Aortic Valve-Sparing Surgery in Marfan Syndrome

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ABSTRACT: **Background:** Patients with Marfan syndrome are referred for cardiac surgery due to root aneurysm with or without aortic valve regurgitation. Because these patients are young and frequently present with normal-appearing aortic cusps, valve sparing is often recommended. However, due to the genetic nature of the disease, the durability of such surgery remains uncertain.

Methods: Between February 2004 and June 2012, 100 patients in our department suffering from aortic aneurysm with aortic valve regurgitation underwent elective aortic valve-sparing surgery. Of them, 30 had Marfan syndrome, were significantly younger (30 ± 13 vs. 53 ± 16 years), and had a higher percentage of root aneurysm, compared with ascending aorta aneurysm in their non-Marfan counterparts. We evaluated the safety, durability, clinical and echocardiographic mid-term results of these patients.

Results: While no early deaths were reported in either group, there were a few major early complications in both groups. At follow-up (reaching 8 years with a mean of 34 ± 26 months) there were no late deaths, and few major late complications in the Marfan group. Altogether, 96% and 78% of the patients were in New York Heart Association functional class I-II in the Marfan and non-Marfan groups respectively. None of the Marfan patients needed reoperation on the aortic valve. Freedom from recurrent aortic valve regurgitation › 3+ was 94% in the Marfan patients.

Conclusions: Aortic valve-sparing surgery in Marfan symdrome patients is safe and yields good mid-term clinical outcomes.

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KEY WORDS: Marfan syndrome, aortic valve root aneurysm, aortic valve-sparing surgery (AVS), David procedure

One of the most common inherited disorders of connective tissue is an autosomal dominant condition known as Marfan syndrome, with a reported incidence of 1 in 3000–5000 individuals [1,2]. This syndrome results from mutations in the fibrillin-1 gene on chromosome 15, which encodes for the glycoprotein fibrillin. Fibrillin is a major building block of microfibrils, which serve as substrates for elastin in the aorta, aortic leaflet [3] and other connective tissues [4].

Aortic root disease, leading to aneurysmal dilatation and often aortic regurgitation, affects about 50% of children and 60–80% of adults with Marfan syndrome [5]. If untreated, this disease could lead to life-threatening aortic dissection, rupture, or both [6,7], conditions that are the main causes of morbidity and mortality in Marfan patients [8].

Replacing the aortic valve and root with a composite valve graft has been the mainstay of surgical treatment of aortic root abnormalities since the technique was introduced by Bentall and de Bono [9] in the 1960s and advanced upon later by others [10-12]. Techniques for aortic valve-sparing root replacement were subsequently introduced by Yacoub in 1979 (remodeling) and David in 1988 (re-implantation) [13,14]. These AVS approaches have been generally accepted by the surgical community not only because Marfan syndrome patients are young and frequently present with normal-appearing aortic cusps, but also to avoid the use of anticoagulation. However, due to the genetic nature of the disease, the durability of such surgery remains uncertain, and concern about potential deterioration of the preserved aortic valve leaflets has created controversy regarding the durability of AVS reconstructions in patients with Marfan syndrome [15-17].

We reviewed our mid-term results with AVS surgery in Marfan and non-Marfan syndrome patients in order to evaluate its safety and durability.

PATIENTS AND METHODS

We conducted a retrospective study that included 100 patients who underwent elective AVS surgery in the cardiac surgery department of Sheba Medical Center during the period February 2004 to June 2012. All 100 patients suffered from aortic aneurysm with aortic regurgitation; 30 of them had Marfan syndrome. Table 1 shows patients' demographic and clinical data obtained at presentation. Marfan patients were significantly younger (33 ± 13 vs. 56 ± 16 years) and had a higher percentage of root aneurysm, compared with ascending aorta aneurysm in the non-Marfan group of patients.

At follow-up, infectious, thromboembolic and bleeding complications were recorded, as recommended by the guidelines of the American Association for Thoracic Surgery and the Society of Thoracic Surgeons. All patients underwent echocardiography during the follow-up period.

