Changes of the Endothelium and Extracellular Matrix in Thoracic Aortic Aneurysm Revealed by Scanning Electron Microscopic Investigations Are there Structural Parallels to Aortic Valve Degeneration?

Mirzaie Masoud1*, Michael Schultz2, Peter Schwartz2, Zaur Guliyev1 and Sheila Fatehpur1

1Department of Vascular Surgery, Lippe-Lemgo Hospital, University clinics OWL, Germany
2Institute for Anatomy, University of Göttingen, Göttingen, Germany

*Corresponding author: Masoud Mirzaie, Head of the Department of Vascular Surgery University Hospital of Lemgo, Germany

Abstract

Objective: Thoracic aneurysms occur most frequently with 60% in ascending aorta and arch, and in 40% the descending aorta, although the etiological factors are different for individual segments. While, depending on localization, factors such as atherosclerosis, bicuspid aortic valve, familial thoracic aortic aneurysm syndrome, Turner syndrome, Marfan syndrome, aortic arteritis in Takayasu’s arteritis, trauma and dissection lead to the formation of thoracic aortic aneurysms, the structural changes of the basement membrane and the exact causes of the mechanism of thoracic aortic aneurysm are not known. The aim of this study was to investigate the pathophysiological origin of thoracic aortic aneurysms from a morphological point of view.

Patients and methods: For this study, between 2007 and 2017, 12 patients with thoracic aortic aneurysms with contraindications to interventional therapy underwent open surgery. All patients underwent multi-detector row CT with three-dimensional (3D) reformation in 3 mm slices and transesophageal echocardiography. Tissue samples were taken from descending aorta of two female (average age, 72.32 years) and 10 male patients (63.12 years), and were fixed for 6 hours in a solution containing 2.5% glutaraldehyde and 0.2 mMol cacodylate. The samples were finally visualized using the digital scanning microscope.

Results: In addition to partial desquamation of the endothelium, severe alterations of the collagen fibers and basal membrane and repair attempts in the form of endothelial islets and deep tears in the fibers, cancellation and destruction of the helical structure of collagen fibers are visible.

Conclusion: In summary, in thoracic aortic aneurysms we found severe structural changes of collagen fibres, endothelium and basement membrane, which occur in a similar form to acquired aortic valve degeneration.

Keywords: Thoracic aortic aneurysm, electron microscopy,
loss of muscle cells and interstitial collections of collagenous fibers and basophilic ground substance [5,6]. The aim of this study was the evaluation of the changes of endocardium and extracellular matrix in thoracic aortic aneurysms.

Materials and methods

Tissue samples

Table 1: Baseline characteristics of the study population.

| Aortic aneurysms (n=10) | Male | Female |
|-------------------------|------|--------|
| Age                     | 10   | 2      |
| (63.12 years)           | (72.32 years) |
| Comorbidities           |      |        |
| Nicotin, active         | 4 (40.0%) | 1 (50%) |
| Ex-nicotin              | 1 (10.0%) | 0     |
| Hypertension            | 8 (80.0%) | 1 (50%) |
| Diabetes                | 4 (40%)  | 1 (50%) |
| Hyperlipoproteinemia    | 4 (40%)  | 0     |
| Hyperuricaemia          | 1 (10%)   | 0     |
| CHD                     | 3 (30%)  | 0     |
| Carcinoma               | 1 (10%)   | 0     |
| Renal insufficiency     | 2 (20%)  | 0     |
| COPD, emphysema         | 2 (20%)  | 1 (50%) |

Continuous variables are presented as an absolute percentage. Abbreviations: CHD: Coronar Heart Disease, COPD: Chronic obstructive pulmonary disease.

Results

Figure 1: Electronmicroscopical view of inner aortic wall, 1000 x magnification: desquamation of endothelial cells from basal membrane with partially dissolved cell junctions and destruction of collagen fibers.

