Abdominal and Thoracoabdominal Aortic Replacement for Marfan Syndrome

10

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Definitions, Classification and Context

Thoracoabdominal aortic aneurysm (TAAA) refers to aneurysmal disease affecting variable extents of the thoracic and abdominal aorta concurrently. TAAA may occur as a primary pathology or secondary to aortic dissection. The extent of aortic involvement in TAAA is defined by the Crawford classification (Fig. 10.1), which is the basis for stratifying prognosis and also determines the surgical approach [1].

In the general population, TAAA is a rare pathology (incidence: 6/100,000 person years) [2] typically affecting the older patient and associated with the usual risk factors for atherosclerosis. The Marfan syndrome (and other Mendelian causes of aortopathy) form a distinct subset within TAAA overall, with a younger age of onset, where traditional risk factors are not a major component. The natural history and characteristics of the disease in this group are different [3, 4].

Of aortopathies in Marfan syndrome, TAAA is a relatively common presentation (accounting for almost a half of all aortic operations [5]) often occurring after or concurrently with a proximal aortic presentation, most commonly an aortic root aneurysm [6, 7]. Abdominal aortic aneurysms (AAA) are rarely observed in

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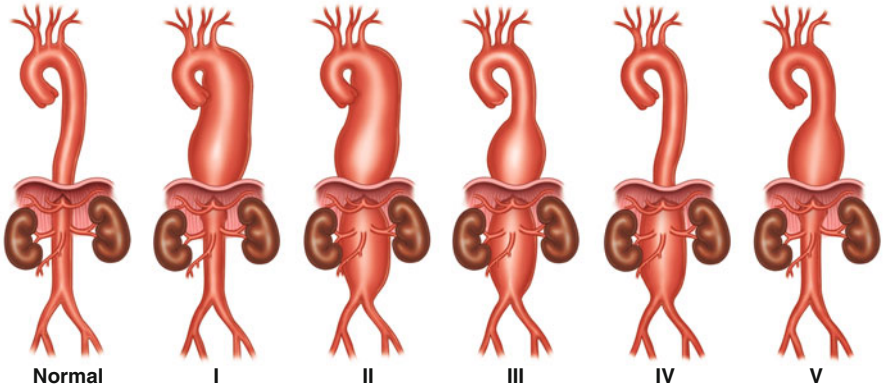

Fig. 10.1 Crawford classification of TAAA extent (from Safi et al., Annals Surgery 2003 [10]). In brief, type I aneurysms extend from the level of the left subclavian artery to the renal arteries; type II, the most extensive and complex to repair, extend from the level of the left subclavian artery to the aortoiliac bifurcation; type III start at or are distal to T6 and affect the lower part of the descending thoracic aorta and the abdominal aorta; and type IV involve the abdominal aorta below the diaphragm but extending up to the diaphragm. Type V is a variant of Type III, more recently defined, involving a lesser extent of the abdominal aorta

isolation in Marfan syndrome, and when they do occur, are observed as part of a TAAA or following prior TAAA repair. Therefore, they will be considered as a subgroup of TAAA for the purposes of this review.

Patient Factors and Selection for Surgery

Owing to the extent of the aorta involved and the corresponding major systemic disruption to blood supply, which is an inevitable aspect of repair, TAAA replacement tends to be associated with a significantly higher burden of mortality and morbidity than other aortic presentations, with few centres worldwide undertaking it. Nevertheless, at the outset, lie the same two questions as for any aneurysm; first, concerning the timing of aortic replacement and second, concerning the best strategies to minimise the surgical risk as far as possible. Both of these attempt to balance the risk from the natural course of the disease (which tends to be aggressive and unpredictable in Marfan syndrome) against the risk of intervention (which is also significant).

