The use of allogenic and autologous tissue to treat aortic valve endocarditis

Francesco Nappi[1], Sanjeet Singh Avtaar Singh[2], Mario Lusini[3], Antonio Nenna[3], Ivancarmine Gambardella[4], Massimo Chello[3]

[1]Department of Cardiac Surgery, Centre Cardiologique du Nord, Saint-Denis, Paris, France; [2]Department of Cardiac Surgery, Golden Jubilee National Hospital, Glasgow, UK; [3]Department of Cardiovascular Surgery, Università Campus Bio-Medico di Roma, Rome, Italy; [4]Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NYUSA

Contributions: (I) Conception and design: F Nappi, SSA Singh; (II) Administrative support: F Nappi, M Chello; (III) Provision of study materials or patients: F Nappi, SSA Singh, M Lusini, I Gambardella; (IV) Collection and assembly of data: F Nappi, SSA Singh, M Lusini, A Nenna, I Gambardella; (V) Data analysis and interpretation: F Nappi, SSA Singh, A Nenna, M Lusini, I Gambardella; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Francesco Nappi, MD. Department of Cardiac Surgery, Centre Cardiologique du Nord, 36 Rue des Moulins Gémeaux, 93200 Saint-Denis, Paris, France. Email: francesconappi2@gmail.com.

Abstract: The surgical treatment of aortic valve endocarditis (AVE) is generally performed using conventional mechanical or biological xenograft prosthesis, with limited use of aortic homograft (Ao-Homo) or pulmonary autograft (PA). Clinical evidence has demonstrated a clear contradiction between the proven benefits of Ao-Homo and PA in the context of infection and the very limited use of allogenic or autologous tissue in everyday clinical practice. This review aims to summarize the most recent and relevant literature in order to foster the scientific debate on the use of the use of allogenic and autologous tissue to treat AVE. The decisional process of the Heart Team should also include the preferences of the patient, his/her family, the general cardiologist or primary care physician. The use of allogenic or autologous valve substitute is beneficial if there is a high risk of recurrence of infection, avoiding extensive adhesiolysis and debridement of synthetic material. In any case, those procedures should be performed by highly trained centers to optimize outcomes.

Keywords: Aortic valve; endocarditis; allogenic; autologous; homograft

Introduction

The incidence of infective endocarditis (IE) is about 3–10 per 100,000 people ranging from 35% (1) to 39.1% (2) in patients with native aortic valve involvement and from 56% (1) to 64.4% (2) in those who have had previous aortic valve surgery. For these reasons, surgical treatment of aortic valve endocarditis (AVE) and the choice of an ideal substitute are often decisive in the resolution of the disease. Over the decades, the challenges associated with aortic valve IE have become increasingly demanding because the patients affected are older with a multitude of

comorbidities (3). This population in high-income countries are often infected by virulent staphylococci that have obscured the strains of penicillin-sensitive streptococci (4,5). The source of the infections responsible for staphylococcal bacteremia is found with increased use of long-term intravenous lines and invasive procedures required for cardiac device implantation (permanent pacemakers, implantable cardioverter defibrillators) (6). In younger patients, the use of intravenous drugs and congenital heart disease have replaced rheumatic heart disease as the main risk factors for aortic IE (7). Likewise, transcatheter valve replacement has revolutionized the management of valvular heart disease

despite the potential that it may be associated with higher rates of IE than surgically implanted prosthetic valves (8).

The surgical treatment of AVE today is generally performed using conventional mechanical or stented/non-stented xenograft prosthesis, although surgeons sometimes prefer the use of aortic homograft (Ao-Homo) or pulmonary autograft (PA) (9). Clinical evidence has demonstrated a clear contradiction between the proven benefits of Ao-Homo and PA in the context of infection and the very limited use of allogenic or autologous tissue in everyday clinical practice (9,10). Moreover, recurrence of infection after valve replacement for IE is a major concern, and accordingly, the optimal valve substitute in this setting has been debated for decades (10-13). The biological substitute remains ideal for certain subgroups of young patients, women with future plans of pregnancy or any other contraindication to anticoagulants (9,14-17), with the caveat of an increased risk of early structural valve degeneration (SVD) (18-20). This category of patient constitutes a point of reference for the use of a homograft or an autograft as an aortic valve substitute in the context of infection because both guarantee excellent hemodynamic performance while avoiding the need for life-long vitamin K-antagonists. However, a reluctance among surgeons to Ao-Homo or PA usage can be explained by the paucity of randomized trials affirming the clinical benefit of allogenic tissues in these categories of patients compared to observational studies (10,14).

