

Incidence and Clinical Impact of Pulmonary Homograft Dysfunction After the Ross Procedure

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Introduction and objectives. We analyzed the incidence, risk factors and clinical impact of pulmonary homograft dysfunction after the Ross procedure in our patients.

Patients and method. All patients were evaluated at 3, 6 and 12 months, and annually thereafter. Patients with a transhomograft pressure gradient greater than 30 mmHg were referred for cardiac magnetic resonance imaging.

Results. At the end of the study, 9 patients (11.8%) showed a transhomograft pressure gradient >30 mm Hg after a mean period of 15.3 months post-surgery. Mean transhomograft pressure gradient was 19.8 (16.2%) (range, 2-100 mm Hg). All patients were in functional class I, except 2 who were in New York Heart Association class II with severe stenosis. These 2 patients were treated percutaneously with stent placement and no reoperation. No association was found between clinical outcome and sex, age or homograft diameter. We found a trend toward greater perioperative use of plasma, platelets and red cells in the group of patients in comparison to controls, although the difference was significant only for postoperative use of plasma (1.7 [3] vs 5.5 [5.3] units; $P < .05$). Cardiac magnetic resonance imaging showed stenosis predominantly in the body of the homograft, whereas the valvular component itself remained competent. Right ventricular hypertrophy was mild or very mild in 7 patients and moderate in 2.

Conclusions. The incidence of some degree of pulmonary homograft dysfunction after the Ross procedure was non-negligible, but its clinical impact seems to be slight. Patients with severe stenosis were treated successfully via a percutaneous approach. The use of blood products might be a risk factor for the development of this complication.

Key words: *Ross procedure. Pulmonary stenosis. Aortic stenosis. Magnetic resonance imaging. Valves.*

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Incidencia e impacto clínico de la estenosis del homoinjerto pulmonar tras el procedimiento de Ross

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Introducción y objetivos. Estudiamos la incidencia, los factores de riesgo y el impacto clínico de la estenosis del homoinjerto pulmonar tras la intervención de Ross en nuestra serie clínica.

Pacientes y método. El seguimiento se realizó a los 3, 6 y 12 meses, y después anualmente. Los pacientes con gradiente a través del homoinjerto pulmonar > 30 mmHg fueron sometidos a una resonancia magnética cardíaca.

Resultados. De los 76 pacientes intervenidos, 9 (11,8%) presentaron un homoinjerto pulmonar > 30 mmHg una media de 15,3 meses después de la intervención. El gradiente medio fue de $19,8 \pm 16,2$ mmHg (rango, 2-100). Todos los pacientes se encontraban en grado funcional I de la New York Heart Association excepto 2, que estaban en grado funcional II con estenosis severa y fueron tratados percutáneamente con *stents*, sin necesidad de reoperación. No encontramos asociación con el sexo, la edad ni el diámetro del homoinjerto. El uso de hemoderivados (hematíes, plasma y plaquetas) fue mayor en el grupo afectado que en el de control, si bien no alcanzó significación estadística, a excepción del uso de plasma en cuidados intensivos ($1,7 \pm 3$ frente a $5,5 \pm 5,3$ unidades; $p < 0,05$). El estudio con resonancia magnética cardíaca demostró afección eminentemente del cuerpo de homoinjerto, con aparato valvular competente. La repercusión en el ventrículo derecho fue muy leve-leve ($n = 7$) o moderada ($n = 2$).

Conclusiones. La incidencia de disfunción del homoinjerto pulmonar no es desdeñable, si bien el impacto clínico parece ser muy discreto y los casos severos se controlan satisfactoriamente de forma percutánea. El uso de hemoderivados podría ser un factor de riesgo para el desarrollo de esta complicación.

Palabras clave: *Procedimiento de Ross. Estenosis pulmonar. Estenosis aórtica. Resonancia magnética. Válvulas.*

ABBREVIATIONS

PHS: pulmonary homograft stenosis.
 TPG: transhomograft pressure gradient.
 NYHA: New York Heart Association functional class.
 RVOT: right ventricular outflow tract.
 MRI: magnetic resonance imaging.
 CsA: cyclosporin A.
 HLA: haplotype A.

