Influence of Patient Age and Implantation Technique on the Probability of Re-Replacement of the Homograft Aortic Valve

Shu K. Ng[1], Mark F. O'Brien[2], Susan Harrocks[2], Geoffrey J. McLachlan[1]

[1]*Department of Mathematics, The University of Queensland, St. Lucia, Queensland,* [2]*Department of Cardiac Surgery, The Prince Charles Hospital, Brisbane, Queensland, Australia*

Background and aim of the study: **Results of valve re-replacement (reoperation) in 898 patients undergoing aortic valve replacement with cryopreserved homograft valves between 1975 and 1998 are reported. The study aim was to provide estimates of unconditional probability of valve reoperation and cumulative incidence function (actual risk) of reoperation.**

Methods: **Valves were implanted by subcoronary insertion (n = 500), inclusion cylinder (n = 46), and aortic root replacement (n = 352). Probability of reoperation was estimated by adopting a mixture model framework within which estimates were adjusted for two risk factors: patient age at initial replacement, and implantation technique.**

Results: **For a patient aged 50 years, the probability of reoperation in his/her lifetime was estimated as 44% and 56% for non-root and root replacement techniques, respectively. For a patient aged 70 years, estimated probability of reoperation was 16% and 25%, respectively. Given that a reoperation is required, patients with non-root replacement have a higher hazard rate than those with root replacement (hazards ratio = 1.4), indicating that non-root replacement patients tend to undergo reoperation earlier before death than root replacement patients.**

Conclusion: **Younger patient age and root versus non-root replacement are risk factors for reoperation. Valve durability is much less in younger patients, while root replacement patients appear more likely to live longer and hence are more likely to require reoperation.**

The Journal of Heart Valve Disease 2001;10:217-225

Biologic valve replacement devices (xenograft and homograft valves) have an important and complementary role in the treatment of valvular heart disease (1-3). The clear advantages of biologic valves are the freedom from anticoagulant-related hemorrhage and a low incidence of thromboembolic events (4,5). During the 1990s, cryopreserved homograft valves became popular because of their advantage in the setting of endocarditis, with a lower probability of persisting endocarditis (6), and because of their better long-term durability (7,8). However, several reports have been published regarding the immune response to cryopreserved homograft valves (9,10). This response raises the question of decreased homograft valve durability in unmatched HLA donor recipients and in younger patients (11,12). The cryopreserved homograft valves can be inserted by a variety of methods, including the subcoronary implantation technique, the cylindrical technique, and as an aortic root replacement (13). Re-replacement of a cryopreserved homograft valve is required because of leaflet failure caused by degeneration and the changing mechanical properties of leaflets, geometric distortion, and replacement valve endocarditis (14). The relationship between structural failure, implantation technique, and patient age at the time of the initial operation provides useful information for the cardiac surgeon and patient if the use of a biologic valve is to be considered.

Herein, we report the results of valve reoperation in a series of patients undergoing aortic valve replacement with cryopreserved homograft valves at the Prince Charles Hospital (1). Estimates are provided of the unconditional probability of valve reoperation and cumulative incidence function of reoperation. The latter is often referred to as the 'actual' risk in cardiac-related literature (15-18).

Presented at the First Biennial Meeting of the Society for Heart Valve Disease, 15th-18th June 2001, Queen Elizabeth II Conference Centre, London, United Kingdom

Address for correspondence:
Professor G.J. McLachlan, Department of Mathematics, The University of Queensland, Brisbane, Queensland 4702, Australia.

J Heart Valve Dis
Vol. 11. No. 2
March 2002

Clinical material and methods

Patients

The study group included 898 patients who underwent aortic valve replacement (primary and subsequent valve replacements) with cryopreserved homograft valves at The Prince Charles Hospital, between June 2, 1975 and July 31, 1998. The valves were implanted by either subcoronary insertion (n = 500), inclusion cylinder (n = 46),or aortic root replacement (n = 352).

In the analysis, the root replacement and non-root replacement (subcoronary insertion or inclusion cylinder) techniques were compared (Table I), in relation to age at implantation and year of first operation. Reoperation of a previously implanted aortic homograft valve and death were the end-points of the study.

