Progress in Pediatric Cardiology 55 (2019) 101121

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Coronary ostial aneurysms following aortic root replacement in patients with familial aortic aneurysm are common and support the need for long-term surveillance

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ARTICLE INFO

Keywords:
Familial aortic aneurysm and dissection syndromes
Aortic root replacement
Coronary ostial aneurysms

ABSTRACT

Background: Following the successful aortic root replacement (ARR) in patients with familial forms of aortic aneurysms (FFAA), few studies have defined the long-term outcomes of the re-implanted coronary arteries. The goal of the study was to describe late coronary complications following ARR in patients with FFAA.
Methods: 40 patients with a genetically confirmed form of FFAA S/P ARR whom had undergone at least 1 CT scan or cardiac MRI study following ARR were identified. All studies were reviewed retrospectively and the coronary ostium were measured offline by two independent observers.
Results: The majority of patients had Marfan Syndrome (80%), 15% had Loeys-Dietz Syndrome (TGFBR1 or TGFBR2), and 2 patients a MYLK or ACTA2 mutation. Mean age at time of ARR was 30.7 years, range 10–65. Mean length of follow-up from ARR 6.2 years, range 0.5–19. At last follow-up, 55% had developed at least 1 coronary complication. Nineteen (48%) had developed a coronary ostium aneurysm and 3 patients coronary ostium stenosis. All patients were alive at last follow-up. No patient had developed a coronary button rupture or dissection. Patients with aneurysms were more likely to have a mutation other than Marfan Syndrome ($p < .05$) and were more likely to have undergone emergent ARR following dissection ($p = .008$). Progressive coronary ostium dilation was rare. Two patients however did develop severe dilation and required button revision, both with TGFBR2 mutation.
Conclusion: Coronary ostium dilation is common following ARR in patients with FFAA. Progressive dilation and risk for coronary button rupture appears to be low. Patients with non-fibrillin 1 mutations, are at higher risk for severe dilation and some may require intervention. Long term surveillance in particular in patients with non-fibrillin1 forms of familial aortic aneurysm and dissection syndrome should be considered.

1. Background

While numerous papers have highlighted excellent outcomes after aortic root replacement (ARR) in patients with familial forms of aortic aneurysms (FFAA), few studies have defined the long-term outcomes of the re-implanted coronary arteries [1,2]. Case reports have documented progressive dilation of the coronary buttons [3] with risk for dissection and rupture in select patients [4–7]. In addition, small case series have reported that patients may be at risk for severe stenosis [4,5]. The goal of this study was to describe late coronary complications following ARR in patients with FFAA [1].

2. Methods

After IRB approval, 108 patients with a history of ascending aortic aneurysms who underwent aortic root replacement and were actively

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https://doi.org/10.1016/j.ppedcard.2019.05.001
Received 29 January 2019; Received in revised form 19 April 2019; Accepted 6 May 2019
Available online 10 May 2019
1058-9813/

being followed in the Wisconsin Adult Congenital Heart Disease Program were identified. Of these, 40 patients had genetically confirmed Marfan Syndrome or a familial aortic aneurysm syndrome and served as our study cohort. All 40 patients had undergone at least 1 computed tomography (CT) scan or cardiac magnetic resonance imaging (MRI) study following their aortic root replacement. The majority of patients, 85%, had a previous CT scan, while the remaining patients had a cardiac MRI. Of the 40 patients, 37 patients had 2 or more studies to allow for analysis of progression over time.

All CT scans were performed using the same acquisition protocol. The thoracic aorta was scanned in the cephalocaudal direction using a single breath hold from the aortic arch to the diaphragm. Acquisition time was 25–30 s. In all cases, 150 ml of contrast was administered with a power injector. All axial images were reconstructed with 180 degree linear interpolation at 1-mm spacing using a standard reconstruction algorithm.

The MRI examinations were performed using a 1.5 Tesla MRI system using similar pulse sequences. Conventional breath-hold contrast-enhanced 3-dimensional MR angiography was performed to visualize the entire aorta and the re-implanted coronary ostia.

