Two Cases of Quadricuspid Aortic Valve: Aortic Regurgitation and Degeneration

Jan Michael Federspiel[1] Thomas Tschernig[2] Matthias Werner Laschke[3] Hans-Joachim Schäfers[4]

[1] Institute for Legal Medicine, Saarland University Faculty of Medicine, Campus Homburg, Building 49.1, Kirrberger Straße, 66421 Homburg, Saarland, Germany
[2] Institute for Anatomy and Cell biology, Saarland University Faculty of Medicne, Campus Homburg, Building 61, Kirrberger Straße, 66421 Homburg, Saarland, Germany
[3] Institute for Clinical and Experimental Surgery, Saarland University Faculty of Medicine, Campus Homburg, Building 65, Kirrberger Straße, 66421 Homburg, Saarland, Germany
[4] Department 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).

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Abstract

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.

Keywords
- aortic regurgitation
- aneurysm
- aortic valve
- 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

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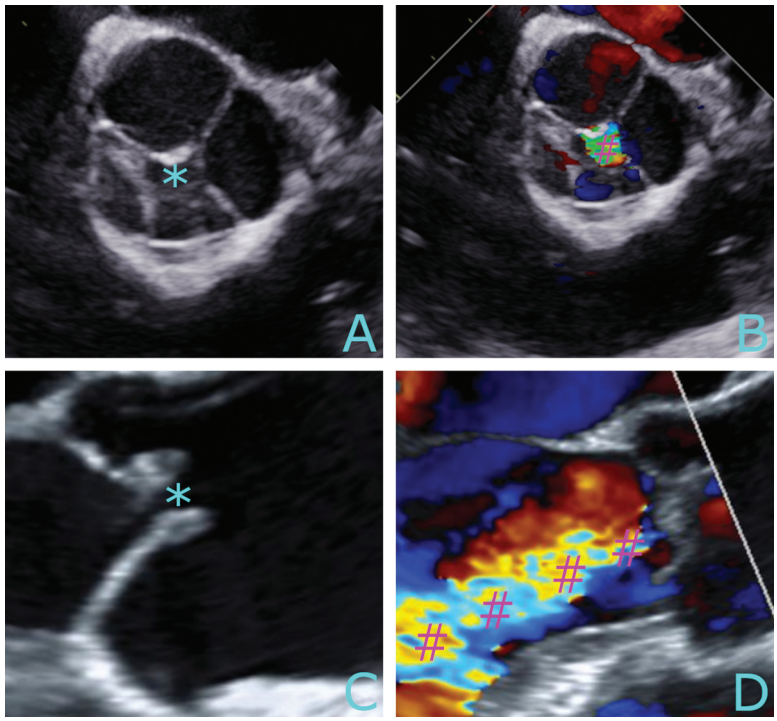

Fig. 1 Echocardiographic findings. Case 1 (**A, B**): short axis of the AV in transesophageal echocardiography. Case 2 (**C, D**): long axis of the left ventricular outflow tract, aortic valve, and root in transesophageal echocardiography. Pictures A and C show brightness mode of the AV without central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

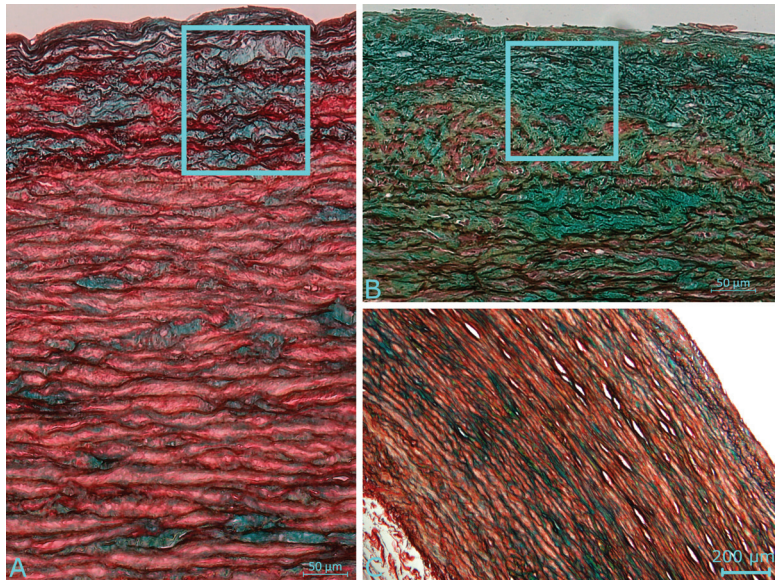

Fig. 2 Histomorphology. Displayed are histological findings (Movat pentachrome-stain) in case 1 (**A**) and case 2 (**B**). As comparison, non-dilated aortic wall of an individual with gross-sectional competent tricuspid AV is depicted (**C**, sample obtained during autopsy). Rectangles (**A, B**) mark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

