



Two Cases of Quadricuspid Aortic Valve: Aortic Regurgitation and Degeneration

Jan Michael Federspiel¹ Thomas Tschernig² Matthias Werner Laschke³ Hans-Joachim Schäfers⁴

¹Institute for Legal Medicine, Saarland University Faculty of Medicine, Campus Homburg, Building 49.1, Kirrberger Straße, 66421 Homburg, Saarland, Germany

²Institute for Anatomy and Cell biology, Saarland University Faculty of Medicine, Campus Homburg, Building 61, Kirrberger Straße, 66421 Homburg, Saarland, Germany

³Institute for Clinical and Experimental Surgery, Saarland University Faculty of Medicine, Campus Homburg, Building 65, Kirrberger Straße, 66421 Homburg, Saarland, Germany

⁴Department for Thoracic- and Cardio-Vascular Surgery, Saarland University Medical Center, Building 57, Kirrberger Straße, 66421 Homburg, Saarland, Germany

Address for correspondence Jan Michael Federspiel, MD, Institute for Legal Medicine, Saarland University Faculty of Medicine, Campus Homburg, Building 49.1, Kirrberger Straße, 66421 Homburg, Saarland, Germany (e-mail: jmfederspiel@outlook.com).

Thorac Cardiovasc Surg Rep 2022;11:e39–e43.

Abstract

Keywords

- ▶ aortic regurgitation
- ▶ aneurysm
- ▶ aortic valve
- ▶ aorta

Background Quadricuspid aortic valve is rare and occasionally associated with aortic regurgitation and ascending aortic dilatation. Recent studies suggest an association of aortic regurgitation with ascending aortic medial degeneration.

Case Description Histologic evaluation of ascending aortic tissue of two individuals with regurgitant quadricuspid aortic valve, one dilated, one non-dilated, yielded comparable degeneration in the Media.

Conclusion Regurgitation of quadricuspid aortic valve may lead to the degeneration of Tunica media of the ascending aorta.

Introduction

Quadricuspid aortic valve (AV) is a rare malformation.¹ For other congenital AV malformations (e.g., bicuspid AV) an association between aneurysm formation and AV morphology was observed.² For the quadricuspid AV (QAV) such an association remains controversial.^{1,3}

For many years AV stenosis was assumed to be involved in aneurysm formation.⁴ Recent studies have shown that aortic regurgitation might be associated with more pronounced ascending aortic degeneration.⁵ In QAV, aortic regurgitation is variable,¹ and echocardiographically usually central, suggesting variable degrees of aortic dilatation as main mechanism of aortic regurgitation. Thus, a more constant

relationship between ascending aorta and QAV seems possible.

To explore such a potential relationship, we studied two cases of regurgitant QAVs, one with grossly dilated (case 1) and one with apparently normal ascending aortic dimensions (case 2).

Case Description

This study was approved by the regional ethics committee (vote #47/14). Both patients gave written informed consent.

Both patients were female and presented with severe, symptomatic aortic regurgitation (▶ **Fig. 1**; Case 1: 31 years, sino-tubular junction 35 mm, ascending aorta 45 mm; case

received
December 23, 2021
accepted after revision
March 7, 2022

DOI <https://doi.org/10.1055/s-0042-1750408>.
ISSN 2194-7635.