Clinical evidence

Professional society recommendations and surgical choices

The use of Ao-Homo is recommended by the position papers of professional societies predominantly on the basis of large observational studies that have reported a benefit with regards to outcomes in infectious endocarditis (9,15-20). Guidelines from The Society of Thoracic Surgeons assigned a Class IIb recommendation (level of evidence B) to the use of Ao-Homo in IE. The choice of allogenic tissue is considered reasonable for native/prosthetic AVE particularly with periannular abscess and extensive annular or aortic wall destruction requiring aortic root replacement or reconstruction, as well as in cases of extensive aortic-ventricular discontinuity (21,22). The AATS 2016 guidelines echo these recommendations indicating the use of allogenic or autologous tissue in destructive native or prosthetic aortic valve IE which surgery

of aortic root; however, the choice of prosthetic bioroot or prosthetic valved conduit with a mechanical or bioprosthetic valve are considered acceptable alternatives although it should be guided by the grade of surgeon's training and experience (22). The degree of infectious involvement of annulus and aorto-mitral curtain are factors that warrant a bespoke surgical strategy (23-25). Furthermore, the involvement of the aortic annulus is also possible with an IE that is limited to a single leaflet requiring precise removal of vegetation as well as aggressive debridement of necrotic material (23-25). This concern is also highlighted in the guidelines when the use of mechanical and stented xenograft is advocated in complex IE and periannular abscess formation provided the valve can be anchored securely to healthy and strong tissue (class IIa level of evidence B). Conversely, the use of homograft or PA has been considered the most appropriate treatment and it is preferable to implantation of a prosthetic valved conduit in case of complex infectious lesions involving native valve or prosthetic valve endocarditis (PVE) in which extensive annular destruction and invasion of the heart structure is noted (21,22). In these patients, radical surgery involving root reconstruction is required with the use of allogenic or autologous substitute. In the presence of IE extending to the aorto-mitral junction with injury of mitral valve and trigonal zone, the choice of double aorto-mitral homograft is suitable either using a monobloc implant or separate bloc with partial mitral homograft insertion (26,27). Despite the recommendations of professional societies, allogeneic or autologous tissue has not been widely promoted, in either patients with an AVE that requires emergency or urgent surgical intervention nor those who are scheduled for an elective intervention. One of the reasons for their limited use is that the superior clinical outcomes associated with the choice of allogenic and autologous tissue for aortic valve replacement (AVR), that has been highlighted in several observational studies (9,15-17), have not been subsequently confirmed in randomized controlled trials (28). This concern is well highlighted in the guidelines where both of these recommendations for the choice of homograft or autograft are categorized as Class II, indicating that there is conflicting evidence and/or a divergence of opinion related to the usefulness/efficacy of this procedure or treatment. The usefulness and efficacy of Ao-Homo or PA is less well established by evidence/opinion (categorized as Class IIb) because data are derived from a single randomized trial or from nonrandomized studies (Level of evidence B) (21,22,28,29).
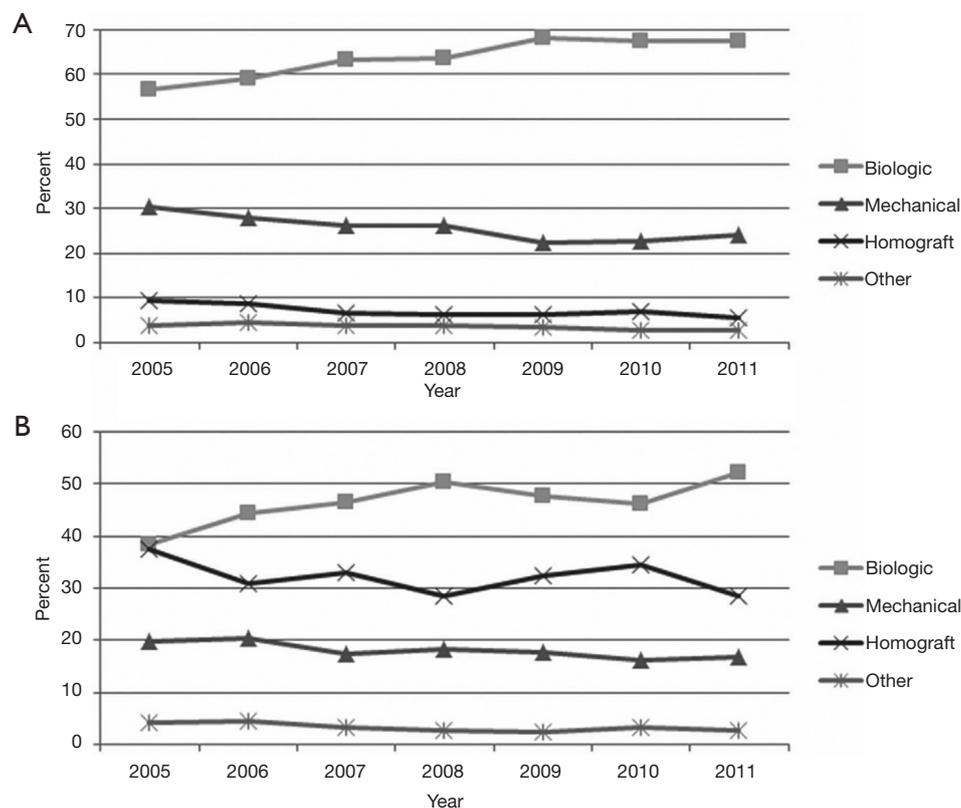
Figure 1 Trend representing the use of substitutes for AVR in endocarditis from 2005 to 2011 in USA (STS database). (A) Native aortic valve endocarditis and (B) Prosthetic valve endocarditis. The P value for the usage trends in both groups was <0.001. (biologic = squares; mechanical = triangles; homograft = x; other = star). Reproduced with permission from Savage *et al.* Ann Thorac Surg 2014;98:806-14.