Identification of At-Risk Marfan Patients

The best outcomes in aortic surgery in general depend on identifying the disease early and planning an elective repair at the correct time [7,9, 10]. A significant proportion of TAAA overall (13–16 %) follow a prior aortic pathology, and in Marfan

syndrome this proportion is a great deal higher (around 50–68 %); a similar proportion of ascending or aortic root operations in Marfan syndrome are followed by subsequent aneurysmal disease in the distal aorta, including TAAA [6–9]. Thus, a close surveillance of known aortic cases in Marfan syndrome is advocated and we would agree with current guidelines that this should involve annual imaging by magnetic resonance angiography (MRA) or computed tomogram angiography (CTA) in a stable postoperative patient and closer surveillance once new pathology is detected [3, 4]. Similarly, surveillance by MRA/CTA of any newly diagnosed Marfan patient and any relatives carrying the familial *FBN1* mutation should be instigated and maintained at appropriate intervals [3].

Specific Considerations in the Marfan Patient

The Marfan patient presenting with TAAA is younger (mean age 39–49 years) and physiologically fitter compared with the majority of TAAA patients (who present at a greater mean age of 68 years and have significant cardiorespiratory comorbidities) [5, 8, 10–12]. The generalised connective tissue dysfunction manifests firstly in a larger extent of aorta involved on presentation. The disease course is more aggressive: Marfan TAAA's demonstrate faster growth rate, earlier rupture and greater propensity to dissection [4, 7, 8, 13]. Furthermore, there is a higher frequency of recurrence, with a tendency for new aneurysm formation in intervening untreated parts of the native aorta or in autologous grafts or patches used for revascularisation of visceral branches of the abdominal aorta [5, 8, 11, 14]. These all suggest that a more durable and a more extensive repair is indicated and indeed some centres advocate a full length aortic repair in any Marfan patient with aortic dissection [15] (Table 10.1).

There appears to be a further group of apparently Mendelian cases of aortopathy who do not meet Ghent criteria or have a *FBN1* mutation. From our own cohort (Ibrahim et al (unpublished)) and others [5, 16], this group appears to be phenotypically intermediate between the proven Marfan group and the sporadic group, or

Table 10.1 Specific considerations in Marfan TAAA patients

Factor	Strategy
Younger age, physiologically fitter	More durable repair (open surgery)
More aggressive/extensive disease & tendency to recurrence	Lower size-threshold for elective repair
	More extensive repair at first presentation
	Open surgery in preference to endovascular options
Generalised connective tissue disorder with tendency for aneurysmal degeneration of intervening (untreated) aorta or autologous grafts/patches	More extensive repair
	Use of pre-fabricated (synthetic) branched grafts as opposed to autologous patches to re-connect visceral/renal vessels

partly overlapping with the Marfan group. Elucidating the spectrum of genetic mutations underlying this group and correlation with phenotype in larger cohorts will allow a more informed or personalised approach to their surgical management; the wider application of high-throughput DNA sequencing technologies will certainly help this in future [17]. However, for the moment, we approach those cases with a strong family history, younger age of onset or phenotypically more aggressive presentation in a similar manner to the Marfan group [3].

Indications for Intervention

A patient with a symptomatic aneurysm of any size should be considered for repair. Symptoms are usually non-specific and include chest, abdominal or back pain or cough. An acute presentation heralds a rapid expansion and possible imminent rupture, requiring emergent investigation and treatment.

For asymptomatic patients (approximately 50 %), aneurysm diameter is used as a guide to predict when the operative risk is exceeded by the risk of rupture, to guide the timing of aortic replacement. It is known that the risk of rupture with respect to aortic diameter is not a linear relationship, and in fact increases steeply above a certain threshold (or "hinge point") [18]. The exact value for the latter is not accurately known either in sporadic TAAA or in the Marfan patient presenting with TAAA. Therefore, a range of size thresholds for intervention have been proposed. Absolute aortic diameter from 5 to 6.5 cm or relative values of twice the normal aortic diameter in the individual patient have been suggested as suitable cut-off points for management [3, 6, 18]. A fast-growing aneurysm (>0.5 cm/year) is also an indication for repair.