Tissue samples were taken from the descending aorta of two female (average age, 72.32 years) and 10 male patients (63.12 years). 8 patients were undergoing emergency surgical resection and four patients elective resection. Preoperative diagnostics and therapy were performed according to the guidelines of the European Society of Cardiology for the diagnosis and therapy of aortic aneurysms. Thus, all patients underwent preoperative thoracic CT angiography with three-dimensional (3D) reformation in 3 mm slices and trans-esophageal echocardiography. The indication for surgery was set for an aneurysm size of > 5.5 cm, for smaller aneurysms the indication was given only in the presence of grade 3 aortic valve insufficiency, and as an emergency in the case of perforation [7]. Table 1 presents summarized data of the basic patient characteristics.

Scanning Electron Microscopy

In order to reveal the morphology of the tissue sample, scanning electron microscopy was performed in all tissue samples. Specimens from the descending aorta were fixed for 6 hours in a solution containing 2.5% glutaraldehyde and 0.2 mMol cacodylate. Afterwards, samples were dehydrated in a series of increasing concentrations of alcohol. After critical point drying, all samples were sputtered with gold-palladium. Samples were visualized using the digital scanning microscope (Zeiss DSM 960, Germany).
Scanning electron microscopical findings. In all samples we studied the endothelial tissue materials which are, for the most part, desquamated. The intervening tissue, collagen and elastic fibers are destroyed, and are infiltrated mainly with red cells. Rarely, are the collagen fibers present in the island form obtained endothelial cells. At higher magnification, deep tears in the fibers, cancellation and destruction of the helical structure of collagen fibers are visible. The remaining endothelial cells are swollen. The intercellular junction is partially disrupted, and only available in a few fibers. The collagen fibers are partially hypertrophied. In such places, the endothelial cells are deposited in the fibers, the lamina elastic interna is for the most part no longer exists (Figures 1, 2). The endothelial cells are present as islands. The surface of the endothelial cells are transformed villi, reminiscent of endothelial cells of the duodenum (Figures 3, 4). The deep defects of the extracellular matrix are covered in places by the normal endothelium as a partial reendothelialisation and give the impression of a deep crater (Figure 5).

Figure 2: Electronmikroscopical view of inner aortic wall, 1500 x magnification, destruction of collagen and elastic fibers with infiltration mainly by red cells, the collagen fibers rarely are present in the island form obtained endothelial cells.

Figure 3: Electron microscopical view of cell island of aortic wall, 1000 x magnification, the endothelial cells are present as islands.
Figure 4: Electron microscopical view of cell island of aortic wall, 2000 x magnification, the surface of the endothelial cells are transformed into villi, reminiscent to endothelial cells of the duodenum.

Figure 5: Electronmicroscopical view of inner aortic wall, 2500 x magnification, the deep defects of the extracellular matrix are in places covered by the endothelium, which lokks irregular. The shape of endothelial coating shows very deep defects in aortic wall.

Discussion

Thoracic aortic aneurysms and dissections constitute a critical condition that often goes undiagnosed with fatal consequences. Besides, various inherited forms discussed, genetic factors are discussed, genetic factors being important in the development of thoracic aneurysms [8,9]. Familial aortic aneurysm (FAA) has been described in such conditions as the Marfan and Ehlers-Danlos syndrome type IV, which are due to defects in the fibrillin-1 and III procollagen genes respectively [10-14]. In this group of a novel locus at chromosome 11q23.3-q24 was detected, a critical step toward elucidating a gene defect responsible for aortic dilatation [15]. Hasham et al. Determined one locus, mapped to 5q13-14, which will enhance the chances to determine persons at risk for aortic aneurysm in non-familial aortic aneurysm diseases [5]. Thoracic aortic aneurysms and infrarenal aortic aneurysms exhibit distinct patterns of gene expression relative to the normal aorta from the same sites [14]. Keramat mapped in familial TAA, a single
Changes of the Endocardium and Extracellular Matrix in Thoracic Aortic Aneurysm
of increased expression of metalloproteinases ADAM10, ADAM17, the synthesized collagen fibers is underlined by the demonstration progression of aneurysmal enlargement [28]. The hypothesis of an aneurysm and provide a potential mechanism for generation and expansion of aneurysms [20]. Smooth muscle cells can exert a tiggr function in the development of inflammatory processes involved in transmural inflammation by increased secretion of GM-CSF [21-23]. The bulk of the extracellular matrix was involved in transmural inflammation, IFN-gamma, IP-10 and mig chemikines are correlated with vascular remodeling and expansion of aneurysms [20]. Smooth muscle cells can exert a tiggr function in the development of inflammatory processes involved in transmural inflammation by increased secretion of GM-CSF [21-23]. The bulk of the extracellular matrix was involved in transmural inflammation, IFN-gamma, IP-10 and mig chemikines are correlated with vascular remodeling and expansion of aneurysms [20].