Follow up

Follow up information was obtained from hospital and outpatient records, and by direct contact with the patient, family, cardiologist and family physician. Follow up was conducted between January 1998 and December 1998, and the closing date for inclusion of events was December 4, 1998 (1). The total follow up time was 6,037 patient-years; maximum follow up was 23.0 years. Structural deterioration (n = 52), endocarditis (n = 17) and technical errors (n = 21) were the reasons for the 90 subsequent valve reoperations; 156 patients died without undergoing reoperation. The survival times of the remaining 652 patients were all censored, these patients having no events of death nor reoperation (Table II). The proportion of censored observations was 67%.

Statistical analysis

The unconditional probability and cumulative incidence function ('actual' risk) of valve reoperation were estimated by adopting a mixture model framework in which the time to reoperation or death without reoperation was modeled as a two-component mixture distribution. The first component, corresponding to reoperation, was expressed in terms of the unconditional probability of reoperation and the conditional distribution of time to reoperation, given that reoperation was required. The unconditional probability of reoperation was modeled by the logistic form (19), and the conditional distribution was modeled in the proportional hazards function domain (20). The second component corresponded to death before reoperation. Estimates were adjusted for two risk factors: patient age at the initial replacement, and an indicator variable denoting the implantation technique (technique = 0 for non-root replacement; technique = 1 for root replacement). The method of maximum likelihood implemented via the EM algorithm (21,22) was used to estimate simultaneously the parameters of the conditional distributions and the coefficients of the risk factors. Details are provided in Appendix I.

It should be noted that, as patients with valve disease have a relatively higher risk of dying than the normal population, the usual classical analysis (Kaplan-Meier actuarial freedom curves) of single end-point (reoperation) was not appropriate (15,18,23). In the setting of competing-risks analysis, the traditional approach is in terms of the so-called latent failure times corresponding to each failure type in the absence of the other (24). This was the approach used by Grunkemeier et al. (15) and McGiffin et al. (25)

Table I: Summary of patients by implantation technique.

Parameter	Non-root replacement	Root replacement	Total
Patients by age (years)			
<30	85	78	163
30-50	129	134	263
50-70	272	130	402
>70	60	10	70
Subtotal	546	352	898
Age (years)			
Mean	51	44	48
Range	3-81	1-76	1-81
Year of implantation			
1975-1979	78	0	78
1980-1984	69	0	69
1985-1989	180	32	212
1990-1994	215	170	385
1995-1998	4	150	154

Table II: Summary of follow up information by implantation technique.

Parameter	Non-root replacement	Root replacement	Total
Follow up (years			
Mean	8.5	3.9	6.7
Total	4,654.0	1,382.0	6,037.0
Maximum	23.0	12.8	23.0
Events			
Reoperation	74	16	90
Death	138	18	156
Events per patient-year (%)			
Reoperation	1.6	1.2	1.5
Death	3.0	1.3	2.6

Table III: Maximum likelihood estimates (±SE) for the logistic model.

Parameter	Estimate (SE)	p-value
Constant	3.082 (0.522)	0.000
Age	-0.067 (0.010)	0.000
Technique*	0.496 (0.166)	0.001

*0 for non-root replacement; 1 for root replacement.

to estimate the actual risk (cumulative incidence function) of reoperation. However, the cumulative incidence function is estimated by combining the estimates of the latent survival functions, and so the effect of a covariate on the latent survival functions may be very different from its effect on the probability of reoperation (26,27). The mixture model approach not only provides a direct interpretation of the impact of risk factors on the probability of reoperation, but also does not have to rely on assumptions about the independence of the competing risks (28).

Results

The maximum likelihood estimates for the logistic model are presented in Table III. Younger patient age ($p < 0.0001$) and root replacement ($p = 0.001$) are seen to be related to higher risk of reoperation. Adjusted odds ratio can also be calculated to estimate the associated relative risk of a reoperation. For example, the odds of requiring a reoperation increase about 1.6 fold (exp{0.496}) for root replacement relative to non-root implantation technique. The estimated probability of reoperation plotted against patient age for non-root and root replacement is shown in Figure 1. For a patient aged 50 years, the probability of reoperation was estimated as 44% and 56% for non-root and root replacement technique, respectively. For a patient aged 70 years, the estimated probability of reoperation was 16% and 25%, respectively.

