PEER REVIEWED FEATURE

The aorta

A central player in hypertension

BENEDICT T. COSTELLO MB BS, FRACP
ANDREW WILSON MB BS, FRACP, PhD

Aortic stiffening occurs progressively throughout life and leads to increased pulse pressure and systolic hypertension. This process is also impacted by cardiovascular risk factors such as diabetes, smoking and renal impairment. Medical therapy directed at this process is not yet available, and as such aortic stiffening contributes to resistant hypertension.

Key points

- **Aortic stiffening occurs progressively throughout life from infancy and can be detected from the third decade, well before end-organ effects occur.**
- **As aortic stiffness progresses, the aorta loses its cushioning function. This reduces the capacity to convert pulsatile to continuous flow, which raises systolic blood pressure (BP) and lowers diastolic BP, thereby reducing coronary artery flow and increasing cardiac workload.**
- **Central (aortic) BP is now known to be a better predictor of cardiovascular risk and mortality than peripheral BP.**
- **Antihypertensive agents can have a different effect on central and peripheral BP and this discordance may be important when accounting for treatment response to specific agents when assessing peripheral BP.**
- **The ability to recognise aortic stiffening early may enable timely interventions to halt the progression of hypertension and break the cycle leading to drug resistance.**

CARDIOLOGY TODAY 2015; 5(1): 18-22

Dr Costello is a Cardiologist and PhD Research Fellow at The Alfred Hospital, Melbourne. Associate Professor Wilson is a Cardiologist at St Vincent's Hospital, Melbourne, and David Blickart Clinical Research Fellow and Principle Research Fellow at the Department of Medicine, University of Melbourne, Melbourne, Vic.

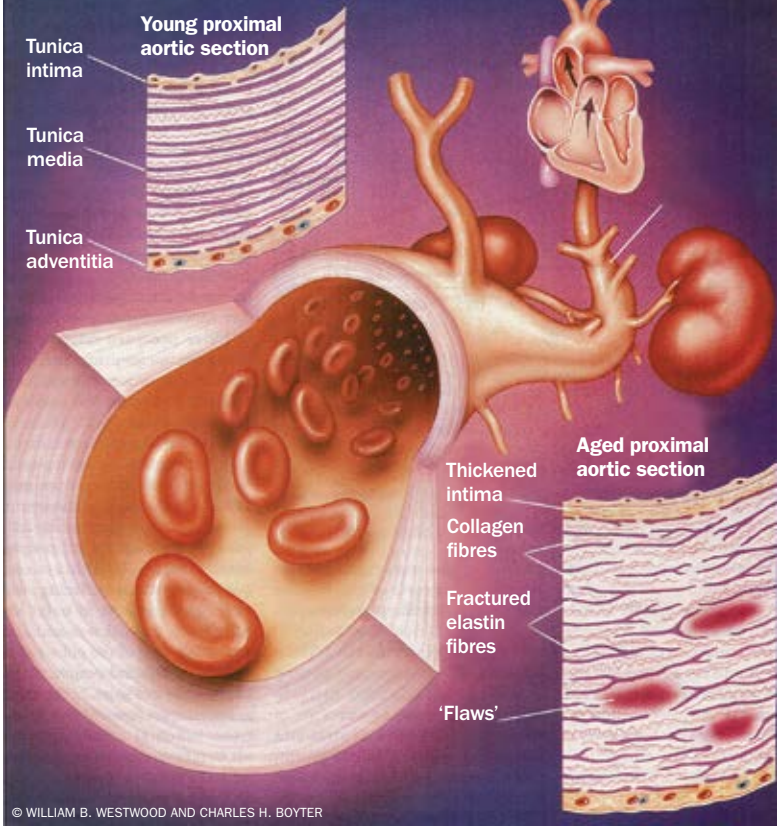

Figure 1. The ageing aorta. In the young, elastic lamellae is orderly arranged in the arterial wall. With ageing, there is a progressive degeneration of the normal architecture: elastin fibres fracture, collagenous material increases and in some areas there is breakdown of structural elements ('flaws'), resulting in aortic stiffening.

