Incidence, Location, Pathology, and Significance of Pulmonary Homograft Stenosis After the Ross Operation

Gerald S. Carr-White, MRCP; Philip J. Kilner, MD, PhD; Jimmy K.F. Hon, MB, ChB; Thomas Rutledge, MBBS; Sue Edwards, BSc; Elisabeth D. Burman, SRN; Dudley J. Pennell, FRCP; Magdi H. Yacoub, FRS

Background—The Ross operation has several theoretical advantages. However, concern exists regarding evolving pathology in the pulmonary homograft.

Methods and Results—Consecutive patients (n = 144; mean age 31 years, range 2 months to 64 years) undergoing the Ross operation were studied between 1993 and 2000. Echocardiographic examination of the pulmonary homograft was performed immediately after surgery, then at yearly intervals for a mean interval of 48 months. Fifteen patients (mean age 37 years) in whom echocardiography revealed peak pulmonary gradients $\geq 30$ mm Hg (mean 46±18 mm Hg) underwent MRI with velocity mapping in a Picker 1.5-T magnet. No patient had more than mild pulmonary regurgitation. Four patients required reoperation for rapidly progressive pulmonary homograft stenosis; in all 4, there was macroscopic and microscopic evidence of a pronounced chronic adventitial reaction, with perivascular infiltration producing extrinsic compression. Freedom from any pulmonary homograft stenosis at 7-year follow-up was 79.7%, with instantaneous hazard falling to zero after 4 years. Freedom from reoperation at 7 years was 96.7%. In those studied with MRI, there was evidence of narrowing of the whole homograft or distal suture line in 14 of 15 patients, with obvious excess surrounding tissue in 11. Mean minimum diameter and peak velocity by MRI were 11±2 mm and 3.2±0.7 m/s, respectively. Multivariate analysis of patient-, surgery-, and homograft-related variables did not reveal any significant risk factors for development of neopulmonary stenosis.

Conclusions—Pulmonary homograft stenosis after the Ross operation is clinically important and appears to represent an early postoperative inflammatory reaction to the pulmonary homograft that leads to extrinsic compression and/or shrinkage. (Circulation. 2001;104[suppl I]:I-16-I-20.)

Key Words: valves ■ surgery ■ magnetic resonance imaging ■ echocardiography

Pulmonary autograft replacement of the aortic valve has potential advantages, including improved hemodynamics, durability, and the ability to grow.1,2 Both intermediate and late results have demonstrated rates of survival and freedom from reoperation that compare favorably with other valve substitutes.3,4 The operation itself, however, involves insertion of a pulmonary homograft, and concern exists about the development of neopulmonary dysfunction, particularly stenosis. The aim of the present study was to describe the incidence and severity of pulmonary homograft dysfunction in a series of 144 consecutive patients. In addition, by using MRI, we hoped to characterize the location and functional significance of the dysfunction, and by combining this with operative histology, to examine the underlying mechanisms. Finally, we attempted to identify potential determinants of pulmonary homograft dysfunction.

Methods

Patient Selection

Consecutive patients (n = 144) operated on by one surgeon (M.H.Y.) at one National Health Service (NHS) trust (the Royal Brompton and Harefield Hospitals NHS trust) between September 1993 and June 2000 were studied. Patient demographics and preoperative variables are shown in the Table. Local ethics committee approval was obtained before the study was begun, and full informed consent was obtained from each patient.

Operative Technique

Cardiopulmonary bypass with moderate hypothermia (30°C) was used, and myocardial protection was achieved by either antegrade crystalloid or cold-blood cardioplegia. All patients underwent aortic root replacement with coronary reimplantation. The right ventricular outflow tract (RVOT) was reconstructed with the use of a large homovital or antibiotic sterilized (either fresh or cryopreserved) pulmonary homograft conduit inserted by either continuous or interrupted 4-0 sutures without inclusion of strips of prosthetic or autologous tissue for support. These suture lines were performed

From the Departments of Cardiology (G.S.C.-W.), Cardiovascular Magnetic Resonance (P.J.K., E.D.B., D.J.P.), and Academic Surgery (J.K.F.H., T.R., S.E., M.H.Y.), National Heart and Lung Institute, Royal Brompton Hospital, London, UK.