AVS = aortic valve-sparing

Table 1. Characteristics of patients with and without Marfan syndrome

	Non-Marfan (n = 70)	Marfan (n =30)	*P* value
Age (yr) mean ± SD (range)	53 ± 16 (17–81)	30 ± 13 (10–58)	0.000
Male gender	54 (77%)	21 (70%)	0.460
Hypertension	31 (44%)	6 (20%)	0.025
Hyperlipidemia	17 (24%)	2 (7%)	0.051
Diabetes	3 (4%)	1 (3%)	1.000
Recent cerebrovascular accident	0 (0%)	0 (0%)	–
Chronic obstructive lung disease	2 (3%)	1 (3%)	1.000
Pulmonary hypertension	33 ± 8	33 ± 7	0.266
Mitral valve disease (mild+)	19 (28%)	14 (48%)	0.073
NYHA class I II III IV	1.5 ± 0.6 43 (62%) 21 (30%) 6 (8%) 0 (0%)	1.3 ± 0.5 21 (70%) 9 (30%) 0 (0%) 0 (0%)	0.264 0.393 0.393 0.393 0.393
Left ventricular ejection fraction (%)	57 ± 6	57 ± 9	0.854
Aortic regurgitation None/trivial Mild Moderate Severe	2.25 ± 0.9 14 (21%) 31 (44%) 19 (27%) 6 (8%)	2.3 ± 1.0 9 (29%) 7 (25%) 11 (36%) 3 (10%)	0.799 0.444 0.444 0.444 0.444
Ascending aortic dimensions (mm)	5.1 ± 0.8	3.9 ± 1.0	0.000
Sinuses of Valsalva (median)	4.2 ± 0.8	4.9 ± 0.7	0.004

Data are presented as number and percentage of patients unless otherwise specified

SD = standard deviation, NYHA = New York Heart Association

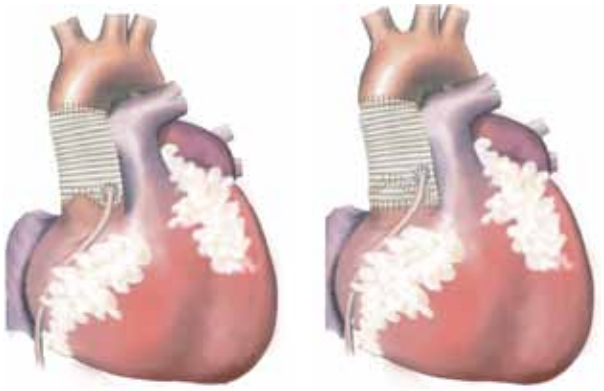
SURGICAL TECHNIQUE

Surgery was performed through standard median sternotomy in all patients. The re-implantation (David I) technique, used in 26 of the Marfan patients (87%), was the most common procedure [Figure 1]. Only one of the Marfan patients underwent surgical remodeling (Yacoub) [19]. In the non-Marfan patients, 16 (23%) underwent the re-implantation (David I) technique and 10 (14%) underwent surgical remodeling (Yacoub). Either direct cusp aortic valve repair or shortening of the cusp-free margin was performed in 20 (29%) of the non-Marfan patients. Only 1 patient (3%) needed aortic valve repair in the Marfan group. The rest of the non-Marfan and Marfan patients – 24 (34%) and 2 (7%) respectively – underwent replacement of the ascending aorta with tube graft from the sinotubular junction. Three Marfan patients (10%) underwent concomitant mitral valve repair and two procedures (7%) were redo operations.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS for Windows (Version 19.0). Categorical variables were expressed as percentages and continuous variables as mean and standard deviation. Categorical variables were compared using Fisher's exact test or the chi-square test and continuous variables were compared using the Student *t*-test for independent variables. The value of significance for analysis was set at 0.05 (two-sided). Kaplan-Meier analysis was used for the evaluation of time-related variables, and the log-rank test was applied.

