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CURRENT TOPICS REVIEW ARTICLE

Etiology of aortic dissection

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Abstract
We discuss the etiology of aortic dissection (AD) from various points of view. The development of AD requires two pathological conditions: medial degeneration and mechanical wall stress. First, histopathological findings of medial degeneration are hypothesized to be due to a loss of elastic fibers and interconnecting elastic fibers. Damage to the vasa vasorum plays a key role in creating an entry site. The clinical causes of medial degeneration include hypertension, aortic aneurysms, obstructive sleep apnea, and connective tissue disorders. Second, mechanical wall stress is supposedly induced by shear stress caused by blood flow, together with hypertension and aortic root movement. Further investigation is necessary in the search for mechanisms responsible for medial degeneration prior to AD development.

Keywords Aortic dissection · Etiology · Medial degeneration · Shear wall stress · Connective tissue disorder · Vasa vasorum

Introduction

Acute aortic dissection (AAD) is a potentially catastrophic condition for which the etiology has been described but remains to be fully elucidated. In addition, although hypertension [1, 2] and Marfan syndrome (MFS) [3] are well-known causes of aortic dissection (AD), their association with this disease are not fully understood. In this paper, we discuss the etiology of AD from various points of view.

AD may develop in response to specific conditions existing with the aorta. This is thought to involve "medial degeneration of the aortic wall", the idea having initially been reported in 1958 [1]. The etiology of AD will be explained with respect to this process, except in response to events such as trauma or iatrogenic disease. In addition, the development of AD needs a "trigger" related to creating an entry site in the aortic wall. The trigger is presumed to be blood flow, which produces shear stress on the aortic wall. Thus, AD development requires two pathological conditions: medial degeneration and mechanical shear stress of the aortic wall. The etiology of AD will be explained according to these two pathological processes.

Medial degeneration of aortic wall

Histopathological findings

Medial degeneration of the aortic wall is considered to be a specific condition that favors the development of AAD. Cystic medial necrosis (CMN) is one of several representative medial degenerations of the aortic wall. However, the terminology for medial degeneration has varied over time. Recently, older terms such as CMN and medionecrosis have been replaced by terms such as mucoid extracellular matrix accumulation, elastic fiber fragmentation and/or loss, and smooth muscle cell nuclei loss [4].

Cystic medial necrosis

Classically, CMN has been regarded as the main cause of AD. Recently, CMN was reportedly observed in only 8–19% of AD patients without MFS [5–7] in whom the degree of CMN was mild. In contrast, it was observed in 40–82% of AD patients with MFS [5, 7], with the degree being severe. Thus, CMN is now not considered to be the main cause of AD without the presence of a connective tissue disorder

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(CTD) such as MFS. CMN of a mild nature is observed with increasing age, and is also observed more often in patients with hypertension [8].

Elastic fiber loss

Elastic fiber is the most important component of connective tissue responsible for the elasticity of the aortic media. Several reports describe how elastic fibers were observed to be decreased in AD [7, 9] (Fig. 1). In contrast, others have reported that elastic fiber loss was not significant in this disease [10]. Additionally, the extent of elastic fiber loss may not be uniform in each case of AD.

Interconnecting elastic fiber loss

Interconnecting elastic fibers are components within connective tissue that bind elastic fibers together and can be seen only by electron microscopy. The loss of interconnecting elastic fibers has been reported in patients with AD [9, 11] and hypertension [11] (Fig. 2). This is thought to be essential in the etiology of the degeneration of the aortic media. The loss of interconnecting elastic fibers may result in difficulty balancing the shear stress present between the intima and adventitia of the aortic wall, resulting in the disruption and detachment of the intima, and causing the creation of an entry site [9].