Correspondence to Professor Sir Magdi Yacoub, Professor of Cardiothoracic Surgery, National Heart and Lung Institute, Royal Brompton Hospital, Sydney St, London SW3 6NP, United Kingdom. E-mail g.carr-white@virgin.net

© 2001 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org
Pulmonary Homograft Stenosis After Ross Operation  Carr-White et al  I-17

**Patient Demographics and Potential Determinants of Pulmonary Homograft Dysfunction**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=144)</th>
<th>Homograft Stenosis (n=25)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>31 (14)</td>
<td>34 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Male, %</td>
<td>78</td>
<td>84</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis, %</td>
<td>23</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Predominant AR, %</td>
<td>41</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>Predominant AS, %</td>
<td>34</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Mixed, %</td>
<td>25</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Previous AVR, %</td>
<td>38</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Pathological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicuspid AV, %</td>
<td>48</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>Rheumatic disease, %</td>
<td>21</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Degenerative, %</td>
<td>31</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Homograft</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size, mm, mean</td>
<td>24</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Fresh, %</td>
<td>82</td>
<td>91</td>
<td>NS</td>
</tr>
<tr>
<td>Frozen, %</td>
<td>18</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Blood group mismatch, %</td>
<td>58</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>Retrieval to preservation, %</td>
<td>66</td>
<td>52</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;24 h</td>
<td>34</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;24 h</td>
<td>51 (28)</td>
<td>47 (15)</td>
<td>NS</td>
</tr>
</tbody>
</table>

AR indicates aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; and AV, aortic valve.

either before or after release of the aortic clamp. Full details of the operative technique have been published elsewhere.5,5

**Echocardiographic Measurements**

Transthoracic echocardiograms were performed with a Hewlett Packard Sonos 500 or 2000 machine. Maximum velocities across the pulmonary homograft were recorded with continuous-wave Doppler. Pulmonary regurgitation was graded by measuring the jet width as a fraction of the width of the RVOT, in addition to measuring the pressure half-time of the continuous-wave trace of pulmonary regurgitation. In each case, 3 consecutive beats were analyzed. Any pulmonary stenosis was defined as a peak gradient ≥30 mm Hg.

**Magnetic Resonance Measurements**

In 15 of the 25 patients with echocardiographic pulmonary valve gradients ≥30 mm Hg, MRI of the pulmonary homograft and right ventricle was undertaken. Imaging was performed with a Picker Edge 1.5-T whole-body system, with prospective ECG gating and a jacket receiver coil. After acquisition of transaxial spin echo multislice images, cine imaging (echo time 14 ms) in an oblique sagittal plane aligned with the RVOT was performed, followed by imaging in an orthogonal slice aligned with the stream through the homograft lumen. This last was used as scout for in-plane phase velocity mapping (echo time 4 ms) in an oblique sagittal plane now better aligned with the RVOT and the narrowest part of the homograft lumen. Image parameters were slice thickness of 6 mm, field of view of 350 mm, and 2×128 phase encoding steps. Peak velocity of the jet, location of the stenosis, and minimum stenosis diameter were recorded. Right ventricular hypertrophy was graded as absent, mild, moderate, or severe on the basis of observation of cine images in the oblique sagittal and transaxial planes, the latter located through the tricuspid valve and right ventricle (echo time 14 ms). Time restraints prevented acquisition of further multiple cine images, hence right ventricular mass and volume were not measured. Comparable early postoperative MRI studies, acquired on a 0.5-T Picker system 6 and 14 days after Ross procedure, respectively, were found to have been performed in 2 of the above patients, which allowed assessment of homograft change since operation. In 5 additional patients who had MRI performed for other reasons 1 to 4 years after Ross operation, diameters of the homograft lumen were measured from oblique sagittal cine images.

**Statistical Analysis**

Statistical analysis was performed with a commercially available software package (SPSS Inc). Comparison of demographic and preoperative or postoperative 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 1-way ANOVA. A P value of <0.05 was accepted as significant. Possible determinants of pulmonary homograft stenosis were assessed by a logistic multiple regression model. Kaplan-Meier analysis was used to represent freedom from dysfunction at various time points.

**Results**

There were 4 deaths in our series. None were related to pathology in the pulmonary homograft.

**Echocardiographic Data**

No patient had more than mild pulmonary regurgitation. Mean echocardiographic follow-up was 48 months (range 7 to 96 months), and at the pre–hospital-discharge early examination, none of the patients had evidence of any homograft stenosis. Twenty-five (17%) of the 144 patients studied developed echocardiographic evidence of some degree of pulmonary stenosis (defined as a maximum postoperative gradient at any time point ≥30 mm Hg), and the progression over time for each of these patients is shown in Figure 1. Of these, 8 had severe stenosis (defined as a peak gradient >50 mm Hg). Kaplan-Meier curves illustrating cumulative freedom from any stenosis (peak gradient ≥30 mm Hg) and reoperation are shown in Figure 2. Reoperation was undertaken when the patient developed either worsening symptoms, an objective deterioration in exercise tolerance, or worsening right ventricular function. The cumulative probability of freedom from reoperation at 1, 2, and 7 years was 98.5%, 96.7%, and 96.7%, respectively. The cumulative probability of freedom from any pulmonary artery stenosis at 1, 2, 4, and 7 years was 86.1%, 83.4%, 79.7%, and 79.7%, respectively. Figure 3 illustrates the instantaneous hazard
function for the development of any pulmonary homograft stenosis over time. The hazard was relatively high in the first year after surgery but rapidly dropped to zero after the fourth year.

