SURGICAL MANAGEMENT OF TYPE A ACUTE AORTIC DISSECTION IN PATIENTS WITH MARFAN SYNDROME: A SINGLE CENTER EXPERIENCE

O. Stiru1*, E. V. Gorduza2, F. L. Dorobantu1, C. A. Parasca1, O. Chioncel1, S. I. Bubenek Turconi1, D. Filipescu1, V. A. Iliescu1

1. Emergency Institute for Cardiovascular Diseases „Prof dr. C. C. Iliescu” Bucharest University of Medicine and Pharmacy” Grigore T. Popa”-Iasi, Faculty of Medicine
2. Department of Mother and Child Medicine
*Corresponding author. E-mail: ovidiu_stiru@yahoo.com

SURGICAL MANAGEMENT OF TYPE A ACUTE AORTIC DISSECTION IN PATIENTS WITH MARFAN SYNDROME: A SINGLE CENTER EXPERIENCE (Abstract)

Introduction Acute aortic dissection is the most common cause of death in patients with Marfan syndrome and untreated aortic root enlargement. Emergency surgery for replacement of the ascending aorta has the potential of life saving procedure, but is associated with high morbidity and mortality. Long-term outcomes after surgical repair of acute aortic dissection type A in patients with Marfan syndrome are limited. Material and methods: We made a retrospective study concerning emergency surgical intervention for acute aortic dissection type A, by Bentall procedure, performed in Emergency Institute for Cardiovascular Diseases „Prof dr. C. C. Iliescu” Bucharest between January 2005 and July 2014. We included 332 patients with type a acute aortic dissection divided into two groups: group A - 16 patients with Marfan syndrome and group B - 316 patients with other etiologies. We analyzed differences between these two groups regarding perioperative characteristics, surgical technique and short and long-term morbidity and mortality. Results: The patients from group A were significantly younger than those in group B (35.1±12.7 years vs. 56.8±7.1 years; p<0.001). Arterial hypertension was three times more common in group B as compared to group A (p<0.001). The incidence of postoperative morbidity, and intraoperative and 30-days mortality death rates were similar between groups, but overall mortality at 10 years was lower in group A (31.3%) vs. group B (44.9 %). Conclusions: Emergency surgical in Marfan syndrome, by Bentall procedure could improve perioperative morbidity and mortality of patients with acute aortic dissection, but need an early diagnosis, proper medical therapy and imagistic surveillance. Keywords: MARFAN SYNDROME, TYPE A ACUTE AORTIC DISSECTION, BENTALL PROCEDURE.

The aortic disease is a severe disorder with bad prognosis. This term encompasses a lot of different of conditions like aneurysm, dissection, atherosclerosis and a general stiffening of elasticity associated with ageing. The etiology is complex and include injury, arterial hypertension, bicuspid aortic valve or genetic disorders like Marfan syn-
drome (MS), Ehler–Danlos syndrome, osteogenesis imperfecta, or Turner syndrome. The aorta has a high degree of elasticity, necessary for the propulsion of blood in the systemic circulation. This feature is allowed by connective fibers, where the major components are elastin and collagen. Any alteration of quantity and/or architecture of these fibers induces mechanical changes that generate aortic disease.

