



OPEN ACCESS

Research article

Inclusion cylinder method for aortic valve replacement utilising the Ross operation in adults with predominant aortic stenosis – 99% freedom from re-operation on the aortic valve at 15 years

Peter D. Skillington^{1,2,*}, M. Mostafa Mokhles³, William Wilson⁴, Leeanne Grigg⁴, Marco Larobina¹, Michael O'Keefe¹, Johanna Takkenberg³

¹Department of Cardiothoracic Surgery, Royal Melbourne Hospital, Australia

²Department of Cardiothoracic Surgery, Epworth Hospital, Melbourne, Australia

³Department of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, Netherlands

⁴Department of Cardiology Royal Melbourne Hospital, Melbourne, Australia

*Email: peter.skillington@mh.org.au

ABSTRACT

Background: To report our experience with the Ross operation in patients with predominant aortic stenosis (AS) using an inclusion cylinder (IC) method.

Methods: Out of 324 adults undergoing a Ross operation, 204 patients of mean age of 41.3 years (limits 16–62) underwent this procedure for either AS or mixed AS and regurgitation (AS/AR) between October, 1992 and February, 2012, implanting the PA with an IC method. Clinical follow up and serial echo data for this group is 97% complete with late mortality follow up 99% complete.

Results: There has been zero (0%) early mortality, and late survival at 15 years is 98% (96%, 100%). Only one re-operation on the aortic valve for progressive aortic regurgitation (AR) has been required with freedom from re-operation on the aortic valve at 15 years being 99% (96%, 100%). The freedom from all re-operations on the aortic and pulmonary valves at 15 years is 97% (94%, 100%). Echo analysis at the most recent study shows that 98% have nil, trivial or mild AR. Aortic root size has remained stable, shown by long-term (15 year) echo follow up.

Conclusions: In an experience spanning 19 years, the Ross operation used for predominant AS using the IC method described, results in 99% freedom from re-operation on the aortic valve at 15 years, better than any other tissue or mechanical valve. For adults under 65 years without significant co-morbidities who present with predominant AS, the pulmonary autograft inserted with this technique gives excellent results.

Keywords: aortic valve, valve stenosis, valve surgery

<http://dx.doi.org/10.5339/gcsp.2013.46>

Submitted: 30 August 2013

Accepted: 7 December 2013

© 2013 Skillington, Mokhles,

Wilson, Grigg, Larobina, O'Keefe,

Takkenberg, licensee Bloomsbury

Qatar Foundation Journals. This is

an open access article distributed

under the terms of the Creative

Commons Attribution license CC BY

3.0, which permits unrestricted use,

distribution and reproduction in any

medium, provided the original work

is properly cited.

INTRODUCTION

For younger adult patients requiring AVR, the Ross procedure has many proven benefits in comparison to other valve substitutes, including absence of need for oral anticoagulation drugs, i.e. Coumadin, better durability than other tissue valve alternatives,^{1–4} excellent haemodynamic function,⁵ improved exercise tolerance,⁶ and possibly improved long term survival.^{2,7,8}

However, its use has been restricted to relatively small numbers of centres with sufficient expertise to achieve good results,^{9–11} and most long term results thus far reporting on implantation of the PA by an unsupported root replacement method, have shown increasing risk of regurgitation of the PA in the second decade, leading to aortic valve re-operation being required.^{12–14} Also, the freestanding root replacement method for PA implantation has shown significant increases in aortic root size¹⁵ with time. The risk for aortic valve re-operation increases when the indication for surgery has been a patient presenting with AR, male gender, and in younger patients presenting with rheumatic valve disease.^{10,12} In addition, the pulmonary valve allograft inserted into the right ventricular outflow tract provides an additional hazard for valve-related complications.^{12,13}

With regard to more recent techniques to improve the PA durability, these have mainly involved either wrapping the autograft with prosthetic materials to prevent the development of later aneurysmal enlargement of the neo-aortic root, thus helping preventing late AR, or inserting the PA inside a Dacron graft.^{16–18} Both of these measures have insufficient follow up duration to determine their success, and involve insertion of significant amounts of prosthetic material, which is against the Ross principle and which may place more strain on the neo-aortic valve leaflets over time as they open and close within a more rigid aortic root. Alternatively, subcoronary implantation of the PA has been proven durable in one particular centre in Germany, but is technically challenging.⁹

The IC method used in this series involves insertion of the PA inside the patient's aortic root, giving it autologous support without need for excessive prosthetic material. This IC method^{19,20} is conceptually different to the technique usually referred to when describing an IC technique,^{21,22} and is the first long term study reported of any IC method involving more than 100 patients and allowing for estimates of outcome far into the second postoperative decade. Patients with predominant aortic stenosis are the focus of this report.

METHODS

Between October 1992 and February 2012, 324 patients underwent AVR utilising the Ross procedure. Of these, in 217 the indication for surgery was predominant AS (either pure AS, or mixed AS/AR). The remaining 107 patients presented with pure AR. Of 217 with predominant AS, 13 patients had the PA inserted using other known techniques (7 root replacements, one subcoronary technique, and in 5, the PA was inserted inside a Valsava dacron graft). For the purposes of this study, the remaining 204 patients with predominant AS who had the PA inserted using an IC method were analysed. The Ethics Committee at the Royal Melbourne Hospital approved the study of these patients and each individual patient gave informed consent for participation in this study.

The demographics of the patients operated on, as well as concomitant procedures performed, can be seen in Table 1. All operations were performed via median sternotomy using cardiopulmonary bypass, aortic cross-clamping and a combination of antegrade and retrograde cardioplegia for myocardial protection. The technique has previously been described,^{19,20} with the sequence of events being:

- Aortic transection and excision of the aortic valve, vertical extension of incision into the non-coronary sinus.
- Narrowing of the aortic root if required to allow for aortic valve/pulmonary valve size mismatch, using quadrangular or wedge excision of the non-coronary sinus. If either the aortic annulus or sinotubular junction diameter exceeds 34 mm., this would contra-indicate use of the inclusion cylinder method because of excessive pulmonary valve/aortic valve mismatch.
- Narrowing and stabilisation of the aortic annulus, if required, using partial circumference external Dacron ring.
- Marking of neocommissural points around the aortic annulus.
- Excision of pulmonary autograft root and insertion of a Cryopreserved pulmonary allograft. These were used exclusively, sourced from tissue banks within Australia.
- Insertion of the PA into aortic root using interrupted 4/0 Prolene sutures at the level of the annulus.