The maximum likelihood estimates for the conditional distributions are presented in Table IV. Increased patient age ($p = 0.028$) and non-root replacement ($p = 0.022$) were seen to be related to higher death rate, given that the patient dies without a reoperation. In addition, given that a reoperation is needed, patients with non-root replacement techniques had

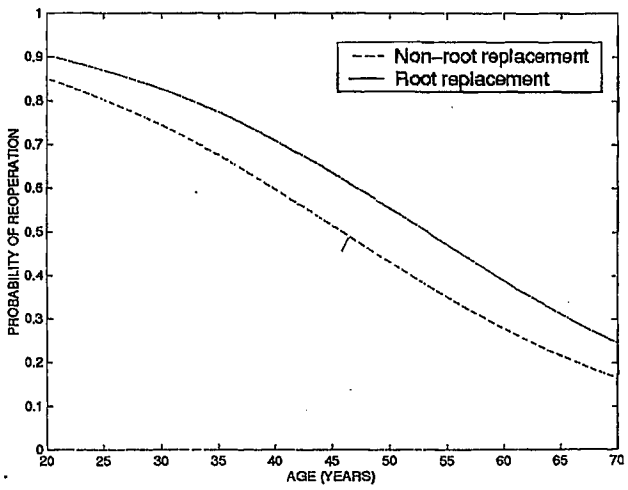
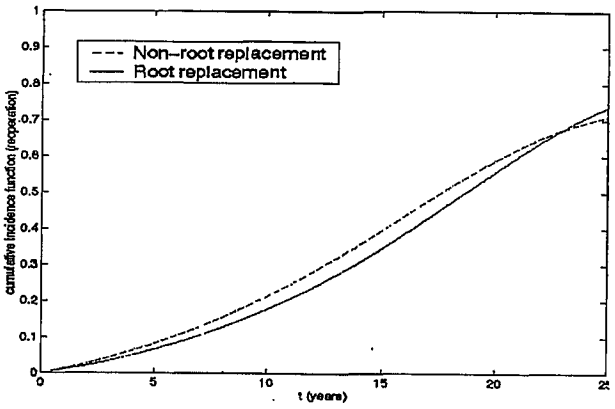
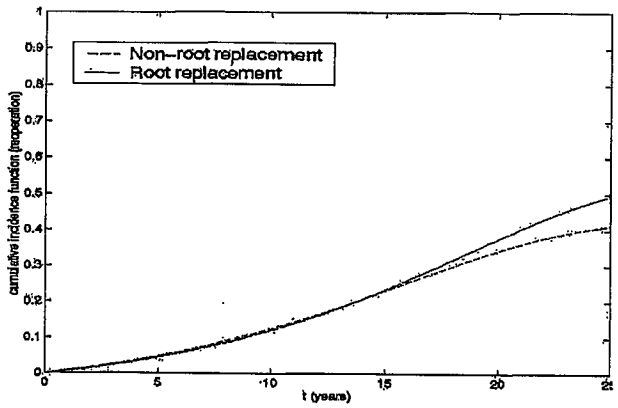


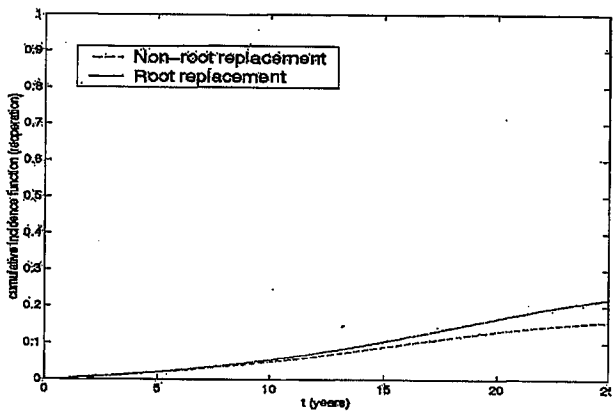
Figure 1: Estimated probability of reoperation at a given patient age.



