Editorial

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Journal of Vascular and Endovascular Surgery
ISSN 2573-4482

2016
Vol. 1 No. 4: 26

DOI: 10.21767/2573-4482.100026

Long-Term Follow-Up Experience on the Aortic Root Surgery in Patients Affected by Marfan syndrome

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Received: October 05, 2016; **Accepted:** October 15, 2016; **Published:** October 20, 2016

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Citation: Nardi P, Saitto G, Ruvolo G. Long-Term Follow-Up Experience on the Aortic Root Surgery in Patients Affected by Marfan syndrome. J Vasc Endovasc Surg. 2016, 1:4.

Background

Marfan syndrome (MFS) is a connective-tissue disorder with dominant autosomal inheritance and a prevalence of around 1/5000 people, mostly caused by mutations in the gene encoding fibrillin-1 [1], characterized by systemic manifestations involving ocular, skeletal, pulmonary and cardiovascular organ systems [2-5]. Prophylactic surgery on the aortic root has been recognised as the most important life-prolonging treatment in patients affected by MFS [6-8], because of the high risk of aortic rupture and/or acute type an aortic dissection [8-10]. Two surgical techniques are now available: aortic root replacement (ARR) with a valved conduit [11], and valve sparing root replacement (VSRR) [12-13]. ARR with a mechanical prosthesis is a safe, low risk and reproducible procedure in these patients, but may lead to thromboembolic and bleeding events due to the anticoagulation therapy [7]. VSRR procedures offer freedom from anticoagulation, but potential deterioration of the preserved aortic valve leaflets has created controversy regarding the durability of valve-sparing procedures in MFS [14-16], with a reported reoperation rate of 1.3% per year [17-18].

Our Clinical Experience

One-hundred and fifty patients affected by Marfan syndrome have been followed at the Marfan Center of the Tor Vergata Policlinic University of Rome. Fifty-nine patients underwent aortic root surgery: aortic root replacement according to modified Bentall-De Bono technique was performed in 30 patients (Bentall Group), whereas aortic root replacement with the re-implantation technique according to David type I operation was performed in 29 patients (David Group). The other 8 patients underwent supracoronary replacement of the ascending aorta (n=3), aortic root remodelling according to the Yacoub procedure (n=2), and mitral valve surgery (3) for mitral regurgitation (1 mitral valve replacement with a mechanical prosthesis, 2 mitral valve repairs). The diagnosis of MFS was made according to the Revised Ghent Criteria published in 2010 [5], and it was confirmed by a multidisciplinary team at our Marfan Center. In a recent series published by our Institution, we have described how these patients are managed at Marfan Center [19]. Transthoracic echocardiography and computed tomography scan or, less frequently, magnetic resonance was performed in elective cases in all patients, while coronary angiography was performed in men over 35 years old and in postmenopausal women. In the setting of a type an acute aortic dissection detected at computed tomography and intraoperative transesophageal echocardiography, surgery was immediately performed without further diagnostic procedures. Our policy was to perform elective aortic root surgery in presence of an aortic root diameter over 45 mm, or in presence of a progressive dilatation of more than 5 mm per year. Type of surgical technique for the replacement of the aortic root repair was dependent on the patient's clinical situation and surgeon and patient preference. On the base of surgical choice, David type I aortic valve re-implantation technique was performed if at the preoperative echocardiography and at the intraoperative inspection aortic leaflets were undamaged and free from sclerosis or calcification; on the contrary, Bentall operation was performed in presence of a moderate or severe aortic valve regurgitation due to a primary disease of the valve and/or depending on the presence of aortic cusps retraction. Since 2001, we have preferred for MFS patients the re-implantation technique over the Yacoub remodelling technique because of the advantage of improved annular stabilization.