Clinical use

Ao-Homo

In patients with active endocarditis who require complex aortic valve surgery, the recurrence of infection rate varies from 2% in recipients of allogenic tissue as reported by Fukushima *et al.* (16) up to 25.4% in those who receive a conventional prosthesis in the first year after implantation as documented in a pivotal study by Musci *et al.* (30). The clinical and echocardiographic evidence of recurrent aortic IE has been reported within the first year in several observational studies (1,30-33). Active endocarditis is a statistically significant risk factor for increased early (1,9,30,31,33) and late mortality (1,9,15-17,30-32,34). In recent years, the choice of polyester graft *in situ* of an infectious injury has gained traction amongst cardiac surgeons for satisfactory outcomes reported with improvements in antibiotic therapy (35). The limited use of allogeneic and autologous tissue may

be due to the renewed enthusiasm for antibiotic therapy before surgery for some cases of PVE (35), avoiding urgent operations (3). Some authors from Harvard Medical School (31,33) reported a significant increase in the proportion of patients treated with allogenic tissue when abscess formation occurs (67% *vs.* 41% for mechanical valve and 30% for xenograft valves, P<0.001) or when the methicillin-resistant Staphylococcus was detected (26 % *vs.* 13% for mechanical prosthesis and 12% for xenograft). This allows us to infer that the Ao-Homo or PA tissue is more likely used in patients with active and severely complicated endocarditis with/without involvement of the heart structure (31). In our experience, the homograft for replacement for aortic and mitral valve disease was used in 56.2% and 21% of patients with active endocarditis who developed periannular abscess and aortic root involvement (9,26) (*Figure 1*).

