SURGERY FOR ACQUIRED HEART DISEASE

PULMONARY AUTOGRAFT VERSUS HOMOGRAFT REPLACEMENT OF THE AORTIC VALVE: A PROSPECTIVE RANDOMIZED TRIAL

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Background: **Pulmonary autografts offer many theoretical advantages. However, the operation is complex, may interfere with right ventricular and pulmonary outflow function, and requires a longer operative time than does the homograft operation. The effects of these potential disadvantages are unknown.** *Methods:* **To clarify these issues we randomized 70 patients undergoing aortic valve replacement to an aortic homograft group (group A = 37 patients; 53%; 34 male, 3 female) or a pulmonary autograft group (group B = 33 patients; 47%; 28 male, 5 female). Ages varied from 12 to 65 years (mean 39 ± 15 years) for group A and from 3 to 54 years (mean 29 ± 15 years) for group B (p = not significant). Eleven patients in group A (30%) and eight in group B (24%) had previous aortic valve surgery. All patients were operated on by the same surgeon. The mean cardiopulmonary bypass time was 113 ± 29 minutes (range 66 to 175 minutes) for group A and 151 ± 31 minutes (range 115 to 226 minutes) for group B ($p < 0.002$). Mean aortic crossclamp time was 85 ± 19 minutes (range 45 to 140 minutes) for group A and 109 ± 20 minutes (range 74 to 164 minutes) for group B ($p = 0.02$). In 32 patients (86.5%) the aortic homograft was implanted as a root with coronary reimplantation. All pulmonary autografts were implanted as a root.** *Results:* **No early or late deaths had occurred in this series at a mean follow-up time of 16 months (range 3 to 21 months). Two patients (one in each group) required reexploration for bleeding. No statistically significant differences were observed between the two groups with regard to ventilatory support (group A, mean 10 ± 8.5 hours; group B, mean 29 ± 85 hours), total blood loss (group A, mean 471 ± 347 ml; group B, mean 543 ± 404 ml), intensive care unit stay (group A, mean 1.2 ± 0.6 days; group B, mean 2 ± 3.7 days), and hospital stay (group A, mean 9.5 = 3.2 days; group B, mean 12 ± 6 days). Postoperatively, all patients are in New York Heart Association class I (93%) or II (7%) (p = not significant). Ejection fraction for the two groups did not change significantly over the follow-up period. Left ventricular mass and diastolic diameter showed progressive regression, with no apparent difference between the two treatment groups to date. Echocardiographic evalu-**

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ation of aortic valve function at 6 months showed good valve function in all patients with no evidence of aortic regurgitation in 80% of both groups. In group B the right ventricular outflow gradient was below 15 mm Hg over the follow-up period. Holter monitoring, available only in 44 patients (63%), showed most of the arrhythmias to be grade 0 to 1 of the modified Lown grading system. ***Conclusion:*** **Although the pulmonary autograft requires a significantly longer operating time, this does not seem to affect early and medium-term outcome when compared with results obtained with aortic homografts. Continued patient evaluation is warranted, particularly with regard to evidence of valve degeneration and right ventricular function and arrhythmias in the long term. (J Thorac Cardiovasc Surg 1997;113: 894-900)**

Untreated aortic valve disease leads to ventricular hypertrophy or dilatation (or both), an adaptive response to pressure or volume overload.[1] Over time, ventricular failure is inevitable.[2] Surgical replacement of the aortic valve interrupts this potentially lethal chain of events and has been shown to be effective even in patients in whom the risks of surgery are high.[3-6] Both the early and long-term results depend to a large degree on the type of valve substitute used. The perfect valve substitute, however, does not exist. In the search for a long-lasting, durable, and nonthrombogenic valve, which has the potential of restoring the normal hemodynamic profile in the aortic root, increased interest has been focused on the aortic homograft and the pulmonary autograft. Although these substitutes were first used clinically many years ago,[7-9] a resurgence of interest in their use for replacement of the failing aortic valve has recently occurred.[10-15]

The potential clinical and hemodynamic advantages of both the aortic homograft and pulmonary autograft over conventional mechanical or xenograft valve prostheses are now widely recognized.[16, 17] When compared with homograft aortic valve replacement (AVR), however, the pulmonary autograft offers even more theoretical advantages, such as the potential for growth in children, increased cellular viability, and enhanced durability and possibly internal innervation of the cusps.[18] These potential advantages are balanced, however, by the increased complexity and longer duration of the operation. Moreover, the potential for coronary arterial injury, the effect of the dissection on right ventricular function, and the exposure of the patient to the disadvantages of two valves at risk are all areas of legitimate concern.