INTRODUCTION

The Ross procedure was first described in 1967¹ and has stood the test of time as a valid option for aortic valve replacement. The hemodynamic advantages,² durability, resistance to infection,³ absence of thrombogenesis^{4,5} and capacity for growth⁶ make the pulmonary autograft a very attractive procedure for use in certain groups of patients. However, the technical complexity, longer surgical time and relative shortage of pulmonary homografts explain why the procedure is still not widely performed. Although the disease involves only the aortic valve, the surgery involves both the aortic and pulmonary valves; the physician must therefore be familiar with, prevent and treat problems associated with the pulmonary homograft.

Pulmonary homograft dysfunction following the Ross procedure can be due to insufficiency, a double lesion or, in particular, stenosis. Some prospective studies⁷ have provided data on the incidence of homograft stenosis, but there is little information on the diagnosis, risk factors, prevention and treatment of this problem.

Because pulmonary homograft stenosis (PHS) is virtually asymptomatic until the advanced stages, serial echocardiographic study is still the usual procedure for patient follow-up. Nevertheless, Doppler echocardiography presents limitations for the study of the right ventricular outflow tract (RVOT) in a relatively high percentage of patients, generally because of the difficulty of finding an adequate acoustic window for anterior visualization of the heart.⁸ As a result, the gold standard for this patient group is presently cardiac magnetic resonance imaging (MRI), as it provides high spatial resolution.⁹

Some studies are available on risk factors in these patients, but the series are small and the results are sometimes contradictory.^{10,11}

Although no standard medical therapy has been established, clinical identification of patients at a higher risk of PHS could lead the physician to consider the selective use of immunosuppressant and/or anti-inflammatory therapies in this subgroup.

The purpose of this study was to assess the incidence and clinical impact of stenosis of the pulmonary homograft after the Ross procedure. Although the number of patients is still small and the follow-up time is limited, we also made an initial estimate of the potential risk factors for the development of this complication.

PATIENTS AND METHODS

Seventy-six patients underwent the Ross procedure at our hospital from 1997 to May 2002. The most frequent aortic lesion was regurgitation (n=32; 42.1%), with congenital diseases (n=47; 61.8%) more prevalent than rheumatic. Mean age was 30.7±13.2 years (range, 1-54) with 12 patients under 15 years old; 73.6% (n=56) were male. A total of 32 patients (50%) had a history of surgery; the most frequent was percutaneous aortic valvuloplasty (n=14; 47%), open commissurotomy (n=10; 13.1%) and resection of subvalvular thickened tissue (n=8; 10.5%). Ten patients (13.1%) had a history of two or more procedures. Twenty-nine patients (38.1%) were New York Heart Association (NYHA) functional class III. Perioperative (first 30 days) mortality was one case (1.3%). No cases of late mortality were reported in our series. Mean follow-up was 27.5±15.1 months (range, 2-54 months), with 100% of the patients completing the follow-up period. A total of 37 patients (48.6%) were followed for over 2 years, and 67 (93%) had a follow-up of more than six months.

All patients underwent surgery with the previously described technique¹² using the autograft as free-standing root. In all cases, we used a pulmonary homograft cryopreserved at -196 °C to reconstruct the right ventricular outflow tract. The grafts had been taken from multiorgan donors and were processed in the Banco Sectorial de Tejidos de Córdoba (Sectorial Tissue Bank of Cordoba), Spain, in accordance with the guidelines of the Asociación Española de Banco de Tejidos (Spanish Tissue Bank Association).¹³ After 6-24 h of antibiotic incubation (vancomycin, tobramycin, co-trimoxazole and amphotericin B), the homografts were bathed in a cryoprotective solution composed of 10% dimethyl sulfoxide in culture medium (TC-199 or RPMI1640) and human albumin; they were then frozen at -1 °C/min to -120 °C, and cryopreserved in liquid nitrogen at -196 °C. For logistical reasons, haplotype A (HLA) typing and ABO compatibility selection were not done. According to the technique, after excising the pulmonary autograft (preserving the first septal branch of the left anterior descending artery in all cases), careful hemostasis of the posterior bleeding area must be achieved, and the aortic reconstruction finished. The pulmonary homografts were implanted by distal suturing with Prolene (Ethicon Ltd., Edinburgh, United Kingdom)

