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ORIGINAL ARTICLE

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The Ross procedure in young adults: over 20 years of experience in our Institution[†]

Stefano Mastrobuoni*, Laurent de Kerchove, Silvia Solari, Parla Astarci, Alain Poncelet, Philippe Noirhomme, Jean Rubay and Gebrine El Khoury

Department of Cardiovascular and Thoracic Surgery, St Luc's Hospital, Catholic University of Louvain, Brussels, Belgium

* Corresponding author. Department of Cardiovascular and Thoracic Surgery, St Luc's Hospital, Avenue Hippocrate 10, 1200 Brussels, Belgium. Tel: +32-2-7646101; fax: +32-2-7643703; e-mail: stm919@mail.harvard.edu (S. Mastrobuoni).

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Abstract

OBJECTIVES: The aim of this study was to evaluate the long-term outcomes following the Ross procedure in young adults in our institution.

METHODS: All adult patients who received a Ross operation between 1991 and 2014 were included in the study. Survival analysis and regression analysis were performed. Survival of the Ross cohort was compared with the age-, gender- and calendar year-matched general population.

RESULTS: Three hundred-and-six patients (mean age: 41.7 ± 9.7, male: 74.8%, bicuspid aortic valve: 58.5%, valve stenosis: 68%) were included in the analysis. There were 7 perioperative deaths (2.3%). Nine patients were lost to follow-up from hospital and completeness of the follow-up was 94%. The median follow-up of the remaining 290 patients was 10.6 years. There were 21 late deaths of which only 3 were valve-related. The overall survival at 15 years since surgery is 88 ± 3% that is comparable with the matched population. Freedom from valve-related deaths was 96.8 ± 2% at 16 years. Freedom from autograft and pulmonary homograft reoperation was 74.5 ± 4.3% at 16 years. Preoperative aortic regurgitation was the only significant predictor of autograft failure over time. Freedom from the combined end point of bleeding/thromboembolism/endocarditis/reoperation was 69.2 ± 4% at 16 years. Perioperative mortality following reoperation was 2.6% and the autograft could be spared in 72% of reinterventions.

CONCLUSIONS: The Ross operation in young adults is associated with an excellent survival in the long term that is comparable with the general population. Although there is a risk of reoperation, incidence of other valve-related events is very low. The use of pulmonary autograft should be considered in any young adult patient requiring aortic valve replacement.

Keywords: Ross procedure • Survival • Long-term outcomes

INTRODUCTION

Aortic valve replacement with the pulmonary autograft, also known as Ross procedure, consists in replacement of the diseased aortic valve with the patient's own pulmonary valve while the latter is usually replaced by a pulmonary homograft. Supposedly, the autograft is the closest substitute to the native valve in terms of physiology and haemodynamic profile, and has no need for anticoagulation [1–3]. Despite these proposed advantages, the technical complexity and the risk of reintervention over time of the autograft, the pulmonary homograft or both [4], have limited its widespread use and the procedure is rarely performed in the USA while it is confined to some centres of excellence in Europe and elsewhere [5].

The aim of this study is to evaluate more than 20 years of experience with the Ross procedure in our institution with particular attention paid to the survival and the risk of valve-related complications over time.

MATERIALS AND METHODS

All adult patients (>18 years of age) who underwent the Ross operation between June 1991 and January 2014 at two hospitals (Cliniques Universitaires Saint-Luc and Cliniques Universitaires Mont-Godinne, Belgium) of the Catholic University of Louvain by two senior surgeons (Jean Rubay and Gebrine El Khoury) were included in this analysis. During this period, the Ross operation was offered to all adult patients with an age up to 55 years requiring aortic valve replacement. This procedure was also considered for older patients (up to 60 years of age) who specifically asked for. Contraindications to this procedure were anomalies of the pulmonary valve detected on preoperative echocardiogram or at intraoperative exploration, and significant comorbidities such as

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morbid obesity and severe chronic obstructive pulmonary disease that make a shorter operation more advisable. Pure aortic regurgitation and a native bicuspid valve were not a contraindication. After discussing the pros and cons of the Ross operation and of conventional aortic valve replacement with either a mechanical or a biological prosthesis, patient's informed consent was obtained. On average, about one-fourth of the eligible patients preferred a valve replacement with prosthesis.