The objective of this study was to prospectively compare the effect of AVR with an aortic homograft or pulmonary autograft on perioperative variables and short- and medium-term clinical performance.

Patients and methods

Patient population. From January 1994 to February 1996, 70 patients, 61 male (87%) and eight female (13%) with an age range from 3 to 64 years, were prospectively randomized to undergo AVR with an aortic homograft (group A, 37 patients; 53%) or a pulmonary autograft (group B, 33 patients; 47%).

Ethical committee approval was obtained before the start of the study. Full informed consent was obtained from each patient before enrollment. The study was designed for patients undergoing isolated AVR regardless of their symptomatic status or ventricular function and included reoperative procedures, bacterial endocarditis, and emergency operations (Table I). Exclusion criteria included the need for double valve replacement or coronary bypass grafting, connective tissue disorders such as Marfan and Ehlers-Danlos syndromes, and autoimmune diseases known to affect the aortic valve and root, such as active rheumatoid arthritis. Patients who had prior rheumatic carditis were not excluded.

Eleven patients in the homograft group (28%) and nine in the autograft group (27%) had undergone previous intracardiac operations (Table I).

Operative technique and procedures. All operations were performed by the same surgeon (M.Y.). Cardiopulmonary bypass with moderate hypothermia (30° C) was used. In both groups myocardial protection was achieved by either antegrade crystalloid or cold blood cardioplegia. In group A, five patients underwent AVR by the two suture line, subcoronary implantation technique. This was used when the size and shape of the available homograft and the patient's aortic root matched well. All the others underwent root replacement with coronary reimplantation.[19, 20] We[11] have previously shown that the two techniques yield comparable results in patients undergoing homovital homograft replacement of the aortic valve. In group B, the proximal anastomosis was performed with interrupted sutures. The right ventricular outflow tract was reconstructed with the use of a large homovital or antibiotic-sterilized pulmonary homograft conduit in all

Table I. *Preoperative data*

Variable	*Homograft*	*Autograft*	*p Value*
Patients (No.)	37 (53%)	33 (47%)	NS
Sex (No.)			
Male	34 (92%)	28 (85%)	NS
Female	3 (8%)	5 (15%)	NS
Age (yr)			
Range	12-65	3-54	
Mean ± SD	39 ± 15	29 ± 15	
Predominant aortic stenosis (No.)	22 (59%)	19 (58%)	NS
Predominant aortic insufficiency (No.)	10 (27%)	10 (30%)	NS
Combined lesion (No.)	5 (14%)	4 (12%)	NS
Clinical symptoms (No.)			
NYHA I	11 (30%)	9 (27%)	NS
NYHA II	18 (49%)	17 (52%)	NS
NYHA III	8 (21%)	6 (18%)	NS
NYHA IV	—	1 (3%)	NS
Echocardiographic data (mean ± SD)			
EF (%)	65 ± 23	66 ± 12	NS
LV mass (gm)	353 ± 135	418 ± 181	NS
Infective endocarditis (No.)	1 (3%)	3 (9%)	NS
Redo procedure (No.)	11 (30%)	9 (27%)	NS

NS, Not significant; *SD,* standard deviation; *NYHA,* New York Heart Association; *EF,* ejection fraction; *LV,* left ventricular.

cases, inserted by continuous 4-0 sutures without inclusion of strips of prosthetic or autologous tissue for support. These suture lines were performed before release of the aortic clamp. In the presence of infective endocarditis, aggressive and complete débridement of the infected and necrotic tissue was performed and no foreign material was used for reconstruction. This subgroup of patients received intravenous antibiotics for 6 weeks after the operation.

Cardiopulmonary bypass and aortic crossclamp times were 113 ± 29 and 85 ± 19 minutes, respectively, for group A and 151 ± 31 ($p < 0.002$) and 109 ± 20 minutes, respectively ($p = 0.02$), for group B. Intraoperative transesophageal echocardiography was used to monitor valve and ventricular function before and after insertion of the graft. Valve function was judged to be good echocardiographically in all patients shortly after release of the aortic clamp.

