Pulmonary homograft muscle reduction to reduce the risk of homograft stenosis in the Ross procedure

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Objective: The Ross procedure has gained increasing interest as an attractive alternative for aortic valve replacement. Despite its advantages, there is a certain risk of structural valve deterioration, especially of the pulmonary homograft as a result of shrinkage and subsequent stenosis predominantly at the muscular annulus. Theoretically, reduction of homograft muscle tissue could reduce this risk.

Methods: From February 1996 through December 2002, a total of 238 patients (mean age 44 ± 13.2 years) underwent the Ross procedure with the subcoronary technique with follow-up investigations before discharge and after 12 and 24 months. To estimate the importance of homograft muscle reduction within our institution-specific risk factor scale for change of transhomograft pressure gradient with time, we performed a generalized estimating equation approach, which identified homograft muscle reduction, higher body surface area in male patients, younger patient age, smaller homograft diameter, blood transfusions, and follow-up time as independent risk factors demonstrating a high β value (-2.8638) for muscle reduction. To find out whether muscle reduction influences transhomograft pressure gradient, we compared patients with (group A, $n = 39$) and without (group B, $n = 199$) muscle reduction. The other mentioned independent risk factors were not different between groups, except for blood transfusions (group A greater than B, $P < .01$), indicating a negative bias for group A.

Results: The maximum pressure gradient across the homograft was lower in patients with muscle reduction before discharge (4.5 ± 2.8 mm Hg group A vs 6.2 ± 3.8 mm Hg group B, $P = .004$) and after 1 (9.3 ± 5.8 vs 13.1 ± 8.4 mm Hg, $P = .028$) and 2 years (10.8 ± 7.6 vs 13.7 ± 7.5 mm Hg, $P = .013$). No significant differences were found concerning homograft insufficiency.

Conclusions: We provide some evidence that transhomograft pressure gradient can be reduced significantly within the first 2 years after operation by homograft muscle reduction. Longer term follow-up is necessary to evaluate this promising operative technique further.

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The pulmonary autograft was inaugurated by Donald Ross¹ in 1967. With its advantages of viability, immunologic identity, comparability with the native aortic valve regarding morphology and hemodynamics, antithrombogenicity, and noiselessness, the pulmonary autograft is gaining growing interest after several publications demonstrating promising midterm results.²⁻⁷ Concerning the pulmonary autograft implanted in the subcoronary technique, the pressure gradient has shown to be excellent, simulating almost normal conditions at rest and exercise.^{7,8} Several patients, however, have some kind of pressure gradient develop across the pulmonary homograft in the right ventricular outflow tract. This occurs predominantly during the first 2 years after implantation, indicating a tissue reaction yet not completely understood^{7,9} that results in shrinkage of the homograft (Figure 1). To date, homograft stenosis has not been shown to be related to surgical factors. We

Abbreviations and Acronyms

AI	= autograft insufficiency
GEE	= generalized estimating equation
PI	= pulmonary homograft insufficiency

observed that shrinkage of the homograft was pronounced in the proximal annulus area, suggesting that implantation of a homograft after reduction of the adjacent allogeneous muscle and replacement with a strip of autologous pericardium might reduce shrinkage of the annular area and thus the transhomograft pressure gradient. To further clarify clinical impact, we performed an echocardiographic follow-up investigation in patients with reduction of homograft muscle and replacement with autologous pericardium relative to patients without homograft muscle reduction.

Patients and Methods**Patient Population**

From February 1996 to December 2002, a total of 238 patients (187 male and 51 female) with a mean age of 44 ± 13.2 years (range 15-70 years) underwent the Ross procedure with the sub-coronary or root inclusion technique, followed by a close follow-up with echocardiographic and clinical examinations (preoperative, postoperative before discharge, and 1 and 2 postoperative years). Clinical follow-up was 99% (1 patient was unavailable for follow-up because he left Germany). Institutional review board approval and informed consent were obtained for each patient.

Operative Procedure

For all patients, extracorporeal circulation with moderate hypothermia (nasopharyngeal temperature 26°C) was used. Crystalloid cardioplegia was applied during the first 2 years of the study; cold blood cardioplegia was used thereafter. After implantation of the autograft with subcoronary or root inclusion technique as described elsewhere,^{7,11} the pulmonary homograft, which was trimmed distally as short as possible (close to sinotubular junction), was inserted. In group A, a strip of pericardium was gained during pericardiotomy and stored in glutaraldehyde solution. This strip (width 20 mm) was sutured onto the homograft annulus after almost complete removal of muscle tissue and was implanted in the right ventricular outflow tract with 5-0 Prolene (Ethicon, Inc, Somerville, NJ) continuous suture (Figure 2). In group B, standard insertion was performed as described elsewhere with homologous muscle that is used for suturing.^{7,11} Homograft diameters were 25.0 ± 1.7 mm in group A and 25.5 ± 1.4 mm in group B (difference not significant). Bypass and crossclamp times were 215 ± 28.3 and 159 ± 23.8 minutes, respectively, in group A and 212 ± 30.9 (difference not significant) and 171 ± 22.9 minutes ($P = .001$), respectively, in group B.