The Marfan syndrome is a disease of connective tissue. It presents an autosomal dominant inheritance and affects 1/5,000 individuals. The majority of cases presents a FBN1 gene mutation. Other mutations (around 10% of cases) concern TGFbR1/2, COL3A1 or ACTA2 genes. The diagnostic evaluation for MS is difficult due to the phenotypic variability, different age depending manifestations, the absence of well-established criteria, and a difficult differential diagnosis. The diagnostic criteria improve the clinical early diagnosis, but accuracy is also important to diminish the deleterious and irreversible consequences of diagnosis errors. The main clinical signs interest ocular, cardiovascular and skeletal systems, but also could be discovered changes in skin, lung or dura. The diagnosis of MS is based on so called Ghent criteria, established in 1991. The revisited Ghent criteria help the clinician in diagnosis of MS. Thus, when is identified a single case in a family, the diagnosis of MS could be established if is present one of the following associations: dilatation of aortic root (Z=2) and ectopia lens; dilatation of aortic root (Z=2) and FBN1 gene mutation; dilatation of aortic root (Z=2) and a clinical score more than 7 or ectopia lens and pathogenic FBN1 gene mutation for dilatation of aortic root. Where the diseases are present in other members of the same family, the diagnosis of MS is sustained by the association between familial history of MS and ectopia lens, dilatation of aortic root (Z=2) or clinical score more than 7. Excepting the dilatation of aortic root and ectopia lens the clinical score contains elements of skeletal, cardiovascular, ocular or skin. The main component of clinical score are: wrist and thumb sign, pectus carinatum, hindfoot deformity, pneumothorax, dural ectasia, and protrusio aceta-buli.

The FBN1 gene is located 15q21 and comprises 65 coding and 3 alternatively spliced exons. It encodes a glycoprotein - fibrillin-1 - with a molecular weight of 350 kD. Fibrillin-1 is a major component of the extracellular micro fibrils, which are connected to extracellular matrix to form sheaths around elastic fibers (Bonetti, 2009). Fibrillin-1 present three types of domains: an epidermal growth factor (EGF) like motif (many of these have a highly conserved calcium-binding sequence (cbEGF)), a latent transforming growth factor beta (TGF-β) binding protein motif and a fusion module. The main type of mutation (>2/3) is a missense mutation that affects the cbEGF modules, but also were described frameshift, splice site and nonsense mutations [Turner et al., 2009]. Except the mutations that concern exons 24–32 usually associated with a severe phenotype (“neonatal Marfan syndrome”) it is impossible to establish a genotype-phenotype correlation in MS.

The major cause of death in MS is acute aortic dissection (1). Without surgical treatment, this condition leads to death in more than 95% cases. Despite advances in surgical technique, the early mortality remains high. Treatment of patients with type A acute aortic dissection and Marfan syndrome is an emergency lifesaving proce-
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dure (2). In a type A aortic dissection, simple replacement of ascending aorta is usually the best option, but when Marfan syndrome is the underlying cause of dissection, this option is not feasible because of important aortic root dilatation (3, 4). Under these circumstances, replacement of the ascending aorta and the entire aortic root represents the adequate surgical treatment (5). This study aimed to identify differences between perioperative characteristics, surgical technique and early and late mortality and morbidity in a group of patients operated for acute aortic dissection with and without Marfan syndrome.

MATERIAL AND METHODS

Patients cohorts

We made a retrospective study on a cohort of 332 patients underwent an emergency surgical intervention for acute aortic dissection type A. This surgical procedure was applied in Emergency Institute for Cardiovascular Diseases “Prof dr. C. C. Iliescu” from Bucharest, between January 2005 and July 2014. We excluded all patients with type B acute aortic dissection and those with type A acute aortic dissection complicated with mesenteric ischemia. The 332 patients were divided into two groups: group A including 16 patients with Marfan syndrome and Group B including the remaining 316 patients with acute aortic dissection by other etiology. We analyzed demographic data and perioperative features of the patients from available patients’ medical records. Information regarding long-term survival was obtained from the National Institute of Statistics/The Register of Persons Records.

Surgery procedures

All patients were evaluated before surgery by transthoracic and transesophageal echocardiography, in order to identify the location of intimal tears and the extension of the dissection.