All studies were reviewed retrospectively offline by two independent observers. The diameters of the re-implanted coronary artery ostium were measured from superior to inferior parallel to the aortic wall (see Fig. 1). A coronary ostium aneurysm was defined as a coronary ostium diameter of ≥10 mm. Progressive dilation was defined as a > 30% increase in coronary ostium diameter on serial imaging. Coronary artery ostium stenosis was defined as a 50% narrowing.

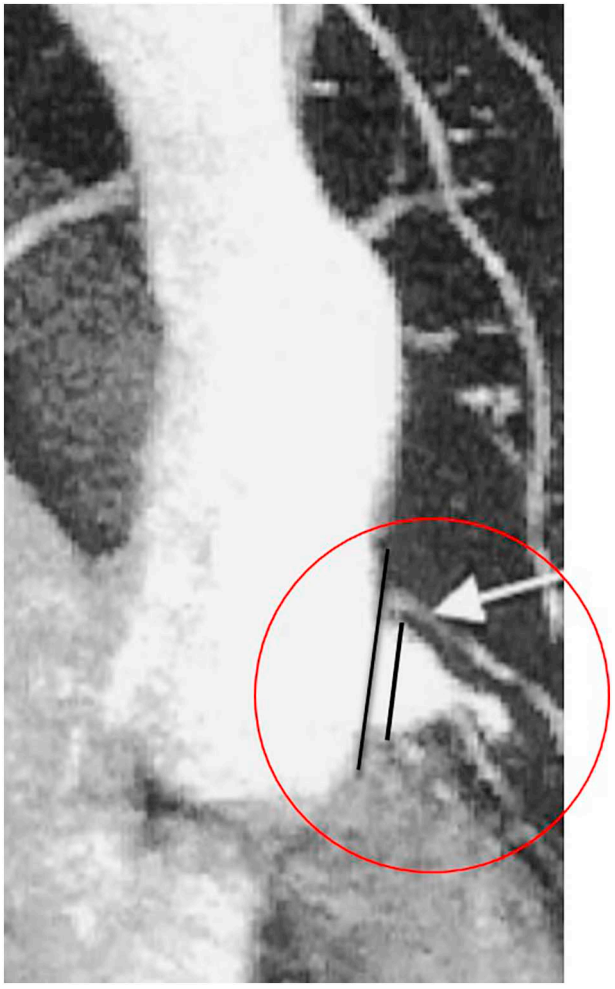

Fig. 1. The diameters of the re-implanted coronary artery ostium were measured from superior to inferior parallel to the aortic wall. Red circle highlights areas of interest on CT scan. White Arrow delineates coronary artery button aneurysm. Black lines demonstrate the technique used to measure the coronary artery ostium diameters.

Table 1
Demographics of study cohort (N = 40).

	N	%
Genetics		
Marfan Syndrome	32	80
Loeys Dietz Syndrome	6	15
ACTA2	1	2.5
MYLK	1	2.5
Elective surgery	32	80
Surgical technique		
Valve sparing aortic root replacement	26	65
Composite aortic root and valve replacement	14	35
Coronary reimplantation using button technique	40	100
Age at time of aortic root replacement (mean)	30.7 years	Range 10–65 years
Length of follow-up from Aortic root replacement (mean)	6.1 years	Range 0.5–9 years

A chart review was also performed and data was collected to allow for analysis of risk factors for coronary ostium complications. Data collected included genotype, gender, age at time of ARR, size of ascending aorta at time of ARR, surgical technique (valve sparing root procedure verses concurrent valve replacement).

2.1. Statistical analysis

Results are presented as frequencies and means. Descriptive statistics, Fisher's exact probability test, the Cochran-Armitage test for trend, and unpaired Student's *t*-tests were performed when appropriate. A p value of < 0.05 was considered significant.