During the study period, both surgeons had a similar surgical approach. The root and inclusion technique have been previously described [6]. Since 2010, we routinely stabilize the autograft through inclusion in a Gelweave Valsalva™ graft (Vascutek, Inchinnan, UK). The technique of Valsalva inclusion has been previously described [7]. The right ventricular outflow tract (RVOT) was reconstructed with a cryopreserved pulmonary homograft in 288 patients (94.1%) and with a stentless xenograft (Medtronic Freestyle® tissue valve, Minneapolis, MN, USA) in 18 cases (5.9%) due to homograft unavailability. Perioperative and postoperative management were also similar in the two hospitals.

The clinical follow-up data were collected by a questionnaire sent to all the patients. When the questionnaire was not returned or incomplete, phone contact was made with the patient or the referring physician. Subsequent hospitalization and routine visit data were collected from hospital records and cardiologists' reports.

The follow-up time was calculated either to death or to the last verified contact with the living patient. The follow-up time for valve-related events was calculated until the last valid assessment of these complications. For the purpose of the study, the follow-up period was closed in June 2014 as to have at least 6 months of the potential follow-up for the last patients operated in 2013. Completeness of the follow-up was calculated according to Clark *et al.* [8]. Morbidity and mortality were reported according to the 2008 Society of Thoracic Surgeons/American Association for Thoracic Surgery/European Association for Cardio-Thoracic Surgery guidelines [9]. Early mortality was defined as any death occurring during hospital stay or during the first 60 days after the operation while any other death was considered a late death. Clinical outcomes of interest included the incidence of systemic embolism, bleeding event, endocarditis and reoperation on the aortic or pulmonary valve for any cause. Reoperations were defined as reinterventions and catheter-based valve procedures on the autograft or the RVOT substitute.

Statistical analysis

Continuous variables were reported as the mean ± SD for variables with a normal distribution or as median and interquartile range (IQR) for non-parametric distributions. Categorical variables were reported as proportions. Survival was estimated with the life-table method in order to compare with the expected survival of a gender-, age- and calendar year-matched Belgian population (estimated with the Conditional method (Ederer II) by means of the mortality rates published by the Human Mortality Database on www.mortality.org, accessed on 1 September 2014). Time-to-event analysis was performed with the product-limit method (Kaplan–Meier). A proportional hazard model (Cox regression) was built to identify significant predictors of reoperation on the autograft or the RVOT substitute over time and predictors of late death. The covariates to include into the final model were selected with a forward stepwise automatic procedure with a probability of entry into the model of 0.15 and a probability of stay of 0.2. Clinically meaningful covariates [age, body mass index (BMI), aetiology of aortic valve disease, bicuspid valve, New York Heart Association functional class, degree of aortic insufficiency, previous aortic valve procedure, predominant form of valve disease (regurgitation vs stenosis) and previous infective endocarditis] and operative variables (use of homograft vs xenograft for RVOT substitute, associated procedures, technique of autograft implantation) were considered for inclusion into the model. The assumption of proportional hazard was checked through the interaction of the candidate predictor with time. Difference in freedom from reoperation on the pulmonary autograft for patients with predominant aortic stenosis versus patients with predominant aortic insufficiency at the time of surgery was assessed by means of the log-rank test.

Results were considered statistically significant at a *P*-value of ≤0.05.

All analyses were conducted with STATA 11.2 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 306 patients were included in the analysis. Patient characteristics and intraoperative data are presented in Tables 1 and 2.