(a) Age group: 20 - 40

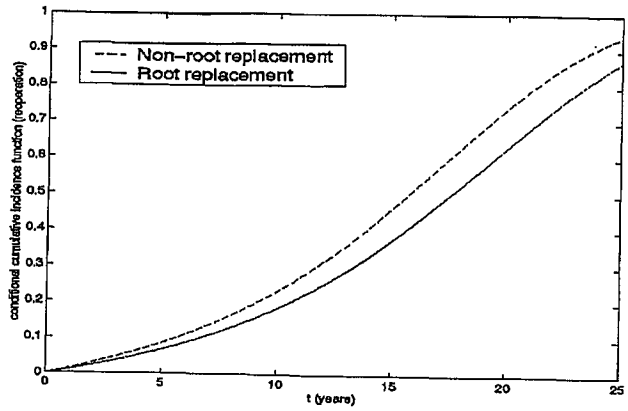


(b) Age group: 40 - 60

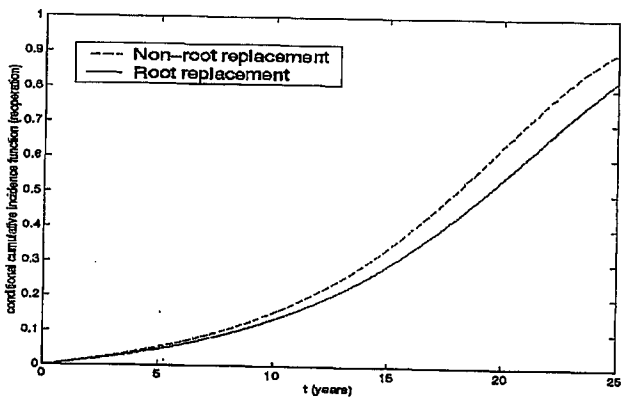


(c) Age group: 60 - 80

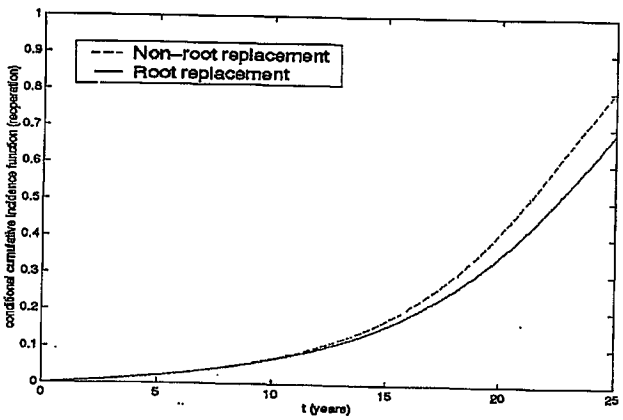
Figure 2: Estimated cumulative incidence function of reoperation versus time t (in years) for specified age groups of patients. a) Age 20-40 years; b) age 40-60 years; c) age 60-80 years.



(a) Age group: 20 - 40



(b) Age group: 40 - 60



(c) Age group: 60 - 80

Figure 3: Estimated conditional cumulative incidence function of reoperation versus time t (in years) for specified age groups of patients. a) Age 20-40 years; b) age 40-60 years; c) age 60-80 years.

Table IV: Maximum likelihood estimates (±SE) for the conditional component distributions.

Parameter	Reoperation		Additional (for death)	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Scale	-4.116 (0.314)	0.000	0.030 (0.009)	0.000
Shape	0.129 (0.014)	0.000	0.108 (0.038)	0.002
Age	0.0004(0.005)	0.532	0.016 (0.008)	0.028
Technique*	-0.336 (0.129)	0.005	-0.610 (0.304)	0.022

*0 for non-root replacement; 1 for root replacement.

a higher hazard rate (p = 0.005) than those with root replacement; the hazards ratio was 1.4 (exp{0.336}).

The estimated cumulative incidence function ('actual' risk) of reoperation plotted against time for various levels of a patient's age is shown in Figure 2. The curves level off to the probability of reoperation before death. The estimated conditional cumulative incidence function (23) of reoperation is shown in Figure 3, which provides the conditional probability of reoperation within a specified time of the initial replacement operation, given that the patient does not die without a reoperation during this period.

Discussion

In our mixture model-based analysis of the aortic cryopreserved homograft valve reoperation data, it was observed that younger age at operation and the implantation technique of root replacement were risk factors for reoperation. Other studies have shown that younger age is a major risk factor for early biologic valve degeneration (1,29), and that root replacement has better results compared with subcoronary implantation (30). The increased probability of reoperation with younger age at operation reflects not only a biologic predisposition to leaflet failure, but also the fact that younger patients have a lower probability of dying than older patients and hence a higher probability of eventually requiring reoperation. As older patients have a higher risk of death before reoperation, the probability of reoperation is mainly related to the risk of death after the initial replacement operation.