Echocardiographic Data Acquisition and Measurements

Patients were examined in left lateral decubitus position. A modified electrocardiographic lead I was continuously recorded. Echo-

Figure 1. Computed tomogram of conventional implanted homograft in right ventricular outflow tract.

cardiographic measurements were determined by two independent observers from video and digitally recorded studies. Transthoracic echocardiograms were performed with a 4-S (2.5-4.0 MHz) ultrasound transducer (SONOS 5500 system; Philips/Hewlett Packard, Andover, Mass) before the operation and after the operation before discharge, followed by two annual intervals. Average values of 5 consecutive beats were taken. Two-dimensional measurements and Doppler investigations were conducted according to the guidelines of the American Society of Echocardiography.¹² Measurements of diameters were taken in standard longitudinal and cross-sectional views. Maximum velocities at homograft level were measured with a continuous-wave Doppler imaging transducer. To assess pulmonary regurgitation, pulsed and continuous-wave Doppler and color flow Doppler imaging were used. In the short-axis view, semiquantitative assessment of pulmonary homograft insufficiency (PI, grade 0 to 3+) was based on the length and width of the regurgitant jet and its extension into the right ventricular outflow tract. Peak systolic pressure gradient was calculated according to the modified Bernoulli equation, $\Delta P = 4 \times v^2$ [m/s], where ΔP is the gradient in millimeters of mercury and v is the peak systolic velocity in meters per second.

Determination of Risk Factors for Homograft Stenosis

Risk factors were investigated by generalized estimating equation (GEE) method as described in a later section.

Comparison of Patients With and Without Replacement of Homograft Muscle

Patients with muscle reduction (group A, $n = 39$, 31 male and 8 female) were compared with patients without muscle reduction (group B, $n = 199$, 156 male and 43 female). Demographic details are depicted in Table 1.

Figure 2. A, Exclusion of homograft muscle tissue. B, Replacement of homograft muscle tissue with autologous pericardial strip. C, Implanted autologous pericardial strip replacing muscle tissue of homograft.

Statistical Analysis

Categorical data are given as total numbers and relative frequencies. Continuous data are given as mean $\pm$ SD. Comparisons between groups were made with the Mann-Whitney *U* test. Comparisons of time-related data were made with the Wilcoxon signed rank test. Insufficiency grades were compared with the exact McNemar test. Statistical analyses were performed with SAS statistical software (version 8.2; SAS Institute, Inc, Cary, NC).

TABLE 1. Demographic data

	With pericardial strip	Without pericardial strip
No.	39	199
Sex (male/female)	31:8	156:43
Age (y, mean $\pm$ SD)	46.0 $\pm$ 15.1	44.1 $\pm$ 12.9
Height (cm, mean $\pm$ SD)	173 $\pm$ 9.4	175 $\pm$ 9.1
Weight (kg, mean $\pm$ SD)	78 $\pm$ 13.9	77 $\pm$ 15.0
Body surface area (m ² , mean $\pm$ SD)	1.9 $\pm$ 0.2	1.9 $\pm$ 0.2
Follow-up (mo, mean $\pm$ SD)	22.6 $\pm$ 3.9	22.7 $\pm$ 4.2

There were no significant differences between groups.

Analysis of GEE Parameter Estimates

GEEs are proposed to analyze longitudinal data with repeated measurements adjusting for possible correlations within the same patients.¹⁰ We applied the GEE model to examine the influences of a number of variables on the basis of longitudinal responses. To select covariables for the multivariate model, univariate analyses were conducted with the following 27 variables possibly affecting transhomograft pressure gradient: sex, weight, height, body surface area, age, preoperative New York Heart Association class, nicotine abuse, hypertension, hyperlipidemia, diabetes mellitus, underlying valve disease (insufficiency, stenosis, combined disease), valve morphology (tricuspid, bicuspid), history of endocarditis, replacement of homograft muscle tissue with pericardial strip, homograft diameter, homograft length, homograft bank origin, use of a decellularized homograft (SynerGraft; CryoLife Inc, Kennesaw, Ga), transfusion (erythrocyte concentrates, fresh-frozen plasma, or platelets), pulmonary hypertension, homograft donor age, bypass and crossclamp times, and length of follow-up. The events per variable were 9. For the GEE model, we used the identity link function combined with a first-order autoregressive structure as working correlation.