In the Marfan syndrome, it is accepted that these thresholds for intervention should be lowered [4, 8, 13]. Any TAAA caused by aortic dissection (Stanford Type B), which in the general population is managed conservatively if uncomplicated, has a poorer prognosis in the Marfan patient, therefore operative intervention is indicated [19]. Furthermore, since it can be argued that the immediate operative risk to the younger, physiologically fitter Marfan patient is lower, earlier intervention is warranted. In summary, we would consider operative intervention in any Marfan patient with an aortic dissection (or family history of dissection), any symptomatic TAAA or an asymptomatic TAAA with maximal diameter >5 cm or growth rate >0.5 cm/year.

Surgical Strategy and Available Modalities

The essential aim is to replace the aneurysm and a variable proportion of surrounding non-aneurysmal aorta with a synthetic graft. The greater extent of involved aorta, and the propensity to recurrent disease means an extensive repair is often warranted at the outset, sometimes involving the whole length of the descending aorta from the termination of the aortic arch in the upper thorax to the aortoiliac bifurcation in the lower abdomen (Fig. 10.2).

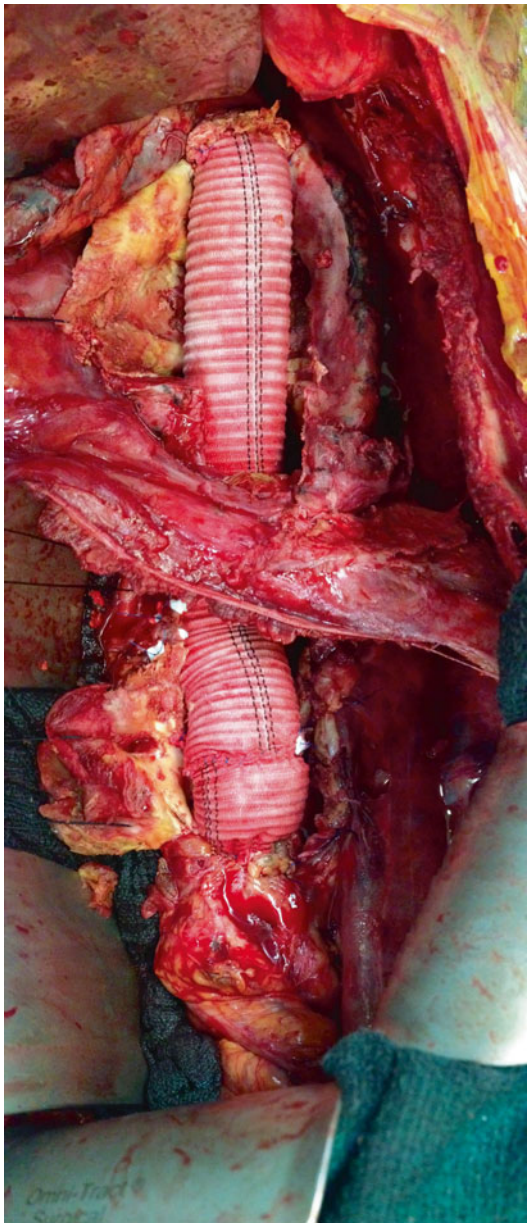

Fig. 10.2 Intraoperative photograph of revascularised thoracoabdominal aorta. A Dacron graft replaces the aorta from the proximal (thoracic) end (top of picture), extending under the diaphragm to the distal abdominal aorta. The continuous *black line* on the Dacron graft starts at the proximal (thoracic) end of the aorta; at the distal (abdominal) end, there is a short extension graft sutured graft to graft. The *black* indicator line is disrupted at this site

The biggest concern in approaching TAAA surgery is in managing the major physiological and metabolic challenge, which arises from disruption of blood supply to most of the thorax, abdomen, all organs therein as well as the lower limbs. These are in addition to the usual challenge of a long general anaesthetic, which carries its own risk of myocardial inhibition, stroke and mortality. Therefore, the

aim is to optimise the patient pre-operatively and, during and after the operation, to utilise all necessary means to support physiology and minimise the ischemic insult to key organs (mainly the spinal cord, kidneys and abdominal viscera).