Figure 1. A schematic drawing of the two root procedures used. The remodeling procedure (left) primarily restores sinus configuration and sinotubular junction. Re-implantation of the valve within a vascular graft (right) additionally corrects dilatation of the aorto-ventricular junction



RESULTS

EARLY OUTCOMES

There were no early deaths in either group. One of the Marfan syndrome patients needed re-exploration of the mediastinum for a suspicion of bleeding that was refuted. There was no perioperative myocardial infarction, infection, or reoperations in the Marfan group. There was one transient ischemic stroke (3%) (in a patient who underwent concomitant mitral valve repair), without residual neurologic deficit. One patient from the Marfan group (3%) developed a heart block that necessitated implantation of a permanent pacemaker. The length of hospital stay was 6.8 ± 6.2 days (range 4–38 days) in the Marfan group.

LATE OUTCOMES

Mean follow-up was 32 ± 30 months (1–94 months) for patients with Marfan syndrome, and 35 ± 25 months (1–86 months) for non-Marfan patients. None of the patients were lost to follow-up, and none died during the follow-up period. There were few major late postoperative complications. One (3%) of the Marfan patients had a transient ischemic stroke without residual neurologic deficits. Five (17%) of the Marfan patients had arrhythmias, 1 (3%) of whom underwent permanent pacemaker implantation. None of the patients needed reoperation on the aortic valve. One patient underwent

Figure 2. Grade of aortic insufficiency preoperatively and at last visit in patients with Marfan syndrome undergoing AVS surgery. Percent of patients is given

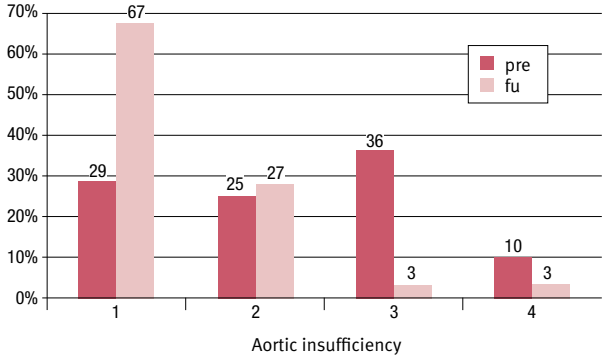
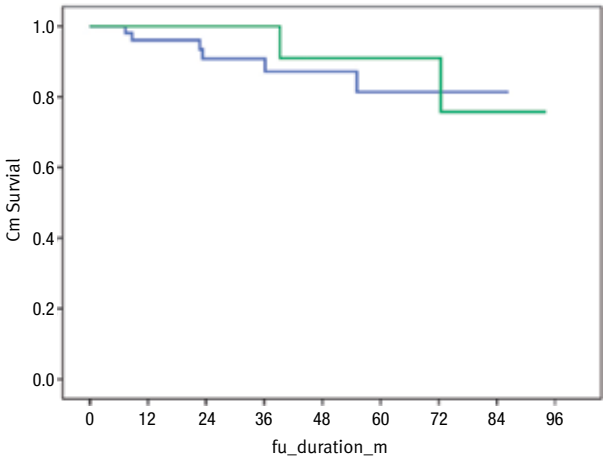


Figure 3. Results of freedom from grade 3 or more aortic insufficiency according to the most recent Doppler echocardiography during follow-up



implantation of a descending aorta stent-graft due to subacute type B aortic dissection and was alive at the end of the follow-up period. Altogether, 96% and 78% of the patients were in New York Heart Association functional class I-II in the Marfan and non-Marfan groups respectively.

Figure 2 summarizes the results of the preoperative and most recent Doppler echocardiographic study in Marfan patients who underwent AVS surgery. At the last visit 20 patients (67%) showed none or trivial aortic insufficiency; in 8 (27%) it was mild, in 1 (3%) it was moderate, and in 1 patient (3%) it was severe. This patient is still asymptomatic and opposes re-operation.