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

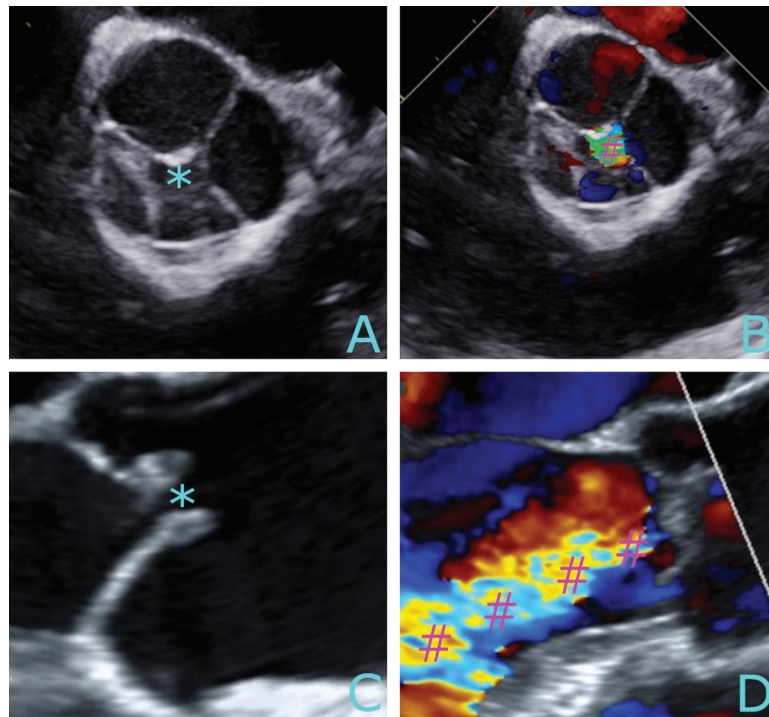


Fig. 1 Echocardiographic findings. Case 1 (A, B): short axis of the AV in transesophageal echocardiography. Case 2 (C, D): long axis of the left ventricular outflow tract, aortic valve, and root in transesophageal echocardiography. Pictures A and C show brightness mode of the AV without central coaptation (*). Pictures B, and D display the regurgitation jet (#) in a color Doppler mode.

2: 49 years, sino-tubular junction 28 mm, ascending aorta 30 mm).

Samples were obtained from the anterior circumference of the aorta approximately 5 to 10 mm above the sino-tubular junction, and immediately fixed (4% phosphate-buffered formalin, Roti-Histofix, Carl Roth, Karlsruhe, Germany). Sections with 3 μm thickness were obtained. Routine (hematoxylin-eosin-, elastica-hematoxylin-eosin-,

Masson-Goldner-trichrome-, Alcian-blue-, toluidine-blue-, Sirius red-, Movat-pentachrome according to Verhoeff-stain) and immunohistochemical stains (Collagen 3A1 [Primary antibody: Anti-Col3A1, Rabbit polyclonal, #ab53076, Abcam, Cambridge, United Kingdom, dilution 1:400; Secondary antibody: Biotinylated Goat Anti-Rabbit IgG, #ab64265, Abcam, dilution 1:100; Chromogen: Diaminobenzidine; Counter stain: Hemalaun according to Mayer], Fibrillin-1 [Primary

Table 1 Results of histological analysis

Parameter	Case 1	Case 2
Histological routine		
Atherosclerosis	Non significant	Mild
Elastic fibers		
Fragmentation/Loss	Mild-focal	Moderate-focal
Thinning	Absent	Absent
Disorganization	Focal	Focal
Smooth muscle cells		
Nuclei loss	Focal-patchy	Focal-patchy
Disorganization	Focal	Focal
Laminar medial collapse	Absent	Absent
Extracellular matrix alterations		
Mucoid extracellular matrix accumulation	Mild-focal-translamellar	Mild-focal-translamellar
Collagen alterations		
Medial fibrosis	Absent	Absent

Table 1 (Continued)

Parameter	Case 1	Case 2
Fiber orientation	Circumferential	Circumferential
Overall medial degeneration	Moderate	Moderate
Morphometry		
Wall thickness	1,451 μm	1,750 μm
Area	15.81 mm^2	19.74 mm^2
Elastin autofluorescence		
% of examined area resembled by autofluorescing elastin	92%	83%
Immunohistochemistry		
Fibrillin-1	Intima: overall weak signal. Media: overall weak signal. Adventitia: strong, areal signal.	Overall, stronger signals. Particularly stronger signals in areas of sub-intimal, medial damage. Otherwise like case 1.
Collagen 3A1	Intima: scattered strong signals. Media: overall weak signal. Adventitia: scattered strong signals, especially in the vasa vasorum.	Overall, stronger signals. Particularly stronger signals in areas of sub-intimal, medial damage. Otherwise like case 1.

Note: Summary of the histological analysis.

antibody: Anti-Fibrillin, Rabbit polyclonal, #ab53076, Abcam, dilution 1:50; Secondary antibody, Chromogen, and counter stain: Same as for Collagen 3A1]) were applied. Additionally, elastic fibers were evaluated by its autofluorescence in confocal microscopy [Mounting: DAPI-Mounting medium, #ab104139, Abcam; Laser excitation: Wavelength approximately 480 nm].