Population-based studies using blood pressure (BP) measured via a cuff at the brachial artery have shown a strong association between hypertension and cardiovascular morbidity, and mortality.[1] It is estimated that there are 1 billion people with hypertension worldwide, and a quarter of these will have 'resistant hypertension', where BP remains above goal (>140/90 mmHg) despite the use of three or more antihypertensive agents of different classes.[2] Fifty per cent of those aged over 60 years are hypertensive, of whom most (80%) have isolated systolic hypertension (ISH).[3] This is characterised by an increase in systolic blood pressure (SBP) but a normal or reduced diastolic blood pressure (DBP).

The aorta has a significant role in the pathogenesis of hypertension, and in the individual response to therapy. There is accumulating evidence that aortic stiffness is an independent predictor of cardiovascular risk, yet there are no established methods to treat this.

This review discusses the properties of blood vessels throughout the body, the difference between central and peripheral BP, and the role of the aorta in drug and exercise treatment of hypertension. It also examines pathological conditions in which the aorta and hypertension have a key role.

Properties of blood vessels

The role of the systemic arterial system is to provide blood continuously to organs at high pressure from the heart as a pump. The arterial system can be divided into the following three anatomical regions:

- the large elastic arteries (aorta, brachiocephalic artery, carotids, etc), which act as a reservoir or an elastic chamber; the aorta

smoothes out the intermittent, pulsatile flow from the heart into continuous flow
- the large muscular arteries, which act as conduits to major organs and can modify flow by altering smooth muscle tone and diameter while keeping mean arterial pressure constant
- the arterioles, which are the major determinant of peripheral resistance and change calibre to regulate mean arterial pressure, thereby providing continuous flow to organs according to need.[4,5]

The elastic properties of the large proximal vessels are due to the collagen and elastin fibres that form a closely meshed matrix. Major changes in the properties of the large elastic vessels occur over a long period of time, and acute changes in the wall properties are passive and usually due to a rise or fall in the distending pressure. The stress of the repetitive nature of pulsatile distension/relaxation in the large elastic arteries is borne out by elastic lamellae. With ageing, this results in elastin fibre fracture and medial degeneration, causing the aorta to stretch so that stresses are transferred from elastin to collagen elements in the wall, and the aorta stiffens progressively (Figure 1). Aortic stiffening occurs progressively throughout life from infancy, and can be detected from the third decade, well before end-organ effects occur.[6]

The process of aortic stiffening is accelerated by diabetes, where vascular wall collagen is modified by glucose and other sugars to form advanced glycation end products (AGE). The AGEs impair the local vasodilating effects of endogenous nitric oxide and interact to increase vascular inflammation, remodelling and atherogenesis.[7] This process induces vascular calcification, which accentuates stiffening of elastic vessels. In addition to diabetes, smoking, chronic renal impairment and hypertension itself contribute to vascular stiffening and calcification; these conditions are also predictors of resistant hypertension, suggesting a causal relationship.

Age-related stiffening of elastic vessels is thought to be the key determinant of resistant hypertension. There is a contribution from renal impairment, as salt and water retention have a physiological role, compounding the reduced capacity of stiffened arteries to act as a buffer.

Age-related vascular changes ('arteriosclerosis') contrast with the arterial changes seen in atherosclerotic disease. Whereas atherosclerosis is a pathological process involving focal narrowing of the intima, arteriosclerosis is a diffuse, dilatory process involving degeneration and calcification of the arterial media. This process is more marked in the large elastic arteries, and leads to dilatation and tortuosity.[8]

The aorta and hypertension

As aortic stiffness progresses, the aorta loses its cushioning function. This reduces the capacity to convert pulsatile to continuous flow, which raises SBP and lowers DBP, thereby reducing coronary artery flow and increasing cardiac workload. A stiffened aorta thus increases impedance to aortic flow, increasing the left ventricular (LV) workload contributing to LV hypertrophy. The combination of increased workload and reduced coronary perfusion leads to ischaemia, fibrosis and LV dysfunction. A high pulse pressure also increases the risk of damage to fragile capillary beds, such as in the brain or kidney (Figure 2).[9]