Steffen *et al.* (36) reported the considerable microbiological advantages of allogeneic tissues in extensive infections of the heart structure, either in native or PVE.

The authors revealed that Ao-Homo tissue treated during cryopreservation process maintains some antibacterial activity over 5 years. Several combinations of antibiotics were tested on cryopreserved allogeneic tissue (gentamicin, piperacillin, vancomycin, metronidazole, amphotericin B, flucloxacillin, meropenem, tobramycin and colistin) and have significant influence on their infection resistance. Ascending Ao-Homo tissue have enhanced bacterial resistance against staphylococcal bacteria (*S. epidermidis* and *S. aureus*) with less bacterial contamination compared to homograft aortic valves. A more effective resistance was found against *P. aeruginosa* using flucloxacillin and *E. coli* with meropenem and colistin (36). Application of antibiotic after thawing the cryopreserved Ao-Homo significantly decreases the recurrence of infections compared to conventional prostheses or Dacron graft in whereby this benefit has not yet been clearly demonstrated (37). Although the risk of vascular graft infection is reduced by pre-treating the prostheses with antibiotics (38,39), the antibiotic/fibrin compound showed a favorable effect of delayed release of antibiotics in the early prevention of the endocarditis recurrence (39). Furthermore, a better understanding of effective concentrations of β-lactam antibiotics may enhance this action by conferring additional immunity to recurrence of infection (39). The better response of allogeneic tissue to antibiotics has been shown in reports where Ao-Homo implants were successfully treated medically after relapse of infection (15-17).

PA

The choice of PA as an aortic valve substitute in the setting of IE has important implications for long-term outcomes and should be carefully selected for specific patients (40,41). In high-income countries, the majority of patients undergoing AVR for IE are elderly (4,5), so surgery of infective aortic valve disease is recommended using bioprosthetic valves (21). By contrast, in some categories of younger patients—such as intravenous drug abusers, previous congenital heart disease, woman with future plans of pregnancy and people with longer life expectancy—who develop IE of aortic valve, the ideal substitute for AVR should provide durable hemodynamics that facilitate an active lifestyle with excellent quality of life. For these patients there is a renewed interest for the use of PA as an ideal substitute in AVR and Ross procedure can be considered to support its use in selected young and middle-aged adults with an aortic valve infection (42-45).

Implantation of the PA in the setting of IE can be performed using two main techniques (46,47). The subcoronary technique may be used for localized infection limited to aortic leaflet and partial involvement of aortic annulus alongside root replacement that may be performed when the infection is extended to the aortic root. The subcoronary insertion has the advantage of limiting the surface of PA exposed to the higher systemic pressures and consequent dilation of vessel wall (46,47). Numerous surgeons prefer to perform the Ross procedure with full root replacement technique and inclusion technique especially in bicuspid/unicuspid aortic valves or in the presence of AI which is marked in aortic IE. A limited number of randomized trials (Level I/Class recommendation A) are available to support performing the Ross Operation in the setting of aortic IE (48-55).

Recently, Ratschiller *et al.* (56) reported the use of Ross procedure in a series of 190 patients. The operation was performed by means of freestanding root replacement technique and 19 patients had acute endocarditis as the indication for operation including 6 patients with bicuspid aortic valves. The clinical follow-up was 100% complete and with a mean of 12.0±5.7 years. The results showed lower in-hospital mortality (5.3%). Echocardiography at hospital discharge revealed at most trivial aortic regurgitation in all patients with no cases of infection relapse that affected the autograft. One patient (0.4% per patient-year) was re-operated 1.8 years after the Ross procedure for endocarditis affecting the pulmonary homograft. The major concern in these patients was the expansion with failure of PA that was noted in three patients (15.8%) for which reoperation was required. The Ross procedure has proven safety and effectiveness as an alternative to prosthetic valve replacement or homograft implantation in selected young patients with acute endocarditis with a low rate infection recurrence (56).