Results

Risk Factors for Homograft Stenosis

The institution-specific risk factor scale for homograft stenosis identified homograft muscle tissue ($P < .01$), higher body surface area in male patients ($P < .01$), younger patient age ($P < .01$), smaller homograft diameter ($P < .01$), blood transfusions ($P = .018$), and follow-up time ($P < .01$) as independent risk factors with a high value for the β parameter of the variable homograft muscle replacement (-2.8638).

Comparison of Patients With and Without Homograft Muscle Replacement

The result of multivariate analysis confirming the influence of homograft muscle replacement on the transhomograft pressure gradient made us compare the patients in group A with those in group B to obtain exact pressure gradients (in millimeters of mercury). All other independent risk factors mentioned were not different between groups, except for blood transfusions (group A more than group B, $P < .01$).

TABLE 2. Homograft pressure gradients

	Follow-up			P value	
	PO	1 y	2 y	PO-1 y	1-2 y
Group A, with pericardial strip					
Maximum pressure gradient (mm Hg)				.0034*	.4747
Mean $\pm$ SD	4.5 $\pm$ 2.8	9.3 $\pm$ 5.8	10.8 $\pm$ 7.6		
Range	1.8-12.6	3.1-21.5	1.9-37.2		
Mean pressure gradient (mm Hg)				.0020*	.3776
Mean $\pm$ SD	2.5 $\pm$ 1.5	5.4 $\pm$ 3.3	6.2 $\pm$ 4.4		
Range	1.0-7.4	1.8-12.3	1.1-21.5		
Group B, without pericardial strip					
Maximum pressure gradient (mm Hg)				<.001*	<.001*
Mean $\pm$ SD	6.2 $\pm$ 3.8	13.1 $\pm$ 8.4	13.7 $\pm$ 7.5		
Range	1.5-32	1.7-49.8	1.6-43.3		
Mean pressure gradient (mm Hg)				<.001*	<.001*
Mean $\pm$ SD	3.2 $\pm$ 1.4	7.1 $\pm$ 4.8	7.6 $\pm$ 4.9		
Range	1.0-8.0	1.0-28.4	1.2-35.0		
P values					
Maximum gradient (mm Hg)	.0042*	.0282*	.0132*		
Mean gradient (mm Hg)	.0056*	.1068	.0664		

PO, Postoperative examination before discharge. *Significant difference.

Mortality

Early mortalities were 1 in group A and 1 in group B. Late mortality was 2 in group A. No deaths were valve related.

Reoperation of the Homograft

In group A, 1 patient (2.6%) had to undergo reoperation on the homograft because of combined pulmonary valve disease with dominant stenosis 13 months after the Ross procedure. In group B, 3 patients (1.5%) underwent reoperation, 2 for PI (14 and 15 months after the initial operation) and 1 for stenosis (16 months after the initial operation).

Homograft Function

The postoperative gradients before discharge showed lower values in group A. One year after the Ross procedure, a significant increase of pressure gradients could be observed in both groups, with higher gradients in group B. During the first postoperative year, there was a further significant increase in group B but not in group A. The maximum pressure gradient 2 years after the Ross procedure was significantly higher in group B ($P = .0132$). Values are depicted in Table 2.

PIs were comparable after the operation before discharge ($P = .7062$), as well as during the first ($P = .7904$) and second years of follow-up examination ($P = .2613$). In group A, there was no significant difference in PI grade in either the postoperative echocardiography before discharge (grade 0 PI 89.3%, grade 1 PI 10.7%, grade 2/3 PI 0%) relative to the first year follow-up examination (grade 0 PI 78.9%, grade 1 PI 21.1%, grade 2/3 PI 0%, $P = .6547$) or the first year relative to the second year follow-up investi-

gation (grade 0 PI 63.9%, grade 1 PI 33.3%, grade 2 PI 2.8%, grade 3 PI 0%, $P = .5637$). In group B a significant increase was documented during the first postoperative year (postoperative examination before discharge/first year grade 0 PI 92.3%/80.6%, grade 1 PI 7.7%/18.7%, grade 2 PI 0%/0%, grade 3 PI 0%/0.7%, $P = .0094$) without further change during the following year (grade 0 PI 76%, grade 1 PI 22.4%, grade 2 PI 1.6%, grade 3 PI 0%, $P = .4545$).

Autograft Function

The autograft showed near physiologic maximum pressure gradients for both groups (group A postoperatively before discharge 10.5 ± 5.1 mm Hg, year 1 6.5 ± 2.8 mm Hg, year 2 5.9 ± 2.2 mm Hg; group B postoperatively before discharge 8.9 ± 5.1 mm Hg, year 1 6.3 ± 3.4 mm Hg, year 2 5.9 ± 3.1 mm Hg) without significant differences between groups. Concerning autograft insufficiency (AI), there were also no differences between groups (group A postoperatively before discharge/first year/second year AI grade 1 or better 100%/100%/100%; group B postoperatively before discharge/first year/second year AI grade 1 or better 100%/97.9%/96.9%, grade 2 AI 0%/1.4%/3.1%, grade 3 AI 0%/0.7%/0%).

