Managing the aorta in patients with a *PRKG1* mutation

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Extremely thin remnant of the aortic sinus wall and mild diffuse elastica fragmentation.

Central Message

Aggressive prophylactic replacement of the proximal aorta should be considered for patients with a pathogenic *PRKG1* mutation and family history of thoracic aortic dissection.

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Video clip is available online.

Around 25% of thoracic aortic aneurysms and dissections (TAADs) result from single gene mutations,¹ including mutations in *PRKG1*.^{2,3} Current American Heart Association/American College of Cardiology guidelines provide recommendations for other mutations, in genes such as *FBN1*, *TGFBR1*, and *MYH11*,^{4,5} but not specifically *PRKG1*. We present a patient with a known *PRKG1* mutation and a story about her family (Video 1).

CLINICAL SUMMARY

A 47-year-old woman with a strong family history of TAAD was found to have a *PRKG1* heterozygous mutation. Her *PRKG1*-positive brother experienced an aortic dissection at age 35 years, a niece died at age 16 years from an aortic dissection, 1 brother died at age 16 days from a congenital heart defect (ie, 3-chambered heart), another brother was stillborn at 7 months, among her 4 daughters, 2 are negative carriers and 2 are *PRKG1* mutation-positive, and 1 granddaughter has the *PRKG1* mutation. Both affected daughters (diagnosed at ages 24 and 22 years) were found to have tricuspid aortic valves, normal ejection fractions, and the older had a 29 mm aortic root whereas the younger had a 23 to 25 mm aortic root and 29 mm ascending aorta. The patient underwent an echocardiogram in her 30s when her brother experienced an aortic dissection, and all measurements were within normal ranges. Following positive genetic testing, an echocardiogram demonstrated a trileaflet aortic valve with trace aortic insufficiency and a left ventricular ejection fraction of 62%. Computed

tomography angiogram revealed a 37 mm aortic root and 38 mm ascending aorta (Figure 1).

The patient experienced significant anxiety regarding possible aortic dissection and eventually underwent a valve-sparing aortic root replacement (David V procedure–Stanford modification, using 32- and 24-mm Hemashield Dacron [Maquet, Rastatt, Germany] grafts) and ascending aorta replacement (as much as possible without circulatory arrest). The distal anastomosis was completed without surgical adjuncts (Figure 2, B). Most

VIDEO 1. Discussion of prophylactic management of the aortic root and ascending aorta in patients with a known *PRKG1* mutation. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32605-9/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32605-9/fulltext).

FIGURE 1. Computed tomography angiography scans before (*left*) and 3 months after (*right*) valve-sparing aortic root and ascending aorta replacement in a patient with a *PRKG1* mutation.

notably, the wall of the proximal ascending aorta and aortic root was exceptionally thin (1 mm), almost as thin as the outer layer of a dissected aorta (Figure 2, A). The right ventricular outflow tract could be visualized through the right coronary sinus wall. The distal ascending aortic wall was about 2-mm thick. The aorta was very fragile, and likely to tear during cannulation of the aortic arch. We used a single 3-0 Ethibond Exel purse-string suture (Ethicon, Bridgewater, NJ) without pledgets for aortic cannulation at the midarch and the cannulation site was reinforced with 5-0 prolene sutures in a figure-8 fashion after decannulation. Histology showed thin aortic media without typical changes seen in patients with Marfan syndrome or Loeys-Dietz syndrome (Figure 2, C and D). She has been doing well for >1 year with a competent aortic valve since her operation (Figure 1). On our patient's postoperative day 4, a 30-year-old cousin with the same *PRKG1* mutation experienced an acute type A aortic dissection with mesenteric malperfusion and necrotic bowel.

DISCUSSION

Although mutation in *PRKG1* has been linked to familial TAAD,^{2,3} there is no evidence to guide the clinical management of affected patients, so clinical decision making is difficult. *PRKG1* encodes a type 1 cGMP-dependent kinase involved in smooth muscle relaxation and contraction^{2,3} crucial in maintaining the integrity of

the thoracic aortic wall throughout life.² Patients with a *PRKG1* mutation present with aortic dissection relatively early in life, around age 31 years (range, 17-51 years; $n = 31$).² In a study by Guo and colleagues,² an acute type A aortic dissection occurred at an aortic root diameter of 37 mm and ascending aorta diameter of 43 mm in a 27-year-old female patient. Gago-Diaz and colleagues³ reported on a female patient who experienced a type B dissection at age 41 years and a type A dissection at age 43 years. Before dissection, the aortic root measured 44 mm and the ascending aorta measured 37 mm. Patients with the *PRKG1* mutation are predisposed to an aggressive form of thoracic aortic disease, experiencing aortic events at relatively young ages and small aortic diameters.^{2,3} Therefore, prophylactic aortic repair should be considered at smaller aortic diameters in affected patients, but specific indications for prophylactic repair remain undecided. Although mutations in *PRKG1* are not the most common cause of genetic TAAD, guidelines regarding this specific presentation are warranted.

In the case presented, the intraoperative finding of an extremely thin aortic wall and strong family history of aortic dissections and death support early aggressive management of the aorta in patients with pathogenic *PRKG1* variants, and if possible, valve-sparing aortic root replacement should be performed. The patient's affected daughters (now aged 26 and 24 years with normal aortic root and

FIGURE 2. A, Valve-sparing root replacement (David procedure) in a patient with *PRKG1* mutation and a thin and fragile aortic wall. Suture for aortic valve implantation was meticulously placed through the aortic annulus, which was strong enough to hold the suture. The *arrow* indicates the extremely thin remnant of the aortic sinus wall. B, Completion of the repair showing the distal anastomosis of the Hemashield Dacron graft to the ascending aorta. C, Moderate, multifocal intralamellar mucoid extracellular matrix accumulation without altering the arrangement of the lamellar units. Medial fibrosis and inflammation were also absent. Thus, overall the media displayed mild-to-moderate medial degeneration. Additionally, there was no evidence of aortitis or dissection (hematoxylin and eosin stain). D, The aortic media also displayed moderate, multifocal elastica fragmentation plus multifocal mild-to-moderate elastic fiber thinning. There was no elastic fiber disorganization, no smooth muscle loss or disorganization, and no laminar medial collapse (elastic Van Gieson stain).

ascending aorta dimensions) continue to be monitored with annual echocardiograms, but the question of when to consider prophylactic aortic repair remains.

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