation may be avoided^{32,40}. In our series, Valsalva graft reinforcement achieved good midterms results in terms of durability but long terms data are lacking. It was not associated with a higher risk of recurrent endocarditis. This modified technique should however be avoided in cases of extensive perivalvular involvement.

When the Ross procedure has to be performed emergently, pulmonary homograft are often unavailable and can be substituted by a large diameter stentless porcine bioprosthesis, as previously described by Juthier et al³³.

The main limitations of our study are its retrospective design, the lack of control group and the small sample size. Thus, the results cannot be extended to the general population.

Conclusion

In the setting of active aortic valve endocarditis, the Ross procedure seems to achieve good short and long-terms results in very well selected patients and in high volume centers.

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Table 1. Preoperative characteristics (n = 38)

Patients' characteristics	
Age, years	33.9 ± 8.1
Male gender	36 (94.7%)
Intravenous drug use	4 (10.5%)
Smoking	28 (73.7%)
Overweight (BMI ≥ 25 kg/m ²)	16 (42.1%)
Euroscore II, %	8.5 [7.7 – 13.8]
NYHA class III-IV	12 (31.6%)
Emergency procedure	6 (15.8%)
Prosthetic valve endocarditis	4 (10.5%)
Indications for surgery	
Congestive heart failure	14 (36.8%)
High degree atrioventricular block	3 (7.9%)
Uncontrolled infection	14 (36.8%)
Systemic embolization	17 (44.7%)
Cerebral embolization	9 (23.7%)
Preoperative echocardiographic findings	
30% ≤ LVEF ≤ 50%	11 (28.9%)
LVEF > 50%	27 (71.1%)
Aortic regurgitation > Grade 2	36 (94.7%)
Suspicion of abscess	15 (39.5%)
Vegetation length ≥ 15 mm	12 (31.6%)

NYHA: New York Heart Association. LVEF: Left Ventricular Ejection Fraction.

Table 2. Microbiological characteristics (n = 38)

Isolated microorganism	
<i>Streptococcus</i> species	17 (44.7%)
<i>Staphylococcus aureus</i>	4 (10.5%)
<i>Staphylococcus</i> coagulase-negative	5 (13.2%)
Other ^a	5 (13.2%)
Negative blood and valve cultures	7 (18.4%)
Septic focus	
Dental	16 (42.1%)
Cutaneous	3 (7.9%)
Gastrointestinal	3 (7.9%)
Genitourinary	2 (5.3%)
Unknown	14 (36.8%)

^a *Gemella morbillorum*, *Tropheryma whipplei*, *Propionibacterium acnes*.

Table 3. Perioperative data (n = 38)

Cardiopulmonary bypass time, min	160.4 ± 7.6
Aortic cross clamp time, min	130.5 ± 5.4
Perivalvular abscess	17 (44.7%)
Bicuspid aortic valve	25 (65.8%)
Associated procedures	
VSD closure (autologous pericardial patch)	3 (7.9%)
Bivalvular endocarditis	7 (18.4%)
Mitral valve vegetectomy	3 (7.9%)
Mitral valve repair (autologous pericardial patch)	3 (7.9%)
Tricuspid valve replacement (mitral homograft ^a)	1 (2.6%)
Autograft implantation technique	
Subcoronary implantation	3 (7.9%)
Full root replacement	30 (78.9%)
Modified Valsalva reinforcement	5 (13.2%)
RVOT reconstruction	
Cryopreserved pulmonary homograft ^a	21 (55.3%)
Stentless porcine root prosthesis	
Medtronic Freestyle (Medtronic, Dublin, Ireland)	15 (39.5%)
St Jude Toronto (Abbott, Chicago, USA)	1 (2.6%)
Shelhigh root (Shelhigh Inc., Millburn, USA)	1 (2.6%)

VSD: Ventricular Septal Defect. RVOT: Right Ventricular Outflow Tract.

^a Provided by European Homograft Bank (Brussels, Belgium)

Table 4. Reoperations after the Ross procedure (n = 8)

Indications for reoperation	Time after Ross	Redo procedures
Severe AR (recurrent endocarditis)	7 months	Mechanical AVR
Autograft and homograft recurrent endocarditis	6 years	Mechanical Bentall and PVR
Autograft dilatation (50 mm) and moderate AR	20 years	Bio-Bentall
Autograft dilatation (50 mm)	21 years	Bio-Bentall
Severe MR and moderate homograft stenosis	16 years	Mitral valve repair and PVR
Autograft dilatation and severe homograft stenosis	14 years	David procedure and PVR
Autograft dilatation and severe homograft stenosis	17 years	Bio-Bentall and PVR
Autograft severe AR (prolapse)	4 years	Mechanical AVR

AR: Aortic valve regurgitation. PVR: Pulmonary valve replacement.

AVR: Aortic valve replacement. MR: Mitral valve regurgitation.

Figures legends

Figure 1. Kaplan-Meier plot of estimated overall survival (estimation \pm standard deviation).

Figure 2. Kaplan-Meier plot of estimated freedom from recurrent endocarditis or reoperation (estimation \pm standard deviation).