3. Results

The demographics for the cohort are shown in Table 1. The majority of patients (80%) in the cohort had Marfan Syndrome defined by the presence of a disease causing mutation in the gene coding for fibrillin 1 and the presence of a dilated ascending aorta [8]. Fifteen percent of the cohort had Loeys Dietz Syndrome secondary to a TGFBR1 or TGFBR2 mutation, and 1 patient each had a MYLK and an ACTA2 mutation. The mean age at the time of aortic root replacement was 30.7 years (range 10–65). The majority of the cohort, 80%, had undergone elective aortic root replacement, with the remaining members presenting emergently after dissection. Overall, 26 patients (65%) underwent a valve sparing root replacement (David Operation) [9] while the remaining 35% underwent composite replacement of the aortic valve and aortic root (Modified Bentall Procedure) [10].

All 40 of the patients had coronaries re-implanted via the button technique [11]. At the time of the button technique, the opening in the graft was never larger than twice the area of the native coronary artery orifice with a maximal opening of 8 mm in diameter. Early in our series, the coronary anastomoses were reinforced with 4-0 Prolene and a narrow straight Teflon strip. After 2012, our center has preferentially used 5-0 polyproplylene and a thin felt strip for coronary anastomosis reinforcement.

Mean time from surgery to last follow up was 6.2 years (range 6 months to 9 years). The mean time from surgery to first CT or MRI was 5 years. As previously mentioned, 93% of patients had serial images available for comparison with an average of 4.1 years between the studies and a range of 6 months to 10 years.

At time of last follow-up, 26 patients (55%) had developed at least one coronary ostium complication. Table 2 is a summary of the coronary ostium complications identified. The most common coronary artery complication noted was a coronary ostium aneurysm, occurring

Table 2
Coronary artery complications (study cohort comprised of 40 patients).

	N	%
# of patients with coronary complications	22	55%
Coronary artery ostium aneurysm	19	48%
Both coronary ostium aneurysmal	11	
Isolated left coronary ostium aneurysm	7	
Isolated right coronary ostium aneurysm	1	
Coronary artery ostium stenosis	3	7.5
Coronary artery disease	4	10

in 19 (48%) patients. Of the 19 patients with ostium aneurysms, 11 had aneurysmal dilation of both coronary ostium; 7 patients had isolated aneurysmal dilation of the left coronary artery (LCA) ostium; and 1 had isolated aneurysmal dilation of the right coronary artery (RCA) ostium. An additional 3 patients, were found to have coronary ostium narrowing on imaging but none had complete obstruction or narrowing that was > 50% the diameter of the native coronary artery. Importantly, all were asymptomatic without evidence of ischemia based on stress testing. Of note, 4 other patients who had CT scans were also found to have coronary artery disease but no patient had significant stenosis defined as ≥50% narrowing of the lumen. Fig. 2 demonstrates examples of coronary artery complications identified.

Risk factors for the development of coronary ostium aneurysms are shown in Table 3. The most significant risk factor associated with the development of coronary ostium aneurysms was the presence of a mutation (TGFBR1, TGFBR2, ACTA2, MYLK) other than a fibrillin 1 mutation, Patients with coronary ostium aneurysms were also more likely to have undergone emergent surgery following an acute dissection, rather than elective aortic root replacement. Age at surgery, procedure type, coronary reinforcement technique, as well as graft size were all not found to be significant risk factors. Importantly, we did not find length of follow-up following aortic root replacement as a risk factor.

In efforts to determine if there was progression in the coronary artery ostium diameters over time, we then evaluated the 37 patients with serial imaging (Table 4). The mean change for the left coronary artery and the right coronary artery from baseline was small at 16 and 11%, respectively. However there was a wide range for both ranging from 0 to 150% for the LCA, and 0–233% for the RCA. Overall, 11 patients (30%) had a > 30% increase in ostium diameters from baseline.

At last follow-up, 2 patients have undergone elective coronary artery button revision after their coronary ostium diameters increased by 150% and 233% respectively. Both patients had a mutation in the TGFBR2 gene. Importantly, no patient has developed a coronary ostium pseudoaneurysm, rupture, or dissection, and all patients were alive at time of chart review.

