Ross Operation: Attractive in theory But, Is it Superior in Daily Practice?

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Despite continuous technological advances, we have yet to develop the perfect means of replacing human heart valves. In the case of the aortic valve, there can be no doubt that the best option available is replacement by another human valve. Pulmonary autograft (the Ross operation) ensures hemodynamic performance very similar to that of the native aortic valve and freedom from anticoagulation. Moreover, the autograft will grow, is more resistant to infection than prosthetic valves and does not cause hemolysis. In theory, all of these advantages make the Ross operation ideal for aortic valve replacement in children, adolescents and young adults. However, the procedure involves implanting a cryopreserved pulmonary homograft to reconstruct the pulmonary outflow tract and is technically much more complex than conventional aortic valve replacement. This complexity is the principal reason few Ross operations are performed in Spain. The Spanish National Register records just 40 Ross operations a year,[1] which means that of the over 3000 patients operated yearly for single aortic valve disease only slightly more than 1% benefit from pulmonary autograft.

Today, the Ross operation can be accomplished with very low mortality (1%-3%) as should be the case with a procedure for patients who are usually young and who present no comorbidity. The Spanish National Register reports 2.4% early mortality among 169 patients at 15 centers.[1] This figure concurs with 2.5% early mortality among more than 2500 patients recorded in the International Registry.[2] In spite of the technical complexity of the procedure, the incidence of perioperative complications is equally low.

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HEMODYNAMIC RESULTS

Whichever surgical technique is used, the effective valve area of the pulmonary autograft is uniformly >3 cm^2, which is similar to that of healthy individuals, and remains stable for years. As in healthy people, the baseline transaortic gradient of the pulmonary autograft is barely detectable and does not increase even with maximal exercise.

It is well known that mechanical and bioprosthetic valve gradients are significantly greater both at rest and during exercise. In a recent randomized study, mean autograft gradient at one year (2.6 mm Hg) was significantly lower than that of a mechanical bivalve (10.9 mm Hg), although this did not lead to a greater reduction in left ventricular mass over the same period.[3] Only aortic homograft results in hemodynamic performance approaching that of the autograft. Some randomized studies have indicated no difference in transvalvular gradients when comparing valve graft types but others have found the autograft ensures better hemodynamic performance during exercise. Definitive proof that the excellent hemodynamic response of the pulmonary autograft means improved clinical results has yet to be presented.

AUTOGRAFT-RELATED PROBLEMS

Pulmonary autograft is highly resistant to degeneration and calcification and it is believed that it could continue to function correctly indefinitely.[4] However, recent experience has indicated autograft replacement due to severe insufficiency is needed by a substantial number of patients. In the Spanish National Register, 4.7% of patients develop moderate or severe aortic insufficiency at 3 years mean follow-up and 3.6% require reoperation. This last figure represents actuarial freedom from reoperation for insufficiency of 94.6% at 6 years.[1] These data coincide with the International Registry which records 91% freedom from reoperation for autograft dysfunction at 10 years and 83% freedom at 25 years.[2] The appearance of autograft insufficiency has been associated with 3

circumstances: baseline valvular heart disease, surgical technique and autograft dilation.

In series including a substantial number of patients with rheumatic valve disease, the incidence of reoperations is greater. Moreover, the presence of rheumatic disease in autografts has been confirmed in echocardiograms and histopathologic analysis of explanted valves. Clearly we cannot ignore these data when recommending patients with rheumatic valve disease undergo the Ross operation, especially if they are younger or the disease is active.

Three different surgical techniques can be used in pulmonary autograft implantation. In two of these techniques, the implant is seated within the native aortic root, either through an incision in the aortic sinus to permit a subcoronary implant or by using the inclusion cylinder method. The third technique involves complete aortic root replacement, does not distort the pulmonary root and preserves its physiology better. The inclusion cylinder method and total aortic root replacement both entail reimplanting coronary arteries. In early trials using subcoronary implants, reoperation for autograft insufficiency was necessary in as many as 45% of patients at 20 years.[5] As total aortic root replacement has become more common, freedom from reoperation for autograft insufficiency has increased significantly from 77% to 88% at 8 years.[6] Moreover, this technique would seem to guarantee the stability of valvular architecture and reduce the likelihood of patients who do not develop insufficiency during the first months doing so later.

Independently of the surgical technique used, a mismatch between the aortic annulus and the pulmonary annulus can cause autograft insufficiency, especially in patients with aortic insufficiency or postoperative aortic annulus dilation. Dilation of the sinotubular joint, whether due to the greater diameter of the native aorta or its subsequent dilation can also cause aortic insufficiency as it reduces coaptation of the leaflets. Echocardiography has shown that pulmonary autografts dilate significantly during the immediate postoperative period and continue to increase in diameter during the first year so that the caliber of the new aortic root is systematically greater than that found in healthy individuals. However, one of the groups with greatest experience of this technique maintains that the new aortic root continues to dilate after the fourth year[6] and that this is the main cause of reoperation for autograft failure.