Table 1: Preoperative characteristics of Ross patients

	n = 306
Mean age ± SD (years)	41.7 ± 9.7
Age group [*n* (%)]	
<30	47 (15.4)
30–50	193 (63.1)
≥50	66 (21.5)
Male (%)	229 (74.8)
Predominant lesion (%)	
Stenosis	208 (68)
Regurgitation	96 (31.3)
Unknown	2 (0.7)
Aetiology (%)	
Bicuspid valve	179 (58.5)
Degenerative	48 (15.7)
Rheumatic	16 (5.2)
Infective endocarditis	25 (8.2)
Prosthetic valve dysfunction	24 (7.8)
Unknown	14 (4.6)
Previous aortic valve intervention (%)	28 (9.2)
Body mass index (kg/m^2) (mean ± SD)	26.3 ± 4.7
Missing values	16 (5.2%)
NYHA functional class (%)	
I	77 (25.1)
II	138 (45.1)
III	84 (27.5)
IV	6 (2)
Missing values	1 (0.3)
Grade of aortic regurgitation [*n* (%)]	
0	77 (25.2)
I	50 (16.3)
II	65 (21.2)
III	99 (32.4)
IV	13 (4.2)
Missing values	2 (0.7)
Left ventricular ejection fraction (%)	
≥50	175 (57.2)
31–49	9 (3)
≤30	0
Missing values	122 (39.8)

Early mortality was 2.3% ($n = 7$). Causes of early death were as follows: 3 cardiogenic shock, 1 respiratory failure, 1 multiorgan failure, 1 haemorrhagic stroke, 1 sudden death.

Nine patients (3%) were lost to the follow-up after 60 days following discharge from hospital. Most of these patients came from abroad, and were referred to our centre for surgery only. The completeness of the follow-up for the remaining 290 patients was 94%. The median duration of the follow-up was 10.6 years (IQR: 4.3–14.8 years) with a total cumulative follow-up of 2938 patient-years.

Long-term survival

There were 21 deaths (7.2%) during the follow-up with a linearized mortality rate of 0.7% patient-year. Three deaths were valve-related (1 due to bacterial endocarditis of both the autograft and the pulmonary homograft, 1 sudden unexplained death and 1 following reoperation on both the autograft and the pulmonary homograft for late failure); 18 deaths were from non-cardiac causes: 9 cancer, 4 infection, 3 alcoholic hepatic cirrhosis, 1 for complications of Alzheimer's disease and 1 trauma. Therefore, freedom from valve-related deaths was 96.8 ± 2% at 16 years since surgery.

Table 2: Operative characteristics of Ross patients

	$n = 306$
Operative technique [*n* (%)]	
Sub-coronary implantation	7 (2.3)
Root	168 (54.9)
Inclusion	131 (42.8)
Cylinder	116 (37.9)
Graft	15 (4.9)
Mean cardiopulmonary bypass time ± SD (min)	163 ± 65
Mean cross-clamp time ± SD (min)	113 ± 56
Concomitant procedures [*n* (%)]	54 (17.7)
Mitral valve repair [*n* (%)]	22 (7.2)
CABG [*n* (%)]	16 (5.2)
Other [*n* (%)]	18 (5.9)

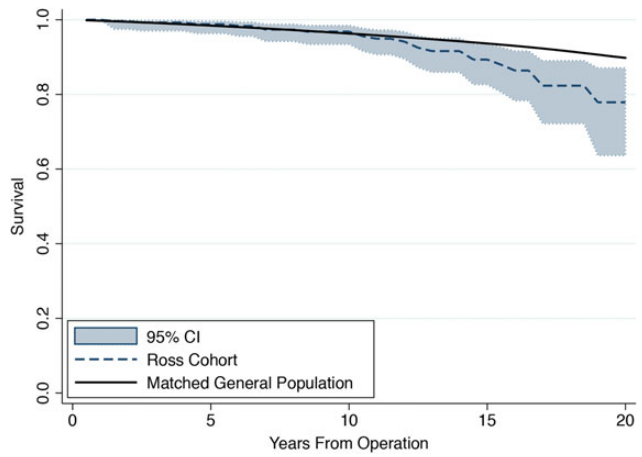

Figure 1: Long-term survival of the Ross cohort including those who underwent autograft replacement during the follow-up (dashed line, with 95% CI of the survival estimates) and that of the age-, gender- and calendar year-matched general population (solid line).

Overall survival is depicted in Fig. 1 together with the expected survival of the age-, gender- and calendar year-matched Belgian population. The two curves start to diverge at 10 years since surgery and the difference becomes statistically significant at 15 years when the cumulative relative survival ratio (RSR) is 0.93 (95% CI: 0.84–0.99). Cumulative RSR at 20 years after surgery is 0.87 (95% CI: 0.71–0.97). Nevertheless, multivariate Cox-regression analysis failed to identify any significant predictor of late death.