4. Discussion

In this study, we demonstrate that coronary ostium aneurysms are common following aortic root replacement in patients with Marfan Syndrome and other genetically confirmed forms of familial aortic aneurysm and dissection syndromes. To our knowledge, very few studies have been published that specifically evaluate the fate of the coronary ostium anastomoses after aortic root replacement. In 2003, Milano and colleagues reported on a series of 71 patients who had undergone aortic

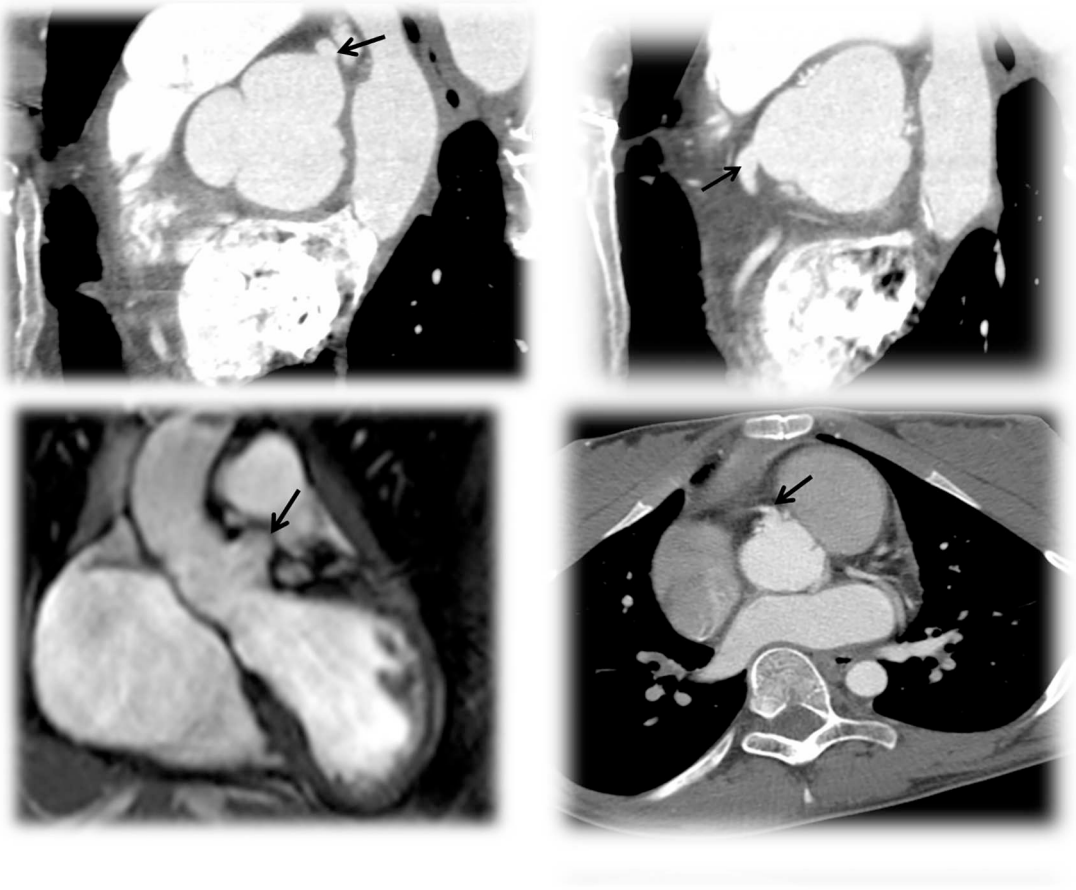

Fig. 2. Examples of coronary artery findings. Left and right upper panels are examples of mild coronary ostium dilation. The left lower panel demonstrates a coronary artery ostium aneurysm. Right lower panel demonstrates an example of coronary ostium stenosis. Coronary artery ostium in each panel are highlighted by black arrow.