DISCUSSION

In this study we analyzed our experience with AVS surgery in patients with Marfan syndrome who presented to surgery electively. Early results showed that the procedure is safe and provides good clinical and echocardiographic results. These early results compare well with other recent series [18-21].

The gold standard for this type of pathology used to be composite replacement of the aortic root and aortic valve with mechanical conduit. Since most Marfan patients present for surgery at a young age, AVS surgery was developed to avoid mechanical prostheses and the complications related to life-long use of anticoagulation. Our mid-term results showed a very low rate of valve-related complications. No late thrombo-embolic and bleeding complications were observed in patients with aortic valve re-implantation, unlike patients with mechanical aortic valves. This supports the objective of avoiding implantation of aortic valve prostheses. Our results are in accord with those previously published by Yacoub and collaborators [22], who described excellent long-term results with valve-sparing procedures in 68 patients with Marfan syndrome, and with recent results published by Settepani et al. [18] and David et al. [19]. Recently, Kallenbach and team [20] published their mid-term results comparing aortic valve re-implantation and composite grafting of the aortic valve and ascending aorta with mechanical valve conduits. Their study results support our findings with regard to early and mid-term postoperative mortality and the incidence of late reoperations. Ongoing, prospective international registry studies comparing early outcomes following valve-sparing and valve-replacing techniques in Marfan patients have shown similar results to those of Kallenbach et al. [20].

The most important adverse effect of valve repair remains valve failure. As mentioned previously, the mean grade of aortic insufficiency improved from 2.3 before to 1.4 post-surgery. At our mid-term follow-up it seemed that once initial repair was satisfactory, there was a modest deterioration of valve function [Figure 3]. It remains to be determined to what extent the structural fibrillin-1 defect can affect stability and durability of the cusps after valve re-implantation in the long-term.

Of note, the Yacoub remodeling technique was used in only one of the AVS surgery patients in the current series. Birks et al. [23] endorsed the remodeling procedure in a retrospective analysis of 82 Marfan patients in 1999. However, their results were marred by relatively high rates of reoperation and aortic regurgitation within 5 to 10 years. Since that time, several groups have expressed concerns that remodeling carries a higher risk for complications (including operative bleeding, progressive annular dilatation, and aortic regurgitation) than the re-implantation technique [16,24,25].

CONCLUSIONS

The analysis of mid-term outcomes with Marfan patients who underwent elective AVS surgery revealed that this procedure is safe and yields good mid-term clinical outcomes, with the added benefit that long-term anticoagulation is not required.

Nevertheless, only true long-term results will be able to clarify the undeniable benefit of AVS surgery in these patients.

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Capsule

De novo mutations in histone-modifying genes in congenital heart disease

Congenital heart disease (CHD) is the most frequent birth defect, affecting 0.8% of live births. Many cases occur sporadically and impair reproductive fitness, suggesting a role for de novo mutations. Zaidi et al. compare the incidence of de novo mutations in 362 severe CHD cases and 264 controls by analyzing exome sequencing of parent-offspring trios. CHD cases show a significant excess of protein-altering de novo mutations in genes expressed in the developing heart, with an odds ratio of 7.5 for damaging (premature termination, frameshift, splice site) mutations. Similar odds ratios are seen across the main classes of severe CHD. The authors find a marked excess of de novo mutations in genes involved in the production, removal or reading of histone 3 lysine 4 (H3K4) methylation, or ubiquitination of H2BK120, which is required for H3K4 methylation. There are also two de novo mutations in *SMAD2*, which regulates H3K27 methylation in the embryonic left-right organizer. The combination of both activating (H3K4 methylation) and inactivating (H3K27 methylation) chromatin marks characterizes 'poised' promoters and enhancers, which regulate expression of key developmental genes. These findings implicate de novo point mutations in several hundreds of genes that collectively contribute to approximately 10% of severe CHD.

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Eitan Israeli

"The world's history is constant, like the laws of nature, and simple, like the souls of men. The same conditions continually produce the same results"

Friedrich von Schiller (1759–1805), German poet, philosopher, historian and playwright