Use of allogeneic tissue to treat infective valvular disease: Has everything been said?

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Mitral homograft before implant.

Central Message

Better a short-term solution or a long-lasting procedure in infective endocarditis? Reconsider homografts.

See Editorial Commentary page 829.

Heart surgery does not always walk forward. It occasionally stops, sometimes retraces its steps. Recently, after the appearance of some interesting reports on the use of homografts for aortic infective endocarditis (IE), it has made quite a jump backward, returning to the situation faced at least 15 years ago. Kim and colleagues¹ questioned the benefit of homografts in aortic position based on the results of a propensity-matched analysis comparing homografts, xenografts, and mechanical prostheses in the setting of IE showing no demonstrable benefit in terms of mortality and resistance to reinfection in the homograft group.

The use of allograft substitutes or autografts is not uniform across European and American units and is greatly dependent on surgeons' individual experience and training. Indeed, as mentioned by Kim and colleagues¹ and in a subsequent editorial by Kirklin,² the technical challenge and the lack of training in these techniques over the last 10 years, coupled with the absence of readily available homograft valves at many centers, has restricted the widespread use of this substitute, confining the "art" of homograft surgery to the hands of a small group of surgeons.² Regardless of these caveats, however, it is undeniable that when such factors as the severity of the destructive process or its extension to the mitral valve are involved, the balance in the choice of the most suitable substitute is critically weighted toward homografts over conventional stented or mechanical prostheses.

The study by Kim and colleagues,¹ although a notable and well-designed contribution, bases its conclusions on a maximum follow-up of 72 months. This hardly compares with the 15- or 20-year follow-up in the studies by Musci and colleagues³ and Yankah and colleagues,⁴ which is of significance when comparing homografts with xenografts or mechanical valves, given that the actual clinical benefit from the use of homografts is expected to emerge in the long term rather than in the short term (ie, better hemodynamics, no warfarin-related complications). In addition,

there was a significant imbalance in the indication for use of homografts, xenografts, and mechanical valves, with the homografts implanted in patients with significantly more serious and complex conditions, including annular abscess, mitral valve involvement, aortomitral junctional abscess, and prosthetic IE. In their propensity score matching analysis, homograft use did not produce a significant benefit in terms of mortality.

The foregoing results seem to challenge the idea introduced by Barratt-Boyes in 1967, and subsequently refined by Ross, Jacoub, and O'Brien, on the use of homografts in patients with IE.⁵⁻⁹ Indeed, for similar patients with IE with differing degrees of extension of the lesion and aggression of the aortic valve, several pivotal observational studies have shown that the use of cryopreserved homograft provides a survival benefit over conventional valve replacement. Successful treatment of circumferential annular abscess root replacement or aortomitral junction abscess using aortic homografts has been reported.¹⁰⁻¹² In 2002, Yankah and colleagues⁴ reported on a 10-year follow-up of 816 patients presenting with complex aortic root IE with periannular abscess and implanted with

Scanning this QR code will take you to a video for the article.

FIGURE 1. Total homograft replacement of the mitral valve after destructive endocarditis with involvement of the entire mitral annulus.

cryopreserved homografts, showing a survival of 91% with a reinfection rate of 3.6% at 10 years. The authors concluded that a properly inserted homograft could provide excellent hemodynamics with reduced risk of reinfection, and that only an undersized mismatch was an actual determinant of reoperation risk.⁴ In 2010, Musci and colleagues,³ in a series including patients with native valve endocarditis, prosthetic valve endocarditis (PVE) and aortoventricular dehiscence, demonstrated satisfactory early and long-term results with a similar low risk of infection recurrence. This was thought to be related to the complete eradication of the infection that is possible with homograft implantation. The use of homografts also would be appropriate in cases of severe destructive endocarditis with aortoventricular dehiscence when reconstruction of the left ventricular outflow tract is required. Musci and colleagues³ reported significantly better outcomes in patients with native valve endocarditis compared with those with PVE. In the context of PVE, Perrotta and colleagues¹³ recently reported their 20 years of experience with homografts and compared outcomes with those of mechanical and biological valves, and documented no significant difference in early mortality or 10-year survival rate, but a statistically significantly lower rate of infection recurrence, with homografts.