Table 3
Risk factors for the development of coronary artery ostium aneurysm.

Risk factor	Coronary ostium aneurysm (N = 19)	No aneurysm (N = 21)	p-Value
% of patients with a non-fibrillin mutation (TGFBR1, TGFBR2, ACTA2, MYLK)	32%	9%	< 0.05
% that had aortic root replacement performed emergently for acute dissection	37%	5%	0.008
Age at aortic root replacement (years)	31.4	30.2	NS
Length of post-operative follow-up (years)	7.3	5.0	NS
% with valve-sparing aortic root replacement	56%	43%	NS
Aortic graft size (mm)	26	27	NS

Table 4
Analysis of patients with serial imaging by CT scan or cardiac MRI (N = 37).

	Variable	Range
Time between studies	4.1 years	0.5–10 years
LCA mean change from baseline	16%	0–150%
RCA mean change from baseline	11%	0–233%
≥30% change of coronary ostium from baseline	11%	
Coronary button revision	5%	
Coronary button rupture/dissection	0%	

root replacement using the modified Bentall Procedure for chronic ascending aortic aneurysm for various aortic root diseases [4]. This study found at a mean follow-up of 4.1 years that only one patient had developed a coronary artery ostium aneurysm and a second patient had developed a coronary button pseudoaneurysm. Interestingly, while Marfan patients represented only 17% of their cohort, both patients who developed a coronary complication in their series had Marfan Syndrome [4]. Tsunekawas and colleagues reported a larger series involving 273 patients operated at their center for a variety of different aortic pathologies, including 93 (34%) Marfan patients [5]. In this series, a variety of different techniques were used to re-implant the coronary arteries, including Bentall's original inclusion technique, the button technique, and a graft interposition technique (Cabrol and Modified Cabrol techniques). At a mean follow-up of 8.8 years, they reported that 6 patients (1.6%) had developed a coronary ostium aneurysm, 4 of which had Marfan Syndrome [5].

Unlike these two previous series, our series included only patients with a genetically confirmed familial thoracic aortic aneurysm and dissection syndrome. In this high risk group, we found a much higher prevalence of coronary ostium aneurysms, with 48% of the cohort having an aneurysm defined as an ostium diameter of > 10 mm. While ostium aneurysmal dilation was noted in the left coronary ostium most commonly (95% of cases), 58% of the patients with ostium aneurysms had dilation of both the left and right coronary ostium. These findings are very similar to the study by Meijboom and colleagues, who reported the fate of the coronary artery ostium in 40 Marfan patients who had underwent aortic root replacement [3]. Similar to our study, they defined a coronary ostium aneurysm as a coronary artery ostium diameter of ≥10 mm. In their study they found coronary ostium aneurysms in 43% of their cohort at a mean follow-up of 5.1 years. Similar to our study, the left coronary ostium was involved most commonly in 59% of their cases, and 41% had dilation involving both coronary ostium.

In our series, we found only two risk factors for coronary ostium aneurysms. Patients with coronary artery ostium aneurysms were more likely to have undergone emergent aortic root replacement following dissection, rather than an elective prophylactic root replacement. Following acute aortic dissection, the aortic wall tissue is highly friable and technical failure during anastomotic construction is a well-known complication [1]. While still rare, early coronary button pseudoaneurysm formation in this setting is well reported [6,7]. As result, finding this as a risk factor for coronary artery ostium dilation was not surprising.

Importantly, our study also demonstrated that the presence of a non-fibrillin genetic mutation was also associated with the presence of coronary artery ostium aneurysm formation. It has been demonstrated in multiple series, that patients with TGFBR1 and TGFBR2 mutations and other forms of familial aortic aneurysm and dissection syndromes have more aggressive disease compared to their Marfan counterparts with likely a higher risk for late complications [2,12,14]. In our series while no patient has developed a coronary artery button pseudoaneurysm, two patients have required coronary button revision, secondary to progressive severe dilation over time. Both of these patients have Loeys Dietz Syndrome. While literature evaluating this association is limited, large centers with growing experience have found similar findings [13]. In the Yale series, of over 500 aortic root replacements, they have encountered only one coronary artery button pseudoaneurysm. Similar to our series, this patient had a pathogenic mutation in the TGFBR2 gene [7].