Diseases causing medial degeneration of the aortic wall (Table 1)

Congenital diseases: connective tissue disorders

Elastic fibers are a component of connective tissue. CTDs show decreased and incomplete elastic fibers, resulting in fragile connective tissue such as in the aortic wall, bone, and lungs. The strength of the aortic media is the most important determinant of the fragility of the aortic wall; a CTD will subsequently lead to the development of AD and an aortic aneurysm. CTDs are also very often caused by genetic disorders. This has led to the suspicion that patients who present

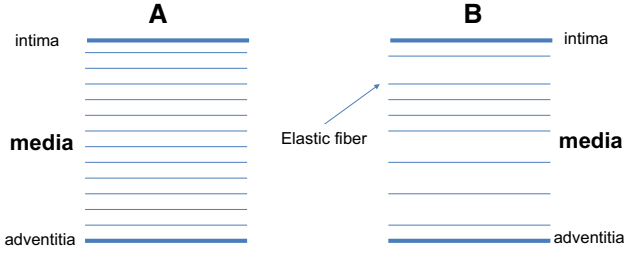

Fig. 1 Elastic fiber loss is obvious in an aortic dissection (**B**) compared to control (**A**)

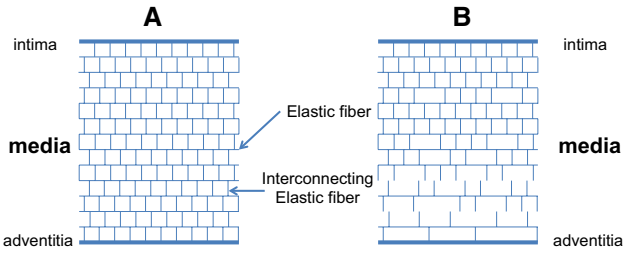

Fig. 2 The loss of interconnecting elastic fibers is more obvious in the external media in an aortic dissection (**B**) compared to control (**A**)

with AAD and who are younger than 40 years of age may have a genetic disorder.

MFS (with *FBN1* mutations) and vascular type Ehlers–Danlos syndrome (vEDS; with *COL3A1* mutations) are well-known genetic diseases. Recently, patients with Loeys–Dietz syndrome (LDS) have been shown to have *TGRBR1* or *TGFBR2* mutations [12], while other CTDs with novel gene mutations, such as *ACTA2* [13], *SMAD3* [14], and *TGFBR* [15], among others, are regularly being discovered. However, all gene mutations causing CTD have not been fully elucidated.

Marfan syndrome MFS is the most common and representative CTD caused by *FBN1* mutations, resulting in skeletal, ocular and cardiovascular problems. The most common and serious finding of MFS is a dilatation of the aortic root [16], which causes a type A AD; in such instances, surgical repair is aggressively performed.

Loeys–Dietz syndrome LDS is caused by *TGFBR1* or *TGFBR2* mutations. The clinical manifestation of LDS is often varied: some cases have a Marfan-like appearance, while other patients look totally normal [17].

Bifid uvula, hypertelorism and the dilatation of branch vessels, such as celiac and supra-mesenteric arteries, from

Table 1 Diseases associated with development of aortic dissection

Diseases	Ratio	References
Hypertension	50–86%	[1, 2, 5, 27–30]
Obstructive sleep apnea	13%	[34]
Aortic aneurysm	9%	[36]
Bicuspid aortic valve	2%	[20]
Connective tissue disorder	< 10%	[26]
Marfan syndrome	5%	[3]
Others	< 5%	[26]
Loeys–Dietz syndrome		
ACT2 mutations		
SMAD3 mutations		
TGFB2 mutations		

the aorta, are thought to be characteristics of LDS [12]; however, these are not commonly observed. Compared to MFS, connective tissue abnormalities are biased toward vascular abnormalities. If a patient has ectopia lentis, LDS is ruled out. Aortic root dilatation, which causes type A AD, is also a very important finding in LDS. Arterial dissection tends to occur with smaller vascular diameters compared to MFS [12]. For example, earlier operative intervention is recommended for ascending aortic diameters of ≥ 42 mm in LDS compared to ≥ 45 mm in MFS [18].

