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In summary, although the pulmonary autografts might be subject to dilatation and insufficiency after the Ross procedure, investigations into the nonstenotic feature could help shed some light on the mechanisms of aortic valve calcification as well as design and fabrication of improved tissue prostheses.

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COR: IIB
why?
LOE: C

REPLY: WHY STILL IIB AND C?

Reply to the Editor:

In a selected group of patients, the Ross operation offers excellent long-term outcomes.¹ Especially in young patients, the Ross operation improves quality of life and increases survival when compared with mechanical valve substitutes.² These findings are related to the advantages of the living pulmonary autograft being implanted in the aortic position.

The letter to the Editor by Ma and colleagues focused on the fact that failure of the pulmonary autograft in aortic position over time is not related to valve stenosis. The reason for this observation remains unclear. Comparing pulmonary and aortic roots using different methodologies will increase our understanding of valve pathophysiology and on the development of aortic valve disease. Histologic analyses, molecular studies, and hemodynamic investigations could be used to accomplish this. Therefore, the letter by Ma and colleagues adds an important piece of information, not only with regards to the Ross operation.

The reason why pulmonary autografts do not develop valve stenosis over time, when implanted in aortic position, remains speculative and most likely multifactorial. As the autograft adopts to the systemic pressure over time, it may be that the length of follow-up may still be too short to observe pulmonary valve stenosis. Autograft age may also play a role in that older autografts could lose their ability to adopt to systemic pressure and, therefore, be more likely to fail over time.

As the autograft is the only “living” valve substitute available for the aortic position, the protective role of viable tissue may be the most important factor. When autografts do fail, it is mainly due to valve regurgitation. Even when this happens, however, the autograft can be preserved either by valve-sparing techniques or by “Ross reversal” in the majority of patients.^{3,4} Correct technical implantation of the tricuspid autograft should exclude valve deterioration over time due to flow alterations causing increased stress on valve cusps.

As the pulmonary autograft has been shown to have principally the same architecture compared with the aortic root, it appears to be the ideal substitute for the aortic position.⁵ One can therefore argue that the current guideline recommendation (2017) is too conservative: “the Ross procedure, when performed by an experienced surgeon, may be considered in young patients when vitamin K antagonist is contraindicated or undesirable.” (Class IIB recommendation, level of evidence C).⁶

Given that there is increasing evidence that the Ross operation is the best procedure to treat aortic valve stenosis in young and middle-aged adults,^{1-4,7,8} one can argue that the guideline level of recommendation should be increased. This has been addressed by surgical experts of the Ross procedure already in 2014.⁹ The letter by Ma and colleagues highlights another important aspect of the advantage of the Ross procedure. It may be time to not only re-evaluate the current guidelines, but to apply this current knowledge on future research in the field of aortic valve disease.

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$$\text{Degeneration} = \left(\frac{\text{Tissue properties,}}{\text{genetic code}} + \text{impact} \right) \times \frac{\text{Time}}{\delta \text{ Normal}}$$

REPLY: DOES ADAPTATION PREVENT CALCIFICATION?

Reply to the Editor:

The authors have to be congratulated for their thoughtful question and the proposed pathway to gain more information on the degeneration of the autograft.¹ They discussed nicely the main predictors including structure and stress, which is shown more generally in the formula shown in Figure 1 for degeneration. The genetic code is the basis of tissue properties being affected (internally eg, by aging and externally eg, by hemodynamic stress) in relation to normal (defined as 1). Degeneration might occur as tissue disruption, elongation, thickening, and mostly later with calcification resulting in valve regurgitation and/or stenosis. The autograft has the same origin and design as the aortic valve, consisting of living, autologous tissue, and operates at low pressure in desaturated blood. During the Ross procedure the autograft is excised, denervated, surgically manipulated, and subjected acutely to systemic pressure and oxygenated blood. The question is whether the autograft can adapt to the new conditions for adequate lifelong function, which is excellent over at least 20 years after the operation albeit with some late decline in function.² Root dilatation and

$$\text{Degeneration} = \left(\frac{\text{Tissue properties,}}{\text{genetic code}} + \text{impact} \right) \times \frac{\text{Time}}{\delta \text{ Normal}}$$

FIGURE 1. General parameters of tissue degeneration related to time and difference (δ) to normal.

leaflet prolapse causing regurgitation are obviously surgically related reasons for nonstructural valve degeneration. But there must be other factors resulting in increasing regurgitation by structural valve degeneration, which was observed in explant studies showing a thickening of autograft leaflets even many years after the operation.³ It remains to be elucidated if the age at operation has some influence on the degree and quality of the adaptation process. For example, the most physiological repair of transposition of the great arteries, the direct spiral anastomosis of the great arteries early in life, warranted near-normal semilunar function after 20 years indicating excellent adaptation.⁴ In this sense, Merryman reported on a coupled response of aortic valve interstitial cells and extracellular matrix stiffness with increasing age that might have an effect on mechanotransduction and thus adaptation.^{5,6}

In addition, even small amounts of unphysiological shear stress and particularly oscillatory shear have been reported to activate endothelial to mesenchymal transformation in adult valves causing cytokine release and a pro-oxidant phenotype initiating inflammation and calcific valve degeneration.^{7,8} It is somewhat difficult to implant the autograft into the aortic root achieving an anatomic situation that is exactly the same as in the original pulmonary position if the autograft worked perfectly. Even if after transplantation of the autograft there is no insufficiency some irregularities in leaflet motion presenting as oscillations of the leaflets might occur leaving the autograft with lifelong unphysiological stress, theoretically hindering the adaptation process and potentially causing degeneration. This might explain in part that over the years in some patients there is a loss of functional excellence especially in patients with primary insufficiency.² Whether the adaptation mechanisms in the Ross autograft are adequate for generating a perfect “normal” aortic valve in all patients or at all and whether they are protective against calcification remains elusive and questionable probably requiring longer follow-up times for clarification. What we can learn is that surgery and especially Ross surgery should be absolutely precise in form and function to imitate nature, thereby reducing the stress on the autograft, which might be beneficial for adaptation with less degeneration over longer time periods.

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