Follow-up. Early mortality was defined as any death within 30 days or during initial hospitalization. Postoperative valve-related morbidity and mortality were evaluated and reported according to standard definitions.[21] All patients had a clinical examination and a chest roentgenogram, electrocardiogram, and color-flow Doppler echocardiogram before discharge, at 6 months, and at yearly intervals after that. Blood velocities were calculated at the level of the left and right ventricular outflow tracts and at the level of the aortic valve orifice, and mean and peak gradients were derived by the modified Bernoulli equation. Aortic valve insufficiency was graded according to the method described by Perry and associates.[22] Regurgitation not severe enough to be measured by these criteria was considered trivial. Left ventricular mass was derived from ventricular dimension.[23] A 24-hour ambulatory electrocardiographic recording was performed within 6 months after the operation.

Statistical analysis. Statistical analysis was performed with a commercially available software package (SPSS, Inc., Chicago, Ill.). Comparison of demographic and preoperative data between groups was performed with the use of an unpaired t test. Comparison of data over time was done with the use of a one-way analysis of variance. A p value of less than 0.05 was accepted as significant.

Results

No early or late deaths had occurred at a mean follow-up of 16 months (range 3 to 21 months). Postoperative complications included reexploration for bleeding in two patients, one in each group, and a low cardiac output state in a 6-year-old child in the autograft group. This patient, who had some features of Shone's disease[24] plus two previous operations (mitral commissurotomy and resection of subaortic membrane with aortic valvuloplasty), required intensive inotropic support and intraaortic balloon counterpulsation complicated by lower limb ischemia requiring fasciotomy and hemofiltration. She was finally extubated on postoperative day 20 and did well. Other complications included left lower lobe atelectasis ($n = 3$), pneumothorax ($n = 2$), and pericardial effusion after implantation of a pulmonary autograft ($n = 1$). No statistically significant differences existed between the two groups

with regard to ventilatory support (group A, mean 10 ± 8.5 hours; group B, mean 29 ± 85 hours), total blood loss (group A, mean 471 ± 347 ml; group B, mean 543 ± 404 ml), intensive care unit stay (group A, mean 1.2 ± 0.6 days; group B, mean 2 ± 3.7 days), and hospital stay (group A, mean 9.5 ± 3.2 days; group B, mean 12 ± 6 days). No significant differences were identified between the two groups with regard to inotropic support requirements and electrocardiographic and biochemical (creatine kinase MB) evidence of postoperative myocardial ischemia.

Postoperatively, all patients are either in New York Heart Association class I (93%) or II (7%), with no significant difference between the two valve groups ($p = 0.57$). No evidence of postoperative endocarditis was seen in either group. No patient had valve-related complications or evidence of valve failure during the follow-up period. The pulmonary autograft group had no evidence of root dilatation during the short follow-up available.

Holter monitoring. Preliminary analysis of Holter monitor data available in 44 patients showed no significant difference between the two groups, with most of the arrhythmias being grade 0 to 1 of the modified Lown grading system.

Hemodynamic follow-up. Postoperative evaluations of aortic valve gradient, degree of regurgitation, ejection fraction, left ventricular diameters and mass, and right ventricular outflow tract gradient were performed at regular intervals.

Ejection fraction for the two groups did not change significantly during the follow-up period. Left ventricular diastolic diameter showed a significant degree of reduction for each group when compared with the preoperative value (analysis of variance versus baseline). At discharge, left ventricular diastolic diameter was reduced by 13% ± 11% and by 16% ± 12% from the preoperative value in the homograft and autograft groups, respectively (p = not significant). Postoperative echocardiographic evaluation of left ventricular mass showed evidence of progressive reduction in both groups, with no significant difference. Mean and peak gradients across the aortic valve were calculated in all patients. At 1 week, the peak gradient was 6.3 ± 3.9 mm Hg versus 6.7 ± 3.1 mm Hg for groups A and B, respectively. No significant differences were recorded from baseline data over the follow-up time.

In group B, the right ventricular outflow tract gradient at the valve level was consistently less than 15 mm Hg throughout follow-up. For the same period, six patients had a trivial degree of regurgitation. None of the patients had clinical evidence of dysfunction of the right ventricle after the operation.