Vascular type Ehlers–Danlos syndrome vEDS is one of various types of EDS, and is caused by *COL3A1* mutations. vEDS is generally characterized by the following findings: translucent skin, easy bruising, fragile arteries, and bowel or uterus perforations. In particular, easy bruising (97%) and translucent skin (77%) are often found in such patients [19]. Stretchy skin is characteristic of classical type EDS, not of vEDS. Disorders of the arteries in this disease do not often include the aorta; instead, supra-mesenteric, splenic, renal and common iliac arteries are more commonly involved [19]. Dissection and rupture of aneurysms of affected arteries are the most common causes of death for patients with vEDS. Compared to MFS and LDS, aortic root dilatation is less commonly found in vEDS; however, the aorta is more fragile. As a result, surgery is only contemplated in potentially fatal complications because of tissue weakness [18].

***ACTA2* mutations** *ACTA2* mutations cause abnormalities of the smooth muscle, resulting in CTDs [13]. Patients with an *ACTA2* mutation lack any obvious physical abnormality making their diagnosis difficult from physical appearance alone, as for MFS.

Bicuspid aortic valve A bicuspid aortic valve (BAV) is found in 9% of patients with AD who are less than 40 years of age; it is found in 2% of all AAD cases [20]. The etiology of BAV is presently under discussion and is thought to be associated with the development of AD in two ways: First, aortic stenosis and regurgitation caused by a BAV may generate mechanical damage to the ascending aortic wall, resulting in aortic dilatation and AD [21]. Second, a BAV may be caused by a genetic disorder complicated by a CTD [22], resulting in aortic dilatation and AD because of a fragile aortic wall [23]. *GATA2* [24] and *NOTCH1* [25] mutations found in patients with a BAV have been reported; however, only a small proportion of patients carried these mutations. Thus, the major cause of a BAV, whether a hemodynamic or genetic disorder, remains unclear.

Others *SMAD3* mutations cause aneurysm–osteoarthritis syndrome, which is characterized by arterial aneurysms, skeletal anomalies and osteoarthritis [14].

Aortic root dilatation causing AD is an important clinical feature of *SMAD3* mutations. *TGFB2* mutations cause Marfan-like clinical features such as aortic root dilatation and skeletal abnormalities. However, ectopia lentis is absent, individuals do not meet the diagnostic criteria for MFS, and AD does not occur at a young age as found in MFS [15].

What is the proportion of AD cases caused by genetic disorders? Patients with MFS comprise 5% of all AD cases [3]. However, with regard to young patients with AD and aortic aneurysms, we have shown that 60% of patients had MFS, 6% had LDS, and 5% had *ACTA2* mutations, while the other 29% of cases were of an unknown origin [26]. Therefore, CTD cases other than MFS may account for less than a half of all MFS cases with AD and aortic aneurysms. MFS and other CTDs may amount to about 10% or less of all AD cases.

Acquired diseases

Hypertension Hypertension is found in 50–86% of patients with AD and is associated with the development of AD in two ways: [1, 2, 5, 27–30]. First, it is related to medial degeneration of the aortic wall. Hypertension reduces the blood flow of the vasa vasorum that nourishes one-third of the external aortic media. Therefore, hypertension causes ischemia and damage to the external media, resulting in the latter's decreased elasticity [31]. Second, hypertension causes mechanical shear stress of the aortic wall [32], resulting in the creation of an entry site. Thus, hypertension is related to both a specific condition that favors the development of AD, and to the mechanical stress that creates an entry site.

Obstructive sleep apnea Recently, obstructive sleep apnea (OSA) has been shown to be an important cause of AD [33, 34]. Yanagi et al. reported that OSA occurred in 13% of all AAD cases [34]. However, it is difficult to fully understand how OSA affects the development of AD. One hypothesis is that negative intrathoracic pressures during apnea may increase the transmural pressure of the aortic wall, causing damage. An increase in sympathetic activity resulting in high blood pressure [33] may be necessary to initiate an entry site. In contrast, a cohort study showed that OSA was not associated with an increased risk of AD [35]. We conclude that evidence for OSA should be aggressively searched for among patients with AD during hospitalization.