Table 1. Patient demographics and concomitant procedures.

No. of Patients		204
Age	Mean	41.3 years
	Limits	16–62 years
Gender	Male	127 (62%)
	Female	77 (38%)
Aortic Valve Lesion	AS	137 (67%)
	AS/AR	67 (33%)
Bicuspid Valve Aetiology NYHA Class		193 (94.6%)
	I	24 (12%)
	II	134 (67%)
	III	44 (22%)
	IV	2 (1%)
Previous Heart Surgery		22 (11%)
	Aortic Valve Repair	14 (6.9%)
	AVR	7 (3.4%)
Concomitant Procedures	Other Heart Surgery	1 (0.5%)
		90 (44%)
	Ascending Aorta	77 (38%)
	-Replacement	31 (15.2)
	-Tailoring Aortoplasty	46 (22.5)
	Subaortic Resection	3 (1.5%)
	CABG	3 (1.5%)
	ASD/PFO	2 (1%)
Miscellaneous	5 (2.5%)	

AS, Aortic Valve Stenosis; AR, Aortic Valve Regurgitation; AVR, Aortic Valve Replacement; CABG, Coronary Artery Bypass Graft Surgery; ASD, Atrial Septal Defect.

- Detachment of coronary ostial buttons, which are brought inside the aortic root and anastomosed to holes created in the pulmonary autograft root.
- Closure of aortic root with direct suture in non-coronary sinus region, enclosing the PA cylinder.
- Distal anastomosis of the PA to patient's native ascending aorta or if the ascending aorta replaced, to the lower end of the Dacron graft used.
- De-airing, removal of aortic cross-clamp and weaning from bypass.
- Check left ventricular (LV) function and aortic valve function with transoesophageal echo (TEE).

There have been some minor changes in technique since the previously described method.¹⁹ The distal autograft to ascending aortic anastomosis now includes the lower aortic root remnant only in the region immediately cephalad to the left coronary ostium. Please see [Figure 1](#) showing the completed IC method.

All patients have been followed up with review by surgeon and/or cardiologist yearly and echocardiograms have been obtained before hospital discharge and 6–12 months after surgery, thereafter every second year. The following echocardiographic measures were assessed: aortic and pulmonary valve function and aortic root size by maximal aortic sinus diameter (mm.).

Statistical analysis

Continuous variables are displayed as mean (SD), discrete variables as counts and proportions. Kaplan-Meier analysis was done to study time-related events such as death and re-operation. In order to calculate 95% confidence limits, the standard error of the estimate of the survival curve was estimated using Greenwood's formula.²³

Analyses of the echocardiographic data

Categorical echocardiographic measurement: To assess the temporal trend of likelihood of conduit regurgitation grades over time after surgery, follow-up transthoracic echocardiograms were analyzed longitudinally for change in percentages of patients in each regurgitation grade across time. A non-linear cumulative logit mixed model^{24,25} was used to resolve a number of time phases on cumulative odds domain to form a temporal decomposition model and to estimate the shaping parameters at each phase. Longitudinal cumulative logistic mixed model^{26,27} for repeated measurements (SAS[®] PROC NLMIXED) was used to implement the temporal decomposition model and to estimate the

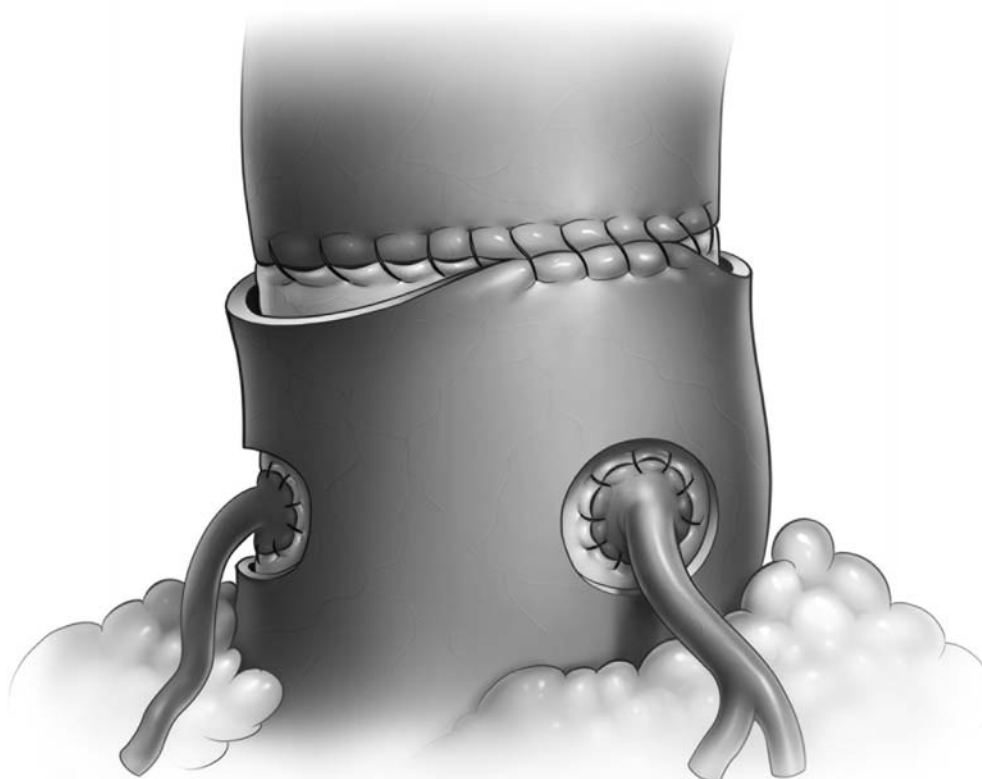


Figure 1. Completed inclusion cylinder method – diagram of aortic root with coronary ostia anastomosed to PA root.

patient-specific probabilities for being in each conduit regurgitation grade. These patient-specific estimates were then averaged to obtain the percentages of patients (prevalence) in each grade.

Continuous echocardiographic measurement: To assess the temporal trend of conduit gradient over time after surgery, follow-up transthoracic echo-cardiographic measurements were analyzed longitudinally for change in mean response across time.²⁸ A non-linear longitudinal mixed model regression^{26,27} (SAS[®] PROC NL MIXED) was used to analyze these continuous repeated measurements.