which contributed to atherosclerotic lesions [17]. In TAA, the Nogo-B mRNA and protein expression are downregulated, which correlate to the formation of aneurysm [10]. The age-associated changes in endothelial nitric oxide synthase expression have not been definitively linked to pathophysiology of aortic aneurysm [18]. As a sign of endothelial inflammatory response the increased VCAM-1 expression has been detected in human aorta with atheromatous changes [19]. In descending thoracic aortic aneurysms as a sign of the transmural inflammation, IFN-gamma, IP-10 and mig chemikines are correlated with vascular remodeling and expansion of aneurysms [20]. Smooth muscle cells can exert a tiggr function in the development of inflammatory processes involved in transmural inflammation by increased secretion of GM-CSF [21-23]. The bulk of the extracellular matrix was involved in transmural inflammation, IFN-gamma, IP-10 and mig chemikines are correlated with vascular remodeling and expansion of aneurysms [20].

Conflict of Interest

I hereby declare that there were no financial or other interests in the execution and evaluation of this work.

References

1. Majumdar R, Miller DV, Ballman KV, Ummkrishnan G, McKellar SH et al. (2007) Elevated expressions of osteopontin and tenasin C in ascending aortic aneurysms are associated with bicuspid aortic valve. Cardiovasc Pathol 16(3): 144-150.
2. Meng YH, Tian C, Liu L, Wang L, Chang Q, et al. (2014) Elevated expression of connective tissue growth factor, osteopontin and increased collagen content in human ascending thoracic aortic aneurysms. Vascular 22(1): 20-27.
3. Kim JH, Na CY, Kim HW, Du Kim Y, Kwon JB, et al. (2010) Integration of gene-expression profiles and pathway analysis in ascending thoracic aortic aneurysms. Ann Vasc Surg 24(4): 538-549.
4. Kimura N, Futamura K, Arakawa M, Okada N, Okamura FH, et al. (2017) Elevated expression of osteopontin and tenasin C in ascending aortic aneurysms are associated with bicuspid aortic valve. Cardiovasc Pathol 16(3): 144-150.
5. Meng YH, Tian C, Liu L, Wang L, Chang Q, et al. (2014) Elevated expression of connective tissue growth factor, osteopontin and increased collagen content in human ascending thoracic aortic aneurysms. Vascular 22(1): 20-27.
6. Kim JH, Na CY, Kim HW, Du Kim Y, Kwon JB, et al. (2010) Integration of gene-expression profiles and pathway analysis in ascending thoracic aortic aneurysms. Ann Vasc Surg 24(4): 538-549.
7. Kimura N, Futamura K, Arakawa M, Okada N, Okamura FH, et al. (2017) Elevated expression of osteopontin and tenasin C in ascending aortic aneurysms are associated with bicuspid aortic valve. Cardiovasc Pathol 16(3): 144-150.
8. Meng YH, Tian C, Liu L, Wang L, Chang Q, et al. (2014) Elevated expression of connective tissue growth factor, osteopontin and increased collagen content in human ascending thoracic aortic aneurysms. Vascular 22(1): 20-27.
9. Kim JH, Na CY, Kim HW, Du Kim Y, Kwon JB, et al. (2010) Integration of gene-expression profiles and pathway analysis in ascending thoracic aortic aneurysms. Ann Vasc Surg 24(4): 538-549.