Reoperations for Pulmonary Stenosis

In the present series, 4 patients underwent reoperation for dysfunction of the pulmonary homograft. In all 4 patients, the indication for reoperation was the rapid development of pulmonary homograft stenosis, with high gradient documented at between 6 and 12 months after surgery. Pulmonary valve re-replacement was necessary at between 12 and 18 months after the original operation. Extensive and prolonged microbiological cultures for bacteria, fungi, and viruses were negative in all 4 patients. The operative findings and histological features of the explanted homografts (Figure 4) were remarkably similar in all 4 cases. At operation, extensive granulomatous tissue was seen encircling the homograft and causing extrinsic compression. Histologically, there was minimal to mild neointimal proliferation and a pronounced chronic adventitial inflammatory fibrotic reaction, with a perivascular lymphocytic infiltrate.

MRI of Patients With Pulmonary Stenosis

MRI allowed good visualization of all 15 stenosed homografts (peak gradient ≥30 mm Hg) studied. Proximal and distal suture lines could usually be identified on cine images as slightly darker regions in the wall, and the point of valve closure could be identified. The narrowing was mainly due to reduction in lumen diameter in the tubular part of the homograft in 10 cases. It was mainly at the distal suture line in 4 cases and mainly due to homograft valvar stenosis in only 1 case. Spin echo appearances in 11 of the 15 cases suggested the presence of regions of nonfat tissue ≥8 mm in thickness adjacent to stenosed homografts. Mean minimum diameter and peak velocity by MRI were 11±2 mm and 3.2±0.7 m/s, respectively. An example is shown in Figure 5, together with the early postoperative image acquired in this case. In both of the patients who had undergone early postoperative MRI, the later study appeared to show reduction in homograft length by ≈40%, as well as reduction in luminal diameter.

Functional Significance of Pulmonary Stenosis

All 25 patients were in New York Heart Association class I or II. One patient had right bundle-branch block on his ECG.

Figure 2. Kaplan-Meier curves illustrating cumulative probability of freedom from (A) any stenosis (peak gradient ≥30 mm Hg) and (B) reoperation.

Figure 3. Instantaneous hazard function curve for developing any pulmonary homograft stenosis (peak gradient ≥30 mm Hg).

Figure 4. Typical histology from explanted pulmonary homograft demonstrating (A) marked chronic inflammatory reaction in adventitia (A) and neointimal hyperplasia (n) and (B) a fibrotic perivascular chronic inflammatory infiltrate in adventitia. M indicates media.
and 1 had electrocardiographic right ventricular hypertrophy. However, in the 15 patients who underwent MRI, at least mild RV hypertrophy was assessed to be present in all 15, with moderate hypertrophy in 8.

Determinants of Pulmonary Homograft Stenosis
The Table details the patient demographics and potential determinants of homograft dysfunction for the entire patient group, as well as for those with pulmonary stenosis (including those who subsequently underwent reoperation). No significant differences between the groups were seen. Multiple logistic regression with patient-, homograft-, and operation-related determinants as end points did not identify any significant determinants. There was no correlation between homograft stenosis and the presence of positive panel reactive antibodies to a wide range of HLA antigens.

Discussion
This study serves to document the changes in pulmonary homograft function during the first 7 years after the Ross operation.

Reoperation for Pulmonary Homograft Stenosis
In the present series, all reoperations were due to rapidly progressive stenosis of the pulmonary homograft, and reoperation was necessary within 18 months of the original operation. This scenario has been described previously in both the adult and pediatric populations. In all 4 cases in the present study, there was a pronounced adventitial reaction that produced extrinsic compression, and this was associated with histology that was suggestive of inflammatory-mediated fibrotic reaction. In all 4 cases, there was no significant calcification or change in the homograft wall, and the cusps were unaffected. Unlike other reports, we could not identify any factors that could predict homograft dysfunction or reoperation. In patients with less severe or more slowly progressive stenosis, stenting has been suggested as a possible option. One such patient in our series has recently undergone primary stenting of the pulmonary homograft with excellent early hemodynamic results. The efficacy and safety of this procedure in this group of patients, however, is still to be clarified.