Variable selection and risk factor analyses: Patient characteristics, conduit properties and procedure related variables were screened for association with postoperative autograft regurgitation, mean and peak autograft gradient, pulmonary allograft regurgitation, and mean pulmonary allograft gradient. In addition, year of surgery (calculated as time interval between first and last surgical procedure) and various transformations (e.g. inverse, natural logarithm) of the available continuous variables were also screened as potential risk factors.

Variable selection, with a P value criterion for retention of variables in the model of 0.05, utilized bootstrap bagging (bootstrap aggregation).^{26,29} This was a four-step process. First, a patient was randomly selected from the original data set to begin a new data set. The original data set continued to be sampled until the new data set was 100% the size of the original. Second, risk factors were identified using automated forward stepwise selection. Third, results of the variable selection were stored. These three steps were repeated 1000 times. Finally, the frequency of occurrence of variables related to group membership was ascertained and indicated the reliability of each variable (aggregation step). All variables with bootstrap reliability of 50% or greater were retained in the guided analysis.

Because of the limited capability of PROC NL MIXED to explore multivariable relations, we initially screened the variables using ordinary multivariable linear regression (PROC REG[®] SAS) and the assumption of independence of observations with liberal entry criteria (0.2) and stay criteria (0.12). This analysis was performed simply to identify possible candidates for our repeated measurements model.

These candidates and their transformations, if any, were entered at once into our model, and then eliminated one by one until all variables remaining had a P value of 0.05 or less. Parametric estimates of continuous postoperative echocardiography measurements are accompanied by asymmetric 95% confidence limits, comparable to ± 2 SE, obtained by a bootstrap percentile method.³⁰ All statistical tests with a p-value of 0.05 or lower were considered significant. The longitudinal analyses of echocardiographic data were performed using SAS9.2 (SAS[®], Cary, N.C.). The deadline for data capture was 15th February, 2012.

RESULTS

Early and late mortality

There have been no early deaths either in hospital or within 30 days post-operative. The 204 surviving patients have been followed up, with only 7 patients lost to late follow up, i.e. 97% complete clinical follow up. An Australian Death Index search confirms that 6 of these patients are alive. The remaining patient lives overseas in Asia and last contact was 6 years after surgery. Thus late mortality follow up is 99% complete. As can be seen from Figure 2a, 15 year survival is 98% (96%, 100%), with only 3 late deaths, all from malignant neoplastic disease (i.e. non-cardiac), occurring at 3, 5 and 10 years post-operatively. Mean late follow up time is 7.84 years (0.1–17.8 years), and encompasses 1576 patient years.

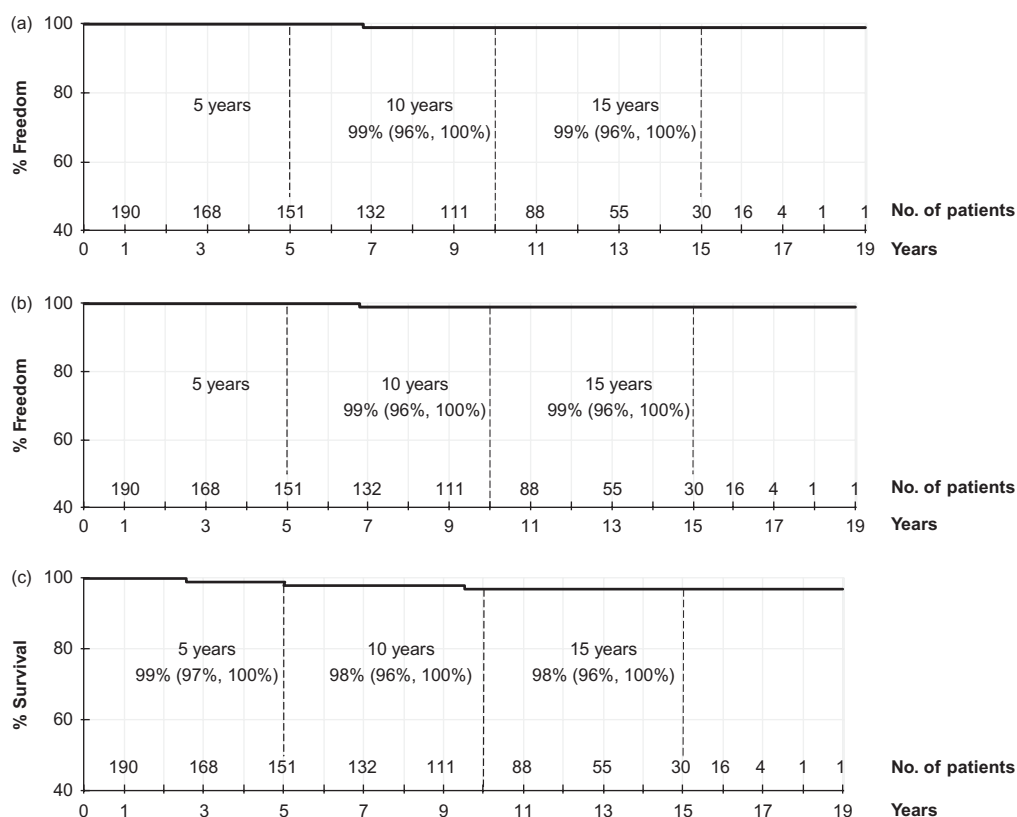


Figure 2. (a) Actuarial survival of entire cohort of 204 patients presenting with predominant AS (Kaplan-Meier). (b) Percent freedom from re-operation on the aortic valve in patients presenting with predominant AS (Kaplan-Meier). (c) Percent freedom from re-operation on both aortic and pulmonary valves for patients presenting with predominant AS (Kaplan-Meier).

In-hospital complications

Early complications after surgery occurred in 50 patients and included the following: acute renal failure defined as doubling of serum creatinine (none required haemofiltration or dialysis) 3 (1.5%), bleeding

requiring return to operating theatre 3 (1.5%), late pericardial effusion requiring drainage 2 (1%), atrial arrhythmias 23 (11%), ventricular arrhythmias 1 (0.5%), pneumothorax 2 (1%), acute myocardial infarction 1 (0.5%), low cardiac output syndrome 1 (0.5%), and deep sternal wound infection 1 (0.5%). There were no cases of post-operative CVA or TIA, respiratory or multisystem failure.