This finding supports the widely accepted assumption that antibiotics are more effective in living and well-vascularized tissue, explaining the higher incidence of recurrent infection in patients who received synthetic derivatives compared with those who received biological allogeneic substitutes. In particular, some strains of *Staphylococcus aureus* and *Streptococcus viridans* are known to be extremely aggressive, with the latter being difficult to detect even with the use of sophisticated techniques, such as mpB genotyping and matrix-assisted laser desorption/ionization time-of-flight systems.¹⁴ In the study by Kim

FIGURE 2. Partial homograft replacement of the mitral valve after extensive endocarditis with commissural lesion.

and colleagues,¹ *S viridans* was isolated in the 38% of the patients who received a mechanical valve. In these conditions, the decision to implant a mechanical valve should be carefully considered given the high rate of recurrence and the elevated risk of mortality after reinfection. In this context, an interesting study conducted in a community hospital serving a highly diverse population in New York City, which captured a real-life picture of patients with IE based on modified Duke criteria, revealed a mortality rate of 27.7% in patients with prosthetic heart valves, compared with only 8.11% in patients with native heart valves.¹⁵

ENDOCARDITIS EXTENSION AND MITRAL VALVE INVOLVEMENT

Another important question is related to the complexity and extension of the infection in IE. If in cases of localized leaflet involvement with vegetations smaller than 10 mm, the question of whether a standard aortic valve replacement will suffice instead of a more destructive approach remains reasonable, then in cases of large abscess formation and extensive annular disease, the need for an appropriate clearance of the infected tissue and adequate reconstruction of the aortic root is more compelling. Kim and colleagues¹ treated more than 40% of patients presenting with abscess formation with mechanical prostheses, which on one hand provides a relatively quick and uncomplicated solution in the short-term, but on the other hand implies accepting the long-term risk of valve reinfection in this more complex operation. In this light, what is the actual benefit of limiting immediate surgery to valve replacement and extending it to more difficult procedures in the long-term?

A similar question might be posed in cases of IE involving the mitral valve alone or in combination with

The aortic valve homograft

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VIDEO 1. The main aspects of homograft evolution, advantages and disadvantages, and indications for use. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(16\)31397-6/addons](http://www.jtcvsonline.org/article/S0022-5223(16)31397-6/addons).

aortic structures. An analysis of the profiles of IE and surgical procedures published by Kim and colleagues (their Table 2)¹ reveals mitral valve involvement in a more than one-half of their 56 patients treated with valve prostheses, including 30 patients with a mechanical valve (38.0%) and 26 patients with a stented xenograft (18.7%) respectively. The 26 patients treated with a xenograft had a follow-up of 72 months, a relatively short and scarcely informative time frame for homografts, compared with other studies reporting outcomes at up to 18 years after treatment.¹⁶ In addition, from a technical standpoint, Obadia and colleagues proposed the use of a monobloc aortomitral homograft in cases of extensive IE involving the aortic root and aortomitral curtain.¹⁷

We also found 11 double homograft valve replacements, including 8 cases of double homograft separate bloc with total mitral homograft implantation and 3 cases of double homograft separate bloc with partial mitral homograft insertion (Figures 1 and 2). However, in our experience we prefer an approach using separate aortic and mitral homografts, which reduces the risk of size mismatch and precludes the need for any reconstruction of the left atrial roof.¹⁸ This approach is normally coupled with the implantation of a prosthetic ring in the mitral homograft, which was found to increase the durability of the mitral homograft in our 8-year follow-up study on mitral homograft replacement.¹⁹ The implantation technique of intraventricular fixation in a side-to-side position on the recipient papillary muscle has provided good results even when mitral tissue is more fragile owing to the presence of infection,^{20,21} with a lower incidence of papillary muscle rupture than has been reported in other series.^{22,23}

Beginning with one of the first implantations in 1994,²⁴ our group has acquired extensive experience in the use of mitral homografts, especially in cases of endocarditic etiology.^{16,20,21} In contrast with Kim and colleagues,¹ in our experience the long-term clinical results of mitral homograft implantation are very encouraging, with rates of freedom from structural valve deterioration (SVD) of 90% at 5 years, 76% at 10 years, and 65% at 15 years and of freedom from reoperation of 88% at 5 years, 80% at 10 years, and 64% at 15 years.¹⁶ The endocarditic etiology, the surgical technique (total vs partial homograft), the

size of the prosthetic ring (30 mm vs larger), and the association with aortic valve surgery were identified as independent predictors of reoperation, although children (age <18 years) had a greater risk of reoperation. SVD resulted in mixed stenosis and insufficiency and was more frequent in patients with a total homograft ($P = .018$ vs partial homograft), patients with a nonendocarditic etiology ($P = .02$ vs endocarditis) and patients who have experienced pregnancy ($P = .016$ vs no pregnancy).^{16,25}

Similar results were obtained in another mitral series from Yankah and colleagues,²³ as well as in a study of the use of mitral homografts in the tricuspid position from Mestres and colleagues,²⁶ and also in a study on growing animals reported by Bernal and colleagues.²⁷ On this basis, the findings of comparable results with mitral homografts and bioprostheses in a cohort of young patients,¹⁹ along with the effectiveness of these biosubstitutes in young females desiring future pregnancy,^{28,29} make homografts an attractive alternative in our opinion.

UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

Undoubtedly, compared with aortic valve replacement, mitral valve replacement with a cryopreserved homograft is more limited in scope and indications, owing mainly to differences in etiology. Indeed, the last several decades has seen a shift in mitral valve disease from a rheumatic to a degenerative etiology, which is best addressed by mitral repair techniques. However, the pathology of IE in children necessitating the use of a substitute that can accommodate the patient's somatic growth remains an important indication for both mitral repair and valve substitutes, as specified by American and European guidelines.^{30,31}

Of note, these guidelines also reflect a parallel renewed interest in stented xenograft prostheses in the aortic position for patients aged <65 years. This orientation is supported by the benefits of biological substitutes in terms of good durability and no need for anticoagulation, and by the possibility of valve-in-valve transcatheter aortic valve replacement in cases of SVD.³² In this context, cryopreserved homografts have already shown not only similar beneficial effects on hemodynamic performance, but also consistent advantages over conventional prostheses, stented xenografts, and mechanical valves in terms of low thrombogenicity, avoidance of life-long anticoagulation, lower rate of neurologic events, improved quality of life during the reproductive years, and risk of reinfection.^{33,34} Moreover, the recent achievements in terms of antibiotic management, pathogenic diagnosis,³⁵ and novel anticoagulants³⁶ surely will play a role in the management of IE (Video 1).

As noted by Stulak and colleagues³⁷ with regard to the use of autologous and allogeneic substitutes to treat both congenital and acquired disease of the left ventricular outflow tract, the use of biological derivatives raises some

ethical issues when the risk of procedure failure or of reoperation is not low. Our group also has faced the problem of longevity of biological substitutes, and has attempted to provide reasonable approaches to dealing for these substitutes' long-term drawbacks.³⁸⁻⁴⁰ Patients need to be informed in detail about the technical issues associated with the use of homografts. As recommended by current guidelines, multidisciplinary decision making regarding valve replacement strategies in IE should take into account the longevity of the biological substitute, the potential recurrence of infection, and the possible need for repeat surgery, which is often associated with extensive cardiac tissue destruction. This is not only required, but emphasized. The choice is best made through a process of shared decision making that includes the patient, the patient's family, an interventional cardiologist, a cardiac surgeon, and as preferred, the patient's general cardiologist or primary care practitioner. In the context of homograft implantation, striking a balance between the risk of SVD with potential valve dysfunction versus a very low incidence of infection recurrence, which would require further complex redo surgery and tissue destruction, should be taken into account when discussing surgical options with the patient.

On the other hand, SVD and calcification of homograft aortic wall is a major drawback of the use of these conduits, leading to technically demanding reoperation with a reported mortality of 4% to 10% and morbidity of 34%.⁴¹ However, unlike prosthetic valves, homografts are affected by reinfection only very rarely, and SVD occurring in homografts carries a significantly lower burden (8.9% early mortality in the series reported by Kowert and colleagues⁴²) compared with redo surgery for an infected prosthetic valve, as exemplified by the 17% operative mortality reported by Grubitzsch and colleagues.⁴³ Indeed, novel transcatheter procedures might be performed with relatively low risk in cases of homograft calcification; for example, Kowert and colleagues⁴² reported 86% survival at 1 year and 77.4% survival at 5 years after homograft redo operation, and deemed transcatheter aortic valve replacement (TAVR) a safe and feasible option in cases where the valve is not infected. However, TAVR is not indicated in cases of noncalcified annuli with massive valve regurgitation, in which treatment for SVD necessitates surgical replacement of the conduit. It has been suggested that in patients with noncalcified annulus and regurgitation (eg, cusp prolapse, cusp rupture) secondary to homograft degeneration, the use of a sutureless valve is a viable option, especially in younger patients^{44,45} and also in patients with homograft reinfection,⁴⁶ whereas TAVR might be safely performed in patients with noninfected calcified SVD with reduced mortality and morbidity.⁴⁷

Nonetheless, evidence suggests that in complex valve surgery for IE, SVD is a much less daunting problem than

recurrent infection. The reoperation for relapsing infection, especially when extended or circumferential abscesses have been treated with prosthetic valves and large amounts of prosthetic materials, such as Dacron patches, is technically demanding and associated with higher mortality. The use of homografts is a reasonable option in cases of extensive abscess, either circumferential (as is typical in cases of PVE) or deep in the aortomitral curtain and interventricular septum. Moreover, homografts have been shown to be useful in cases of relapsing infection after a David or Bentall operation for root endocarditis.⁴⁸ However, in cases of less aggressive lesions and vegetations smaller than 10 mm, the use of allogeneic tissue is recommended only in the pediatric population when necessary to accommodate somatic growth (Video 1).

In conclusion, regardless of the important limitations related to the lack of surgical training and inconsistent homograft availability, in patients with IE, the choice between a short-term solution burdened by the risk of reinfection (ie, xenograft or mechanical valve) and a more surgically demanding but longer-lasting procedure (ie, homograft) should be carefully weighed and serve as the main topic of discussion in cardiac teams.

In other words, should we more often apply the maxim "do it once, and do it well" in extensive IE?

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Authors have nothing to disclose with regard to commercial support.

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