From Figure 1, it can be seen that root-replacement patients have a greater chance of requiring reoperation than patients with non-root replacement. The reason for this is that patients with root replacement appear more likely to live longer. This result is demonstrated in Table II by a higher percentage death per patient-year for non-root replacement patients (3.0%, versus 1.3% per patient-year for root replacement), and higher risk of death for those patients (negative estimate for the coefficient of the technique indicator variable in Table IV). However, this result should be treated with some caution because the duration of follow up and surgical experience were different between these two implantation techniques. From Figure 3, it can be seen that a patient aged 70 years at the time of the initial replacement operation, has only a conditional probability of 0.07 of having to undergo a reoperation within the next 10 years, given that he/she does not die first without a reoperation. This implies that older patients will have less of a chance of 'outliving' the cryopreserved homograft valve. As the age of the patient at the time of the initial replacement operation decreases, the conditional cumulative incidence function of reoperation increases. As biologic valves will eventually need replacement if the patient lives for a sufficiently long time after the initial replacement operation, the estimates of probability and conditional cumulative incidence function of reoperation provide useful information to the cardiac surgeon and patient if they are to consider choosing a mechanical valve rather than a biologic valve.

References

1. O'Brien MF, Harrocks S, Stafford EG, et al. The Homograft aortic valve: A 29-year, 99.3% follow up of 1,022 valve replacements. J Heart Valve Dis 2001;10:334-345
2. Thomson HL, O'Brien MF, Almeida AA, et al. Haemodynamics and left ventricular mass regression: A comparison of the stentless, stented and mechanical aortic valve replacement. Eur J Cardiothorac Surg 1998;13:572-575
3. Hammermeister K, Sethi GK, Henderson WG, et al. Outcomes 15 years after valve replacement with a mechanical versus a bio-prosthetic valve: Final report of the Veterans Affairs randomized trial. J Am Coll Cardiol 2000;36:1152-1158
4. Perier P, Bessou JP, Swanson JS, et al. Comparative evaluation of aortic valve replacement with Starr, Björk, and porcine valve prosthesis. Circulation 1985;72(suppl.):III-40-III-45
5. Naegele H, Bohlmann M, Doring V, et al. Results of