and by proximal suturing in the same way, generally after the ischemia period. All patients received oral anti-inflammatory therapy with 500 mg of Solusprin® every 12 hours for the first month after the surgery.

After the operation, all patients underwent clinical and echocardiographic follow-up studies at discharge, 3, 6 and 12 months, and yearly thereafter. The studies were performed by two experienced cardiologists using the Acuson Sequoia 256 echocardiography system. Although cardiac output was not routinely estimated, the studies were performed after 5 minutes of rest under baseline conditions and in the absence of clinical evidence suggesting a hyperdynamic state that could potentially affect the transvalvular velocity measurements. The pressure gradient was calculated from the modified Bernoulli equation using the transvalvular flow velocity. High-resolution (1.5 Tesla) cardiac MRI with morphological and functional analyses was performed in patients who developed a transhomograft pressure gradient (TPG) above 30 mm Hg.

The measurements are expressed as mean \pm standard deviation. The χ^2 test, Fisher's exact test and Student's *t* test were used for the univariate analysis. Because we still do not have complete data on the homograft and the number of patients is still limited, we decided to postpone the multivariate analysis for future studies. The probability of the homograft being free of stenosis and the need for a repeat procedure was calculated using the Kaplan-Meier method. Statistical significance was set at a *P* value of less than .05, and SPSS Ver. 8 was used for the data analysis.

RESULTS

The mean peak gradient of the pulmonary autograft was 6.7 ± 5.5 mm Hg. The mean intraoperative diameter of the pulmonary annulus was 23.5 ± 2.7 mm (range, 19-30), whereas the mean diameter (24.7 ± 2.8 mm; range, 19-35) of the pulmonary homograft was slightly, but significantly,

higher ($P < .01$). During the echocardiographic follow-up, 9 patients (11.8%) developed TPG > 30 mm Hg, although only 4 (5.2%) had TPG > 50 mm Hg. Table 1 indicates the clinical profile of this subgroup of patients. The mean peak TPG assessed with Doppler echocardiography at the last follow-up was 19.8 ± 16.2 mm Hg (2-80 mm Hg), with the mean remaining stable after the first 12 months. The mean time to development of a TPG above 30 mm Hg was 15.4 months (range, 6-36). Although the relationship between the TPG and the time after surgery was not linear ($r = 0.257$), we did observe that patients who reached a higher peak TPG, did so earlier, typically in the first six months.

With regard to the location of the stenosis, the mean diameter of the pulmonary homograft, as measured by echocardiography, decreased significantly with respect to the graft diameter at the time of implantation (20.9 ± 7.4 mm [range, 11-40] vs 24.7 ± 2.8 mm [range; $P < .001$]). However, MRI study of the patients with PHS showed that the stenosis affected the entire length of the homograft, particularly the supralvalvular portion. We lack quantitative data to illustrate this finding because no baseline MRI images were available (Figures 1 and 2). The valve apparatus remained competent in all cases, a finding that supports endovascular treatment of this complication.

Repercussions on the right ventricle included very mild hypertrophy in 7 patients and moderate hypertrophy in 2. Two patients presented right bundle branch block.

Only 2 patients showed mild homograft regurgitation, and no case of endocarditis was recorded. No patient presented clinically or echocardiographically significant right ventricular dysfunction. Two cases presented mild-to-moderate tricuspid regurgitation that was present prior to surgery.