The histological grading was performed according to the consensus statements on aortic pathology.^{2,6} Results are displayed in ►Table 1 and ►Fig. 2. Immunohistochemical stains were evaluated regarding signal intensity and distribution. Elastin autofluorescence was analyzed by determination of the area resembled by fluorescing elastin.

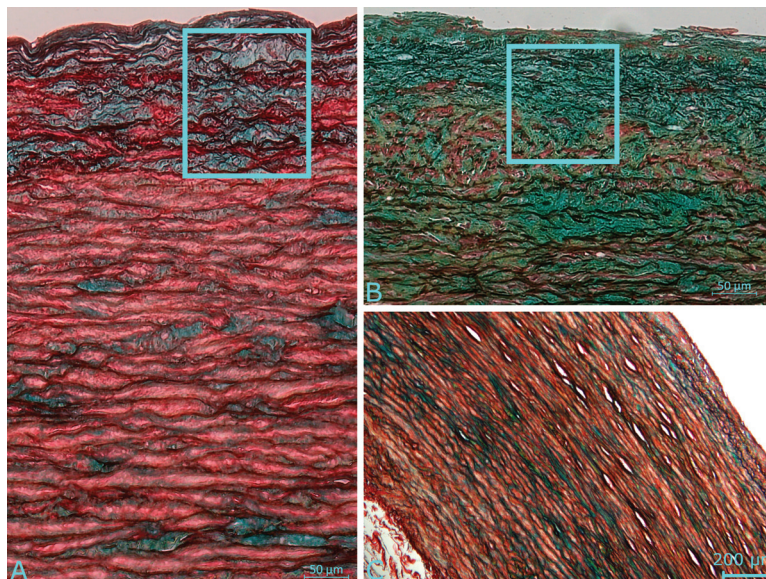


Fig. 2 Histomorphology. Displayed are histological findings (Movat pentachrome-stain) in case 1 (A) and case 2 (B). As comparison, non-dilated aortic wall of an individual with gross-sectional competent tricuspid AV is depicted (C, sample obtained during autopsy). Rectangles (A, B) mark areas with translamellar mucoid extracellular matrix accumulation leading to the diagnosis of moderate overall medial degeneration.