Late re-operation on aortic and pulmonary valves

- (a) Neo-aortic valve for progressive AR. One patient developed moderate aortic regurgitation 3 years following surgery, and this resulted in symptomatic, enlarging left ventricular dimensions, leading to re-do AVR at 7 years. The freedom from re-operation on the neo-aortic valve for this problem can be seen in [Figure 2b](#), which reveals 99% (96%, 100%) freedom at 15 years post-operatively.
- (b) Endocarditis of aortic and pulmonary valves (3 patients). There was one case of aortic valve endocarditis, one case of pulmonary valve endocarditis, and one case of both aortic and pulmonary valve endocarditis occurring at 3, 7 and 9 years post-operatively. All three cases underwent re-operation successfully. Except for the case of lone endocarditis affecting the aortic valve in which the infection was peri-aortic and the pulmonary autograft valve preserved (as it was functioning normally), the other three infected valves (in 2 patients) required replacement. The cumulative incidence of endocarditis is 0.19%/pt/yr of follow up.
- (c) Pulmonary valve for structural valve degeneration: there have been no re-operations necessary for this complication. Thus the freedom from all re-operations on aortic and pulmonary valves (see [Figure 2c](#)) is 97% (94%, 100%) at 15 years.

Late non-aortic or pulmonary valve cardiac re-operations

During the period prior to 1997, bicuspid aortic valve related aortopathy was not fully appreciated as an entity that could lead to later further dilatation of the mid ascending aorta. Four patients operated on between 1992–1996 (inclusive) exhibited mild enlargement of the mid ascending aorta (maximum 4.5 cm. diameter). In these patients, none of whom underwent a procedure on the ascending aorta at their initial surgery, progressive later enlargement of the ascending aorta was noted, without any change in aortic root size or aortic valve function. In each case, the ascending aorta was replaced electively once the ascending aortic diameter exceeded 5.0 cm. diameter. Two of these cases required hemi-arch replacement as well, and in the other two cases, near total arch replacement was required. These secondary operations were performed 7, 11, 12 and 15 years respectively after the primary operation. None of these cases required further surgery to either the aortic or pulmonary valves. Thus, these cases were not considered to be in the category of re-operations on either aortic or pulmonary valves. In addition, a further fifth patient developed severe mitral valve regurgitation two years after surgery, and required a mitral valve replacement using a mechanical prosthesis.

Late echo-Doppler data

- (a) Aortic valve function: Echocardiographic follow-up on autograft regurgitation. Regurgitation was graded as 0 for no regurgitation, 1+ trivial, 2+ mild, 3+ for moderate, and 4+ for severe. Because of low frequency (2 patients with a total of 7 observations) in grade 3+ this grade was collapsed together with 2+ and is treated as one category. None of the patients had 4+ AR. As can be seen in [Figure 3a](#) there is no general trend for increasing severity of post-operative AR over time. Mean aortic valve (autograft) gradients are between 4–5 mmHg, with no change over time (see [Figure 3b](#)).
- (b) Aortic root size: The maximum aortic root diameter has been assessed, with measurements in mm. The assessments have been performed before surgery, one week after surgery, at one year post-operative, and then second yearly intervals. Because echocardiograms are performed every second year routinely, after three years, results for year 4, 5 post-operative, are included under 5 years, etc. As can be seen from [Figure 4](#), mean aortic root size, as measured by maximum aortic size diameter increases very slowly with time. The mean pre-operative diameter is 33 (28, 38) mm. and this increases to 35 (32, 38) mm. at 15 years post-operative. This equates to 0.13 mm increase in aortic root size per year, i.e. minimal increase in aortic size over time.