All patients were functional class I except for 2, who were functional class II with TPG > 100 mm Hg. These patients were treated percutaneously with a

TABLE 1. Clinical Characteristics of Patients With a Transhomograft Pressure Gradient (TPG) Above 30 mm Hg

Case	Sex	Age, Years	Etiology	Prior Procedure	TPG, mm Hg	Latency, Months	Reoperation*
1	Female	14	Congenital	No	100	12	Yes (stent)
2	Male	36	Rheumatic	No	70	36	No
3	Male	7	Congenital	PV	65	9	No
4	Male	33	Rheumatic	No	48.5	13	No
5	Male	16	Congenital	PV	42	22	No
6	Male	38	Rheumatic	OC	110	6	Yes (stent)
7	Male	16	Congenital	No	31	13	No
8	Male	37	Rheumatic	No	30	22	No
9	Male	44	Rheumatic	AP	31.3	6	No

*Repeat procedure on the right ventricular outflow tract, including percutaneous treatment. Latency indicates time to detection of obstructive gradient; PV, percutaneous valvuloplasty; OC, open commissurotomy; AP, aortic prosthesis.



Figure 1. Cardiac magnetic resonance imaging of a patient who underwent the Ross procedure. Transhomograft pressure gradient was 30 mm Hg. The sagittal view of the right ventricular outflow tract reveals narrowing of the pulmonary homograft conduit and the presence of an area with an inflammatory appearance in the anterior aspect of the graft (arrow).



Figure 2. Cardiac magnetic resonance imaging of a patient who underwent the Ross procedure. There is severe pulmonary homograft stenosis (transhomograft pressure gradient of 100 mm Hg). The valve remains competent, with the stenosis appearing in the homograft conduit.

Palmaz stent in the pulmonary homograft (Figure 3). The angiographic and hemodynamic results were very satisfactory, with a residual TPG < 15 mm Hg. Two patients with TPG of 65 and 70 mm Hg are being closely monitored at this time and will probably be

similarly treated in the near future.

Figure 4 shows the freedom from stenosis with TPG > 30 mm Hg (considered moderate) and > 50 mm Hg (severe), respectively, according to the Kaplan-Meier method. Figure 5 indicates the freedom of