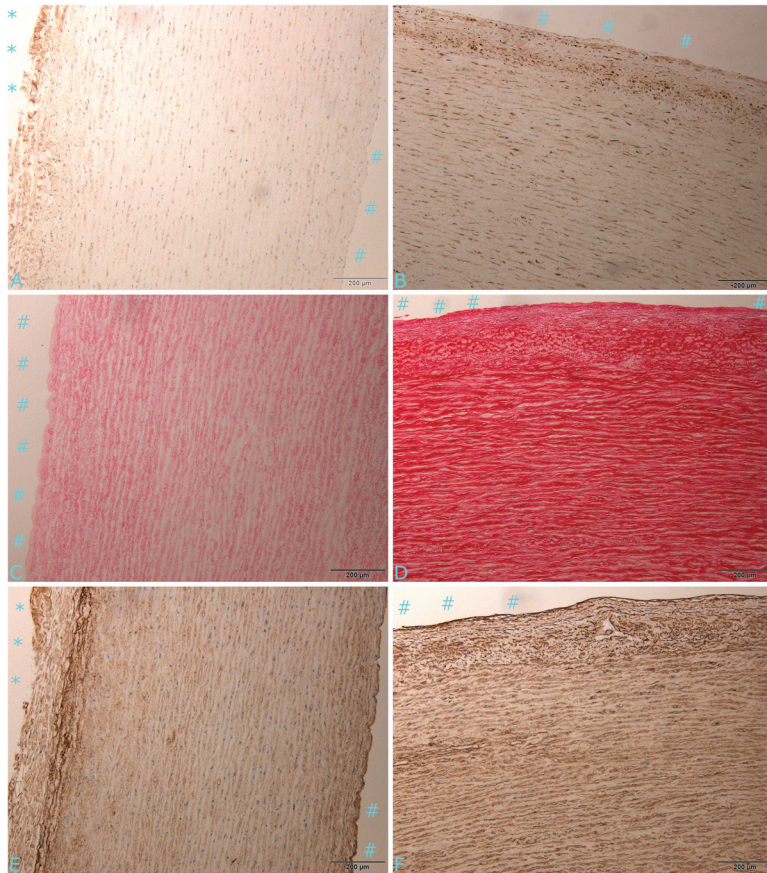


Fig. 3 Collagen and fibrillin-1. Displayed are fibrillin-1- (A, B), Sirius red- (C, D), and collagen 3A1-stain (E, F) for case 1 (A, C, E) and case 2 (B, D, F). Synopsis of Sirius red- and Collagen 3A1-stain reveals that, especially in areas of mucoid extracellular matrix accumulation and elastic fiber degeneration, collagen aggregates, particularly Collagen 3A1. Also, fibrillin-1 aggregates in these areas. Symbols: Aortic lumen—#; outside —*.

Discussion

The exact pathophysiological mechanism of ascending aortic dilatation in the setting of congenitally malformed AVs is not yet determined. Recent studies on the tricuspid AV suggest a relevant impact of aortic regurgitation independent of AV morphology.⁴ The two presented cases of regurgitant QAV showed a similarly moderate degeneration of the ascending aorta, like previously described for regurgitant tricuspid AVs.⁴ This *might* indicate, that a certain degree of aortic

dilatation may be a causative factor in the pathogenesis of aortic regurgitation. But vice-versa aortic regurgitation may lead to aortic degeneration with consecutive dilatation, may be indicated by less, and weaker signals of Collagen 3A1, Fibrillin-1 (►Fig. 3), and fluorescing elastin (►Fig. 4) in the dilated aorta.

Summarizing, further research analyzing the association between aortic degeneration and regurgitation in the AV morphologies is required to better define both—the role of AV malformations and AV diseases in aneurysm formation.

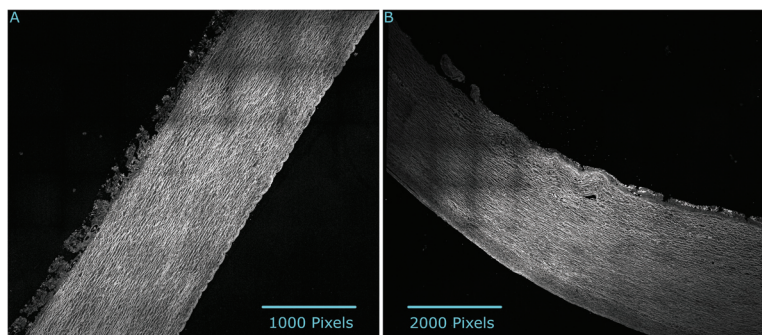


Fig. 4 Elastin autofluorescence. A pixel represents 0.57 μm. The bright lines depict the fluorescing elastin. Other, none or less fluorescing components of the aorta are displayed black or gray. Besides elastin, erythrocytes emit light due to excitation too. (A) Case 1. (B) Case 2.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

In mourning for Prof. Dr. med. P. A. Schabel, we want to thank him for his year-long support and guidance. We thank Ms. Tanja Schwab for Performing the histological stains. We thank Prof. Dr. Peter Lipp for his support with the confocal microscope.

Data Availability Statement

The data underlying this manuscript are available in the article itself.

References

- 1 Idrees JJ, Roselli EE, Arafat A, et al. Outcomes after repair or replacement of dysfunctional quadracuspid aortic valve. *J Thorac Cardiovasc Surg* 2015;150(01):79–82
- 2 Halushka MK, Angelini A, Bartoloni G, 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(03):247–257
- 3 Lin Y, Yin K, Wang Y, et al. Clinical characteristics and surgical outcomes of dysfunctional quadracuspid aortic valve. *J Surg Res* 2018;229:223–229
- 4 Wilton E, Jahangiri M. Post-stenotic aortic dilatation. *J Cardiothorac Surg* 2006;1:7
- 5 Balint B, Federspiel JM, Schwab T, Ehrlich T, Ramsthaler F, Schäfers HJ. Aortic regurgitation is associated with ascending aortic remodeling in the nondilated aorta. *Arterioscler Thromb Vasc Biol* 2021;41(03):1179–1190
- 6 Stone JR, Bruneval P, Angelini A, et al. Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology: I. Inflammatory diseases. *Cardiovasc Pathol* 2015;24(05):267–278