The surgical strategy implied resection and replacement of the dilated segment (aortic root, ascending aorta or aortic arch) with a prosthetic graft, and exclusion of access intimal tear. Surgery was performed via standard median sternotomy with total cardiopulmonary bypass (CBP). Depending of the integrity of the peripheral vessels, cannulation is initiated via right axillary artery or right femoral artery for arterial access and right atrium for venous return. A vent was placed in the left ventricle via the right superior pulmonary vein. Myocardial protection with cold blood cardioplegia was initiated through retrograde route after cross clamping the ascending aorta. Completion of cardioplegia is achieved after transverse aortotomy at the level of ascending aorta and administration of the remaining dose of cold blood cardioplegia via direct cannulation of both coronary ostia. Inspection of the ascending aorta and the aortic valve was performed, together with the resection of the segment including the proximal entry tear, followed by repair or replacement of the aortic valve, as needed. After reaching a mean temperature of 25-28°C, during circulatory arrest the aortic clamp was removed and the entire aortic arch was examined and replaced whenever an aortic arch tear has been identified. The distal anastomosis with prosthetic collagen impregnated low porosity graft was then completed under circulatory arrest with anterograde selective cerebral perfusion. Teflon strips and sometimes biological glue were used to reinforce the distal suture lines. After completion of the distal anastomosis, the prosthetic graft and the great vessels are de-aired, and extracorporeal circulation is restarted after a cross clamp is placed on the prosthetic graft. Finally, in
the supracommissural aortic repair the proximal anastomosis is performed in a similar fashion using Teflon strips and biological glue. In the Bentall procedure we use a premanufactured conduit with Valsalva sinuses and a mechanical valve, each coronary button was sutured with Prolene 6.0 to the Valsalva part of the premanufactured conduit. Eight surgeons performed the operations throughout this period, using a similar perioperative and surgical strategy according to current available guidelines and hospital’s established protocols.

**Bentall procedure**

As the abnormalities found in patients with Marfan syndrome often compel to replacement of the ascending aorta and the aortic valve with a composite prosthesis containing a mechanical or bio prosthetic cardiac valve enclosed in a tubular polyester graft, operation referred to as the Bentall procedure. The patient is placed on cardiopulmonary bypass using a single venous two-stage cannula, with the arterial cannula in the femoral artery. The ascending aorta is clamped, retrograde cardioplegic solution is administered in the coronary sinus and a vent catheter is placed through the right superior pulmonary vein to the left atrium and left ventricle. The ascending aorta is clamped, retrograde cardioplegic solution is administered in the coronary sinus and a vent catheter is placed through the right superior pulmonary vein to the left atrium and left ventricle. The ascending aorta aneurysm is opened via a vertical incision. Traction stitches are placed above each aortic valve commissure to expose the aortic root and the aortic valve is excised. The coronary arteries are mobilized with buttons of sinus aorta and the remaining sinus aorta is removed. After calibration of aortic annulus, the composite prosthesis is sewn to the aortic annulus using mattress stitches of 2-0 braided polyester with PTFE felt pledges, starting from the right coronary sinus. Reimplantation of the coronary arteries requires direct anastomosis of the coronary ostia to the graft, but it can also involve a bypass graft or a polyester extension depending on the position of the ostia in relation to the aneurysm or dissection. The right coronary anastomosis is performed after completing the left coronary anastomosis, with deep bites into the aorta using continuous stitches of 6-0. The distal end of the graft is then shortened to allow a direct end-to-end anastomosis.

**Statistical methods**

Continuous variables are presented as mean ± standard deviation and compared using the Student t-test. Discrete variables were expressed as counts and percentages and comparisons between groups were done with the \( \chi^2 \) or Fisher’s exact test, when appropriate. Five-year survival rates were estimated using Kaplan-Meier analysis and comparisons between groups were performed with the log-rank test. A two-sided P-value of 0.05 was considered significant for all tests. All analyses were conducted using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA).

**RESULTS**

Preoperative data are presented in Table 1. Only two statistical significant differences were discovered: patients with Marfan syndrome were significantly younger than patients of group B (35.1±12.7 vs. 56.8±7.1 years; p<0.001) and arterial hypertension was more common among patients’ form group B (79.7% in group B vs. 25% in group A; p<0.001).