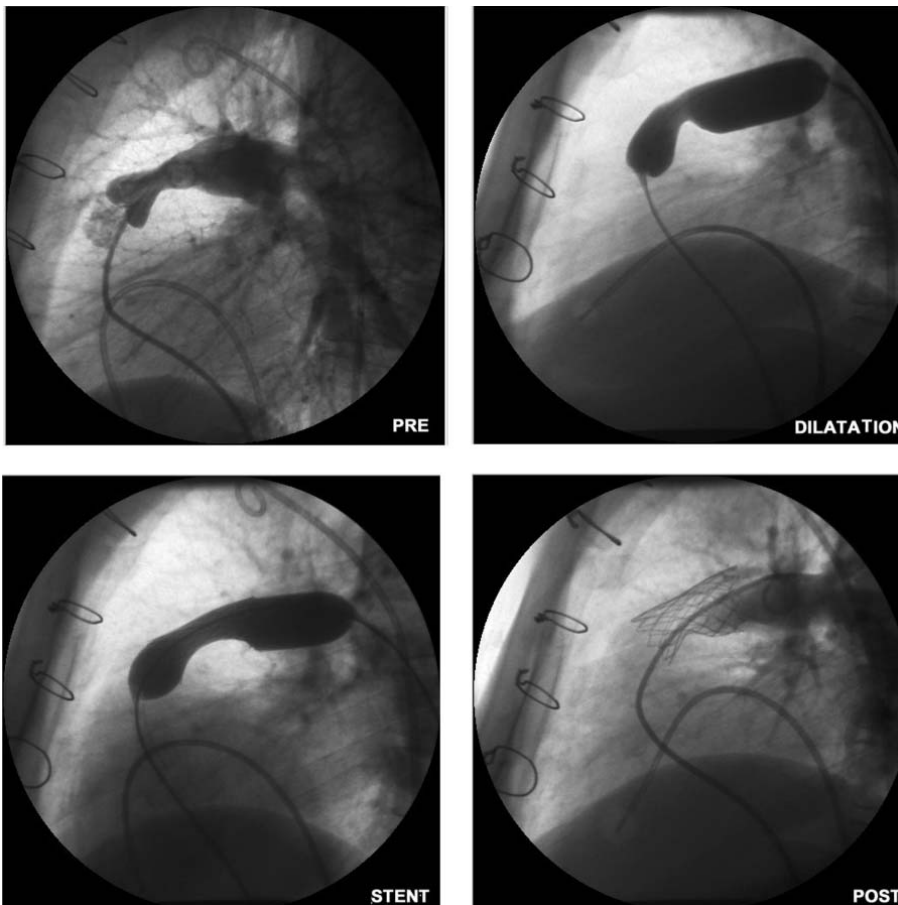


Figure 3. Angiography, balloon dilatation, Palmaz stent placement in the pulmonary homograft conduit and final results in a patient with severe pulmonary homograft stenosis treated percutaneously in the Interventional Cardiology Department of our hospital. The initial transhomograft pressure gradient decreased from 110 to 15 mm Hg after stent placement.

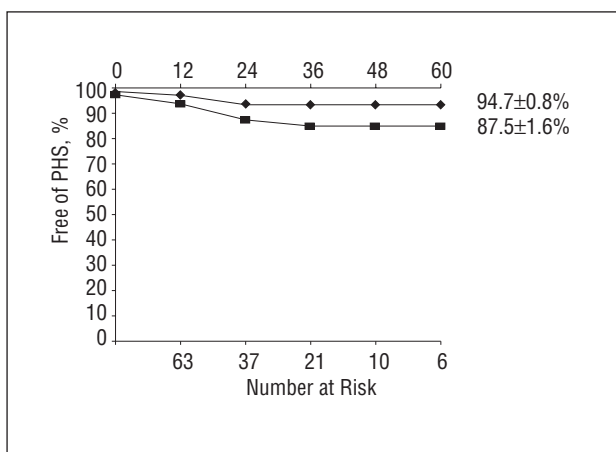


Figure 4. Freedom from mild-to-moderate (TPG>30 mm Hg, bottom line) and severe (TPG>50 mm Hg, top line) stenosis in our clinical series. PHS indicates pulmonary homograft stenosis; TPG, transhomograft pressure gradient.

repeat procedure (surgical or percutaneous) on the RVOT. To date, 87.5% of the patients remain free of significant stenosis, 94.7% are free of severe stenosis and 97.4% had no repeat procedure. No patient in our series underwent repeat surgery by the end of the study.

The univariate analysis indicated no association with age, sex or diameter of the pulmonary homograft used (Table 2). Although the overall use of blood products was greater in the patients with pulmonary stenosis than the controls, there were no significant differences between the groups in the use of any of these products except plasma units administered during the postoperative period.

DISCUSSION

Although the Ross procedure has been used for more than 3 decades, it was not implemented in our hospital until the late 1990s.^{12,14} The numerous advantages of the pulmonary autograft have been confirmed over time, with this procedure considered a good option for the management of aortic valve disease,^{15,16} particularly in children, women of childbearing age and young patients in general. Potential complications include diseases of the pulmonary homograft, which have been a subject of interest in recent times. Although the percentage of repeat operations is relatively low, the percentage of patients who develop a significant transhomograft pressure gradient is not negligible; moreover, it is not clear how this affects the right ventricle. The risk factors reported include young age of the recipient and donor, short ischemia time and cryopreservation of the homograft, and small grafts.^{10,11}

To date it has not been shown that ABO mismatching is important in the development of PHS, a finding