Comments

We reported the use of cryopreserved homograft for AVR in 210 patients (9) either using a free-hand subcoronary implantation technique or as root replacement with coronary reimplantation (*Figure 2A,B*). More than half of the patients had endocarditis, with 21% showing evidence of abscess formation (*Figure 2C*) and nearly a quarter had associated valvular or coronary procedures. Although the comparison of the two techniques was not our primary objective, we did not find significant differences between
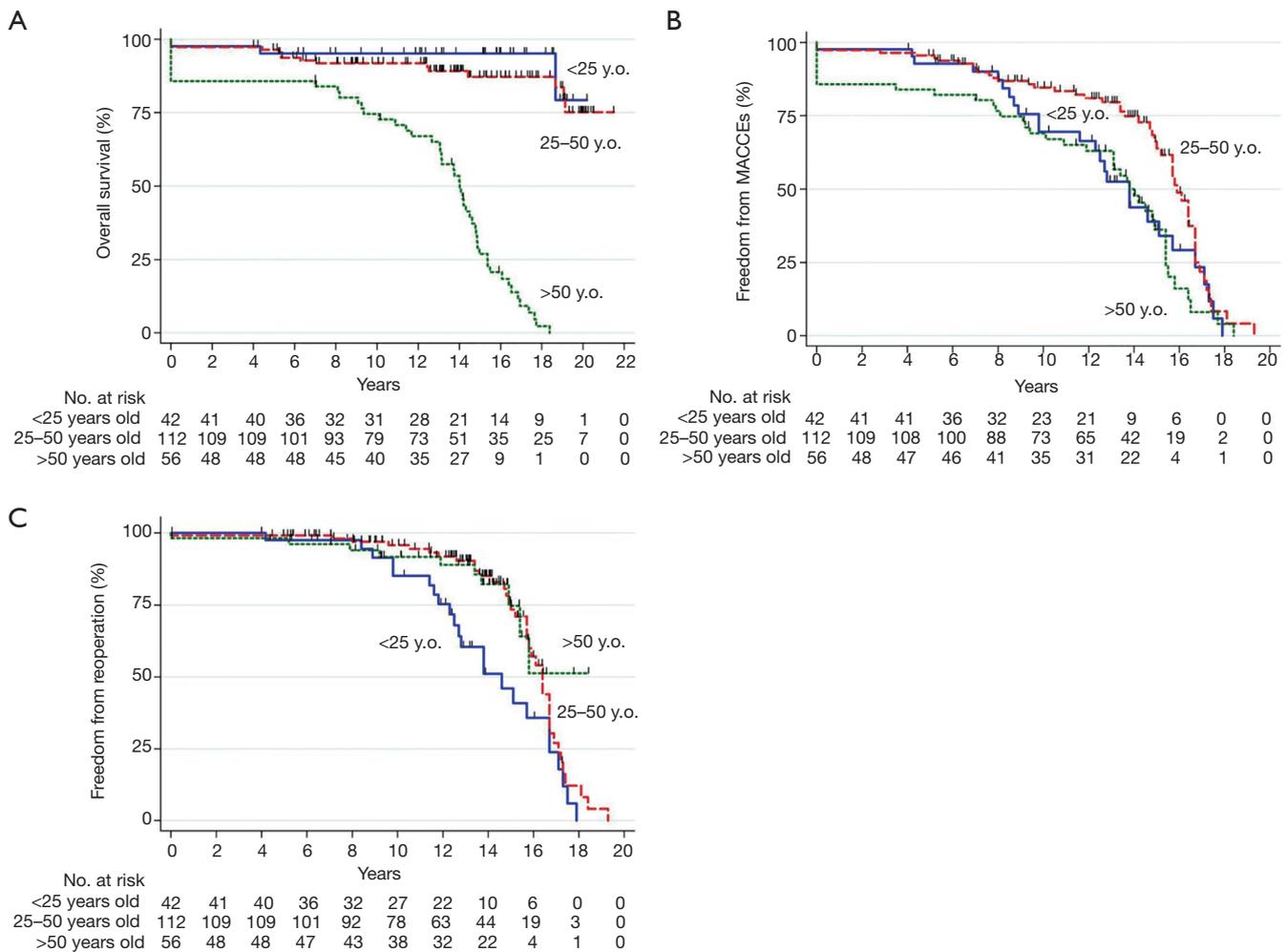
Figure 2 Endpoints among age groups. (A) Overall survival; (B) freedom from MACCEs; (C) freedom from reoperation. MACCE, major adverse cardiac and cerebrovascular events.