Valve-related complications

No patient presented valve thrombosis but systemic embolism or major bleeding events occurred in 20 patients (6.9%) during the follow-up: 10 stroke, 6 transient ischaemic attack and 4 bleeding, although none of these events were fatal. The linearized rate of thromboembolic/bleeding events was therefore 0.7% patient-year.

Three patients (1.03%) presented infective endocarditis (1 on the autograft that underwent replacement, 1 on the pulmonary homograft that was successfully treated with antibiotics and 1 on both valves that died without surgery). The linearized rate of bacterial endocarditis was therefore 0.1% patient-year.

Reoperation

There were no early (during the same hospitalization) but 39 (13.4%) late aortic or pulmonary valve reoperation (28 on the autograft, 3 on the pulmonary homograft and 8 on both valves) for a linearized rate of autograft/pulmonary valve reintervention of 1.4% patient-year. Median interval of reoperation was 9.1 years (IQR: 5.3–13.4 years).

Indications for reoperations were as follows: severe aortic regurgitation ($n = 20$, associated with ascending aorta dilatation in 7 cases), root dilatation with varying degrees of aortic insufficiency ($n = 15$), isolated pulmonary homograft stenosis ($n = 2$), endocarditis ($n = 1$) and stenosis of the distal anastomosis of the pulmonary homograft ($n = 1$). Concomitant moderate-to-severe pulmonary regurgitation or stenosis was present in 8 cases.

The pulmonary autograft was repaired in 26 cases (72%) by means of valve-sparing root replacement (14 reimplantation technique, 1 remodelling) or cusp repair ($n = 11$). Further, the autograft was repaired in 14 (82%) out of 17 patients re-operated in our centre. In the remaining 10 cases, the aortic valve was replaced by a mechanical prosthesis ($n = 4$), Bentall operation ($n = 2$), aortic homograft ($n = 2$), biological prosthesis ($n = 1$), stentless xenograft ($n = 1$).

The pulmonary homograft was replaced by another homograft in 7 cases and by a stentless xenograft in 2 cases. Percutaneous transcatheter balloon dilatation of the pulmonary homograft and enlargement of the pulmonary artery with a pericardial patch were performed in 1 case each. Perioperative mortality at reintervention was 2.6% ($n = 1$).

Three patients underwent a second valve reoperation due to recurrence of aortic regurgitation after autograft repair in 2 cases and following replacement with a homograft in 1 case. Three more patients underwent 5 mitral valve replacements during the follow-up.

Freedom from reoperation on the autograft and from reoperation on the RVOT was 75.6 ± 4.3% and 90.5 ± 3.5%, respectively at 16 years. Nevertheless, freedom from autograft reoperation was significantly better for patients with predominant aortic valve