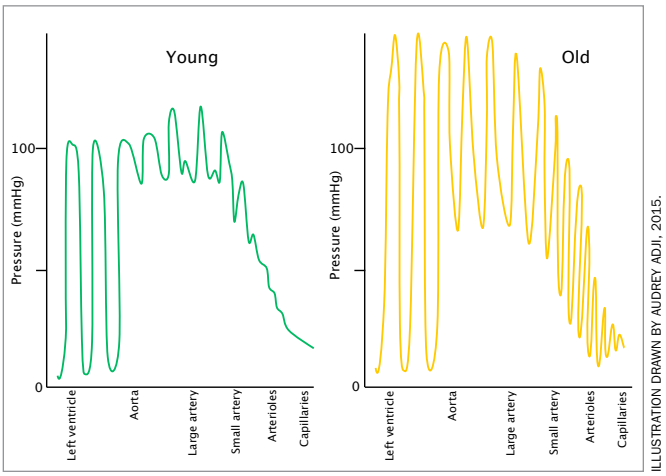

ILLUSTRATION DRAWN BY AUDREY ADJI, 2015.

Figure 2. A schematic diagram of the pulsatile pressure change between the left ventricle and capillaries of a young subject and an older person with arterial stiffening. Pulsations are not absorbed in the large arteries of the older subject and extend into the microcirculation.
Adapted from O'Rourke MF and Hashimoto J,[5] with permission from Prof M. O'Rourke.

Pulse wave velocity (PWV) is the gold standard for measuring large vessel stiffness. It can be measured by taking simultaneous recordings of pressure waves at two points, usually the carotid and femoral arteries.[10] Aortic stiffness increases the PWV, which in turn increases central aortic and LV pressure augmentation by reducing the time taken for reflected waves to reach the ascending aorta (Figures 3 and 4). This increase in central pressure continues the cycle of matrix degradation and vascular calcification, further increasing aortic stiffness.

Central (aortic) blood pressure

Although mean BP and DBP are relatively constant throughout the vascular system, it is well recognised that SBP and pulse pressure are higher in the more muscular peripheral arteries (e.g. the brachial artery) than in the more elastic central arteries (e.g. aortic, carotid and coronary arteries).[11] This disparity in BP is known as pulse pressure amplification.[11] The magnitude of amplification is greater in people with healthy compliant arteries and diminishes with age,[12] and can result in the potential for markedly different central BPs (SBP and pulse pressure) between patients, despite having the same peripheral BP. Importantly, recent evidence indicates that the central (aortic) BP is a better predictor of cardiovascular risk and mortality than peripheral BP,[11,13,14] because central SBP is a determinant of LV afterload and central DBP a determinant of coronary circulation.

It has also been shown that antihypertensive agents can have a different effect on central and peripheral BP and the discordance may be important when accounting for perceived treatment response to different agents when assessing peripheral BP.[15]

Central BP can be measured directly at angiography or estimated using a number of methods. The best validated method is applanation tonometry, whereby the radial artery waveform is detected