The operative data are reported in Table 2. These data showed only two significant differences. In Marfan syndrome group the replacement of aortic root and first portion of ascending aorta was more frequent applied (81.3% vs. 33.2%, p<0.001). Similar
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value concerned the replacement of aortic root and entire ascending aorta more fre-
quently applied in Marfan syndrome (56.3% vs. 18.4%, p=0.001).

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Preoperative characteristics</th>
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<tbody>
<tr>
<td><strong>Group A (n=16)</strong></td>
<td><strong>Group B (n=316)</strong></td>
</tr>
<tr>
<td>Gender (female)</td>
<td>37.5% (6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.1±12.7</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>25% (4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0% (0)</td>
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<tr>
<td>Renal impairment</td>
<td>18.8% (3)</td>
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<table>
<thead>
<tr>
<th>TABLE II</th>
<th>Operative data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A (n=16)</strong></td>
<td><strong>Group B (n=316)</strong></td>
</tr>
<tr>
<td>Arterial cannulation sites</td>
<td></td>
</tr>
<tr>
<td>Axillary artery</td>
<td>56.3% (9)</td>
</tr>
<tr>
<td>Ascending Aorta</td>
<td>12.5% (2)</td>
</tr>
<tr>
<td>Femoral artery</td>
<td>25.0% (4)</td>
</tr>
<tr>
<td>Axillary and Femoral artery</td>
<td>0% (0)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>253.3±81.1</td>
</tr>
<tr>
<td>Cross clamp (time)</td>
<td>168.0±54.8</td>
</tr>
<tr>
<td>Cerebral perfusion (%)</td>
<td>33.3 % (5)</td>
</tr>
<tr>
<td>Circulatory arrest (min)</td>
<td>20.3±26.0</td>
</tr>
<tr>
<td>Temperature Circulatory arrest (ºC)</td>
<td>24.4±5.4</td>
</tr>
<tr>
<td>Aortic segment replaced</td>
<td></td>
</tr>
<tr>
<td>Aortic root and first portion of ascending aorta</td>
<td>81.3% (13)</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>6.3% (1)</td>
</tr>
<tr>
<td>Aortic root and entire ascending aorta</td>
<td>56.3% (9)</td>
</tr>
</tbody>
</table>

*CPB – cardio-pulmonary bypass.

All patients with Marfan syndrome had aortic insufficiency at the time of diagnosis, and the majority of them had grade 4 aortic regurgitation (11/16 patients). The Bentall modified operation (BMO) was performed in 11 patients, while in the rest cases were applied other type of surgical interventions.

Postoperative characteristics were evaluated but we did not found any significant differences between groups concerning mechanical ventilation time (106.6±252.5 hours in group A vs. 211.4±397 hours in group B, p=0.15) or length of stay in the intensive care unit (8.9±15.6 days in group A as compared to 13.8±19.5 in group B; p=0.25).

Follow-up was 100% complete as data were received from the National Institute of Statistics / the Register of Persons Rec-
The mean follow-up of the study was 4 years (standard error ±2.76 years, min 1 day, max 10.2 years, and median 3.8 years) with x patients at the end of the study. Intraoperative death rate was similar in both groups without statistical significance (12.5% in group A vs. 6.0% in group B; p=0.27). The incidence of postoperative morbidity was not significantly different between the two groups, with the main incidents being: stroke, mediastinitis, and multisystem organ failure in both group. The only major difference was the acute kidney disease present in only 18.8% patients from Marfan syndrome group compared with 58.2% in group B (p=0.007). Also, we not found statistical significance differences regarding 30-day mortality (18.3% in group A compared with 30.1% in group B; p=0.9). Similar results we found the one-year mortality (7.7% in group A vs. 9.2% in group B; p=0.87) and mortality at 10 years (31.3% in group A vs. 44.9% in group B; p=0.28).