the choice of surgical insertion. The use of Ao-Homo was associated with an overall mortality and cardiac mortality rate of 38.1% and 30.5% respectively, and the rate of structural valve deterioration requiring repeat surgery was 27.1%. There was no early recurrence of infection with only 4 late recurrence of endocarditis. The composite outcome of major adverse cardiac and cerebrovascular events (MACCE) (all valve-related mortality, valve-related morbidity, thrombosis, bleeding, neurologic events, endocarditis, rehospitalization for heart failure, and worsening New York Heart Association class) was 50.6%±4.1% at 15 years. The use of allogenic tissue was also associated with no difference in clinical outcomes between pregnant women and the other patients (9). Our results were similar to the findings of the Cleveland Clinic

and another study from Sweden (57,58). We also used the PA as a substitute for AVR in IE in limited cases (young and middle-aged patients with both bicuspid and tricuspid valve anatomy). In our series, no cases of recurrent PA endocarditis occurred at up to 23 years of follow-up which was unique to our center (59) (*Figure 2*).

The clinical benefits associated with the use of Ao-Homo or PA were more evident in women with future plans for pregnancy. Pregnancy gravidity was not found to be a significant effect modifier on the functionality of allogenic tissue. This finding was confirmed by Romeo *et al.* (14) who described the use of homograft as a conduit for right ventricular outflow tract (RVOT) reconstruction in women with future plans for pregnancy. All women survived pregnancy, 20.2% and 23.8% of newborn were small for
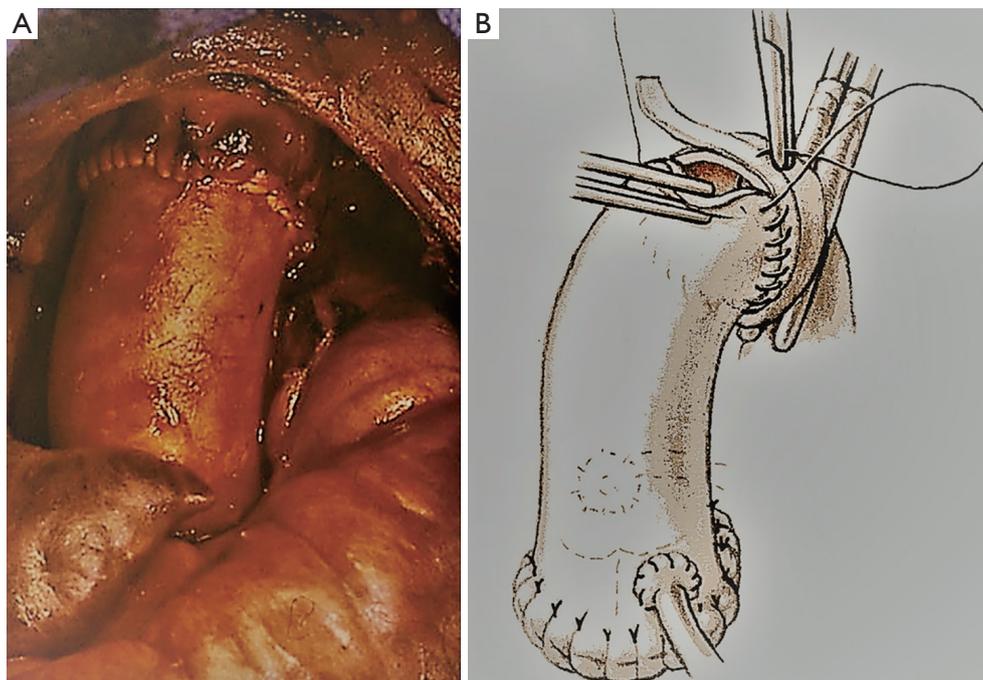
Figure 3 Valve endocarditis following the Bentall procedure replacement of the valved conduit with a homograft including the whole ascending aorta (A) or the arch (B).

gestational age or premature. These results (9,14) offers a biologic mechanism to explain the observed advantage in clinical outcomes; however, the higher incidence of pre-term delivery and children small for gestational age deserves further in-depth investigations (14,42-44).