True aortic aneurysms We previously found a true aneurysm was a complication in 24% of all cases with AAD; 9% of all AAD cases originated specifically from an aortic aneurysm [36]. We should be mindful that the final features of a true aneurysm include not only an aortic rupture, but

also the development of AD. The aortic wall dilates while its structure is intact (intima, media, and adventitia) during the first stage of an aortic aneurysm. However, in the final stage, the aneurysmal wall, composed of three wall structures, breaks down and becomes thinner. Thus, AD sometimes occurs after the development of such broken down and thin aneurysmal walls.

Inflammatory aortic diseases Inflammatory aortic diseases, such as Takayasu aortitis, giant cell aortitis, and Behçet's disease, have been previously described in case reports but are unlikely to be a cause of AD. The main inflammatory lesion of Takayasu aortitis is composed of aortic media and medial necrosis and the fragmentation of elastic fibers [37]. Typical inflammatory lesions of Takayasu aortitis are found in neck vessels and subclavian arteries. The aortic root is also common as a site of inflammatory lesions, and aortic regurgitation with dilatation of the ascending aorta is related to AD.

Pregnancy and steroid use In pregnancy, an increased circulatory blood mass raises blood pressure and causes aortic wall stress. Pregnancy is thus thought to be a risk factor for AD [38]. However, many pregnant patients who develop AD often have CTDs such as MFS, while pregnant patients without MFS are unlikely to develop AD [39]. Long-time steroid use also disturbs the production of collagen fibers, resulting in a fragile aortic wall and the development of AD [40].

Atherosclerosis The association of atherosclerosis with the development of AD has been previously discussed elsewhere [41, 42]. AD can develop at the site of a penetrating ulcer that is caused by atherosclerosis; however, the frequency of occurrence is not high. In general, atherosclerosis is thought not to be associated with the development of AD [41]. In patients with AD, the extent of atherosclerosis can be from mild to moderate, while the development of AD is sometimes observed to cease at an atherosclerotic site of aortic aneurysm [36].

Aortic wall stress

Disruption of aortic intima caused by medial ischemia with shear stress

The aortic wall is composed of three layers: the intima, media, and adventitia. The media is the thickest layer and is responsible for the elastic property of the aorta. Nutrients and oxygen for two-thirds of the internal media are supplied by perfusion from the lumen of the aorta, while nutrients for one-third of the external media is supplied by the vasa vasorum [43]. As described above, hypertension damages the vasa vasorum, which is rich in the external media, resulting in external medial ischemia and a decrease in its elasticity [31]. In contrast, two-thirds of the internal media is unlikely to be ischemic, and its elasticity is unlikely to be reduced. Thus, differences in elastic properties between the inner and outer media plus the shear stress of the aortic wall, which is caused by blood flow proportional to hypertension [32], may eventually lead to detachment of the layers to cause AD [31]. Most AD develops in one-third of the external media [44].

Vertical swinging motion at the aortic root

The aortic root moves vertically according to the beating of the heart. The aorta is anchored by three branch vessels from the aortic arch. Therefore, the aorta at the origin of these three vessels, where an entry site is often created, is exposed to strong mechanical stresses [45]. In fact, a finite element model shows that two centimeters distal from the aortic root, the origin of the brachiocephalic artery and the aortic isthmus are exposed to strong stresses [46].

Progression of AD in the media

During the development of AD, blood flows into the aortic wall through an entry site and runs in the direction of the adventitia. In an experimental model, blood flow that reaches the first one-third of the external media turns in a cranio-caudal direction, resulting in the extension of a dissection [47]. Thus, AD often progresses in this first one-third of the media [45, 47], which is the border for nutrition that is supplied by the vasa vasorum or perfusion from the aortic lumen. Any impairment of the vasa vasorum would mean a reduced blood supply and an increased fragility of the media, which may be associated with the development of AD.