10. Kimura N, Futamura K, Arakawa M, Okada N, Okamura FH, et al. (2017) Elevated expression of osteopontin and tenasin C in ascending aortic aneurysms are associated with bicuspid aortic valve. Cardiovasc Pathol 16(3): 144-150.
5. Hasham SN, Guo DC, Milesicz DM (2002) Genetic basis of thoracic aortic aneurysms and dissections. Curr Opin Cardiol 17(6): 677-683.
6. Takeda N, Komuro I (2019) Genetic basis of hereditary thoracic aortic aneurysms and dissections. Journal of Cardioiology 74(2): 136-143.
7. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, et al. (2014) ESC Committee for Practice Guidelines (2014) Guideline of the European Society for Cardiology (ESC) for diagnosis and therapy of Aortic diseases. Eur Heart J 35(41): 2873-2926.
8. Tromp G, Kuivaniemi H, Hinterseher I, Carey DJ (2010) Novel genetic mechanisms for aortic aneurysms. Curr Atheroscler Rep 12(4): 259-266.
9. Ostberg NP, Zafar MA, Zgiganshi BA, Elefteriades JA (2020) The Genetics of Thoracic Aortic Aneurysms and Dissection: A Clinical Perspective Biomolecules 10(2): pp. 182.
10. Robinson PN, Arteaga-Solis E, Baldock C, Collod-Béroud G, Booms P, et al. (2006) The molecular genetics of Marfan syndrome and related disorders. J Med Genet 43(10): 769-787.
11. El-Hamamsy I, Yacoub MH (2009) Cellular and molecular mechanisms of tigecicular aortic aneurysms. Nat Rev Cardiol 6(12): 771-786.
12. Pinard A, Jones GT, Milewicz DM (2019) Genetics of Thoracic and Abdominal Aortic Diseases Aneurysms, Dissections, and Ruptures. Circulation Research 124(4): 588-606.
13. Verstraeten A, Meester J, Peeters S, Mortier G, Loesys B, et al. (2020) Chondrodysplasias and Aneurysmal Thoracic Aortopathy: An Emerging Tale of Molecular Intersection. Trend in molecular medicine 26(8): 783-795.
14. Vaughan CJ, Casey M, He J, Veugelers M, Henderson K, et al. (2002) Basoon identification of a Chromosome 11q23.2-q24 locus for familial aneurysm disease, a genetically heterogeneous disorder. 103(20): 2469-2475.
15. Koenig SN, LaHaye S, Feller JD, Rowland P, Hor KN, et al. 2017 Notch1 haploinsufficiency causes ascending aortic aneurysms in mice. JCI Insight 2(21): e91353.
16. Kemmati AR, Sadeghpour A, Farahani MM, Chandok G, Mani A, et al. (2010) The non-syndromic familial thoracic aortic aneurysms and dissections maps to 15q21 locus. BMC Med Genet 11: 143.
17. Marin EP, Moeckel G, Al-Lamki R, Bradley J, Yan Q, et al. (2010) Identification and Regulation of Reticulin 4B (Nogo-B) in Renal Tubular Epithelial Cells. Am J Pathol 177(6): 2765-2773.
18. Wächtl T, Pernet V, Weinmann O, Shui Y, Guzik-Kornacka A, et al. (2013) Nogo-A is a negative regulator of CNS angio genesis. Proc Natl Acad Sci 110(21): 1943-1952.
19. Wang X, Searle AK, Chen YC, Peter K (2017) P6268 Downregulation of vascular cell adhesion molecule-1 using targeted microbubbles for the delivery of microRNA-126: treatment and prevention of abdominal aortic aneurysm, Eur Heart J 38(1): eho493.P6268.
