The Big Aortic Root Study: evaluation of personalised external aortic root support

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None declared.

Introduction

If there is one condition for which the terrifying analogy 'sitting on a time bomb' might be appropriate, aortic dissection is it. In acute ascending aortic dissection, at a heartbeat, the victim's situation changes from having an intact aorta conveying blood throughout the body, to having a rent in the aortic wall running from the root along a variable length of the aorta, potentially extending into its branches. Rupture into the pericardium may result in death within minutes or hours. It is very unusual for victims of this catastrophic event to survive untreated for more than a few days after the onset.

There are people with genetically determined aortic disease for whom this is predictable, most notably those with Marfan syndrome. It is predictable in the sense that, if the disease follows its natural course, about two thirds of them will die from aortic dissection, most commonly as young adults. What is not predictable is when this catastrophe will occur. Aortic dissection is relatively uncommon. Data collected by the London Cardiovascular Project for example showed that only about 100 patients a year reach hospital in the city to have the diagnosis made but 20% die despite having emergency surgery [1]. The basis of our management of this situation is to detect that they have a vulnerable aortic root, to assess the situation by measurement and continued monitoring and then to intervene.

Conventionally the intervention is to replace the aortic root. This is accepted as a matter of routine for patients with Marfan aortopathy. Indeed, the risk of death in current practice in the best hands is remarkably small but clearly root replacement is a major undertaking. It takes two to three hours on cardiopulmonary bypass with interruption of normal myocardial perfusion for 90 minutes to two hours [2]. The brain is at risk from the hazards of air and particulate emboli, in addition to the effects of bypass itself, and added to that is commonly a period of total circulatory arrest to make a safe, secure anastomosis to the remaining aorta. More often than not the aortic valve is replaced. Because these are young people, on average in their 30s, they are expected to outlive several tissue valves so a mechanical valve is the commonest solution. The penalty is a 1.3% annual combined rate of embolism, bleeding and endocarditis [3]. The rate appears small until you do the calculations. A 30-year-old might realistically hope for another 40 years of life: that is a cumulative hazard of over 50%; they are more likely than not to have a significant valve related event which may be fatal or permanently life changing. After several iterations valve sparing surgery is an alternative but the failure of the re-suspended aortic valve is its vulnerability; the combined rate of valve related events is 1.9% or a cumulative lifetime rate of about 75%.

An alternative now available [4] is to operate before the aorta has enlarged and ensleeve it in a soft pliable porous mesh, made to measure, fitted to the most vulnerable part of the aorta, from the aortoventricular junction to the arch of the aorta, beyond the brachiocephalic artery. This procedure is a personalised external aortic root support [Figure 1a-e].

Evaluation from 'first in man'

The first operation

The idea was first proposed at the Marfan Association meeting in 2000 by an engineer with Marfan syndrome. It was very carefully worked out in collaboration with the cardiac morphologist Prof Robert Anderson, of the Institute of Child Health, and academic engineers at Imperial College in London. In 2004 we were ready for the first clinical implant and the inventor Tal Golesworthy, as he had hoped and intended, was the first recipient [5].

The first 10

After 10 patients had been operated on we conducted a very carefully controlled and blinded study of the technical outcome. The preoperative and all postoperative cardiac magnetic resonance (CMR) images from three to thirty-four months after operation were collected, two to four studies per patient depending on the length of follow-up, making a total of 28 images. We also assembled images of 37 un-operated Marfan patients and made duplicates to assess read-reread variability. We presented 102 cropped and anonymised CMR

Figure 1b: The model is used to sculpt by rapid protyping a replica of the individual's aorta.

Figure 1c: On that is manufactured a mesh sleeve which as can be seen is soft and pliable.

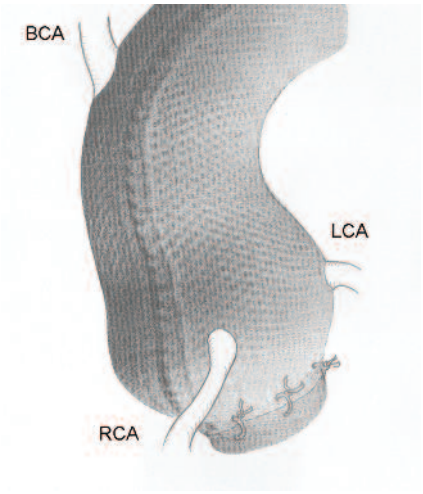

Figure 1d: It is opened along its longitudinal seam and openings are made for right and left coronary arteries (RCA, LCA) and the brachiocepalic artery (BCA).