AD without entry site

The term "intramural hematoma (IMH)" is defined as AD without an entry site and is a histopathological term. In Japan, we use the term "non-communicating false lumen" instead of IMH according to the "Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection (JCS 2011)" [48]. This is because the existence of an entry site is very difficult to determine in a clinical setting. Small intimal tears are not all detected by a computed tomography scan, even with a direct view. However, whether AD without an intimal tear can actually exist for a long period of time is controversial. Hirst et al. reported a lack of intimal tears in 4% of 505 autopsy cases of AD [1]. The International Registry of Acute Aortic Dissections reported that IMH

comprised 6% of 2830 AD cases [49]. About 5% of AD cases may lack an entry site.

If AD cases without an intimal tear actually exist, this may support the idea that medial degeneration is the first step in the development of AD. In ordinary cases, medial degeneration would cause disruption and detachment of the intima, which may then create an entry site resulting in a communicating false lumen. In contrast, a non-communicating false lumen can develop in two ways: one is by blood flow in the media without re-entry that becomes stagnant, and coagulates wholly within the false lumen, including the entry site. The other is supposedly by rupture of the vasa vasorum causing hematoma in the media. In some limited cases of AD with a non-communicating false lumen, medial degeneration may cause a rupture of the vasa vasorum prior to an emerging entry site. These ideas are only hypotheses and have not, to date, been supported by sufficient evidence. Whether AD cases without intimal tears exist or not is one of the keys to resolving the mechanisms involved in their development.

Conclusions

AD may develop on the basis of medial degeneration, and mechanical aortic wall stress. Histopathological findings of medial degeneration are hypothesized to be a loss of elastic fibers and interconnecting elastic fibers. The clinical causes of medial degeneration include hypertension, aortic aneurysms, OSA, and CTDs. In addition, mechanical wall stress is supposedly induced by shear stress caused by blood flow, together with hypertension and aortic root movement. Damage to the vasa vasorum plays a key role in creating an entry site.

Thus, although the etiology of AD has been extensively discussed; it however, has not been fully elucidated. Further investigation is necessary in the search for mechanisms responsible for medial degeneration prior to AD development.

Compliance with ethical standards

Conflict of interest The author declares no competing financial interests.

References

1. Hirst AE Jr, Johns VJ Jr, KIime SW Jr. Dissecting aneurysm of the aorta: a review of 505 cases. Medicine (Baltimore). 1958;37:217–79.
2. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The international registry of acute aortic dissection (IRAD): new insights into an old disease. JAMA. 2000;283:897–903.
3. Nienaber CA, Fattori R, Mehta RH, Richartz BM, Evangelista A, Petzsch M, et al. International registry of acute aortic dissection. Gender-related differences in acute aortic dissection. Circulation. 2004;109:3014–21.
4. Halushka MK, Angelini A, Bartoloni G, Basso C, Batoroeva L, Bruneval P, et al. Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology: II. Noninflammatory degenerative diseases—nomenclature and diagnostic criteria. Cardiovasc Pathol. 2016;25:247–57.
5. Wilson SK, Hutchins GM. Aortic dissecting aneurysms: causative factors in 204 subjects. Arch Pathol Lab Med. 1982;106:175–80.
6. Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. Am J Cardiol. 1984;53:849–55.
7. Nakashima Y, Kurozumi T, Sueishi K, Tanaka K. Dissecting aneurysm: a clinicopathologic and histopathologic study of 111 autopsied cases. Hum Pathol. 1990;21:291–6.
8. Carlson RG, Lillehei CW, Edwards JE. Cystic medial necrosis of the ascending aorta in relation to age and hypertension. Am J Cardiol. 1970;25:411–5.
9. Kageyama N, Ro A, Tanifuji T, Kumagai T, Murai T, Fukunaga T. The histopathologic study of elastic laminar and interconnecting elastic fiber in aortic media: Implications for aortic dissection (Japanese). J Jpn Coll Angiol. 2005;45:1003–9.
10. Roberts WC, Vowels TJ, Kitchens BL, Ko JM, Filardo G, Henry AC, et al. Aortic medial elastic fiber loss in acute ascending aortic dissection. Am J Cardiol. 2011;108:1639–44.
11. Nakashima Y, Shiokawa Y, Sueishi K. Alterations of elastic architecture in human aortic dissecting aneurysm. Lab Investig. 1990;62:751–60.
12. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006;355:788–98.
13. Morisaki H, Akutsu K, Ogino H, Kondo N, Yamanaka I, Tsutsumi Y, et al. Mutation of *ACTA2* gene as an important cause of familial and non-familial non-syndromatic thoracic aortic aneurysm and/or dissection. Hum Mutat. 2009;30:1406–11.
14. van de Laar IM, van der Linde D, Oei EH, Bos PK, Bessems JH, Bierma-Zeinstra SM, et al. Phenotypic spectrum of the SMAD3-related aneurysms-osteoarthritis syndrome. J Med Genet. 2012;49:47–57.
15. Boileau C, Guo DC, Hanna N, Regalado ES, Detaint D, Gong L, et al. TGFB2 mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. Nat Genet. 2012;44:916–21.
16. Détaint D, Faivre L, Collod-Beroud G, Child AH, Loeys BL, Binquet C, et al. Cardiovascular manifestations in men and women carrying a FBN1 mutation. Eur Heart J. 2010;31:2223–9.
17. Akutsu K, Morisaki H, Takeshita S, Sakamoto S, Tamori Y, Yoshimuta T, et al. Phenotypic heterogeneity of Marfan-like connective tissue disorders associated with mutations of the transforming growth factor-β receptor gene. Circ J. 2007;71:1305–9.
18. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2873–926.
19. Oderich GS, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. J Vasc Surg. 2005;42:98–106.