Discussion

The present prospective randomized study has served to define the influence of the use of the pulmonary autograft for AVR on patient outcome, clinical status, and left ventricular and valve function during the first 2 years.

Pulmonary autograft implantation is a longer and more extensive operation than homograft implantation. However, this did not have a significant impact on patient survival and postoperative outcome when the amount of blood loss and blood product requirement, ventilatory and inotropic support necessary, and length of intensive care unit and hospital stay were compared between the two patient groups. Consequently, hospital costs between the two treatment groups were judged to be similar.

Evidence of a comparable amount of blood loss and blood product requirement between the two groups is of particular interest in view of the more extensive dissection required in the harvesting of the pulmonary autograft. The exposure of the right ventricular outflow tract is an additional potential source of bleeding, and delayed pericardial effusion (one case in our series) might be related to minor vascular and lymphatic leakage from this area.

In this study we did not exclude patients with poor left ventricular function or those requiring emergency operations, and we have observed no early or late deaths at a mean follow-up time of 16 months. This result compares favorably with previous studies reporting on the use of different valve substitutes.[25-28] This could be due to the excellent hemodynamic performance of the two types of replacement valves used in this series, particularly in patients with active bacterial endocarditis or diminished left ventricular function.

Although the potential for coronary artery injury during the Ross operation is widely recognized, postoperative monitoring of myocardial ischemia by biochemical means (creatine kinase MB) and electrocardiographic evaluation failed to show a significant difference between the two procedures.

Cardiac function for the two groups, as measured by ejection fraction, did not show any significant difference in the postoperative period. Postoperative echocardiographic evaluation of left ventricular diameter and mass instead showed a progressive

degree of regression in both groups, and this trend is maintained over the follow-up period. At discharge, the degree of regression of the left ventricular diastolic diameter was averaging 14.5% when compared with baseline, confirming the impact of the valve substitutes used on ventricular hemodynamics and function. The postoperative changes of left ventricular mass in the two groups over the follow-up period showed relatively fast progressive regression of hypertrophy, which was similar in the two groups.

Postoperative echocardiographic evaluation of aortic valve function at 6 months revealed no evidence of aortic regurgitation in more than 80% of patients in both groups, with trivial regurgitation in less than 15% and mild regurgitation in less than 6%. This trend appears to be maintained over the follow-up period.

In all patients who had a Ross procedure, the gradient across the right ventricular outflow tract was below 15 mm Hg. A small percentage of these had a trivial degree of regurgitation (18%), indicating that the use of a large pulmonary homograft conduit for this purpose can give good results, at least in the short term. None of the patients in group B had evidence of apparent right ventricular dilatation or dysfunction as viewed by two-dimensional echocardiography.

Postoperatively, all patients are in New York Heart Association class I (93%) or II (7%), with no significant difference between the two valve groups ($p = 0.57$). No patient had valve-related complications or evidence of valve failure during the follow-up period.

We conclude that although pulmonary autograft implantation is a technically more demanding operation than aortic homograft implantation, with a longer aortic crossclamp time and cardiopulmonary bypass time, both procedures carry a low risk of death and equivalent risks of complications. Hospital stay and resource utilization appear to be comparable. No clear evidence of ischemic damage was found in the two groups. Left and right ventricular function appear to be preserved within a medium-term follow-up.

Continued patient evaluation, particularly with regard to evidence of valve degeneration and arrhythmias in the long term, is warranted.

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Discussion

Dr. Robert C. Robbins *(Stanford, Calif.).* This is an extremely important paper for those of us who are interested in doing the Ross procedure. The objectives of Dr. Santini and his associates were satisfactorily achieved in that no deaths and no complications, early or late, occurred in this impressive series. They are also to be congratulated on sticking to a prospective randomized trial, since this is the first large-scale trial that I am aware of that addresses this issue.

I have a couple of questions specifically addressing the randomization. Were these patients all randomized? They were at two hospitals, the Brompton and Harefield, and they were all Mr. Yacoub's patients. Am I correct in assuming that all the patients who were referred for AVR were randomized regardless of the hospitals, or were the patients randomized separately between the hospitals?

