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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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REPLY FROM THE AUTHOR: WHY DON'T PULMONARY AUTOGRAFTS CALCIFY IN THE AORTIC POSITION?

Reply to the Editor:

I have been following my first 212 consecutive patients who had the Ross procedure with periodical clinical and echocardiographic assessments since 1990.¹ To the end of June 2019, I had reoperated on the pulmonary autograft in 24 patients because of aortic insufficiency, partial dehiscence of the pulmonary autograft from the intervalvular fibrous body, or dilatation of the neo-aortic root, either isolated or in combination with pulmonary valve homograft replacement. On the basis of this and other studies on longitudinal outcomes after the Ross procedure, Drs Ma, Zhang, and Wang from Shanghai raised the question, “Why don’t pulmonary autografts calcify in the aortic position?” in a letter to the Editor.

I reviewed the operative notes and pathological reports on all patients who had reoperation on the pulmonary autograft and there was no mention of calcification in the cusps or annulus in any of my patients. However, I have also reoperated on 9 other patients who had the Ross procedure in other institutions and 1 patient had calcified annulus and

small islands of calcification in the left coronary cusp but aortic insufficiency was the indication for reoperation. That patient had the pulmonary autograft implanted in the subcoronary position 27 years earlier and he was 68 years old at the time of reoperation. My own series of Ross patients were relatively young (median age, 34 years; interquartile range, 28-41 years)¹ and that could be the reason we did not see any calcification in the pulmonary autografts. It might take 2, 3, or more decades for the pulmonary autograft cusps to calcify and become stenotic and the Ross procedure might not last that long.

Drs Ma, Zhang, and Wang’s potential reasons for the lack of calcification of the pulmonary cusps with consequent aortic stenosis as a mode of failure after the Ross procedure such as increased mechanical stress, higher oxygen saturation, histological and molecular structure differences between the aortic and pulmonary valves, and duration of follow-up are all valid. In addition to all that, I would add that lack of adaptation of the pulmonary valve is responsible for fragmentation of its fibrous and elastic tissues and distortion of the normal histology with thinning and elongation of the cusps with consequent aortic insufficiency instead of cusp calcification and stenosis. Ischemia might also play a role in this degenerative process because the neurovascular connections of the pulmonary root are severed during the operation. Finally, I firmly believe that older age adversely affects adaptation although my personal data are inadequate to prove my contention. In my hands the pulmonary autograft of younger patients is much more durable than in older patients. Similarly, adaptation of the aortic valve cusps after reimplantation of the aortic valve into a tubular Dacron graft (the so-called “David operation”) is far superior in younger than in older patients, that is, that type of repair is more durable in young adults than in older patients.

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