Echocardiographic Pulmonary Stenosis
At 7 years of follow-up, a total of 17% of patients in our series had developed peak pulmonary homograft gradients $\geq 30$ mm Hg. This is in contrast to the low reoperation rates. This is due in part to our end point being the development of any pulmonary stenosis (defined as a peak gradient at any time point $\geq 30$ mm Hg), which was chosen to illustrate the entire spectrum of dysfunction. Figures 1 and 2 demonstrate that in the majority of patients who develop stenosis, this becomes clinically apparent within 2 years of surgery, there being no new cases of stenosis detected after the fourth year of follow-up. To investigate this further, 15 of the 21 patients with echocardiographic gradients between 30 and 60 mm Hg underwent MRI. This produced clear pictures of the location of the narrowing, which demonstrated that in 10 of the 15 patients we studied, the narrowing was due to a reduction of the lumen of the tubular part of the homograft. We do not have a matched control group, but in the 2 patients studied early after operation by MRI and in 5 additional patients 1 to 4 years after Ross operation who were scanned for other clinical indications, there was no evidence of significant homograft narrowing, and minimum homograft lumen diameter was 17 to 26 mm. Eleven of the 15 stenosed homografts had MRI evidence of excess tissue around the homograft compatible with an adventitial reaction producing extrinsic compression in the manner of those undergoing reoperation. In the 2 patients who had early postoperative as well as later MRI, reduction in homograft length and diameter would be compatible with tissue shrinkage and/or compression.

Mechanism of Pulmonary Homograft Dysfunction
For reconstruction of the RVOT, pulmonary homografts appear to have advantages over aortic homografts, and in the present series, all patients received pulmonary homografts. The operative findings and histology in combination with the magnetic resonance images suggest that the underlying mechanism in our patients was predominantly inflammatory in nature. Unlike other series, in our patients, this was manifested solely as progressive stenosis rather than regurgitation. Raised early postoperative pulmonary homograft velocities and degeneration have been reported previously, as well as an inflammatory mechanism sug-
gested from raised temperatures postoperatively and from postmortem studies. The present study supports these findings and extends them by demonstrating that this mechanism appears to be the main cause in a patient population that encompasses the entire spectrum of surgical practice. The cause of the inflammatory cell proliferation is unclear. Although microbiological cultures were consistently negative, occult chronic infection or a chronic mediastinitis, possibly as a reaction to the homograft, cannot be excluded. The reaction may be immunologically mediated in a manner similar to that seen in chronic rejection. This would be supported by the chronic lymphocytic infiltrate; however, the lack of histological changes in the homograft wall and the excessive mediastinal fibrotic reaction do not support this putative mechanism. Indeed, in the present series, panel reactive antibodies were noncontributory. Alternatively, early postoperative stretching and lengthening of the homograft may cause the release of tissue factors responsible for the reaction. Multivariate analysis did not show any potential determinants of stenosis; in particular, there were no differences in patients receiving fresh or cryopreserved homografts. Whether the newer generation of artificial conduits, those developed from the pulmonary arterial wall, or even tissue-engineered valves will produce a lower incidence of those developed from the pulmonary arterial wall, or even tissue-engineered valves will produce a lower incidence of inflammatory stenosis remains to be seen. The present study describes and characterizes an inflammatory reaction around the pulmonary homograft, but we did not investigate further any of the above hypotheses. Additional studies are necessary to determine the underlying mechanism.

**Significance of Pulmonary Homograft Stenosis**

The clinical significance of mild increases in pulmonary homograft velocities is debatable; as expected, the velocities obtained by MRI were lower because of the ability to map velocity in the middle of the stenotic jet and avoid any aliasing effect. All 15 patients who underwent MRI were in New York Heart Association class I or II. However, the presence of right ventricular hypertrophy in all the patients suggests that this level of obstruction may have functional significance over a longer period of time.

**Conclusions**

In the present study, we have demonstrated that in patients who undergo the Ross procedure, evolving pulmonary homograft stenosis is an uncommon but clinically important problem. Despite this, the mortality, morbidity, and freedom from reoperation figures for pulmonary autograft surgery, both in the present series and in others, compare favorably with those for other valve substitutes. The early development and clinical progression, magnetic resonance images, and histology of the explanted homografts suggest that the predominant mechanism is inflammatory, although the precise mechanism is unclear. The present study, therefore, has implications regarding the monitoring of patients after the Ross operation, from both a clinical and a research point of view. We have highlighted the fact that follow-up of pulmonary homograft function is critically important in the first 2 years after surgery, and where possible, those with echocardiographic gradients should undergo MRI. In addition, the present study raises the possibility that in the future, immune modulation may further improve clinical results for patients undergoing this operation. For example, patients with early pulmonary homograft stenosis and evidence of extrinsic compression may benefit from prophylactic anti-inflammatory treatment.

**Acknowledgments**

Dr Carr-White is a British Heart Foundation Junior Research Fellow. Dr Yacoub is a British Heart Foundation Professor of Cardiac Surgery. Many thanks to Dr Mary Shepphard for histological pictures and expert advice.

**References**

Incidence, Location, Pathology, and Significance of Pulmonary Homograft Stenosis After the Ross Operation

Circulation. 2001;104:I-16-I-20
doi: 10.1161/hc37t1.094545

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/suppl_1/I-16

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/