20. Januzzi JL, Isselbacher EM, Fattori R, Cooper JV, Smith DE, Fang J, et al. Characterizing the young patient with aortic dissection: results from the international registry of aortic dissection (IRAD). Am Coll Cardiol. 2004;43:665–9.
21. Hahn RT, Roman MJ, Mogtader AH, Devereux RB. Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves. J Am Coll Cardiol. 1992;19:283–8.
22. Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. J Am Coll Cardiol. 2004;44:138–43.
23. Bonderman D, Gharehbaghi-Schnell E, Wollenek G, Maurer G, Baumgartner H, Lang IM. Mechanisms underlying aortic dilatation in congenital aortic valve malformation. Circulation. 1999;99:2138–43.
24. Padang R, Bagnall RD, Richmond DR, Bannon PG, Semsarian C. Rare non-synonymous variations in the transcriptional activation domains of GATA5 in bicuspid aortic valve disease. J Mol Cell Cardiol. 2012;53:277–81.
25. Garg V, Muth AN, Ransom JF, Schluterman MK, Barnes R, King IN, et al. Mutations in NOTCH1 cause aortic valve disease. Nature. 2005;437:270–4.
26. Akutsu K, Morisaki H, Okajima T, Yoshimuta T, Tsusumi Y, Takeshita S, et al. Genetic analysis of young adult patients with aortic disease not fulfilling the diagnostic criteria for Marfan syndrome. Circ J. 2010;74:990–7.
27. Suzuki T, Isselbacher EM, Nienaber CA, Pyeritz RE, Eagle KA, Tsai TT, et al. Type-selective benefits of medications in treatment of acute aortic dissection (from the international registry of acute aortic dissection [IRAD]). Am J Cardiol. 2012;109:122–7.
28. Li Y, Yang N, Duan W, Liu S, Yu S, Yi D. Acute aortic dissection in China. Am J Cardiol. 2012;110:1056–61.
29. Howard DP, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM, et al. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. Circulation. 2013;127:2031–7.
30. Pape LA, Awais M, Woznic.ki EM, Suzuki T, Trimarchi S, Evangelista A, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the international registry of acute aortic dissection. J Am Coll Cardiol. 2015;66:350–8.
31. Angouras D, Sokolis DP, Dosios T, Kostomitsopoulos N, Boudoulas H, Skalkeas G, et al. Effect of impaired vasa vasorum flow on the structure and mechanics of the thoracic aorta: implications for the pathogenesis of aortic dissection. Eur J Cardiothorac Surg. 2000;17:468–73.
32. Gao F, Guo Z, Sakamoto M, Matsuzawa T. Fluid-structure interaction within a layered aortic arch model. J Biol Phys. 2006;32:435–54.
33. Sampol G, Romero O, Salas A, Tovar JL, Lloberes P, Sagales T, et al. Obstructive sleep apnea and thoracic aorta dissection. Am J Respir Crit Care Med. 2003;168:1528–31.
34. Yanagi H, Imoto K, Suzuki SI, Uchida K, Masuda M, Miyashita A. Acute aortic dissection associated with sleep apnea syndrome. Ann Thorac Cardiovasc Surg. 2013;19:456–60.