aortic valve replacement with pulmonary and aortic homografts. J Heart Valve Dis 2000;9:215-220
6. McGiffin DC, Galbraith AJ, McLachlan GJ, et al. Aortic valve infection: risk factors for death and recurrent endocarditis. J Thorac Cardiovasc Surg 1992;104:511-520
7. Dossche KM, de la Riviere AB, Morshuis WJ, et al. Cryopreserved aortic allografts for aortic root reconstruction: A single institution's experience. Ann Thorac Surg 1999;67:1617-1622
8. Homann M, Haehnel JC, Mendler N, et al. Reconstruction of the RVOT with valved biological conduits: 25 years experience with allografts and xenografts. Eur J Cardiothorac Surg 2000;17:624-630
9. Hawkins JA, Breinholt JP, Lambert LM, et al. Class I and class II anti-HLA antibodies after implantation of cryopreserved allograft material in pediatric patients. J Thorac Cardiovasc Surg 2000;119:324-328
10. Shaddy RE, Lambert LM, Fuller TC, et al. Prospective randomized trial of azathioprine in cryopreserved valved allografts in children. Ann Thorac Surg 2001;71:43-47
11. Dignan R, O'Brien MF, Hogan PG, et al. Influence of HLA matching and associated factors on aortic valve homograft function. J Heart Valve Dis 2000;9:504-511
12. Hogan PG, Duplock L, Green M, et al. Human aortic valve allografts elicit a donor-specific immune response. J Thorac Cardiovasc Surg 1996;112:1260-1267
13. O'Brien MF, McGiffin DC, Stafford EG. Allograft aortic valve implantation: Techniques for all types of aortic valve and root pathology. Ann Thorac Surg 1989;48:600-609
14. Christie GW, Barratt-Boyes BG. Identification of a failure mode of the antibiotic sterilized aortic allograft after 10 years: Implications for their long-term survival. J Card Surg 1991;6:462-467
15. Grunkemeier GL, Jamieson WRE, Miller DC, Starr A. Actuarial versus actual risk of porcine structural valve deterioration. J Thorac Cardiovasc Surg 1994;108:709-718
16. Miller CC, III, Safi HJ, Winnerkvist A, Baldwin JC. Actual versus actuarial analysis for cardiac valve complications: The problem of competing risks. Curr Opin Cardiol 1999;14:79-83
17. Grunkemeier GL, Anderson RP, Starr A. Actuarial and actual analysis of surgical results: Empirical validation. Ann Thorac Surg 2001;71:1885-1887
18. Grunkemeier GL, Wu YX. Interpretation of nonfatal events after cardiac surgery: Actual versus actuarial reporting. J Thorac Cardiovasc Surg 2001;122:216-219
19. Farewell VT. The use of mixture models for the analysis of survival data with long-term survivors. Biometrics 1982;38:1041-1046
20. Cox DR. Regression models and life-tables (with Discussion). J Roy Statist Soc B 1972;34:187-220
21. Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data via the EM algorithm (with Discussion). J Roy Statist Soc B 1977;39:1-38
22. McLachlan GJ, Krishnan T. The EM Algorithm and Extensions. Wiley, New York, 1997
23. Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? Statist Med 1993;12:737-751
24. David HA, Moeschberger ML. The Theory of Competing Risks. Griffin, London, 1978
25. McGiffin DC, Galbraith AJ, O'Brien, MF, et al. An analysis of valve re-replacement after aortic valve replacement with biologic devices. J Thorac Cardiovasc Surg 1997;113:311-318
26. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Statist 1988;16:1141-1154
27. Pepe MS. Inference for events with dependent risks in multiple endpoint studies. J Am Statist Assoc 1991;86:770-778
28. Ng SK, McLachlan GJ, McGiffin DC, O'Brien MF. Constrained mixture models in competing risks problems. Environmetrics 1999;10:753-767
29. Choudhary SK, Mathur A, Chander H, et al. Aortic valve replacement with biological substitute. J Card Surg 1998;13:1-8
30. Lund O, Chandrasekaran V, Grocott-Mason R, et al. Primary aortic valve replacement with allografts over twenty-five years: Valve-related and procedure-related determinants of outcome. J Thorac Cardiovasc Surg 1999;117:77-90
31. Efron B. The Jackknife, the Bootstrap and Other Resampling Plans. SIAM, Philadelphia, 1982

Appendix I: Mixture modeling approach

In the context of the valve-reoperation problem, we let T denote the time to either a reoperation or to death without a reoperation. In the mixture model framework, the survival function of T is modeled as:

$$S(t;x) = \pi_1(x)S_1(t;x) + \pi_2(x)S_2(t;x) \quad (1)$$

where x = *(age, technique)* is a vector of covariates (*technique* = *0* for non-root replacement; *technique* = *1* for root replacement), $S_1(t;x)$ denotes the conditional survival function given the patient undergoes a reoperation, and $\pi_1(x)$ is the probability of reoperation. The second component corresponds to death before reoperation.

The probability of reoperation is taken to have the logistic form (19):

$$\pi_1(x;\alpha) = \frac{\exp(a+b * age + c * technique)}{1 + \exp(a + b * age + c * technique)} \quad (2)$$

where $\alpha = (a,b,c)^T$; the superscript T denotes vector transpose. It is assumed that the conditional survival function for reoperation $S_1(t;x)$ belongs to the Gompertz family with proportional hazards (20); that is, the conditional hazard function is specified parametrically as:

$$h_1(t;\theta_1,x) = \exp(\lambda_1 + \beta_1 t)\exp(\gamma_1 * age + \xi_1 * technique),$$

where λ_1 and $\beta_1 > 0$ are the scale and shape parameters of Gompertz distribution, respectively, and $\theta_1 = (\lambda_1, \beta_1, \gamma_1, \xi_1)^T$. As a reoperation is eventually needed if a patient were to live for a sufficiently long period following the initial replacement operation, it means that the conditional hazard function for death will be greater than the conditional hazard function for reoperation. Hence, the conditional survival function for death $S_2(t;x)$ is specified by a constrained approach (28) to model the dependency between failure times of death and reoperation:

$$S_2(t;x) = S_a(t;x)S_1(t;x), \quad (3)$$

where $S_a(t;x)$ denotes some additional survival function. We assume here that $S_a(t;x)$ has the Weibull form with proportional hazards; that is

$$h_a(t;\theta_a,x) = \lambda_a\beta_a t^{(\beta_a-1)}\exp(\gamma_a * age + \xi_a * technique),$$

where λ_a and $\beta_a > 0$ are the scale and shape parameters of Weibull distribution, respectively, and $\theta_1 = (\lambda_a, \beta_a, \gamma_a, \xi_a)^T$. With Eqn. (3), given that a patient will die without a reoperation, his/her conditional hazard function can be viewed as being equal to the conditional hazard function for reoperation plus an additional hazard denoted here by $h_a(t;x)$ (28).