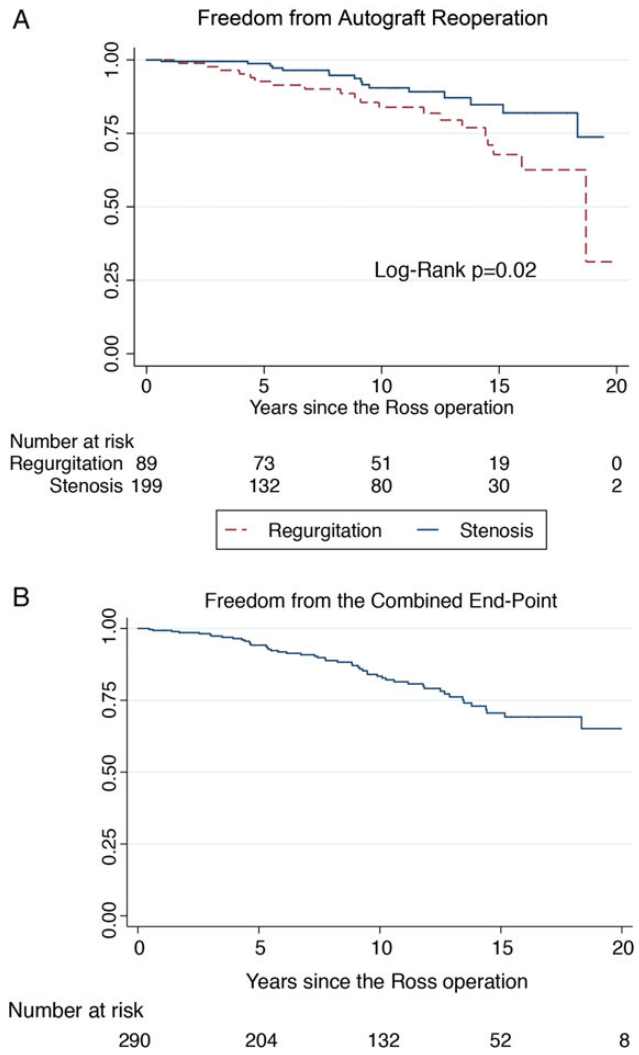

Figure 2: (**A**) Kaplan–Meier curve representing the freedom from reoperation on the autograft/RVOT substitute over time according to the predominant form of aortic valve disease. (**B**) Kaplan–Meier curve representing the freedom from the combined end point of major bleeding/systemic thromboembolism/endocarditis/reoperation on the autograft/RVOT. RVOT: right ventricular outflow tract.

stenosis compared with patients with predominant insufficiency at the time of surgery (Fig. 2A) (82.7 ± 5.1 vs 65.3 ± 7.6, $P = 0.02$).

Freedom from any valve (autograft or pulmonary homograft) and from all cardiac reoperation were 74.5 ± 4.3% and 70.6 ± 4.5%, respectively at 16 years. Nevertheless, freedom from autograft replacement was 92.0 ± 2.5% at 16 years. Freedom from the combined end point of bleeding/thromboembolism/endocarditis and reoperation was 69.2 ± 4% at 16 years (Fig. 2B).

Univariate Cox-regression analysis revealed aortic regurgitation as predominant form of valve disease, and young age at operation as significantly associated with late autograft failure. Other covariates including bicuspid aortic valve, previous aortic valve surgery, gender and BMI were not significantly correlated with autograft failure. Nevertheless, at multivariate analysis only aortic regurgitation was still significantly associated with late autograft failure with a hazard ratio (HR) of 2.02 (95% CI: 1.04–3.94). The technique of autograft implantation (root vs inclusion) is not associated with the risk of late failure.

Significant risk factors for RVOT substitute reoperation over time are previous endocarditis (HR: 8.5, 95% CI: 1.7–43.9), younger age at operation (HR: 0.9, 95% CI: 0.82–0.99) and BMI (kg/m^2) (HR: 1.13, 95% CI: 1.01–1.26). The use of pulmonary homograft vs stentless xenograft is not associated with risk of late RVOT reoperation.

Echocardiographic studies

Two hundred and fifteen patients (85.7%) out of 251 who did not require reoperation on the autograft/RVOT substitute had a transthoracic echocardiogram at a median follow-up of 9 years (IQR: 4–13 years). At last available echo, 188 patients (87.4%) had none or mild (<2+/4) aortic insufficiency (AI) while 27 (12.5%) presented ≥2 AI. Notably, only 1 patient had a 3+ AI and none had severe AI. Further, 21 patients (9.8%) presented ≥2+ pulmonary homograft regurgitation and only 7 patients (3.3%) presented a peak gradient through the pulmonary homograft >40 mmHg.

DISCUSSION

The choice of a valve substitute for aortic valve replacement in young adults (<60 years of age) can be particularly challenging. On the one hand, a bioprosthetic valve, whether stented or homograft, has been associated with over 50% risk of reoperation at 15 years with the highest risk of reoperation in patients less than 40 years of age [10, 11]. On the other hand, mechanical prostheses have a low risk of reoperation but carry a significant risk of valve-related complications in the long-term, namely bleeding and thromboembolic events. With both types of valve prostheses, long-term survival is lower than the expected survival of the age- and gender-matched reference population [12–14].