In-Hospital Results

Out of One-Hundred and fifty MFS patients followed at our Marfan Center since 2008, 67 (45%) patients underwent surgery. Thirty patients underwent Bentall operation (Bentall Group), 29 underwent David operation (David Group); other surgical procedures were performed in the other patients. Mean patient age of the entire population, 36 men and 31 women, was 35 ± 12 years (range 12 to 62 years). Thirty-nine of 67 patients (58%) were in New York Heart Association (NYHA) class I, twenty-four (36%) in class II, three (4%) in class III and one (2%) in class IV. Fifty-nine patients (88%) underwent elective surgery, while eight patients (12%) needed for emergent surgery.

Focalizing the analysis on the Bentall Group (n=30) and David Group (n=29), mean patient age was 35 ± 12 years (range, 12 to 62 years). As compared with the David Group, in the Bentall Group a depressed left ventricle ejection fraction expressed as value less than 45% was more frequent (P<0.0001), left ventricle end-diastolic (LVEDD) and end-systolic (LVESD) diameters, aortic root and ascending aorta diameters were greater (P=0.01, P=0.006, P=0.002 and P=0.009, respectively). Most importantly, Bentall Group in comparison with David Group showed a higher rate of concomitant moderate-to-severe aortic regurgitation (AR) (P<0.0001).

No operative mortality was recorded. David Group has shown longer CPB and cardiac ischemic times (P=0.02 and P=0.05, respectively). A higher rate of concomitant coronary artery bypass grafting (CABG) was observed in the Bentall Group (17% vs. 7%), but this difference was not statistically significant.

Five patients (2%) required mediastinum re-exploration for bleeding. Postoperative in-hospital stay was of 6 ± 2 days in David Group vs. 11 ± 6 days in Bentall Group (P=0.001). Echocardiography performed at discharge showed in the David Group a persistent AR ≥ 2+ in 2 cases (7%).

Follow-up Results

All patients are followed at our Marfan Center, with a clinic and an echocardiographic evaluation every six months, before and after surgery. All patients with prosthetic valves were maintained on a regimen of oral warfarin sodium. All the patients were maintained on β-adrenergic-blocking agents or on angiotensin-II receptor-1 blockers after surgery.

No patient was lost at follow-up. Median and mean duration of the follow-up was 72 months and 97 ± 82 months (range from 1 to 369), respectively.

There were 2 late deaths in the general population operated on, with an overall 10- and 20-year survival rate of 94±4%, for both intervals. At 20-years (mean follow-up 97 ± 82, range 1-369 months), no prosthesis-related major bleeding or thromboembolic events were observed; 20 year survival was 94 ± 6% in Bentall Group and 100% in David Group, respectively (P=0.32), freedom from re-intervention for aortic valve dysfunction was 100% in the Bentall Group and 75 ± 13% in the David Group (P=0.04). In particular, the difference became significantly relevant after the first 8-year period of follow-up. Freedom from all-cause death, myocardial infarction, stroke, prosthetic valve-related complications, re-intervention on any aortic segment was 69 ± 12% in Bentall Group and 67 ± 14% in David Group (P=NS).

Four patients in the David Group underwent reoperation on the aortic root for failure of the surgical technique, while other 2 patients developed severe aortic insufficiency secondary to endocarditis from *Staphylococcus aureus* 129 and 98 months after aortic valve re-implantation, respectively. Both of them underwent aortic valve replacement with a mechanical prosthesis valve.

Echocardiographic Data at Follow-up

Two patients in David Group had an aortic regurgitation grade ≥ 2+ at the last follow-up. In the Bentall Group, as compared to preoperative values, LVEF (56 ± 6% vs. 52 ± 8%, P=0.03), LVEDD (56 ± 7 mm vs. 61.5 ± 12 mm, P=0.04), and LVESD (35 ± 6 mm vs. 42 ± 12 mm, P=0.01) significantly improved.