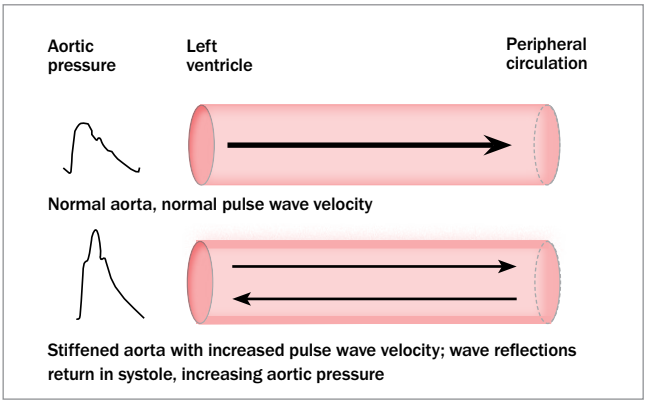

Figure 3. Simple conceptual model of the aorta as a vascular cushion. The elastic aortic/arterial model is a simple tube with the left ventricle at one end and peripheral circulation at the other end. In young adults, the pressure waves travel slowly to the periphery, are reflected and return to the heart as the aortic valve shuts, so aiding coronary perfusion during diastole. In older people, the stiffened aorta has higher wave velocity, so that the reflected waves return early to the heart, in systole, thus augmenting pressure during systole and leading to relative reduction in pressure during diastole. This limits the capacity to ensure adequate coronary flow.

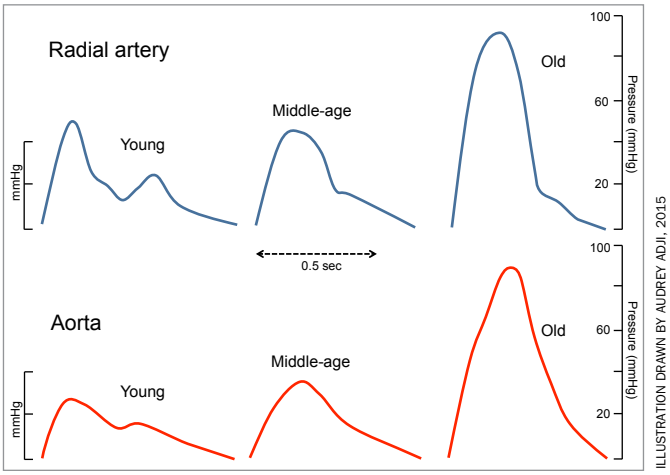

ILLUSTRATION DRAWN BY AUDREY ADJI, 2015

Figure 4. A schematic diagram of the pressure wave forms measured in the radial artery and ascending aorta in a young, middle-aged and elderly woman. The pulse pressure is increased almost four-fold in the aorta and two-fold in the radial artery.

Adapted from O'Rourke MF and Hashimoto J,[5] with permission from Prof M. O'Rourke.

noninvasively and converted to an aortic waveform using a mathematical model.[16] Applanation tonometry can be time consuming (up to 30 minutes) and requires a trained operator; however, with experience the time taken to perform this can approach five minutes.

A number of devices have been developed to noninvasively estimate central BP using a traditional oscillometric cuff. The cuff measures the BP and wave form of the pulse wave to derive an estimate of central pressure.[17-19] More recently, central pressure estimation using magnetic resonance imaging (MRI) has been validated against applanation tonometry.[20]

Central BP obtained in the office can predict future mortality as effectively as the reference standard of 24-hour ambulatory blood pressure monitoring.[21] Furthermore, the use of central BP obtained in the office has been tested against the conventional use of brachial pressure in a randomised study.[22] This study demonstrated the benefits of using central BP to guide therapy, with the use of less medication to achieve BP control and no adverse effects on LV mass, aortic stiffness or quality of life.

Therapeutic effects on hypertension and the aorta

Pharmacotherapy

There are two main targets of antihypertensive therapy. Diuretics (loop diuretics, thiazides, aldosterone antagonists) modulate the capacity of the body to handle volume and salt, especially when glomerular filtration rate declines with age and stiffened vessels are unable to act as a buffer. The second mainstay of treatment targets vascular smooth muscle relaxation and includes ACE inhibitors, calcium channel antagonists and alpha-receptor antagonists. Peripheral arteries, arterioles and, to a lesser extent, the venous system are the physiological targets of vasodilating therapies. Arterial dilating drugs 'trap' wave reflection in the peripheral arteries and reduce central SBP.[10] At this stage no pharmacological agents have been shown to effectively improve the function of the elastic vessels. Attempts have been made to target AGEs, and, although early experimental experience was promising,[23] the efficacy of these agents has not been supported by the results of larger clinical trials.[24]

The ability to recognise aortic stiffening early may enable timely interventions to halt the progression of hypertension and break the cycle leading to drug resistance.