Our study also provides insight into whether there is progressive coronary artery button dilation over time. In the series by Meijboom and colleagues, they found that coronary ostial aneurysms were more frequently seen in patients who underwent aortic root replacement before 35 years of age, likely serving as a marker of more aggressive disease [3]. Time after operation, however, did not influence the prevalence of coronary ostial aneurysms. As result, the authors concluded that while common, coronary ostium aneurysms were likely not progressive and develop due to perioperative stretch of the native aortic wall used as part of the button technique [3]. In our series, we also did not find length of follow-up as a risk factor for coronary ostium aneurysm formation. Unlike the Meijboom study, however, we had serial imaging available for review in 93% of our cohort. Although the analysis was limited by the variable time interval between serial imaging studies, we feel our results support their conclusion that, in general, while coronary ostium aneurysms are common, the risk for progressive coronary ostium dilation is relatively low. In our series, the mean percent change from baseline for the left and right coronary ostium was only 16 and 11% respectively, with only 30% of the cohort having > 30% increase in diameter from baseline at a mean follow-up of 4.1 years. Certain patients, however, such as those with non-fibrillin mutations, may be at higher risk for progressive dilation overtime, and may require closer surveillance.

In addition to aneurysms, we did demonstrate that a small number of our patients had coronary ostium narrowing (3 patients). Importantly, no patient with narrowing of the ostium had significant obstruction and all had a negative stress test with no evidence of inducible myocardial ischemia. The study by Tsunekawa et al., similarly found that a small number of their patients (1%) had developed coronary ostium narrowing but all these patients too were asymptomatic [5]. The long-term clinical impact of coronary ostium narrowing over time is unknown. In our series, while not a primary goal of this study, we did note the presence of coronary artery disease in 4 patients who had underwent a CT scan. As this patient population ages, the risk of coronary artery disease increases, and the presence of concurrent proximal coronary ostium narrowing and coronary artery disease would be a concern. This is even more concerning, given it remains unclear whether patients following aortic root replacement experience chest pain during episodes of myocardial ischemia given many of these patients may be de-innervated following their aortic root replacement.

5. Limitations

Our paper has several limitations. First, we are a tertiary referral center and as result are subject to referral bias. Most importantly, it is limited by its retrospective design, which covers a long time period with variable intervals between imaging studies as well as variable imaging modalities from patient to patient. This reflects our lack of a universal accepted postoperative surveillance program until 2013. Since 2013, all patients following valve sparing root replacement undergo an echocardiogram prior to discharge and then at 6 months, 12 months, and then annually. In addition, at the 6 month postoperative visit, all patients undergo imaging with cardiac MRI or CT angiography to allow for three-dimensional reconstruction to best evaluate the repair sites and the coronary anastomoses. Repeat imaging with CT or MRI is then performed every 2–3 years.

6. Conclusion

Despite these limitations, we feel that our study confirms that coronary ostium dilation is common following aortic root replacement in patients with genotype positive forms of familial aortic aneurysm and dissection syndrome. While coronary ostium dilation is common, progressive dilation and risk for coronary button rupture and pseudoaneurysm formation, appears to be low. Patients with non-fibrillin 1 mutations appear to be at much higher risk for severe ostium dilation and some may require intervention. Similarly coronary ostial narrowing, while rare, also does occur. Further studies to determine the long-term clinical importance of coronary ostial complications in this patient population are warranted. Until this data is available, long term surveillance, in particular in patients with non-fibrillin1 forms of familial aortic aneurysm and dissection syndrome, should be considered.

Disclosure

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Conflicts of interest

The authors report no relevant disclosures and no conflicts of interest.

Funding

There was no external funding for this project.

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