These findings all indicate the importance of matching autograft and native aortic root annulus and sinotubular junction diameters through additional surgical procedures aimed to reduce or prevent dilation. Measures such as these have significantly reduced the incidence of aortic insufficiency and the need for reoperation in the most recent series.[6,7] A further simple and intuitively appropriate measure is the exhaustive, long-term monitoring of blood pressure in these patients.

HOMOGRAFT-RELATED PROBLEMS

In contrast to aortic root replacement procedures, it is clear that most patients present some evidence of pulmonary stenosis despite the standard practice of reconstructing the pulmonary outflow tract with a homograft of a diameter greater than that of the recipient pulmonary annulus. Presence of stenosis is indicated by transpulmonary gradient that is barely detectable in the immediate postoperative period but increases during the first 2 or 3 years to stabilize later. As a result, pulmonary homografts produce higher gradients and more reduced effective valve areas than in patients' pulmonary arteries. These differences become especially apparent with exercise. However, in a few patients stenosis does seriously affect hemodynamic performance.

In this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA, Aranda et al[8] analyze the incidence and implication of stenosis in the largest series of Ross procedure patients recorded in Spain. In operations performed at the Hospital Reina Sofía (Córdoba, Spain), 12% of 76 patients presented significant stenosis (gradient >30 mm Hg) of the pulmonary homograft during a follow-up averaging just over 2 years. In fewer than half of these patients, stenosis was severe (gradient >50 mm Hg). The incidence of this complication is similar to that published by American and European researchers with wide experience of this technique. The University of Toronto group found gradients of >20 mm Hg in 29% and >40 mm Hg in 4% of patients, respectively, during a mean follow-up period of 3 years.[9] The National Heart and Lung Institute of London recorded stenosis >30 mm Hg in 17% and >50 mm Hg in 6% of patients studied during a mean follow-up of 4 years.[10] These figures constitute actuarial probability of freedom from significant homograft stenosis of 87% at 5 years and 80% at 7 years.[8,10] The immediate risk of developing homograft stenosis is greater in the first year and diminishes rapidly to almost disappear after year 4.

However, probability of reoperation for homograft stenosis is very low. Only 3 of 169 patients in the Spanish National Register needed reoperation for implant replacement or percutaneous homograft dilatation. This figure represents actuarial freedom from reoperation of 98% at 5 years,[1] similar to the 97% at 7 years of the National Heart and Lung Institute series.[10] In the International Registry, with a longer follow-up period, actuarial freedom from reoperation for homograft failure is 92% at 10 years and 85% at 25 years.[2] By contrast with pulmonary autografts implanted in the aortic position, the incidence of homograft-related regurgitation is

infrequent. Regurgitation, when it does occur, is almost always mild.[10]

Pulmonary homograft stenosis is usually found in the tubular section, especially above the valve sinuses, and is accompanied by a reduction in length. This "retraction" does not affect valve leaflets and therefore does not compromise their competence. As Aranda et al[8] comment, some patients have a weakness for this particular complication. Stenosis is not a condition that develops after a specific postoperative time lapse. Rather, some patients develop stenosis to a greater extent. In these individuals, stenosis is diagnosed in the first months and indicates a possible reaction against the homograft.

Although the Ross operation is a genuine valve transplant, neither ABO nor HLA compatibility are required. Apart from logistical reasons, this seems justified by the known absence of antigens to this system in valvular leaflets. However, these grafts present a variable proportion of viable cells capable of surface antigen expression and of triggering the recipient's HLA antigen response. As these findings would lead us to expect, it has been found that more than half of patients develop new anti-HLA antibodies after the operation and that this is directly related to the magnitude of the incompatibilities in the system.[11] The production of antibodies against the graft is greatest at 12 months postoperatively which coincides with greater severity of homograft illness. Curiously, in this and other similar studies[10] no relationship has been found between immune response and degree of homograft stenosis. So, clinically the importance of this immune response remains controversial although a consensus is growing around the role it plays in the development of homograft dysfunction and the need for reoperation. Aranda et al[8] also support the theory of an immune mechanism. The greater consumption of blood-derived products, especially plasma, found among patients who develop homograft stenosis might be related to the known immunomodulation that these circumstances entail or to the transmission of preformed antibodies to counter ABO or HLA antigens. However, this relationship has not been confirmed by other studies.[11]

Based on operative findings and histopathologic analysis of explanted homografts, other researchers suggest a non-specific inflammatory mechanism that causes the marked adventitious fibrosis which surrounds and compresses the homograft and contrasts with the absence of minimal intimal proliferation.[10] The cause of this excessive inflammatory reaction has not been clarified although it might be related to the freeing of growth factors as a response to surgical manipulation of the homograft or postoperative mechanical stress.