Invasive procedures

The use of radiofrequency ablation to denervate the renal arteries had shown promise in lowering BP, particularly in patients with resistant hypertension. Early studies showed significant BP reduction, both in animal models and subsequently in clinical trials, leading to widespread use globally.[25] However, a recent large multicentre trial of renal artery denervation involving sham procedures in the control arm did not demonstrate a significant BP reduction with this technique.[26] This may be explained by the difficulty treating hypertension in subjects with advanced arteriosclerosis and vascular calcification, in whom altering arteriolar tone is less effective.

Exercise

People with hypertension, decreased aortic compliance or arteriosclerosis find exercise more difficult, and are under-represented in studies of haemodynamic changes with exercise. It is well established that endothelial function improves with exercise by allowing the smaller, more muscular arteries to respond to training.[27] During exercise there may be a disproportionate rise in PWV and peripheral BP when compared with central pressure. There is evidence that aerobic exercise slows the progress of arterial stiffening and improves central

haemodynamics; however, it is unlikely to reverse the arteriosclerotic process.[28]

Thoracic aortic aneurysm

Not only does the breakdown of the elastic matrix contribute to aortic stiffness, it is also thought to be a key component in aortic aneurysm and dilatation, a pathological finding common in long-standing hypertension. The development of aortic aneurysms is due to a combination of genetic predisposition and clinical factors including hypertension and fatiguing effects of stress (mechanical effect).

The classic example of a genetic disorder leading to aortic dilatation is Marfan syndrome, an autosomal dominant condition carried by the gene *FBN1*, which encodes the connective protein fibrillin-1.[29] Patients with Marfan syndrome are more likely to have aortic aneurysm, and a tendency for these to rupture at a lower diameter. Bicuspid aortic disease and other connective tissue diseases also increase the risk of aneurysm.[30] Genetic predisposition in the absence of syndromic features poses a diagnostic challenge. Genetic mutations have been identified in families with increased rates of thoracic aneurysm and dissection, and this condition is given the label 'familial TAAD – thoracic aneurysm and dissection'.[31]

Hypertension and dissection

Elevation in BP is likely to be a key player in the timing of acute aortic dissection and rupture. Observational studies have recognised the association of periods of exertion or emotional stress with dissection. There are numerous case examples of weightlifters presenting with dissection and requiring urgent surgery. Subsequent studies have shown central aortic pressure can reach as high as 300 mmHg during extreme weightlifting, causing significantly increased wall stress and increasing the risk of rupture.[32] Similarly, times of emotional stress have been identified as precursors to acute rupture, again suggesting that acute elevation in aortic pressure can precipitate this presentation.

Summary

The aorta has a key role in hypertension, with increased vessel wall stiffness leading to a wider pulse pressure and systolic hypertension. The process is progressive and impacted by cardiovascular risk factors such as diabetes, smoking and renal impairment. Medical therapy directed at this process has yet to be proven effective, and as such aortic stiffening contributes to resistant hypertension.

Pulse pressure amplification explains the higher recorded BP in the brachial artery compared with the aorta. There are devices to estimate central BP noninvasively, and the use of central BP to guide antihypertensive management is the subject of ongoing research. **CT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