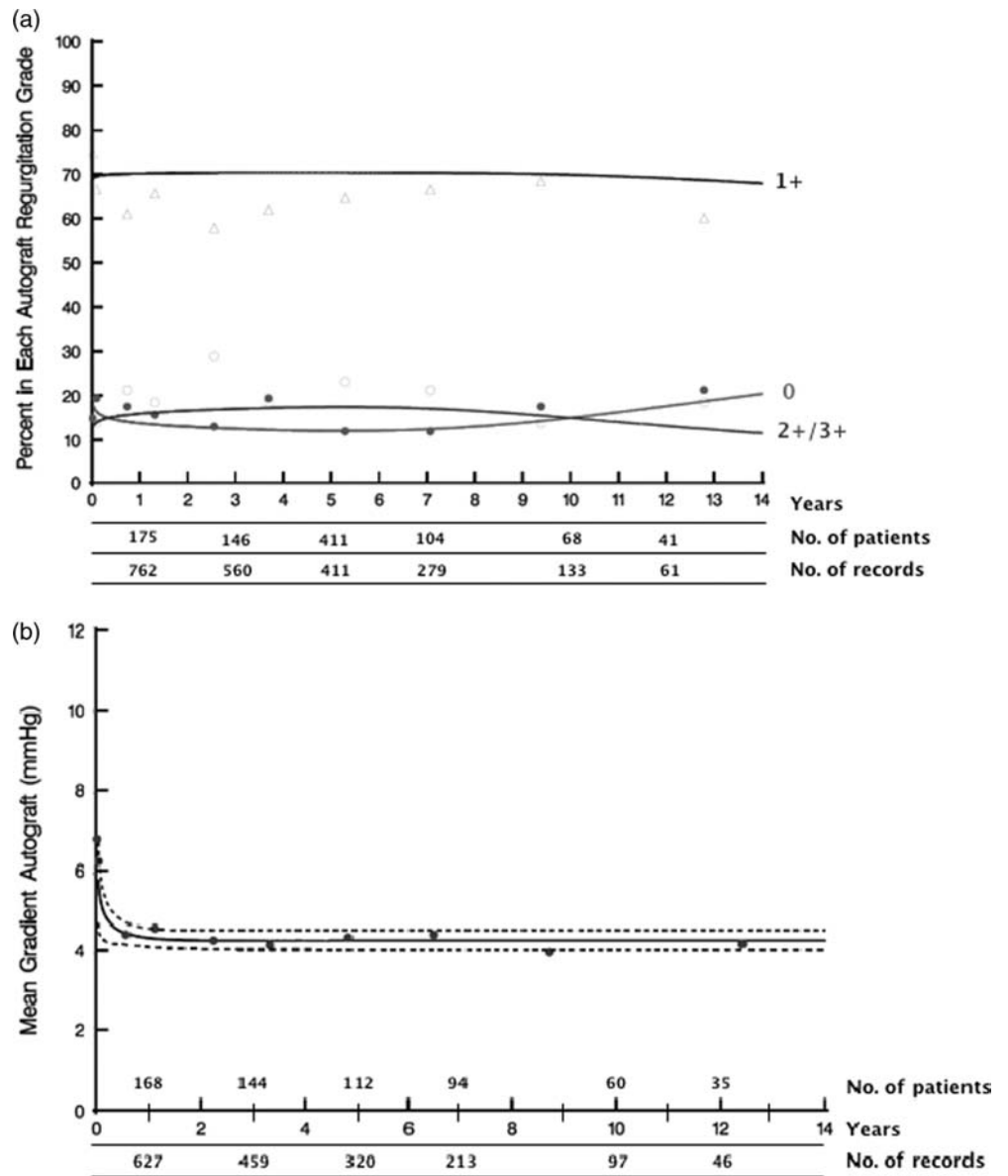


Figure 3. (a) Temporal trend of aortic regurgitation after the Ross procedure. Solid lines represent percentage of patients (mean effect) in each grade at various time points. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting. Aortic regurgitation was graded as 0 for no regurgitation, 1+ trivial, 2+ mild, 3+ for moderate, and 4+ for severe. Because of low frequency (2 patients with a total of 7 observations) in grade 3+ this grade was collapsed together with 2+ and is treated as one category. None of the patients had 4+ AR. (b) Solid lines are parametric estimates of mean autograft gradient from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

(c) Pulmonary valve function: The mean late pulmonary valve gradient, measured by Doppler study is 10 mmHg (limits 2–44). There are 6 patients with mean gradient between 20 to 30 mmHg, and 3 where this gradient exceeds 30 mmHg, i.e. only 4.4% in excess of 20 mmHg. Analysis of patients with pulmonary valve gradients in excess of 20 mmHg mean, shows that these gradients have appeared between 6–18 months after surgery, and then plateaued without further elevation over time. Right ventricular size, function and wall thickness have remained normal in these patients. Please see [Figure 5a](#) for the temporal change in

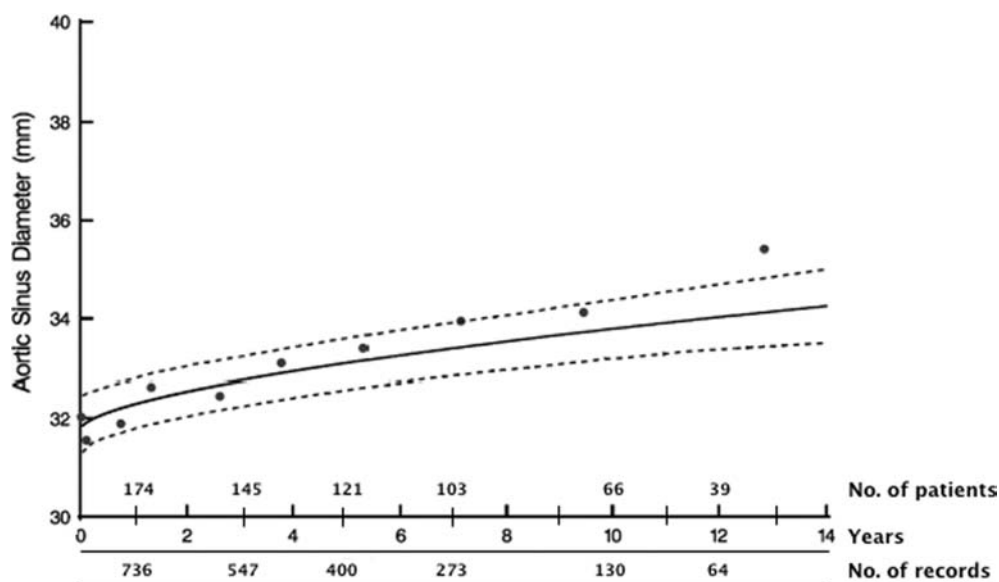


Figure 4. Temporal trend of echo derived maximum aortic root size, as assessed by maximum aortic sinus diameter (mm.). Solid lines are parametric estimates of mean aortic sinus diameter from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

pre-operative pulmonary valve gradient with time. Risk factors associated with increased post-operative pulmonary allograft gradient can be seen in Table 2. In summary, older recipient age, male patient gender, and earlier year of surgery were found to be associated with higher pulmonary allograft gradient during follow-up of patients after the Ross procedure. Older donor age, on the other hand, was associated with a lower allograft gradient. However, older donor age was found to be associated with an increased risk of higher PR (Table 3). The temporal trend in pulmonary valve regurgitation grade can be seen in Figure 5b.

NYHA Class: 99% are NYHA Class I, at most recent evaluation, 1% in NYHA Class II.

DISCUSSION

This is the first report of a large and long-term experience with the Ross procedure employing an inclusion cylinder technique, with results extending far into the second post-operative decade. It shows that the use of this surgical technique in patients with predominant aortic stenosis provides a durable solution that is far superior to any other surgical technique and any other biological or mechanical valve substitute. Originally described as a method for implantation of the PA or an aortic allograft, the author has modified the technique¹⁹ in order to retain the root replacement principle which ensures early neo-aortic valve competence.

With this technique, the patient's aortic root, rather than being discarded or substituted by prosthetic material to wrap around the PA, is retained as an autologous support around the autograft, the main advantage being to prevent its later enlargement which has been shown to lead to neo-aortic root aneurysm, and also, in an unsupported root replacement, to progressive aortic regurgitation, the main reason for late left-sided re-operation after the Ross procedure.¹³ The method employed is different to previous descriptions of the inclusion cylinder or intra-aortic implant techniques.

Late echo-Doppler assessment in this series shows that the IC method used limits expansion of the autograft root, with only 2 mm. increase in maximum diameter during 15 years of follow up. There have been no cases of neo-aortic root aneurysmal enlargement noted in the follow up period either. This would appear to be the reason for excellent late results with this technique, with only one re-operation being necessary for progressive AR or structural valve degeneration of the autograft, leading to 15 year freedom from re-do AVR for this problem, of 99% (96%, 100%), as well as trivial incidence of moderate or greater late AR shown in 2 (1%) patients only, during the follow up period.