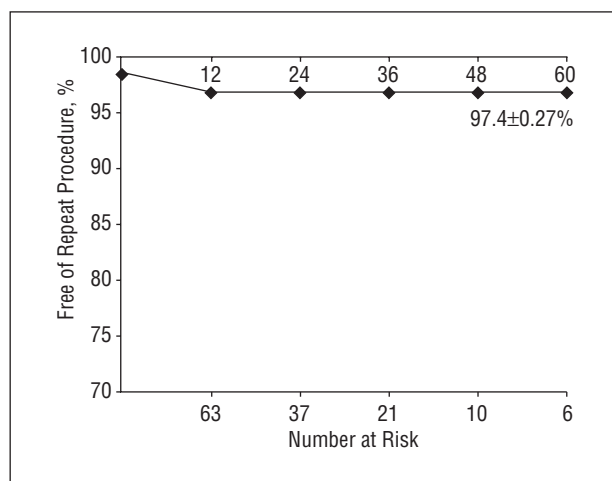


Figure 5. Freedom from repeat procedure (surgical or percutaneous) on the pulmonary homograft. RVOT indicates right ventricular outflow tract.

consistent with data indicating that there are no ABO antigens in the valve leaflets of cryopreserved homografts.¹⁷

In contrast with the trend observed in this preliminary study, blood transfusions have been associated with a higher infection rate after cardiac surgery because of immunomodulation.¹⁸ Nevertheless, the presence of preformed antibodies against HLA or ABO antigens that are not found in the blood products (particularly red blood cells and plasma) may be one factor contributing to the immunoinflammatory response against the homograft.

For logistical reasons, routine HLA or ABO typing between the homograft and the recipient has not been considered to date. However, various studies with aortic homografts show that viable cells capable of expressing surface antigens persist, despite the

TABLE 2. Univariate Analysis of the Risk Factors for the Development of Pulmonary Homograft Stenosis*

Variable	Total Group	TPG Group >30 mm Hg	P
Age, years	28.5±12.7	27.2±12	.71
Sex, female/male	1/8	16/56	.67
RBC during surgery	2.7±3.8	4.6±7.7	.48
Plasma during surgery	4.2±3.2	6.2±5.6	.34
RBC in ICU	2.9±3.4	6.2±5.6	.12
Plasma in ICU	1.7±3	5.5±4.9	.039
Total RBC	5.7±7.2	11±11.6	.21
Total plasma	6±6.2	9.8±9.7	.27
Total blood products	11.7±13.4	20.8±21.1	.24
Homograft diameter, mm	24.7±2.8	25.3±1.8	.56

*TPG indicates transhomograft pressure gradient; the blood products are quantified as units of packed red blood cells, frozen fresh plasma and platelets, respectively; RBC, packed red blood cells; ICU, Intensive Care Unit.

cryopreservation process.¹⁹ A recent study published in *Circulation*²⁰ reported that 54% of patients develop HLA-I antibodies after the surgery, and the probability of these antibodies appearing is directly proportional to the degree of incompatibility of the HLA-A and HLA-B loci. Although this study does not report a statistically positive association between the degree of HLA-A or HLA-B incompatibility and the degree to which the homograft is affected, an association should not be ruled out because of the relatively short follow-up (15±6 months) and the small sample size, as well as the small group of patients who were immunocompatible. In fact, the authors did find signs of this association in its extended study.²¹

Follow-up of surgically treated patients shows that homograft dysfunction usually occurs as supravalvular stenosis, with annulus shrinkage and shortening.⁷ Histological study of the explanted homografts shows a characteristic chronic adventitial inflammatory response with perivascular fibrosis and neointimal hyperplasia,²² a pattern reminiscent of that seen in chronic graft vasculopathy after heart transplantation.²³ Although the mechanism suggested by these findings is immunological, the frequent presence of an excessive mediastinal fibrotic-inflammatory reaction does not rule out the possibility that the underlying mechanisms are strictly non-specific inflammatory mechanisms and are mediated by tissue factors.⁷ In light of these data, it is not unreasonable to question the use of immunosuppressants for PHS prophylaxis after the Ross procedure. Since Sandoz first introduced cyclosporin A (CsA) in 1978, this drug has been used in thousands of transplant patients with a high degree of safety and efficacy.²⁴ Its modulatory effect on T-lymphocyte response through the inhibition of its main mediator (interleukin [IL]-2) significantly slows aggression against non-immunocompatible grafts. Cyclosporin A has been shown to inhibit and slow the development lesions in aortic allografts in rats.²⁵ This effect includes inhibition of induced intimal hyperplasia.²⁶ The lesions found in aortic or pulmonary homografts that are not protected with immunosuppressants are not observed in the aortic wall of heart transplant patients.²⁷ Despite its deleterious effect on the lipid profile, CsA is also effective in the prevention and treatment of chronic valve disease in the graft.²⁸ It is not associated with the development of pulmonary hypertension in transplant patients, and in fact has been shown to be effective in the treatment of this condition when associated with autoimmune diseases such as systemic lupus erythematosus.²⁹ Furthermore, it has been shown in experiments that CsA does not slow autograft growth, but does prevent homograft rejection.³⁰ Experimental studies have shown that CsA would also be effective for inhibiting the production of other inflammatory

