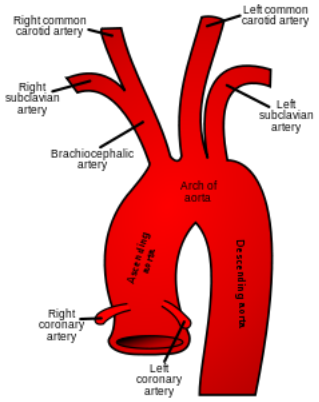
Aortic arch dilatation.

“The ascending aorta is a portion of the aorta commencing at the upper part of the base of the left ventricle on a level with the lower border of the third costal cartilage behind the left half of the sternum. It passes obliquely upward, forward, and to the right, in the direction of the heart's axis, as high as the upper border of the second right costal cartilage describing a slight curve in its course, and being situated, about 6 centimetres behind the posterior surface of the sternum. The total length is about 5 centimetres.



Source: Wikipedia.org: Ascending aorta

The aortic root is the portion of the aorta beginning at the aortic annulus and extending to the sinotubular junction. It is sometimes regarded as a part of the ascending aorta, and sometimes regarded as a separate entity from the rest of the ascending aorta. A thoracic aortic diameter greater than 3.5 cm is generally considered dilated, whereas a diameter greater than 4.5 cm is generally considered to be a Thoracic Aortic Aneurysm. Still, the average diameter in the population varies by for example age and sex. The upper limit of the standard reference range of the ascending aorta may be up to 4.3 cm among large, elderly individuals.” (1)

As a general rule in adults, the diameter greater than 4 cm is considered to indicate dilatation. Known causes can include hypertension, arteriosclerosis, aortic valve disease, congenital heart disease, connective tissue diseases. The elastic tissues in the aortic wall undergo increasing stiffening, less able to sustain (bounce back) from the mechanical pressures as blood is pumped from the left ventricle leading to dilatation.

The last decade has shown an increase in the relevance of inflammation and its mediators in vascular biology; thus, the role of inflammation during atherogenesis is now a matter of intense investigation. Basic science studies proved that elements belonging to both innate and adaptive immunity can be involved in the formation, progression and complication of atherosclerosis and the progressive wall changes.

Plasma levels of circulating inflammatory molecules, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been shown to be predictive of future cardiovascular disease (CVD), and drugs which modify their levels can reduce the risk of myocardial infarction and stroke. It has been shown that an inflammatory response can develop in the arteries of animal models of hypertension. The predominant inflammatory response is mediated via Interleukin-6 and this cytokine is found in increased quantity in this tissue.

Innate immunity is first line of defence and is programmed to detect molecular motifs called pathogen-associated microbial patterns (PAMPs) via specialized receptors. Toll-like receptors (TLRs) are the most characterized pattern - recognition receptors (PPRs) so far. TLRs and their ligands are critical in atherogenesis. (5)

Preventing vascular ageing

Preventing vascular aging is complex and requires early intervention and management. Arteriosclerosis is all about increasing stiffness in the vessels, and results from reversible and irreversible components, and are responsible for the elevated blood pressure that continues with ageing, with increasing risk of cardiac, cerebrovascular and chronic renal disease. The majority of treatments target the consequences rather than the cause.

At a cellular level, ageing can be determined by the length of telomeres, small segments of DNA that bind the DNA and are essential for maintaining DNA integrity during replication. As cells age, the telomeres become shorter. This vascular ageing is thought to be from oxidative stress, and the presence of reactive oxygen species (ROS) and oxidized low-density lipoprotein (LDL) below the intimal lining of the vessels. Also involved is modification of collagen, especially in diabetes. These processes lead to aortic stiffening, dilatation and wall hypertrophy. This arterial ageing is accelerated by hypertension, impaired glucose tolerance, diabetes, dyslipidaemia and smoking, along with other inflammatory and autonomic processes.

Research suggests that this root enlargement is caused by excessive signalling by transforming growth factor β (TGF-β) that can be mitigated by treatment with TGF-β -blockers, particularly angiotensin 11-receptor blockers (ARBs.) (2) The arch dilatation is known to be caused by the oxidative stress response.

People with hypermobility, with increased stretch of blood vessels (or compression), causes increased baroreceptor signalling (ref Prof Pete Smith). A lot of mast cells are around major key branch points (including the root of the aorta) and histamine is a co-factor in sensory nerve activation thresholds. There is an increased propensity to dilate at those points, but this may simply be mechanical, at points where higher pressures are being experienced.

It seems apparent that elevated homocysteine, which is a common accompaniment of the MTHFR mutation is one of the risks for developing this dilatation. Increased homocysteine induces oxidative stress and latent matrix

metalloproteinases (MMPs) causing ECM (extracellular matrix) remodeling and aneurysm formation.

Research has demonstrated that a type of blood pressure tablet, the ARBs, seem to slow the progress of this dilatation, and early studies would suggest there is actual repair, possibly at a DNA level with repair of telomeres. So this is where we start in practice, to stop the process using a combination of ARB (eg Atacand or Micardis) and vitamin B12 which appears to improve function of the defective enzyme in the MTHFR pathway Traditional management in Marfan's has been with β-blockers, and in progressive disease, the combination of ARB and β-blocker appears to be synergistic. (4) In patients with increasing dilatation despite attention to causes and already taking an ARB, the combination would appear to be the next step. Recent reversal of an arch dilatation when an Interleukin-6 Receptor Inhibitor was started for rheumatoid arthritis provides an interesting and exciting look for future management.

It is thought we can halt the progression of the dilatation by removing the inflammatory responses by dealing with the genetic problems of the MTHFR mutation and the mechanical sources in the thoracic outlet. Trials are well underway using angiotensin-renin blockers in stabilizing this dilatation. These (especially Atacand) have been employed for Marfan's syndrome where the risk of dissection and death is much higher.

There are guidelines for the dilatation, which do not include the current research, but do suggest that the echocardiogram be checked yearly, or twice yearly if the aortic root has enlarged to 4.5 cm at which time you would need a specialist opinion. The yearly echocardiogram should be done on the same machine and if there is progression despite treatment, I would recommend an earlier referral as this association with elevated homocysteine is as yet unexplored territory and the management at research level. The dilating aorta can be surgically corrected if necessary, but we hope to stop this being required by halting and hopefully reversing the process, something that is looking promising with early research results.

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