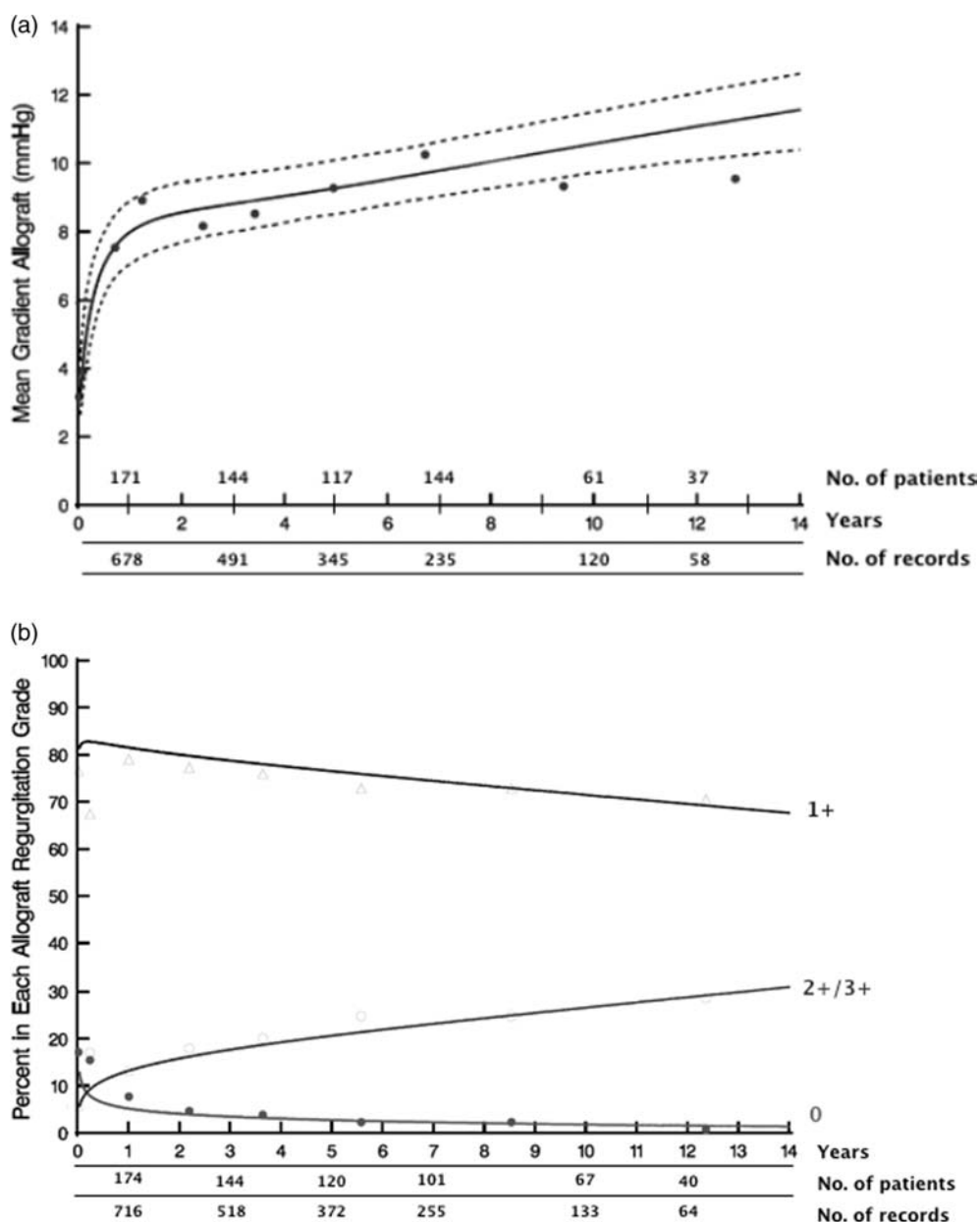


Figure 5. (a) Solid lines are parametric estimates of pulmonary allograft gradient from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting. Pulmonary allograft regurgitation (PR) was graded as 0 for no regurgitation, 1+ trivial, 2+ mild, 3+ for moderate, and 4+ for severe. Because of low frequency (9 patients with a total of 14 observations) in grade 3+ this grade was collapsed together with 2+ and is treated as one category. None of the patients had 4+ PR. (b) Temporal trend of pulmonary allograft regurgitation after the procedure. Solid lines represent percentage of patients (mean effect) in each grade at various time points. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

Late survival in this series is excellent also, with only 3 late deaths 98% (96%, 100%) survival at 15 years, none of which are cardiac related, all due to cancer. Many late deaths after tissue AVR have been shown in various series to be due to cardiac causes including heart failure, arrhythmias, re-operation and endocarditis. By minimising late aortic valve dysfunction and re-operation, presumably this should improve survival. It has been shown that in particular younger adult patients who undergo aortic valve replacement, there is a considerable excess mortality compared to the general population.³¹

Table 2. Pre-OP Risk factors associated with post-op pulmonary allograft gradient.

Factor	Estimate \pm SE	P	Reliability
Recipient age*	0.0254 \pm 0.0070	0.0004	100
Male patient gender	0.0934 \pm 0.0207	< .0001	82.9
Donor age#	-0.1040 \pm 0.0293	0.0005	100
Timing/period of surgery^	0.1618 \pm 0.0319	< .0001	89.1

*During bootstrap analyses inverse of age was found to be most reliable and this variable was used in the multivariate analyses. #During bootstrap analyses the natural logarithm of donor age was found to be most reliable and this variable was used in the multivariate analyses. ^During bootstrap analyses the natural logarithm of 'timing of surgery' was found to be most reliable and this variable was used in the multivariate analyses.

Table 3. Pre-OP Risk factors associated with post-op pulmonary allograft regurgitation.

Factor	Estimate \pm SE	P	Reliability
Donor age*	0.7521 \pm 0.2840	0.0088	96.9

*During bootstrap analyses inverse of donor age was found to be most reliable and this variable was used in the multivariate analyses.