There are three potential modalities available: open surgical replacement, which is carried out via thoraco-laporotomy or endovascular stent graft placement or by a combination of the two (known as the "hybrid" technique). In reality, open surgical replacement is the gold standard in Marfan syndrome and endovascular options are only indicated in special conditions. The focus of this chapter will therefore be on open surgery, followed by a discussion of endovascular techniques.

Preoperative Preparation

Pre-operative optimisation focuses on four critical areas: the heart, neurovascular supply, lungs and kidneys. Though coronary artery disease or strokes are not common in the MFS patient, it is important to rule out left ventricular dysfunction (by echocardiogram and/or exercise stress testing) as well as significant carotid disease (by carotid duplex ultrasonography). Though the main risk factors for pulmonary complications include smoking history or COPD (which may be less common in the Marfan patient compared with other TAAA patients), intra-operative factors such as thoracotomy, diaphragmatic incision, unilateral lung collapse and operative site involving the thorax contribute to the fact that pulmonary complications comprise the most common following TAAA repair. Pulmonary function tests, spirometry and arterial blood gases are carried out with desirable targets of FEV1 >1.0 L, pCO_2 <4.5 kPa and in borderline cases, a period of 1–3 months optimisation and smoking cessation to optimise the patient's condition. The arterial supply to the kidneys is assessed (with a view to pre-operative or intraoperative revascularisation) and pre-operative dialysis is undertaken if necessary.

Open Surgery – Procedural Details and Key Considerations

The operative technique has been described in detail previously [10]. Here we shall briefly outline the key events and issues, which impact on the overall care of the patient.

The approach depends upon the extent of involved aorta. In the most extensive TAAA (Crawford types I and II, Fig. 10.1), which form the majority of TAAA seen in Marfan syndrome, a single long thoraco-laporotomy incision beginning at the tip of the scapula, passing anteriorly through the fourth or fifth intercostal spaces and extending in the midline of the abdomen is used. This allows access to, and adequate exposure of, the whole length of the descending thoracic and abdominal aorta. The left lung is collapsed to allow access to the heart and thoracic aorta. Left heart bypass is instigated. This takes oxygenated blood from the left atrium or a left pulmonary vein and returns it via a pump system, distal to the repair site, usually the femoral artery, ensuring ongoing distal aortic perfusion while the repair proceeds

(the brain, head and neck and upper limbs will be perfused proximally via the aortic arch vessels, which are proximal to the repair and therefore not disrupted). The abdominal aorta is approached and exposed by retroperitoneal dissection.

After full exposure, the aorta is sequentially clamped and opened, beginning at the proximal thoracic aorta. A synthetic graft is sewn onto the proximal, normal aorta above the aneurysm. Intercostal vessels (from a critical watershed area of T7–T12) are selectively implanted back into the graft. The proximal aspect of the graft is now in direct connection with the proximal aorta and, once isolated from the rest of the graft by a clamp, allows the re-implanted intercostal vessels to be perfused through it, while the rest of the repair takes place distally. After clamping and opening the abdominal aorta, the visceral vessels (coeliac plexus, superior and inferior mesenteric arteries) and renal arteries are explanted and perfused via separate cannulas from the left heart bypass system. The distal end of the graft is sewn onto the distal abdominal aorta. The visceral and renal arteries are then anastomosed on to the graft. The graft now forms a continuous conduit from the proximal thoracic aorta down to the distal abdominal aorta, with perfusion to the spinal cord and abdominal viscera maintained through their re-implanted vessels.