20. Yan H, Hu Y, Akk A, Ye K, Bacon J, et al. (2019) Interleukin-12 and -23 blockades mitigates elastase-induced abdominal aortic aneurysm. Pham Sci Rep 9: 10447.
21. Ijaz T, Tilton RG, Brasier AR (2016) Cytokine amplification and macrophage effector functions in aortic inflammation and abdominal aortic aneurysm formation. J Thorac Dis 8(8): 746-754.
22. Takeda N, Hara H, Fujiwara T, Kanaya T, Maemura S, et al. (2018) TGF-β Signaling-Related Genes and Thoracic Aortic Aneurysms and Dissections. Int J Mol Sci 19(7): 2125.
23. Hara H, Takeda N, Fujiwara T, Yagi H, Maemura S, et al. (2019) Activation of TGF-β signaling in an aortic aneurysm in a patient with Loey-Dietz syndrome caused by a novel loss-of-function variant of TGFBR1. Hum Genome Var 6(6).
24. Gurung R, Choong AM, Woo CC, Foo R, Sorokin V, et al. (2020) Genetic and Epigenetic Mechanisms Underlying Vascular Smooth Muscle Cell Phenotypic Modulation in Abdominal Aortic Aneurysm. Int J Mol Sci 21(17): 6334.
25. Harman JL, Dobnikar L, Chappell J, Stokell BG, Dalby A, et al. (2019) Epigenetic regulation of vascular smooth muscle cells by histone H3 lysine 9 dimethylation attenuates target gene induction by inflammatory signaling. Arterioscler Throm Vasc 39(11): 2289-2302.
26. Liu B, Song Y, Zhou Y, Liu Y, Qiu T, et al. (2018) Cyclic Mechanical Stretch Induced Smooth Muscle Cell Phenotypic Changes in Cerebral Aneurysm Progression by Reducing Collagen Type IV and Collagen Type VI Levels. Cell Physiol Biochem 45(3): 1051-1060.
27. Mirzaie M, Schultz M, Schwartz P, Coulbably M, Schöndube F, et al. (2003) Evidence of woven bone formation in heart valve disease. Ann Thorac Cardiovasc Surg 9(3): 163-169.
28. Trompoulis IK, Oxford JT, Cowan DB, Aagnostopoulos CE, Rokas C, et al. (2009) Differential expression of collagen V and XI alpha-1 in human ascending thoracic aortic aneurysms. Ann Thorac Surg 88(2): 506-513.
29. Jana S, Chute M, Hu M, Winkelkraut G, Owen CA, et al. (2020) ADAM (a Disintegrin and Metalloproteinase) 15 Deficiency Exacerbates Ang II (Angiotensin II)–Induced Aortic Remodeling Leading to Abdominal Aortic Aneurysm. Arterioscler Thromb Vasc Biol 40(8): 1918-1934.
30. Geng L, Wang W, Chen Y, Cao J, Lu L, et al. (2010) Evaluation of ADAM10, ADAM17, MMP-2 and MMP-9 expression with media degeneration features CaCl2-induced thoracic aortic aneurysm in a rat model. Exp Mol Pathol 89(1): 72-81.
31. Jiao Y, Yao B, Zhang B, Hao DC, Sun QF, et al. (2017) Role of MicroRNA-103a Targeting ADAM10 in Abdominal Aortic Aneurysm. BioMed Res Int, 2017(3): 1-14.
32. Yang I, LeBlanc MF, Cano I, Saez-Torres KL, Saint-Geniez M, et al. (2020) ADAM10 and ADAM17 promote mediate proinflammatory cytokine-induced and constitutive cleavage of endomucin from the endothelial surface. J Biol Chem 295(19): Jbc.RA119.011192.
Citation: Mirzaie M, Michael S, Peter S, Zaur G, Sheila F. Changes of the Endocardium and Extracellular Matrix in Thoracic Aortic Aneurysm Revealed by Scanning Electron Microscopic Investigations are there Structural Parallels to Aortic Valve Degeneration?. Adv Card Res 3(2)-2020. ACRR.MS.ID.000159. DOI: 10.32474/ACR.2020.03.000159