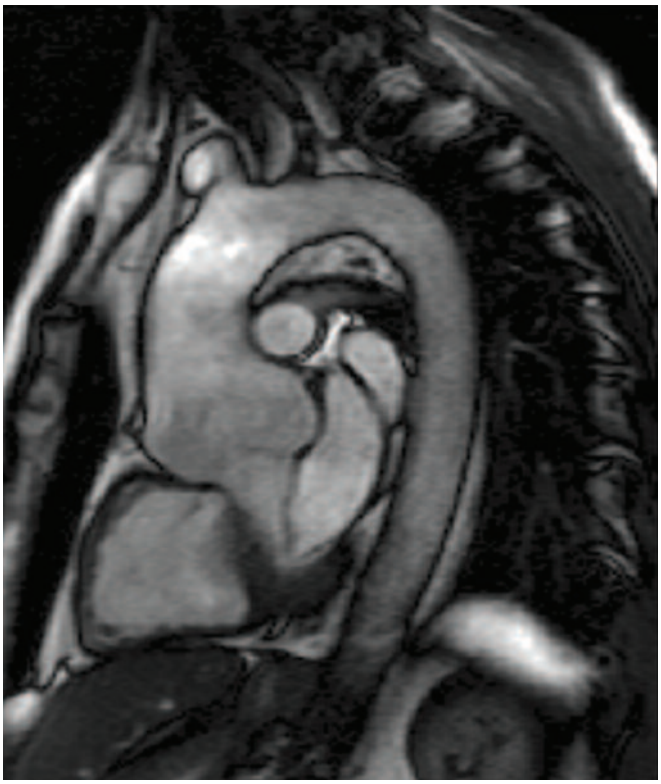

Figure 1a: From the patient's cardiac magnetic resonance image or computed tomography (CT) the measurements of the aorta are captured and used in a process of computer aided design.

Figure 1e: The MRI of the first patient imaged nearly eight years later showing that the root architecture is held exactly as before.

images in random sequence to an entirely independent, experienced vascular radiologist to make the measurements. There was no further expansion and in eight of ten patients the aortic dimensions were reduced to nearer the normal range [6]. The aortic root has subsequently been held stable in all cases.

The first 20

After 20 patients we made a comparison of perioperative hazards and burden of care with 20 matched patients having root replacement in exactly the same time frame. Since the inception of this surgery at the Brompton, most patients who met the criteria had the new external support operation. We asked colleagues in Birmingham and at St Thomas's Hospital in London for data on their patients having standard root replacement. Without any patient identifiers or knowledge of the outcome we constructed by minimisation on preoperative variables (age, root size, any aortic regurgitation) a matched control group. We quantified the sparing of bypass time, myocardial ischaemia, operation time, blood product usage, and hospital stay. There are very evident reductions in perioperative hazards [2].

The first 30

When we had 30 patients with more than one year of follow-up we analysed outcomes in this patient cohort. These

results have been presented in Chicago at GenTAC 2012 (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) and in Houston at CTACS 2013 (Current Trends in Aortic and Cardiovascular Surgery). There was a robust scepticism from some participants. Valve sparing root replacement is technically demanding and has had a substantial iterative learning period, with multiple versions. In contrast, personalised external support has been carried out to the same technique since its inception in 2004 and is, at face value, disarmingly simple. It has its dangers, not least dissecting below the left coronary artery, but the need for a high level of intraoperative craft skill has largely been replaced by preoperative measurement and a personalised engineered design. With over 140 patient / years of follow-up there have been no valve or aortic root events in marked contrast to the meta-analysed data on valve sparing surgery [3].

The Big Aortic Root Study

We are planning and actively seeking collaborators for the Big Aortic Root Study (BARS). Embedded within this would be decision-making nodes where random allocation would be an option – it depends on the view of all those who want to join to play a part in designing BARS. One thing on which all the contenders agree is that a randomised trial would be difficult [7]. It is noteworthy however that while the contending operations have come into practice by trial and error [8] (and there have been many errors along the way) their protagonists now call for a trial and we agree with them. There is prior experience of designing studies in surgery [9] and we will trawl for any and all good ideas.

The 'big' in the proposed title serves two purposes. An aneurysm is an aorta bigger than it should be. People with Marfan syndrome are particularly prone to root aneurysm but so are people with other forms of aortopathy. Marfan syndrome itself is heterogeneous. Marfan syndrome was first 'framed' [10] by a constellation of clinical features but over time the diagnostic frame has shifted with incorporation of new knowledge. For all those prone to dissection due to aortopathy, a unifying pathology, 'cystic medial necrosis' was suggested as a useful diagnostic frame. Then fragmented fibrillin offered a biochemical / connective tissue diagnostic frame. The identification of a gene on chromosome 15 (unfortunately there are several) advanced understanding but the genetically framed diagnosis has not replaced assessment of aortic shape, size and expansion in the decision of whether or not to operate. Furthermore, with over 600 different mutations of the fibrillin gene it has so far not been possible to link the specific genotype with a specific phenotype. As far as this surgery is concerned it addresses one part and one part only of these syndromes: the aortic root. If the patient has a big and enlarging aortic root, there appears to be a risk of dissection and sudden death. Conversely, for people with morphological normal aortic roots, we would have no justification for proposing any intervention on the root. In that sense we propose a study of patients with big aortic roots.

A pragmatic study needs to be 'big'. A tried and tested way is to recruit patients into a first stage which is as inclusive as possible. It is proposed that patients who are being assessed with a view to soon or eventually undergoing aortic root surgery can be recruited into BARS so that during the evaluation data are collected and patients are fully informed by protocol. In many instances there will be a most appropriate or clearly preferred option but if there is uncertainty, allocation to one course of action or another, can be made by randomisation.

The role of patients in this research

Cardiology News highlighted in 'Listening to the Voice' (February/March 2013) the importance of patient involvement. In that the inventor, first patient and key member of the project team is a Marfan 'patient', we feel we are ahead of the game in that regard and we have many patient accounts on our website (http://www.marfanaorticrootsupport.org/experiences.php). These are patients who have had external support so it would be valuable to include patients in the project team with different experiences or family members with multiple experiences.

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