Comments

In MFS patients the best surgical technique to be adopted remains still controversial, especially related to the younger age of the MFS population. The re-implantation technique should reasonably be preferred in MFS patients because of native aortic valve preservation, avoiding potential thromboembolic or bleeding events related to the need for anticoagulation therapy. Moreover, avoiding warfarin therapy is advisable in young women whishing a pregnancy. Although some surgeons believe that MFS itself is not a risk factor of aortic valve-sparing procedure failure [23], a recent study [20] Coselli and Co-workers reported that following aortic valve-sparing procedures 7% of MFS patients were affected by a residual aortic valve insufficiency more than mild at 1 year after surgery, showing a worse outcome of these patients in comparison with non-MFS patient population (0%,) (P=0.02). In fact, MFS patients have a weakness of the aortic valve leaflets that is usually uncommon in other patients presenting with aortic root aneurysms. Fleischer *et al.* found immunohistochemical abnormalities of fibrillin in aortic valves of MFS patients and concluded that the widespread use of aortic valve-sparing repair procedures in patients affected by MFS in light of these findings should be carefully re-examined [21].

Our policy consisted on an aggressive surgical approach, performing elective aortic root surgery in presence of an aortic root diameter ≥ 45 mm, or in presence of a progressive dilatation of the aortic root of more than 5 mm per year. The early indication took also account of previously reported findings showing an increased risk of type an acute aortic dissection in MFS patients in presence of an aortic root diameter less than 50 mm [7]. Jondeau and Co-workers recommended surgical treatment of the aortic root in MFS population when the diameter reaches 50 mm; however, they reported also a 0.3% per-year risk of aortic rupture and/or dissection at aortic root diameters less than 50 mm [22].

No operative mortality was recorded in our series; other Authors reported an overall 30-day mortality between 0% and 2% [6,23,24]; a longer extracorporeal circulation and aortic cross-clamp times required for David valve-sparing procedure did not increase the risk.

No statistically significant differences were found in our series between the overall 15-year survival rates in the two Groups (100% in David Group and 94 ± 6% in Bentall Group, respectively). In Bentall Group there was only a late death in a patient that had previously undergone two cardiac surgery procedures. Cameron et al. found an overall survival of 75.6% at 20 years among 372 patients with previous ARR; this difference could be related to the high percentage of patients with type A AAD in this work [6].

Freedom from MACCE was similar in the two Groups. The risk of thromboembolic and bleeding events due to oral anticoagulation following ARR with a mechanical valve is still a challenge, with a reported rate of 0.7-24%; aortic-valve sparing procedure seems an attractive option to avoid the risk related with anticoagulation therapy. In the largest series of MFS patients to date, Cameron et al. reported that thromboembolism was the most common late complication after Bentall operation with a freedom from thromboembolic events of 89.8% at 20 years [6]. As also previously reported, in a mid-term period of follow-up in our series we did not recorded prosthetic-related major bleeding or thromboembolic events [25]. This could be likely related to the younger age of the MFS population, which has a good compliance to the anticoagulation therapy and to the close clinical follow-up of MFS patients after surgery at our Marfan Center. Moreover, the rate of thromboembolism after Bentall operation with mechanical valved conduit is generally better than that reported for isolated aortic valve replacement with a mechanical valve, perhaps because no suture knots are left inside the prosthetic valve conduit when Bentall procedure is performed.

In our experience, both the surgical techniques are good options for MFS patients. In particular, David procedure seems to be a viable and good option for the first 8-10 years after surgery in MFS patients, especially it could be an attractive approach for young women whishing a pregnancy; anyway, recurrence of aortic regurgitation after this period could occur, maybe related to a primitive and progressive degeneration of the aortic leaflets not observed at the first operation. In fact, in our previous study we have observed at 8 years of follow-up a 91% freedom from reoperation for the David re-implantation [25]. Therefore, we suggest Bentall operation should be preferred to David re-implantation in MFS patients: low in-hospital mortality and morbidity, the very satisfactory long-term results make this operation as the best surgical treatment in MFS patients. A close attention at follow-up in a Marfan Center may probably reduce the complications related to the anticoagulation therapy and can sometimes prevent any emergency situation in this category of patients.

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