The process of clamping the aorta interrupts normal blood flow to the branches of the aorta, causing widespread end-organ ischaemia for that duration: this period is known as the "cross clamp time" [20]. The direct effects of extensive end-organ ischemia as well as secondary effects from ischemia-reperfusion injury - which is a process of cytokine and free radical release from reperfused vascular beds, leading to damage to the lungs, heart and possibly the spinal cord - are the major concern in TAAA [20, 21]. The main complication is paraplegia from spinal cord ischemia, which in the past was as high as 30 % [22, 23]. These effects are reduced by minimising cross-clamp time, which itself depends upon the technical proficiency and speed by which the operation is undertaken. However, the ischemic insult during the cross-clamp period can be further significantly mitigated by the use of a number of adjuncts, resulting in improvements in patient outcomes beyond what is achievable by technical factors alone – these adjuncts have been shown, collectively to prevent between 1 in 5 and 1 in 20 permanent neurological deficits, or in other words represent a reduction in risk of 72 % overall [10, 21]. They include measures either to reduce metabolic demand to a minimum level or to maintain blood flow to critical organs during the cross-clamp period: systemic hypothermia (which may be moderate systemic hypothermia at 32–34° Celsius or deep hypothermic circulatory arrest), use of the left-heart bypass circuit to maintain distal perfusion, and selective perfusion of visceral and renal arteries whilst their branches are disconnected from the aorta. Specific measures for the spinal cord include: intraoperative and postoperative CSF drainage [10, 23–26], identification and re-implantation of intercostal vessels of T8–L2 or the artery of Adamkiewicz, which are thought to comprise a critical arterial supply to the spinal cord [10, 21, 27–30], use of intraoperative motor and sensory evoked potentials to assess the adequacy of spinal cord blood supply/reperfusion [10, 31–33], and (in some cases) localised epidural cooling [34]. Certain pharmacological agents such as steroids, mannitol and free-radical scavengers have also been proposed [35]. To prevent pulmonary complications and prolonged

post-operative ventilatory requirements, care is taken to minimise lung trauma and protect the phrenic nerves throughout the procedure.

Post-operative Management

Immediately post-operatively the patient is managed on the intensive care unit with haemodynamic parameters maintained to optimise perfusion and oxygen delivery and minimise fluctuations in blood pressure, particularly periods of hypotension (which compromise spinal cord perfusion). Mean arterial pressure is maintained between 90 and 100 mmHg, haemoglobin concentration at >10 g/dL, cardiac index at >2 L/min, CSF pressure <10 mmHg (as spinal cord blood flow is counteracted by CSF pressure). The spinal drain remains in situ for 2–3 days postoperatively. Careful attention is paid to the development of respiratory complications. Once stabilised, the patient convalesces on the general ward and is rehabilitated to their usual life-routine. Beta-blockers are continued indefinitely post-operatively and moderate exercise limitation is advised (to avoid major haemodynamic stresses such as from contact sports and isometric exercises e.g. weight lifting).

Endovascular and Hybrid Open/Endovascular Options as an Alternative to Open Surgery

Whereas in open surgery, the diseased segment is effectively removed and replaced with a synthetic graft, the endovascular technique involves placing a stent-graft within the existing aorta, to bypass the aneurysmal section. It is introduced in its collapsed state across a wire, via a peripheral artery – usually the femoral artery-guided into the correct position and deployed to its full diameter under fluoroscopy. The graft-size is preselected so that, at maximum diameter, it anchors itself to the normal-diameter aorta proximal and distal to the aneurysmal segment, by radial force alone. For extensive aneurysm, custom-designed grafts also allow fenestrations or branches to allow perfusion of key aortic branch vessels, which would otherwise be excluded by the stent. Alternatively, the Hybrid technique, involves a limited operation to revascularise key branches (visceral and renal arteries) by creating a bypass from an unaffected peripheral branch before inserting the stent [36–42].

Overall, this modality, as a result of its minimally invasive approach, has the advantage of lower anaesthetic risk and lower short-term mortality and morbidity [43, 44]. However, in the Marfan patient its routine use is precluded by a higher rate of technical failure and limited durability resulting from a faster growing aorta. This can predispose to "endoleak" (leakage between the stent and native aorta) and tendency to recurrent disease in the intervening untreated aorta [45, 46]. Biomechanically and pathologically, one might also question the compatibility of a stent graft with the Marfan aorta: evidence of reduced aortic compliance [47], early elastolysis and loss of smooth muscle cell to elastic lamella connections [48, 49] and an earlier

predisposition to dissection and aneurysmal dilatation all suggest that the application of a stent graft which relies on radial force for anchoring may adversely interact with an already compromised aortic structure. The most severe adverse events encountered include retrograde dissection and aortic perforation, but more frequently, endoleak and the need for multiple further corrective procedures are the main concern [8].