The development of homograft stenosis seems not to be related to surgical technique but, rather, to properties of the homograft itself, of the recipient and of circumstances in which it was preserved, all of which have yet to be clarified. Research into this problem highlights the influence of the younger donor age versus with recipient age, the shorter time lapse prior to freezing the homograft and using it, as well as graft caliber and factors related to the short- and mid-term development of pulmonary stenosis. Most of these circumstances imply increased cellularity of the homograft. A certain synergy clearly exists between these factors as a linear relationship has been established between the number of factors and the degree of homograft stenosis.

Homograft dysfunction is asymptomatic until it reaches a very advanced stage, when it produces gradients >60 mm Hg or >80 mm Hg. This means that early detection and non-invasive diagnostic follow-up are fundamental. Consequently, Doppler echocardiography is extremely useful although it is limited in many patients due to poor transthoracic visualization of the pulmonary homograft. High resolution spatial imaging techniques, such as magnetic resonance or computed tomography are also of use. Follow-up for homograft dysfunction is especially important in the first 2 years when the risk of developing homograft stenosis is greatest. Most patients with moderate or severe stenosis develop significant right ventricular hypertrophy, which can have major long-term clinical repercussions.[10]

Evidence that early or severe homograft dysfunction appears in response to recipient reaction against the graft, as happens in the transplant of other tissues, opens the door to a range of therapeutic strategies. Preoperative determination of donor-recipient compatibility should reduce rejection although it would complicate the already limited availability of homografts. The administration of immunosuppressive drugs might mitigate this process but it would do so at the expense of introducing the morbidity that this entails, making the procedure less attractive. Without doubt, homograft "decellularization" seems a less burdensome way of reducing histopathologic alterations produced by recipient reaction against the graft. To achieve this, specimens taken from older donors or cadavers, or prepared over a longer period can be used. These grafts could be revitalized with endothelial cells taken from the receptor by tissue engineering techniques in order to try and improve their longevity. Finally, homograft stenosis can be prevented by using oversized specimens, as is standard practice, or reducing inflammatory response by administering specific drugs, especially to those patients who have significant transpulmonary gradients at any early stage.

Only incapacitating symptoms or depressed right ventricular function are indications for some kind of intervention. The nature of the homograft stenosis

permits percutaneous balloon dilatation and stenting to avoid restenosis, as Aranda et al describe.[8] Initial results are excellent as they produce a substantial reduction of gradient, but mid- and long-term evolution are as yet unknown.

ROSS OPERATION VERSUS VALVE PROSTHESIS

The objective of cardiovascular medicine is to ensure years of quality life for patients with heart disease. Agreement exists that the pulmonary autograft has fulfilled its objectives perfectly for many years, especially among younger patients. In children and adolescents, bioprosthetic valves degenerate quickly, anticoagulation is an essential accompaniment of mechanical valve implants that is especially undesirable, and the inevitable growth of the patient almost always leads inexorably to reoperation. For all of these reasons, homografts and autografts prove especially attractive for this age group. Various studies have compared these two options and agree that freedom from valve-related complications is greater with the autograft. Recent experience with pediatric patients shows that long-term probability of freedom from valve-related complication survival following the Ross operation approaches 80% at 8 years.[12]

In young adults, <50 years, the advantages of the pulmonary autograft are not so obvious. In general, incidence of all valve-related complications (thromboembolism, valvular thrombosis, anticoagulation-related bleeding, dehiscence and endocarditis) is lower for pulmonary autograft than for valve replacement with a bioprosthetic or mechanical valve. Only homografts produce a similar incidence of complications to that associated with the Ross operation. However, data of comparative randomized long-term studies are not available but clinical results do not differ significantly from those for aortic valve replacement by mechanical valves in patients from similar age groups. Today, new prosthetic valves have been developed that ensure highly satisfactory hemodynamic performance and which in the not-too-distant future will require less severe anticoagulation therapy and offer self-monitoring strategies that are easier for the patient to handle. The implantation technique is simple, safe and reproducible; it involves limited intraoperative ischemia and is extremely durable.

These results show that increased recommendation of patients for pulmonary autograft depends on proving the efficacy of strategies designed to reduce the incidence of autograft and homograft dysfunction and on the results of prospective studies that permit us to define the profile of patients who benefit from the procedure. Whatever the future holds, Professor Concha and his group deserve our congratulations for excellent results, a laudable dedication to the development of this complex technique and their invaluable dedication to spreading the word about the Ross operation in Spain.

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