This observation is not confirmed in our experience with the Ross procedure where we observe a late survival comparable to the general age and gender matched population.

Endocarditis remains an infrequent, although serious hazard for all patients undergoing AVR,^{16,32,33} regardless of the prosthesis used. In this series, there have been 3 patients who developed this complication, either on the aortic or pulmonary valves, or on both. Thus, the cumulative incidence of endocarditis in the patients with predominant AS is 0.19%/pt/yr, which is less than the overall rate of prosthetic valve endocarditis associated with other bioprostheses and mechanical valve prostheses.³²⁻³⁴

The pulmonary valve replacement (PVR) remains the Achilles' heel of the Ross procedure. A proportion of patients after PVR with a pulmonary allograft (the PVR of choice in the Ross procedure) develop stenosis of the pulmonary allograft, probably of immunological or inflammatory basis. In this series, six of 204 patients have mean pulmonary valve (PV) gradients between 20 and 30 mmHg, and two between 30 and 40 mmHg. One patient was found to have an allograft gradient of 44 mmHg two years postoperative, unfortunately this patient was lost to follow up. No patients have required re-intervention for this problem with the threshold for re-operation being the development of a mean PV gradient in excess of 40 mmHg, development of right ventricular enlargement or hypertrophy or development of symptoms. There is a slight trend for increasing pulmonary allograft regurgitation with time. It is highly probable that some patients will require re-operation on the PV in the future. Options will include percutaneous PVR or surgical PVR. If surgical PVR is required, it can be performed with cardiopulmonary bypass support, although without the need for aortic cross-clamping, with the heart continuing to beat throughout the procedure. This minimizes mortality and morbidity, if required in the future.

Thus, the freedom from all surgical re-interventions on either the aortic and pulmonary valves in this series of 204 patients presented, utilising the IC method is 97% (94%, 100%) at 15 years. This is better than many series of mechanical AVR patients (33-35), with the latter group not infrequently requiring late re-operation for issues such as prosthetic valve endocarditis, pannus obstruction and paravalvular leak.

Of course, the freedom from re-operation on the neo-aortic valve in this series will require further study, and it is assumed that some degree of valve degeneration could be expected after 15 years even if the pulmonary autograft valve remains viable, with no leaflet degeneration. Of course, Ross operation recipients have an advantage vs. mechanical valve subjects in that patients undergoing a Ross operation do not require anticoagulation with Coumadin and have better haemodynamic performance of the aortic valve than mechanical valve recipients.⁵

Important limitations of this study include the fact that not all patients who are referred for a Ross procedure, ultimately have this operation performed. The reasons for exclusion include older age and excessive co-morbidities (especially in patients in their late 50s and 60s), because of the increased operation risk that would entail, patients with Marfan's syndrome and other connective tissue disorders, patients with more than minor coronary artery disease or mitral valve disease. Also patients

with excessively dilated aortic roots. As mentioned in the methods section, if either the patient's aortic annulus or sinotubular junction exceeds 34 mm. diameter, a Ross operation utilising the inclusion cylinder method described is not appropriate because of excessive pulmonary valve/aortic valve size mismatch. The author would still manage a number of these cases by utilising the Ross principle, inserting the pulmonary autograft inside a Valsava dacron graft. Approximately 2% to 3% of patients have a structurally abnormal pulmonary valve, precluding a Ross operation. It is estimated that approximately 10% of all patients referred for a Ross procedure do not have a Ross utilising an inclusion cylinder method. However, if one looks at younger patients under the age of 50 years, the exclusion rate would fall to less than 5%.

In summary, long term follow up extending to 19 years in adult patients having a Ross operation for predominant aortic stenosis using an IC method, shows excellent patient survival and outstanding autograft durability. Enclosing the pulmonary autograft root in the patient's own aortic root provides autologous support for the autograft and has been shown to prevent late enlargement of the neo-aortic root with very low rate of late progressive AR, such that only 1 re-operation has been required for this problem, and with the remaining patients showing stable aortic valve function at late echo-Doppler assessment. In young adult patients with predominant AS who require AVR, the option of a Ross procedure employing the IC method should be considered in a centre of expertise that is successful in applying this method.

FUNDING SOURCES

The Ross Procedure and Cardiac Surgery Trust.

M. Mostafa Mokhles is funded by a Mosaic grant of the Netherlands Organisation for Scientific Research (NWO 017.006.058).

DISCLOSURES

None.

Acknowledgements

The authors would like to thank Tonia Iacuone for assistance with retrieval of references and typing of the manuscript. Also Mardi Malone for assistance with submission of the manuscript.

REFERENCES

- [1] Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ, Steyerberg EW, van Herwerden LA, Grunkemeier GL, Habbema JD, Bogers AJ. Prognosis after aortic valve replacement with the Carpentier-Edwards pericardial valve: use of microsimulation. *Ann Thorac Surg.* 2005;80:825–831.
- [2] El-Hamamsy I, Eryigit Z, Stevens LM, Sarang Z, George R, Clark L, Melina G, Takkenberg JJ, Yacoub MH. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. *Lancet.* 2010;376:524–531.
- [3] David TE, Puschmann R, Ivanov J, Bos J, Armstrong S, Feindel CM, Scully HE. Aortic valve replacement with stentless and stented porcine valves: a case-match study. *J Thorac Cardiovasc Surg.* 1998;116:236–241.
- [4] O'Brien MF, Stafford EG, Gardner MA, Pohlner PG, Tesar PJ, Cochrane AD, Mau TK, Gall KL, Smith SE. Allograft aortic valve replacement: long-term follow-up. *Ann Thorac Surg.* 1995;60:S65–S70.
- [5] Oury JH, Doty DB, Oswald JD, Knapp JF, Mackey SK, Duran CM. Cardiopulmonary response to maximal exercise in young athletes following the Ross procedure. *Ann Thorac Surg.* 1998;66:S153–S154.
- [6] Porter GF, Skillington PD, Bjorksten AR, Morgan JG, Yapanis AG, Grigg LE. Exercise hemodynamic performance of the pulmonary autograft following the Ross procedure. *J Heart Valve Dis.* 1999;8:516–521.
- [7] Yacoub MH, Klieverik LM, Melina G, Yacoub MH, Klieverik LM, Melina G, Edwards SE, Sarathchandra P, Bogers AJ, Squarcia U, Sani G, van Herwerden LA, Takkenberg JJ. An evaluation of the Ross operation in adults. *J Heart Valve Dis.* 2006;15:531–539.
- [8] Brown JW, Ruzmetov M, Shahriari A, Rodefeld MD, Mahomed Y, Turrentine MW. Midterm results of Ross aortic valve replacement: a single-institution experience. *Ann Thorac Surg.* 2009;88:601–607, discussion 607–8.
- [9] Sievers HH, Hanke T, Stierle U, Bechtel MF, Graf B, Robinson DR, Ross DN. A critical reappraisal of the Ross operation: renaissance of the subcoronary implantation technique? *Circulation.* 2006;114:1504–1511.
- [10] David TE, Woo A, Armstrong S, Maganti M. When is the Ross operation a good option to treat aortic valve disease? *J Thorac Cardiovasc Surg.* 2010;139:68–73, discussion 73–5.
- [11] Sievers HH, Stierle U, Charitos EI, Hanke T, Gorski A, Misfeld M, Bechtel M. Fourteen years' experience with 501 subcoronary Ross procedures: surgical details and results. *J Thorac Cardiovasc Surg.* 2010;140:816–822, 822 e1–5.
- [12] Elkins RC, Thompson DM, Lane MM, Elkins CC, Peyton MD. Ross operation: 16-year experience. *J Thorac Cardiovasc Surg.* 2008;136:623–630, 630 e1–5.
- [13] Klieverik LM, Takkenberg JJ, Bekkers JA, Roos-Hesslink JW, Witsenburg M, Bogers AJ. The Ross operation: a Trojan horse? *Eur Heart J.* 2007;28:1993–2000.