In specific instances however, owing to the much lower anaesthetic risk, this can be a useful alternative and we have utilised endovascular or hybrid techniques as a 'last ditch' measure in a systemically unstable patient who is unlikely to survive open surgery [42, 50]. Such procedures may form the basis for a more definitive repair once the patient is stabilised.

Outcomes for TAAA Replacement

The reported post-operative outcomes for open surgical replacement of TAAA in Marfan syndrome from experienced centres are good. Outcomes in TAAA patients overall, including Marfan syndrome have improved significantly since these procedures were first undertaken. This partly reflects the experience of the centres from which these outcomes are reported. Centres undertaking a higher volume of procedures show better patient outcomes particularly in relation to TAAA (a concept known as volume outcome relationship) [51]. The major outcome measures in TAAA surgery are early mortality and spinal cord ischaemia in the short term (conventionally measured within 30 days of the operation) and, in the long term, all cause mortality/survival and the need for re-intervention.

When considering short-term mortality, figures are comparable or lower in Marfan TAAA patients (0–6.5 %) [5, 8, 11, 12] compared with TAAA overall (5–14 %) [8, 10, 11, 52, 53]. In a direct comparison of TAAA operations for 31 (mainly Marfan) patients with connective tissue disorder versus 226 patients without, Dardik et al. found that 30 day mortality was almost half in the connective tissue disorders group compared with the wider group (Table 10.2). This probably reflects the lower age and lower burden of major cardiorespiratory comorbidity in those with Marfan syndrome compared with the older sporadic group.

On the other hand, rates of symptomatic spinal cord ischaemia (presenting with either a temporary or permanent paraplegia) are probably higher in the Marfan group, reflecting the fact that the Marfan group has a greater extent of aorta involved – over 50 % of Marfan TAAA patients present with the Crawford type II TAAA (the most extensive form) [5, 8, 11]. Extent of aortic disease, specifically presenting with Crawford type II TAAA is probably the major risk factor for the development of post-operative spinal cord ischemia (conferring between a 4 and 20-fold greater risk, compared with other types and is also the most responsive to protection by the use of intra-operative adjuncts) [10, 25]. In the same study, multivariate analysis also revealed the importance of comorbid risk factors for the development of spinal cord ischaemia post-operatively including: age, smoking, renal dysfunction and history of cerebrovascular accident [10]. In a smaller comparative

Table 10.2 Outcomes for Marfan TAAA replacement

Study	Le Maire 2006	Dardik 2002	Mommertz 2008	Kaltat 2007	Pacini 2013
Patient group	Marfan	Marfan	Marfan	Marfan	Marfan Endovascular (meta-analysis)
No.	178	28	22	19	54
Details	From a larger cohort of 398 aortic operations in Marfan patients	From a larger cohort of 31 patients with inherited connective tissue disorder (28 Marfan, 3 Ehlers Danlos) and 226 sporadic cases	From a larger cohort of 206 TAAA cases	Cohort of 22 Marfan patients with TAAA, 19 surgically operated	Systematic review and meta-analysis of 12 studies presenting data for endovascular treatment in Marfan patients
Male	62 %	61 %	–	64 %	75 %
Mean age	39	48.6	40	38	41
Pathology					
I	19 %	26 %	27 %	11 %	
II	57 %	52 %	50 %	79 %	
III	14 %	29 %	18 %	11 %	
IV	10 %	6 %	5 %		
Other	9 %[a]		36 %[d]		
Dissections	71 % (65 % chronic)	52 %	100 %	100 %	100 % (79 % chronic)
Emergency	7 %	7 %	9 % (rupture)	26%[e]	32 % (urgent & emergency)
Short term outcomes (within 30 days)					
Mortality	3 %	6.50 %	0 %	0 %	2 %
Spinal cord ischemia	4 %	19.4%[b]	0 %	0 %	2 %
Re-operation rate (technical failure)	5 %		5 %	15.7%[f]	30 %[g]
Other	Lung 22 %, Cardiac 11 %, Renal 8 % Stroke 1 %	Lung 10 % Cardiac (MI) 6 % Renal 13 % Stroke 0	Lung 14 % Cardiac 9 % (MI = 0), Renal 0 %	Lung:11 % Renal-support 0 % Stroke:5 %	
Length of stay (ICU stay) in days		14 (6.4)		19(8)	13