mediators, such as monocyte tissue factor,³¹ which could provide an important additional benefit in the control of the non-specific inflammatory component in homograft disease.

These data support the hypothesis that pulmonary homograft dysfunction is primarily mediated by a specific immunological mechanism, and therefore could theoretically be prevented with CsA. Aspects such as the dosage, the duration of treatment and the choice of the most adequate drug are attractive from the scientific point of view, but perhaps not from the practical or ethical standpoint. Because of the low incidence of clinically significant homograft disease, the effectiveness of interventional or surgical management of these diseases, the not negligible toxicity of the various immunosuppressant therapies³² and the fact that, unfortunately, the mechanism behind PHS is still uncertain, prophylactic use of these drugs in all operated patients does not appear acceptable at this time. Because the characteristics of the homograft appear to be extremely important for the development of PHS, a deeper understanding of aspects related to the selection of the most appropriate grafts and the forms of preservation is vital, as other authors have already stated.³³

Considering that aortic valve disease is the second leading cause of heart surgery in our setting and that a substantial percentage of those treated are young patients,³⁴ every effort should be made to achieve optimal, effective, long-lasting treatment.

CONCLUSIONS

Although the hemodynamic advantages of the pulmonary autograft are unparalleled, the associated morbidity is still a potential drawback of this technique. Homograft stenosis, which appears to have a multifactorial origin, develops within the first two years and reaches severe levels in only a small subgroup of patients. In our limited experience, we have found that the most aggressive cases also progress more quickly, reaching severe gradients within the first 6 months. From the clinical standpoint, the condition is apparently asymptomatic until the TPG is very high (e.g., >100 mm Hg). Magnetic resonance imaging shows a decrease in the size and diameter of the pulmonary annulus. The repercussions on the right ventricle appear late, and only with elevated TPGs.

Among the factors analyzed, only the use of blood products such as plasma in the postoperative period appears to be significantly associated with stenosis risk. Although longer follow-up periods in studies with large series are necessary, this finding suggests that the presence in plasma of preformed antibodies may be related to the immunoinflammatory reaction that leads

to fibrotic “shrinkage” of the homograft. This evidence will be further investigated later, once we have more patients, a longer follow-up time and all the homograft data (e.g., freezing time, donor age and use of amphotericin B, among others) to ensure a reliable multivariate analysis.

Future efforts should focus on providing scientific evidence to support this or other suspected etiologies and on early screening of patients at risk for complications, in order to selectively use anti-inflammatory/immunosuppressant strategies. Because the data from both our study and others indicate that the viability of cryopreserved homografts may be deleterious because antigenicity is maintained, we have begun to use an early thawing protocol for the homograft. The clinical results obtained with this protocol will be assessed in upcoming years.

In conclusion, the incidence of pulmonary homograft stenosis is not negligible, its clinical repercussions are acceptable and its therapeutic management is apparently safe and effective. Among the risk factors, the use of blood products during the postoperative period could be an additional factor that triggers this complication. Although the follow-up time of our series is still short, we feel that the advantages offered by pulmonary autografts greatly outweigh the disadvantages of using homografts in the treatment of aortic valve disease in young patients.

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