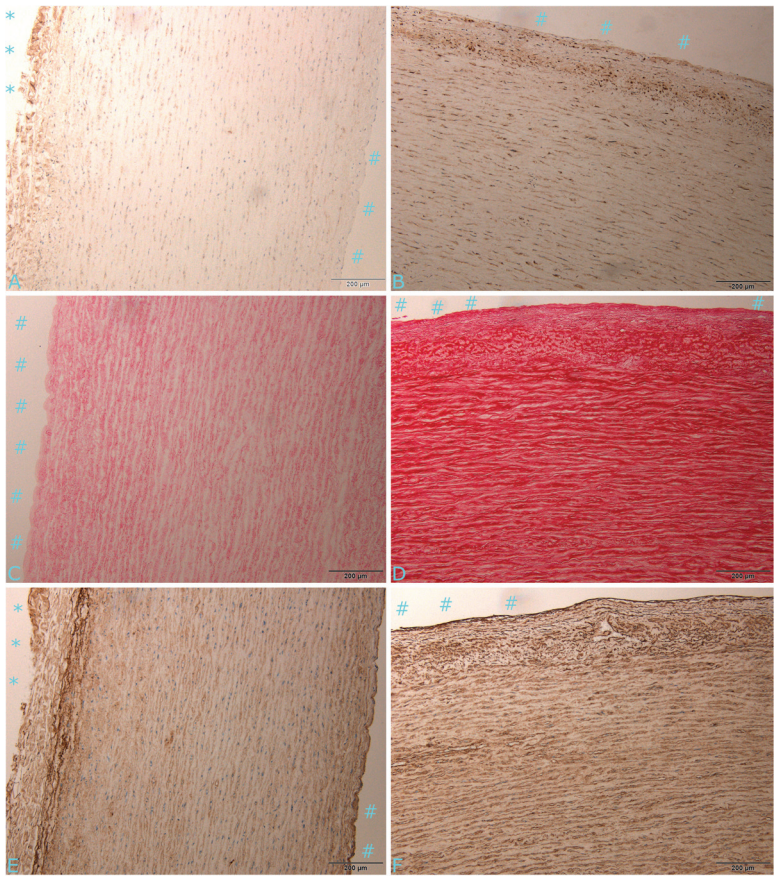

Fig. 3 Collagen and fibrillin-1. Displayed are fibrillin-1- (**A, B**), Sirius red- (**C, D**), and collagen 3A1-stain (**E, F**) for case 1 (**A, C, E**) and case 2 (**B, D, F**). Synopsis of Sirius red- and Collagen 3A1-stain reveals that, especially in areas of mucoid extracellular matrix accumulation 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.

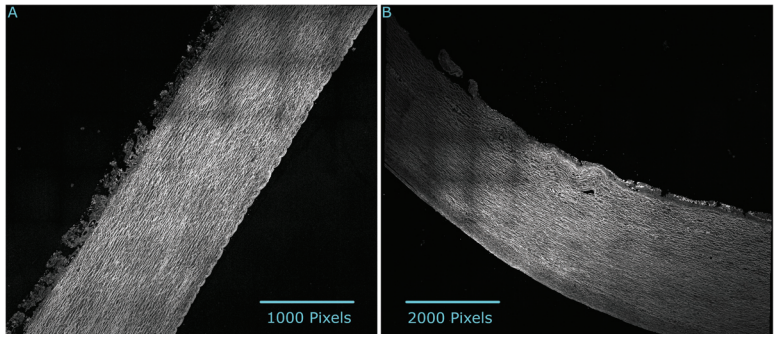

Fig. 4 Elastin autofluorescence. A pixel represents 0.57 µm. The bright lines depict the fluorescing elastin. Other, none or less fluorescing components of the aorta are displayed black or gray. Besides elastin, erythrocytes emit light due to excitation too. (**A**) Case 1. (**B**) Case 2.

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Conflict of Interest
None declared.

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

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