DISCUSSION

Marfan is a systemic connective-tissue, autosomal-dominant inherited disorder characterized by mutations in the fibrillin-1 gene (FBN1), with a prevalence of approximately 1 in 5000 individuals (6). There is no sex, racial, or ethnic predilection, and one third of cases present without previous family history (7). Management of Marfan syndrome with cardiac symptoms includes medical treatment with beta blockers and regular screening to assess the progression of the aorta dilatation to a significant diameter aneurysm, when surgical treatment is required to prevent to prevent dissection or rupture (8). Abnormalities frequently found in patients with Marfan syndrome include aortic root dilatation, associating aortic insufficiency due to aortic annulus dilatation or bicuspid aortic valve.

Replacement with a composite graft containing a mechanical valve and a polyester tube graft - the modified Bentall operation - is the gold standard for such patients with corresponding aortic valve cusps pathology (9-11). For young patients with isolated aortic insufficiency with pliable aortic valve cusps, however, valve sparing root replacement might be a good option in experienced institutions (12). Yacoub and colleagues in 1983 introduced the aortic valve remodeling technique with replacement of the ascending aorta and the sinuses of Valsalva (13). David described replacement of the aorta with native aortic reimplantation into a prosthetic tube graft (12). For the past several years, the David aortic valve reimplantation operation has been the procedure of choice for patients with aortic root enlargement and pliable aortic valve cusps (14). Patients with severe damaged cusps are not good candidates for valve sparing operations (15).

Surgery for acute type A aortic dissection remains associated with high operative mortality and morbidity, and adding a long and complex aortic valve sparing may not be the safest approach (10). Current ESC/EACTS guidelines for the management of valvular heart disease state that, surgery should be considered in patients with Marfan syndrome with risk factors (family history of dissection, size increase 2 mm/year in repeated examinations) or who have aortic root disease with a maximum ascending aortic diameter of ≥45 mm (Class II a, Level C evidence) (16).

In a study analyzing the impact of surgical intervention in patients with Marfan syndrome, Ohsubo et al. showed that valve preserving aortic root reconstruction result-
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ed in improved postoperative quality of life compared with Bentall operation, by reducing late complications related to anticoagulants (17). Unfortunately, in patients presenting in the acute setting of aortic dissection, valve-sparing root replacement or reconstruction is often not possible. After initial repair of an ascending aortic aneurysm, a significant number of patients have subsequent surgeries at other sites throughout the aorta, indicating that Marfan syndrome is a disease involving the entire aorta. Some studies show that patients with Marfan syndrome who had a dissection at the time of the first aortic surgery were more likely to require subsequent aortic surgery than those who underwent prophylactic composite graft repair of an aortic aneurysm (18).

As with any reconstructive procedure, these operations must be performed with intraoperative echocardiography to assess valve morphology and function at the end of the procedure. Restoration of normal aortic cusp geometry is the single most important technical aspect of aortic valve–sparing operations. In addition, to have a competent valve with no or only a minimal central AI at the end of the procedure, no cusp should be prolapsing, and the coaptation height has to be well above the level of the nadir of the aortic annulus.

Finally, patient selection also is important. Patients with severe AI before surgery often have damaged cusps and are not good candidates for this operation. Most of our patients had normal or near-normal cusps on.

Study limitations

This study has several limitations, especially related to the retrospective design of the study and the small number of patients in group A. Under these circumstances, advanced analysis, such as multivariable analysis, is unreliable. Nevertheless, our study provides meaningful information on management of patients with Marfan syndrome presenting with acute aortic dissection.

CONCLUSIONS

Due to the unstable condition of patients with Marfan syndrome presenting with acute aortic dissection, the Bentall operation was the most common surgical procedure performed in our cardiac surgery hospital. The operative mortality was relatively high, but not different in comparison with group without Marfan syndrome. The long-term survival of the patients with type A acute aortic dissection and Marfan syndrome was suboptimal. Early diagnosis and regular CT and EET surveillance of patients with Marfan syndrome and a proper medical therapy could reduce the incidence of the aortic dissection or aortic rupture, and may improve the results by making elective valve sparing operation feasible.

REFERENCES