Our analysis has revealed that aortic valve replacement with the pulmonary autograft is associated with 88 ± 3% survival at 15 years, including those patients who required reoperation during the follow-up which although different well compares to that of the general matched population. It is also noteworthy that the whole cohort showed an excellent survival despite the fact that 9.2% of patients had had a previous aortic valve procedure and 12.4% of patients had concomitant mitral or coronary surgery.

Previous reports [15–17] have observed a median survival at 15 years after the Ross operation of ∼93%, comparable to the age- and sex-matched reference population. Difference in mean age at operation (42 years in our series vs 36 in Andrea *et al.*'s and 34 in David *et al.*'s series), in the mean follow-up (∼8 years in Andrea *et al.*'s vs 10 years in ours) and nonetheless intrinsic differences in the reference populations may account for this difference between the series. Long-term survival in our cohort is also similar to that reported by da Costa *et al.* [18].

Mokhles *et al.* [19] have shown in a propensity-score matched analysis that survival after the Ross procedure and after mechanical valve replacement were similar and were also comparable to that of the general population. However, it must be noted that an important selection bias may affect the results of this study. On the one hand, the Ross cohort was indeed a heterogeneous group of patients included in the German-Dutch Ross Registry and coming from 12 different centres with different expertise with the Ross operation. On the other hand, the mechanical-aortic valve replacement (m-AVR) patients came from a single centre, and were enrolled in the early self controlled anticoagulation trial II trial with optimal anticoagulation self-management. Moreover, the mean follow-up of Ross patients and m-AVR were only 5.1 and 6.3 years

respectively, which is too short a period to see a significant difference in survival in a population of young patients. Furthermore, Andreas *et al.* [20] have showed that in a real-world setting where the oral anticoagulation of patients with a mechanical aortic valve is managed by family doctors or laboratories, survival with the Ross operation was significantly better than m-AVR at 15 years (93 vs 75%) and was also comparable with that of the general population. We consider the Ross operation a better option compared with m-AVR in any young adult patient in the 'real-world' setting whenever aortic valve replacement is indicated. Regression analysis failed to identify significant predictors of late deaths but a very low incidence of valve-related complications such as bleeding, thromboembolism and infective endocarditis should be necessarily linked to the improved survival of the Ross cohort. Incidence rates of these complications in our series are also similar to the pooled estimates of the meta-analysis by Takkemberg *et al.* [4]. However, it is noteworthy that except for 1 case of endocarditis and 1 reoperation on the autograft, these complications were never fatal.

The risk of reoperation on the autograft or the RVOT substitute is a major objection to this procedure. Our series shows similar results to previous reports [15, 18] in terms of long-term freedom from valve reoperation but are significantly lower than the results reported by Charitos *et al.* [21] and David *et al.* [16]. Different patient characteristics, aortic valve and root pathology, technique of implantation of the autograft and nonetheless surgeon experience probably account for this discrepancy in the rate of reoperation between the series. With a freedom from autograft/RVOT substitute reoperation at 16 years of ∼75%, it means that 1 patient out of 4 will need a reoperation before 20 years after the Ross operation.

Similar to previous reports [16, 18, 19, 22, 23], our analysis confirms the association between preoperative aortic regurgitation and late autograft failure, whereas the presence of a bicuspid valve per se was not significantly correlated with this negative outcome. However, it should be noted that at present time pure aortic regurgitation would be treated with valve-sparing techniques rather than with the Ross procedure in our centre. Therefore as we have currently adopted the Ross procedure only for eligible patients with aortic stenosis, we may expect in the future a freedom from reoperation on the autograft failure as high as over 80% at 16 years after surgery. Moreover, we did not see any significant improvement in the rate of late failure with the inclusion technique compared with the root technique. As previously observed, the inclusion technique protects the autograft from late dilatation but does not prevent the occurrence of leaflet prolapse [6]. A few years ago, we have introduced the stabilization of the autograft with the inclusion into a Gelweave Valsalva™ graft (Vascutek, Inchinnan, UK) before root implantation. As we have previously described [7], this is a simple procedure aimed at preventing further dilatation of the autograft, and is simpler than the cylinder-inclusion technique. Nevertheless, our experience with this technique is at this point still too limited to observe any significant difference compared with the cylinder-inclusion. A longer follow-up is needed to figure out if this technical improvement is associated with any significant clinical benefit. Although aortic regurgitation is associated with a higher risk of failure compared with aortic stenosis with a HR of 2.02, late autograft dilatation and failure may occur also in patients with predominant stenosis. Therefore, our practice is to support the autograft also in patients with predominant stenosis every time we use the root technique.