Table 10.2 (continued)

Study	Le Maire 2006	Dardik 2002	Mommertz 2008	Kaltat 2007	Pacini 2013
Long term outcomes					
Mean follow-up period	5 years	5 years	38 months	56 months	30 months
Survival	98 %	>54%[c]	100 %	90 %	88 %
Re-operation rate	2 %				18 %

Summary outcome data from major series reporting open TAAA repair for Marfan syndrome (columns 1–4) compared with meta-analysis of all available endovascular outcomes in Marfan TAAA (column 5). I–IV refer to Crawford classification of TAAA

[a]Completion/reverse elephant trunk

[b]Though no sign diff in paraparesis rate, multivariate analysis showed presence of CTD as possible predictor of paraparesis post op (OR 1.2–70, p = 0.03)

[c]This series showed no significant difference in long term survival in Marfan patients compared with sporadic patients

[d]Arch aneurysms concurrent with TAAA

[e]This includes two ruptures

[f]One SMA thrombosis

[g]25 % early endoleak rate and 5 % conversion to open surgery

study, Dardik et al showed a small but statistically significant increased risk of spinal cord ischemia in patients with connective tissue disorder compared to those without [11].

In terms of long-term survival and outcome after TAAA replacement, no significant difference in long-term survival between MFS and non-MFS patients has been observed. Long-term survival is affected by a number of factors including age, smoking, renal dysfunction, emergency presentation, and anatomy, specifically Crawford type II TAAA. The use of adjuncts, which aim to maintain perfusion during aortic clamping are protective. These data suggest that early detection and elective treatment of TAAA is beneficial, particularly in the face of more extensive aortic involvement and more aggressive natural history as seen in the Marfan syndrome.

Whilst giving excellent results in non-MFS sporadic cases, outcomes of endovascular techniques in Marfan syndrome show a high rate of technical failure in terms of endoleak and high corresponding re-intervention rates [45, 46]. Pacini et al undertook a systematic review of 54 Marfan patients with aortic dissections from 12 publications. In this metanalysis, short term mortality was low (2 %). Early endoleak (within 30 days of the procedure) occurred in 22 % of patients overall and in 30 % of chronic dissections [46], significantly higher than rates reported for non-MFS patients (which are between 7 and 12 %) [43, 54]. It has been suggested that early endoleak is not as prevalent when the proximal aspect of the stent is overlapped with an existing synthetic graft, although existing evidence as a whole does not support this notion [45, 46]. In the long term (over a mean duration of 2.5 years after operation) this group had endoleak and reintervention rates of 18 % each (compared with

1–9 % endoleak rate in non-MFS aortas) [42, 43, 50, 54, 55] and a 12 % mortality, with a mean age of death of 41 years. Overall, current outcomes support the surgical approach to TAAA replacement, which uses early open surgery as the first option and endovascular strategies in specific conditions where open surgery is precluded.

Conclusions

TAAAs are the most extensive and some of the most surgically complex of aortopathies. In Marfan syndrome, they are further complicated by a more aggressive pathology including faster growth rate and greater propensity to dissection in the MFS patient. This requires early detection and surveillance, which in the future, will be aided by the more widespread application of new genomic technologies, allowing more detailed genotype-phenotype correlation and risk-stratification. Early elective replacement and an extensive repair at first presentation minimises recurrence and the need for further procedures. Open surgery, though in the past marred by very high mortality and morbidity, is now the gold standard for treatment as technical developments over the past three decades have allowed good long-term outcomes and durability. When carried out at experienced centres this has allowed Marfan syndrome patients to experience comparable outcomes to TAAA patients overall. Endovascular options have very limited scope in this group but may be a useful alternative in very specific situations where open surgery is not possible.

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