Discussion

Pulmonary autograft replacement of the diseased aortic valve has several advantages, such as excellent hemodynamics, durability, potential to grow, viability, immunologic identity, antithrombogenicity, and noiselessness. Especially noteworthy, the survival after the Ross procedure is higher than those with other valve substitutes.^{13,14} The insertion of a

valved conduit in the right ventricular outflow tract (preferably pulmonary homograft) is necessary in the Ross procedure. There is concern about the development of pulmonary homograft dysfunction, especially homograft stenosis. Several publications have described the problems of shrinkage and valve degeneration.¹⁵⁻¹⁸ A number of risk factors for failure or stenosis of the homograft in the right ventricular outflow tract—predominantly occurring during the first 12 to 24 postoperative months—have been evaluated, including small homograft diameter, young recipient age, younger donor age, aortic homografts, shorter duration of cryopreservation, and longer aortic crossclamp time.¹⁹⁻²² In our institutional analysis, the independent factors influencing homograft pressure gradient during the first 2 years after operation were homograft muscle reduction, higher body surface area in male patients, younger patient age, smaller homograft diameter, blood transfusions, and follow-up time. Patients with and without reduction of muscle tissue were comparable with respect to sex, age, follow-up time, and homograft diameter. Moreover, patients with muscle reduction had lower pressure gradients even though they received a greater number of blood transfusions, which was a predictive factor for development of homograft stenosis.

Other investigators have not found any predictive factors for homograft dysfunction or reoperation but have found a pronounced adventitial reaction producing extrinsic compression, associated with histologic features suggestive of inflammatory-mediated fibrotic reaction.²³ To date, surgery has not been reported on as a predictive factor.

Because most stenoses occur during the first 2 postoperative years, with stable pressure gradients thereafter, we performed echocardiographic examinations postoperatively before discharge and after 1 and 2 years.^{23,24} Also after 5 postoperative years, we found the same results, with significantly lower gradients in group A (maximum/mean transhomograft pressure gradients in group A $11.1 \pm 5.5/5.6 \pm 2.5$ mm Hg and in group B $16.4 \pm 9.9/8.6 \pm 5.8$ mm Hg, $P = .0168/.0118$). Only pulmonary homografts were implanted. The location of pulmonary homograft stenosis has been described to occur in the tubular part of the homograft in the distal suture lines, rarely in the valves themselves,²³ but predominantly at the annular area. These findings were in accordance with our own unpublished computed tomographic results of echocardiographically proven homograft stenosis. This was the rationale for the applied surgical technique, the excision of homograft muscle tissue with subsequent replacement with autologous pericardium (Figure 3). We investigated this operative technique with multivariate GEE analysis and found that the reduction of muscle tissue of the donor pulmonary homograft had a high influence on the progression of the transhomograft pressure gradient (β of -2.8). Because of this finding, we compared two groups of patients: group A, patients with reduction of muscle tissue and its

Figure 3. Computed tomogram of homograft in right ventricular outflow tract with implanted autologous pericardial strip.

subsequent replacement with autologous pericardium, and group B, patients without such reduction. Patients with replacement of muscle tissue (group A) already had lower maximum pressure gradients across the homograft postoperatively before discharge, as well as at 1 and 2 years. No differences were found between groups concerning the grade of PI. These results provide evidence that the operative strategy of extinguishing as much extrinsic tissue as possible can help to avoid increasing transhomograft pressure gradients during the first 2 years.

In group A, autologous pericardium preserved with glutaraldehyde was used to replace the resected subvalvular muscle tissue to provide adequate material for homograft implantation. This material may undergo shrinkage or dilatation, however, and thus become unpredictable with respect to long-term results. We therefore recently replaced muscle tissue with Gore-Tex (W. L. Gore & Associates, Inc, Flagstaff, Ariz) instead of pericardium because it has a lower risk of changing dimension with time. It is most important to follow the scalloped arrangement of the annuli of the homograft valve to warrant almost complete resection of muscle tissue.

This study has some limitations. It is a retrospective analysis rather than a prospective, randomized trial. Nevertheless, the demographic data and those factors having an influence on pressure gradient, except for blood transfusion, were comparable between the groups. The group with muscle resection had more blood transfusions, indicating a negative bias. Although this group showed lower pressure gradients (strengthening the value of the muscle resection)

examinations of panel reactive antibody assays or inflammatory indicators would be desirable to analyze any immune or inflammatory responses.

In conclusion, almost complete muscle resection of homograft seems to provide promising results. Long-term studies are necessary to evaluate this encouraging operative technique further.

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