The risk of reoperation on the RVOT substitute constitutes the second major objection to this operation. Freedom from reoperation on the RVOT was 90.5% at 16 years, in line with other series [17, 19, 22]. Our multivariate analysis revealed age, BMI and previous endocarditis as significantly associated with the risk of RVOT substitute failure over time whereas the type of RVOT substitute was not. The role of young age on the degeneration of the RVOT valve was observed also by Weimar *et al.* [17]. However, due to the limited number of events on the RVOT, and the small number of cases where a stentless xenograft was used, these estimates should be considered with caution. Previous reports [24] have indeed found a significant risk of reoperation on the RVOT associated with the use of stentless xenograft and therefore in our current practice the homograft is the substitute of choice for RVOT reconstruction. We also observed that only a minority of patients who did not undergo reoperation presented significant pulmonary homograft regurgitation or stenosis at last available echocardiogram. However, it must be noted that the median follow-up echo in this subgroup was only 9 years. The longer echo follow-up will give us more insight on the fate of the RVOT substitute in the long term. Isolated RVOT reoperation occurred in <1% of patients but up to one-fourth of patients who required reoperation on the autograft also needed RVOT substitute replacement. This supports the hypothesis that the underlying pathology rather than the surgical technique of implantation is linked to the late failure of this procedure. Therefore, further understanding of the aortic pathology and patients' selection may further improve the late outcome of the Ross operation.

Nevertheless, perioperative mortality in reoperation was a reasonable 2.6% and the autograft could be preserved with valve-sparing procedures in over 70% of redo in our experience. Rate of autograft repair was also similar between the root and the inclusion technique. Although reoperation can be technically more demanding in the presence of the Inclusion technique, we did not observe an increased risk of major perioperative complications following reoperation in the presence of this technique of implantation. Therefore, freedom from valve replacement was a high 92% at 16 years, extending the scope of the autograft use. These results are therefore significantly better than any AVR with bioprostheses in young adults [2, 10, 14]. Further, survival of patients who required reoperation was not significantly different at 16 years compared with those who did not. Finally, although the use of combined end points is debatable because they give the same weight to events of different nature and with variable impact on patient health, our analysis shows a freedom from the combined end point of around 70% at 16 years or, in other words, that over two-thirds of patients have not experienced any adverse valve-related event since the operation.

Study limitations

Our study has several limitations that should be taken into account. Although our patients were prospectively followed in our centre, their long-term medical treatment was managed mainly by their referring physicians. Therefore, differences in individual treatment and lack of standardization may have an impact on the outcomes that is unknown. In addition, echocardiographic follow-up was not available in every patient and the median interval of the last available scan was below 10 years. We cannot exclude that some patients, although asymptomatic, may have autograft or pulmonary homograft dysfunction. Finally, the limited number of patients and of adverse events precludes any robust statistical analysis for the identification of significant predictors of failure.

CONCLUSIONS

In conclusion, our study shows that the Ross operation is associated with an excellent survival at 15 years that is comparable with the matched general population. Although there is a significant risk of failure and need for reoperation, however due to a very low rate of valve-related complications, the majority of patients will not experience any adverse events up to 15 years from surgery. The Ross operation should be therefore considered, and discussed with every young adult patient requiring aortic valve replacement.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

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Dr E. Charitos *(Lübeck, Germany):* The Brussels team is to be congratulated for presenting their experience with over 300 young patients requiring a Ross procedure over the time course of 25 years. I have two questions and a small comment.

One of the criticisms of the Ross procedure and the results of the Ross procedure has often to do with patient selection. The critique we see often is what exactly drives the good results after the Ross procedure? Is it patient characteristics or is it some benefits of the autograft procedure? With this in mind, sometimes in order to evaluate the Ross procedure we need to study not only the patients who received the Ross procedure but also the patients that did not. In the absence of a randomized trial, this aims to investigate the role of patient characteristics on the outcomes. During your 20-year experience, how many patients, approximately, were screened or considered for the Ross procedure? Do certain patient characteristics, haemodynamics, comorbidities or surgeon preference play a role in selecting patients for the Ross procedure in your cohort? With what criteria do you decide if a young patient will receive a Ross procedure or a conventional aortic valve replacement? Perhaps you could elaborate a little bit on your patient selection process.