- [14] Frigiola A, Ranucci M, Carlucci C, Giamberti A, Abella R, Di Donato M. The Ross procedure in adults: long-term follow-up and echocardiographic changes leading to pulmonary autograft reoperation. *Ann Thorac Surg.* 2008;86:482–489.
- [15] Hanke T, Stierle U, Boehm JO, Botha CA, Matthias Bechtel JF, Erasmi A, Misfeld M, Hemmer W, Rein JG, Robinson DR, Lange R, Hörer J, Moritz A, Ozaslan F, Wahlers T, Franke UF, Hetzer R, Hübler M, Ziemer G, Graf B, Ross DN, Sievers HH, German Ross Registry. Autograft regurgitation and aortic root dimensions after the Ross procedure: the German Ross Registry experience. *Circulation.* 2007;116:1251–1258.
- [16] Juthier F, Banfi C, Vincentelli A, Ennezat PV, Le Tourneau T, Pinçon C, Prat A. Modified Ross operation with reinforcement of the pulmonary autograft: Six-year results. *J Thorac Cardiovasc Surg.* 2010;139:1420–1423.
- [17] Slater M, Shen I, Welke K, Komanapalli C, Ungerleider R. Modification to the Ross procedure to prevent autograft dilatation. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu.* 2005;181–184.
- [18] Koul B, Al-Rashidi F, Bhat M, Meurling C. A modified Ross operation to prevent pulmonary autograft dilatation. *Eur J Cardiothorac Surg.* 2007;31:127–128.
- [19] Skillington PD, Fuller JA, Grigg LE, Yapanis AG, Porter GF. Ross procedure. Inserting the autograft using a fully supported root replacement method; techniques and results. *J Heart Valve Dis.* 1999;8:593–600.
- [20] Skillington PD, Grigg LE. Insertion of the pulmonary autograft as an inclusion cylinder—modifications to existing techniques. *J Heart Valve Dis.* 1995;4:374–378.
- [21] Elkins RC, Santangelo K, Stelzer P, Randolph JD, Knott-Craig CJ. Pulmonary autograft replacement of the aortic valve: an evolution of technique. *J Card Surg.* 1992;7:108–116.
- [22] Pacifico AD, Kirklin JK, McGiffin DC, Matter GJ, Nanda NC, Diethelm AG. The Ross operation—early echocardiographic comparison of different operative techniques. *J Heart Valve Dis.* 1994;3:365–370.
- [23] Collett D. *Modelling Survival Data in Medical Research.* London: Chapman and Hall; 1994:22–26.
- [24] Blackstone EH, Rajeswaran J. A non-linear cumulative logit mixed model with time varying phases and coefficients. Conference proceedings, XXIII International Biometric Conference, Montreal, Canada 2006.
- [25] Gillinov AM, McCarthy PM, Blackstone EH, Rajeswaran J, Pettersson G, Sabik JF, Svensson LG, Cosgrove DM, Hill KM, Gonzalez-Stawinski GV, Marrouche N, Natale A. Surgical ablation of atrial fibrillation with bipolar radiofrequency as the primary modality. *J Thorac Cardiovasc Surg.* 2005;129:1322–1329.
- [26] Blackstone EH. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. *J Thorac Cardiovasc Surg.* 2001;122:430–439.
- [27] Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. *Analysis of longitudinal data.* 2nd ed. New York: Oxford University Press; 2002.
- [28] Mason DP, Rajeswaran J, Murthy SC, McNeill AM, Budev MM, Mehta AC, Pettersson GB, Blackstone EH. Spirometry after transplantation: how much better are two lungs than one? *Ann Thorac Surg.* 2008;85:1193–1201, 1201 e1–2.
- [29] Breiman L. Bagging predictors. *Mach Learn.* 1996;24:123–140.
- [30] Efron B, Tibshirani RJ. *An introduction to the bootstrap.* New York: Chapman and Hall/CRC; 1998.
- [31] Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol.* 2000;35:747–756.
- [32] Zellner JL, Kratz JM, Crumbley AJ 3rd, Stroud MR, Bradley SM, Sade RM, Crawford FA Jr. Long-term experience with the St. Jude Medical valve prosthesis. *Ann Thorac Surg.* 1999;68:1210–1218.
- [33] Butchart EG, Li HH, Payne N, Buchan K, Grunkemeier GL. Twenty years' experience with the Medtronic Hall valve. *J Thorac Cardiovasc Surg.* 2001;121:1090–1100.
- [34] Lund O, Nielsen SL, Arildsen H, Ilkjaer LB, Pilegaard HK. Standard aortic St. Jude valve at 18 years: performance profile and determinants of outcome. *Ann Thorac Surg.* 2000;69:1459–1465.