The mixture model (Eqn. 1) is fitted by maximum likelihood via the EM algorithm (21,22). The standard errors of estimates of the parameters can be computed by applying the non-parametric bootstrap approach (31) with the resampling scheme modified for the competing-risks problems (28). Let $\hat{\alpha}$, $\hat{\theta}_1$ and $\hat{\theta}_a$ be the maximum likelihood estimate of α, θ_1 and θ_a, respectively, the estimated probability of reoperation can be obtained by putting $\hat{\alpha}$ into Eqn. (2). The estimated cumulative incidence function (*actual* risk) of reoperation is given by

$$\pi_1(x;\alpha)\{1 - S_1(t;\theta_1,x)\}.$$

As a patient can avoid a reoperation by dying first, it is relevant to consider the conditional probability of a reoperation within a specified time t after the initial operation given that the patient does not die without a reoperation during this period. This conditional cumulative incidence function (23) for reoperation is estimated by:

$$\frac{\pi_1(x;\alpha)\{1 - S_1(t;\theta_1,x)\}}{\pi_1(x;\alpha) + \pi_2(x;\alpha)S_a(t;\theta_a,x)S_1(t;\theta_1,x)}.$$

Meeting discussion

SIR MAGDI YACOUB (Harefield, UK): Dr O'Brien, excellent results. I have some questions and a comment. I am intrigued by the difference in survival, and that you have not entered it into a multivariate analysis. Like you, we introduced that technique earlier, in 1976, and we were nervous about the free root. Also like you, we thought exactly about mismatch between the donor and recipient tissues, and to optimize the component parts to make sure that there would be no distortion. We were very cautious about what would happen to the root in terms of dilatation and/or calcification. Dilatation has not occurred - and neither did it occur in your patients. Calcification has occurred, but it has not been a major problem. When we compared the series for the first time, there was no difference in survival or rate of degeneration between the subcoronary implants and the roots. It took about 20 years to show that. Indeed, in a multivariate model, the use of a root was a predictor of better survival, as with your study. So I am intrigued by that, because you showed better survival and less degeneration. The better survival excited us quite a lot. My next question is, what are your selection criteria? You clearly have a younger group of patients. We have tended to use a homograft for everybody, regardless of ventricular function or age, whenever we could. At one time we

had 1,000 homografts a year available to us, but not now - and you have the same problem! So, what are your selection criteria? You did say in the younger age group, but in terms of sickness as well?

DR. MARK O'BRIEN (Brisbane, Australia): In terms of patient selection, the presence of comorbidity or left ventricular function or poor left ventricular function would not be contraindications. Selection is dictated by a more ideal recipient age, the supply of the homograft, and the presence of endocarditis. Supply can be critical, such that when we see patients in the ideal age range, who would really benefit, we request the appropriate size valve. Patients often have to wait for a valve, and on occasion they cannot wait any longer and have to receive another device. If we had a better supply of homografts, as we had 10 years ago, we would be using two, three, four times the volume. So selection does not really become important in the analysis. We have put all the data through a multivariate analysis. The statistician has gone beyond actual and actuarial curves, looking at the competing risk of death, and further analysis. It has certainly shown that the root replacement will more likely need a reoperation, because the patients are surviving longer than the subcoronary group.

MR. YACOUB: Was there a better survival in the multivariate model?

DR. O'BRIEN: Yes, there was. But my disappointment is that ultimately the valve will deteriorate if the patient lives long enough.

DR. CARLOS DURAN (Missoula, Montana, USA): May I ask you whether there was a difference in reoperation rate among patients under 20 years of age who underwent subcoronary implantation versus root replacement?

DR. O'BRIEN: No, I think it was the same. The other big thing, of course, with this, like all studies, is that the subcoronary group have a much longer follow-up, and the root mean follow-up isn't long enough yet. But I think the statisticians made allowances for that, anyway. In the young, the immune response is greater, irrespective of the implantation technique.