The aorta
A central player in hypertension

BENEDICT T. COSTELLO MB BS, FRACP; **ANDREW WILSON** MB BS, FRACP, PhD

References

1. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-1913.
2. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA 2003; 290: 199-206.
3. Colhoun HM, Dong W, Poulter NR. Blood pressure screening, management and control in England: results from the health survey for England 1994. J Hypertens 1998; 16: 747-752.
4. Belz GG. Elastic properties and Windkessel function of the human aorta. Cardiovasc Drugs Ther 1995; 9: 73-83.
5. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol 2007; 50: 1-13.
6. Redheuil A, Yu WC, Wu CO. Reduced ascending aortic strain and distensibility: earliest manifestations of vascular aging in humans. Hypertension 2010; 55: 319-326.
7. Basta G, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. Cardiovasc Res 2004; 63: 582-592.
8. Niederhoffer N, Lartaud-Idjouadiene I, Giummelly P, Duvivier C, Peslin R, Atkinson J. Calcification of medial elastic fibers and aortic elasticity. Hypertension 1997; 29: 999-1006.
9. Williams B. The aorta and resistant hypertension. J Am Coll Cardiol 2009; 53: 452-454.
10. Nichols WW, O'Rourke MF, McDonald DA. McDonald's blood flow in arteries: theoretic, experimental, and clinical principles. 6th ed. London, New York: Hodder Arnold; 2011, p. 607.
11. Avolio AP, Van Bortel LM, Boutouyrie P, et al. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. Hypertension 2009; 54: 375-383.
12. Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet 2007; 370: 591-603.
13. Roman MJ, Devereux R, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension 2007; 50: 197-203.
14. Pini R, Cavallini MC, Palmieri V, et al. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARe Dicomano Study. J Am Coll Cardiol 2008; 51: 2432-2439.
15. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006; 113: 1213-1225.
16. Nelson MR, Stepanek J, Cevette M, Covalciuc M, Hurst RT, Tajik AJ. Noninvasive measurement of central vascular pressures with arterial tonometry: clinical revival of the pulse pressure waveform? Mayo Clin Proc 2010; 85: 460-472.
17. Weber T, Wassertheurer S, Rammer M, et al. Validation of a brachial cuff-based method for estimating central systolic blood pressure. Hypertension 2011; 58: 825-832.
18. Lin AC, Lowe A, Sidhu K, Harrison W, Ruygrok P, Stewart R. Evaluation of a novel sphygmomanometer, which estimates central aortic blood pressure from analysis of brachial artery suprasystolic pressure waves. J Hypertens 2012; 30: 1743-1750.
19. Costello BT, Schultz MG, Black JA, Sharman JE. Evaluation of a brachial cuff and suprasystolic waveform algorithm method to noninvasively derive central blood pressure. Am J Hypertens 2014; Sep 5 [Epub ahead of print].
20. Quail MA, Steeden JA, Knight D, Segers P, Taylor AM, Muthurangu V. Development and validation of a novel method to derive central aortic systolic pressure from the MR aortic distension curve. J Magn Reson Imaging 2014; 40: 1064-1070.
21. Huang C-M, Wang K-L, Cheng H-M, et al. Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities. J Hypertens 2011; 29: 454-459.
22. Sharman JE, Marwick TH, Gilroy D. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP GUIDE study. Hypertension 2013; 62: 1138-1145.
23. Kass DA, Shapiro EP, Kawaguchi M. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. Circulation 2001; 104: 1464-1470.
24. Fujimoto N, Hastings JL, Carrick-Ranson G, et al. Cardiovascular effects of 1 year of alagebrium and endurance exercise training in healthy older individuals. Circ Heart Fail 2013; 6: 1155-1164.
25. Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 2010; 376: 1903-1909.
26. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014; 370: 1393-1401.
27. Heffernan KS, Fahs CA, Iwamoto GA, et al. Resistance exercise training reduces central blood pressure and improves microvascular function in African American and white men. Atherosclerosis 2009; 207: 220-226.
28. Otsuki T, Maeda S, Iemitsu M, et al. Vascular endothelium-derived factors and arterial stiffness in strength- and endurance-trained men. Am J Physiol Heart Circ Physiol 2007; 292: H786-H791.
29. Cañadas V, Vilacosta I, Bruna I, Fuster V. Marfan syndrome. Part 1: pathophysiology and diagnosis. Nat Rev Cardiol 2010; 7: 256-265.
30. Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. N Engl J Med 2014; 370: 1920-1929.
31. Spin JM. Gene mutations and familial thoracic aortic aneurysms: a walk on the mild side. Circ Cardiovasc Genet 2011; 4: 4-6.
32. Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. J Am Coll Cardiol 2010; 55: 841-857.