35. Teng HI, Huang CC, Chiang CH, Huang PH, Chung CM, Lin SJ, et al. Sleep apnea and risk of aortic dissection: a nonrandomized, pair-matched cohort study. J Chin Med Assoc. 2016;79:422–7.
36. Tamori Y, Akutsu K, Kasai S, Sakamoto S, Okajima T, Yoshimuta T, et al. Coexistent true aortic aneurysm as a cause of acute aortic dissection. Circ J. 2009;73:822–5.
37. Miller DV, Isotalo PA, Weyand CM, Edwards WD, Aubry MC, Tazelaar HD. Surgical pathology of noninfectious ascending aortitis: a study of 45 cases with emphasis on an isolated variant. Am J Surg Pathol. 2006;30:1150–8.
38. Nasiell J, Lindqvist PG. Aortic dissection in pregnancy: the incidence of a life-threatening disease. Eur J Obstet Gynecol Reprod Biol. 2010;149:120–1.
39. Oskoui R, Lindsay J Jr. Aortic dissection in women < 40 years of age and the unimportance of pregnancy. Am J Cardiol. 1994;73:821–3.
40. Reilly JM, Savage EB, Brophy CM, Tilson MD. Hydrocortisone rapidly induces aortic rupture in a genetically susceptible mouse. Arch Surg. 1990;125:707–9.
41. Roberts WC. Aortic dissection: anatomy, consequences, and causes. Am Heart J. 1981;101:195–214.
42. Creager MA, Jones DW, Easton JD, Halperin JL, Hirsch AT, Matsumoto AH, et al. American Heart Association. Atherosclerotic Vascular Disease Conference. Writing Group V: Medical decision making and therapy. Circulation. 2004;109:2634–42.
43. Heistad DD, Marcus ML, Law EG, Armstrong ML, Ehrhardt JC, Abboud FM. Regulation of blood flow to the aortic media in dogs. J Clin Investig. 1978;62:133–40.
44. Osada H, Kyogoku M, Ishidou M, Morishima M, Nakajima H. Aortic dissection in the outer third of the media: what is the role of the vasa vasorum in the triggering process? Eur J Cardiothorac Surg. 2013;43:e82-8.
45. Beller CJ, Labrosse MR, Thubrikar MJ, Robicsek F. Role of aortic root motion in the pathogenesis of aortic dissection. Circulation. 2004;109:763–9.
46. Beller CJ, Labrosse MR, Thubrikar MJ, Robicsek F. Finite element modeling of the thoracic aorta: including aortic root motion to evaluate the risk of aortic dissection. J Med Eng Technol. 2008;32:167–70.
47. Mitsui H, Uchida H, Teramoto S. Correlation between the layer of an intimal tear and the progression of aortic dissection. Acta Med Okayama. 1994;48:93–9.
48. Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection. (JCS 2011)—Digest Version—JCS Joint Working Group. https://www.jstage.jst.go.jp/article/circj/77/3/77_CJ-66-0057/_pdf.
49. Harris KM, Braverman AC, Eagle KA, Woznicki EM, Pyeritz RE, Myrmel T, et al. Acute aortic intramural hematoma: an analysis from the international registry of acute aortic dissection. Circulation. 2012;126(11 Suppl 1):91–6.