You also mentioned a small survival deviation in the Ross patients compared to the general population, and in the manuscript you performed further subgroup analysis investigating which age and gender subgroups has a relative lower survival. We have to understand, however, that mortal events in young individuals are rare events. On the other hand, cardiac and cardiac-related morbidity and mortality are much more frequent in heart-operated patients than in the general population. In that sense, one should not be surprised if the survival of the Ross patients will at some point deviate from the general population. This makes epidemiological sense. However, when and if the survival of these patients deviates, it is important to know how much it deviates. All studies until now show that the survival of the Ross patients is remarkably close to the survival of the general population.

In your manuscript you do a further subgroup analysis. I personally find the subgroup analysis of 21 events in six further subgroups rather precarious for formulating causal inferences. I am not sure if the finding that women between 30 and 50 years have a relative survival which is lower than that of the general population is true, I don't know if this finding is maybe a false positive finding.

Similarly, in the manuscript you mentioned that the xenografts in the right ventricular outflow tract did not result in increased failure, and I think this should be considered with caution. From the data from the Ross registry we see that the hazard for reoperation with biological valves in the right ventricular outflow tract is almost an order of magnitude higher than homograft. But in the manuscript you rightly acknowledge that your study might be underpowered to investigate the performance of xenografts in the right ventricular outflow tract.

My second question has to do with the fact that it is remarkable that you could salvage almost 72% of the failing autografts with either a valve repair or a valve-sparing technique. Have you observed any association between the original operative technique and the repairability in case of reoperation? Are some techniques more repairable than others?

So my first question has to do about your selection criteria for the Ross procedure and the second question about the repairability of the various techniques.

Dr Mastrobuoni: Regarding patient selection, I can say that we are very liberal. That means that we would screen every young patient that means above 18 and up to 50 years old, for these procedures. Even if a 56–57-year-old patient comes for valve replacement in our centre, we would consider him for the Ross, especially if the patient asks for it because he read about it on the Internet or because his cardiologist told him, we would consider him for this procedure. So, we would consider every young adult patient for the Ross procedure.

Of course, we have to also be realistic, and reviewing our analysis, for example, of the patient who died early after the operation, I remember a lady who was severely obese, with diabetes, hypertension, she was young, 45, but it was a long procedure. So retrospectively I could say she was not the best candidate. So if you start doing it, of course, with a better patient selection, you surely will have better results, as in everything.

So for our indication in a young patient whom we would consider, we will discuss with the patient the pros and cons, the risk of reoperation but advantages of not having oral anticoagulation and the low incidence of the related complications.

So, as you said, of course, we had a few women in our series; 30% of our patients were women. We did this group analysis, but, the numbers are limited. Interestingly we found that the only subgroup where the survival diverged from the expected survival was in women between 30 and 50. But again, the numbers are very limited.

I totally agree with you that a guy that has been operated on the heart, I don't think it is realistic to expect a survival that is the same as a guy who has not been operated on the heart. So, having a survival that is almost the same at 15 years, I think it is a very good result.

Regarding the pulmonary homograft, yes, we used the stentless xenograft in a dozen patients, so the numbers are very limited, and we had only 11 reoperations on the pulmonary homograft. So, we didn't find this a significant risk factor. Rather we found, young age of the recipient and BMI as a risk factor for late pulmonary homograft failure, but again, the numbers are very limited to have robust power.

And finally regarding the reoperation, we think that despite shifting from a root to inclusion and now a vascular inclusion technique, the risk of reoperation is about the same. What changes is the mechanism of late failure. We were able to repair the autograft in our centre in over 80% of the cases. I think that probably with the inclusion technique the reoperation is a little bit more complicated. However, we have a large experience in our centre on aortic root surgery and aortic root reoperation, so it is not a big deal. But surely it is a little bit more complicated.