Safety and effectiveness of allogenic and autologous substitutes over conventional prosthesis in recurrence of endocarditis has been widely reported in several observational studies, although a difference in resistance to infection between the valve and aortic wall of allogenic tissue noted (increased resistance in homograft ascending aorta tissues) (15-17,36,37). It is possible that the adaptive remodeling allows the PA to mimic the highly refined anatomical changes and function of the neo-aortic root which intervenes as a protective mechanism both in the leaflet and in PA wall (60). The remodeling process is largely mediated by valvular endothelial and interstitial cells, which undergo activation and phenotypic changes when exposed to the systemic circulation providing greater resistance to the leaflets (60-62).

Re-do surgery in cases of re-infection is particularly challenging with increased risks of morbidity and mortality (1,9,30-34). Infection relapse involving synthetic prostheses or prosthetic materials are daunting and more technically demanding than infection relapse of a homograft valve replacement. We noted that extensive adhesiolysis was necessary to access the heart when synthetic material is implanted compared to homografts (9,26). Our experience also revealed that the foreign material constituting the stent of mechanical or biological prosthetic valves evokes a strong inflammatory reaction and might cause denser adhesions complicating the operation (9,23,26) (*Figure 3*).

Several limiting factors to using Ao-Homo and PA probably come from patient choice, influenced by the surgeon who has to ethically weigh up the risk of failure of the procedure and re-operation, which are not infrequent (9,18-20,50,63). For example, when a PA is used, external reinforcement of the PA with a prosthetic Dacron graft has been proposed to circumvent its late expansion but data on the long-term results of this approach are lacking (64). Nonetheless, experimental models of the Ross operation have shown the risk of migration of polyester into the PA wall with the development of complications related to the onset of the immune-inflammatory processes and to the biomechanical impairment of the PA (65-68). Some recent studies have shown a high adaptability to remodeling of PA when systemic pressures exert unexpected wall

stressors. The phenomenon of remodeling can be induced by polyesters with gradual reabsorption favoring a process of neo-arterialization (69-71). Wall cells of PAs implanted in the aortic position start expressing Ki67, a marker of proliferation and differentiation that leads to extracellular matrix remodeling, in the form of increased smooth muscle actin production (60). These results pave the way for the use of semi-absorbable scaffolds that have the dual effect of avoiding the expansion of the neoaortic root while providing greater solidity to the wall (61,62,69).

Finally, the heart team discussion cannot neglect the patient's preference. A very extensive operation might be a daunting prospect for patients. Clinicians should detail the steps of the procedure, the potential complications and the postoperative course to facilitated informed consent and decision-making (3,23). Patients should be made aware of the complexity of the disease and on the potential need of extensive debridement to achieve good and stable results. The risk of reoperation for SVD of Ao-Homo or PA failure must weighted against the durability of the bioprosthetic valve as an alternative to allogenic or autologous tissue (9,10,18-20,50,63).

Five main points are required for guiding the choice of valvular substitute for AVE during the process of shared decision-making that includes the patient, the patient's family, a cardiologist, a cardiac surgeon, and ideally, the patient's general cardiologist or primary care physician:

(I)   The technical issues involving Ao-Homo or PA usage that may pose difficulties during surgery (especially in young patients);

(II) The age of the patient may guide the choice of the prosthesis even in complex valve endocarditis and widely infected field when allogenic or autologous tissue are recommended;

(III) The risk for a repeat operation when the use of Ao-Homos or PAs is preferred over the conventional prostheses;

(IV) The use of allogenic or autologous valve substitute is beneficial if there is a high risk of recurrence of infection, avoiding extensive adhesiolysis and debridement of synthetic material;

(V)   The rule of societies including religious education that may impose restrictions on the use of allogenic or autologous valve substitute.

Acknowledgments

Footnote

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