Dr. Santini. The patients were randomized in one single institution and then were operated on in two different institutions. All the patients who came to our attention and fulfilled the criteria were randomized; therefore we did not randomize those patients who did not consent to the randomization. Patients referred to the institution for one of the two procedures received that procedure specifically without randomization.

Dr. Robbins. You noted that there was no statistically significant difference between the age of the two groups. How were procedures distributed in patients who were less than 10 years old (four autografts and no homografts) and for those patients older than 50 years old (14 homografts and only three autografts). Is that just luck of the draw, or did other factors influence this?

Dr. Santini. The patients had been genuinely randomized, so I think it is just by chance. There was no bias, no attempt to perform an autograft in a younger population. Because this is an ongoing study, this difference that is evident now with 70 patients may be obliterated later on.

Dr. Robbins. The fact remains that the mean age for the patients receiving pulmonary autografts was 10 years less than that of patients receiving homografts, and that could have some effect on the study. It will be interesting to see how this works out with larger numbers.

It appears that the first five homografts were implanted with a freehand technique and the remainder of the 37 were done with root replacement with coronary reimplantation. If this is correct, can you explain why you changed?

Dr. Santini. We decided after the first few patients to adopt the root replacement for both techniques to make the two procedures as uniform as possible. I do not think the type of procedure used would have an appreciable effect, but in comparing two groups I think it was important to try to adopt the same procedure for both.

Dr. Robbins. I agree that that would be important.

What about your technique for doing the autograft? You said that you used interrupted running sutures. Does that mean that three sutures are placed at the commissures and run in between?

Dr. Santini. That was for the distal suture line. For the proximal suture lines we have always used interrupted 4-0 Ethibond sutures (Ethicon, Inc., Somerville, N.J.). The distal suture line has been done with Prolene sutures (Ethicon) interrupted three times.

Dr. Robbins. I see. You use a homograft for root replacement, and when a pulmonary translocation is performed the proximal sutures are interrupted.

Dr. Santini. Yes.

Dr. Robbins. When you are reconstructing the right ventricular outflow tract, is the clamp on or off? How does that affect the crossclamp time?

Dr. Santini. Both the distal and proximal anastomoses have been done with the crossclamp off.

Dr. Robbins. Were the patients who received the autografts receiving continuous retrograde cardioplegia? Was there any difference between the two groups in how the cardioplegic solution was given?

Dr. Santini. I think the numbers in this cohort of patients are too small to identify any statistically significant difference. When the groups have more patients, approaching 100 or 200, it might be easier to make that assessment.

Dr. Robbins. Did the transesophageal echocardiogram change anything that you did during the operation? Were there ever any cases in which you went back and changed the way that the grafts were implanted because of excessive regurgitation?

Dr. Santini. No. Transesophageal echocardiography has been used at the very beginning of the procedure to assess the incompetence of the pulmonary valve, particularly for the autograft group, and then off bypass to

evaluate the competence of the aortic root and the aortic valve, but in no case have we had to go back on bypass to modify the operation.

Dr. Robbins. I hope you will continue to randomize patients, and I hope you will come back in 15 to 20 years to answer this question: Is it worth the time and the effort to put the patients through a more complex operation because of less valve deterioration with the pulmonary autograft?

Dr. John P. McDermott *(Redding, Calif.).* In the past 4 years, 75% of our patients who have received AVR have been more than 75 years old. The mean ages for your populations for the homograft and pulmonary translocations have been in the 30- to 35-year-old range. Do you have an opinion about a cutoff in terms of age or other noncardiac medical issues that would affect your decision to do the pulmonary translocation? In what types of older patients have you done this procedure?

Second, would you expect the longer cardiopulmonary bypass times to cause more complications in the older patients than in the younger age group?

Dr. Santini. In the inclusion criteria, the oldest patient in whom we decided to perform this operation was 60 years old, but then we decided to base this decision on a biological age rather than a chronological age. We therefore performed either of the two procedures whenever we were expecting at least 15 years of survival. On the basis of our experience, I think this should be the criterion. For older patients, I would not embark on a procedure that is definitely longer, particularly because these older patients may have additional clinical conditions that contraindicate a longer bypass time than is necessary with a more conventional AVR, whatever the prosthetic device.

Dr. McDermott. Am I correct that your oldest patient in the translocation group was 60 years old?

Dr. Santini. On the basis of this study, I think the autograft can be offered to patients 60 years old.