DR. DURAN: But with a follow up of seven or eight years you should be able to know what has happened in these young patients, although I recognize that the number of patients might be too small to draw conclusions.

DR. O'BRIEN: No difference. And I showed you with a bigger published series that the same outcome happened in this younger aged patient group.

DR. J. J. M. TAKKENBERG (Rotterdam, The Netherlands): I read your recent publication in the *Journal of Heart Valve Disease* carefully, and when I look at freedom from reoperation at about 10 years, it seems to be somewhat in favor of the subcoronary implantation technique - even though there are considerably more technical failures in this group compared with the root replacement group. So, is the durability actually improved in the root replacement technique group compared with subcoronary implantation when you are not taking into account these early technical failures?

DR. O'BRIEN: That is an excellent question, the answer to which we have long sought. When we did this analysis a few years ago we could not prove any difference in the durability. In this new analysis, according to the statistician's curves, there is now that difference. It is small such that I personally think that whether it is subcoronary or whether it is a root replacement, ultimately the durability is very close to being the same. The only problem is that the subcoronary group is going to come in earlier with a reoperation and that such patients have a decreased survival compared with the root replacement group. This makes death a greater competing risk in the subcoronary group.

DR. DURAN: Let me go back to the question about the patients under 20 years of age. Perhaps I am influenced by the problems we had in Saudi Arabia where the majority of our patients were under 20. This is a very difficult group because whatever you do is not satisfactory. Was there anything special in the mode of structural deterioration of these valves or roots? You mentioned calcification. Can you expand on this?

DR. O'BRIEN: Yes, that is true. The most calcified valves were in the young group, this calcification occurred within two or three years, and it was so unlike the mode of degeneration in the older age group. Even looking at the whole study echocardiographically, our department showed the same thing, that the mode of degeneration and the stenosis appeared more likely in the younger age group than in the older age group. This, of course, opened up the whole etiology that we would attribute to being an immune response in that younger age group.

DR. DURAN: I don't recall, but were there many rheumatic cases in this group?

DR. O'BRIEN: No. Most of them were congenital. At least 50% or more of the whole series were congenital.

MR. YACOUB: Whilst it is true that degeneration, and particularly calcification, is common below the age of 30 - and I do not know the cut-off point - Dr. O'Brien mentioned that there are patients who have homograft replacement at the age of three who have a good function until the age of 25. So it is not an invariable - true, it is very common, but it is not invariable - which stresses the point that we just do not know. And to complicate the picture further, it is not directly related to the immune response, neither the antibody-mediated nor cell-mediated. So is it metabolic, or is it a mix-

ture of different things?

DR. DURAN: The question is that after listening to this, when we go home, we will not feel very comfortable placing a homograft in these patients.

MR. YACOUB: Absolutely not, but if I am pushed and I cannot do the Ross operation, I will use homografts. We started randomizing above the age of nine between homografts and autografts, arguing that we do not know whether the Ross operation by two operations is going to be worse than repeated operations, taking the point that reoperation is not a disaster. As Lord Brock used to say, mitral valvotomy, revalvotomy, you must get used to the idea that this is just a way of life, and you are not going to kill the patient. But soon we found that homograft failure was too common. As you say, Mark, there were patients coming back at three and four years, which we thought totally unacceptable. So we went back to the ethical committee and went up to the age of 18 now. So anybody below the age of 18 will definitely get an autograft, anybody above the age of 18 will get the randomization, knowing that in the younger age group between 18 and your cutoff point, at about 34 or so, there is still an increased incidence of homograft degeneration. But it could be tolerable in comparison to the autograft.

DR. DURAN: Well, maybe it is alright to be biased, but perhaps a patient under 20 should have a St. Jude valve.

MR. YACOUB: There are things which we do not do. I mean, what happens if the St. Jude patient gets thromboembolism, what happens to ventricular function and coronary flow, and so on? Unless you have solid data, it is easy to be biased, isn't it?

DR. O'BRIEN: The anticoagulant-related hemorrhage and thromboembolism rates per 100 patient-years are about 3% with the St. Jude valve. So you may not be chairing this session in two years' time if you were to have a St. Jude mechanical valve today. (Laughter)

DR. DURAN: Since I am apparently biased towards a mechanical valve, I understand the implications very well.