

Amyloid deposition in surgically resected aortic valves

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Background

Amyloid deposition is variably reported in aortic valves (AVs), with a frequency between 15% and 82% in published series. However, its true incidence, proteomic characteristics, and clinical significance remain unclear. A detailed assessment of surgically resected aortic valves was undertaken with the following aims: 1) employ robust methodology to further characterize AV amyloid incidence, 2) determine the proteomic signature of such deposits, and 3) investigate clinical importance of this finding.

Methods

100 consecutive surgically resected AVs (11/2018-2/2019) were identified through institutional records. Clinical material was semiquantitatively scored for the degree of calcium and inflammation present. Congo red (CR) histochemistry was performed to determine the presence and morphology of CR+ deposits. A subset of cases with adequate CR+ deposits underwent liquid chromatography-tandem mass spectrometry (LC-MS/MS) and electron microscopy. Relevant clinical information was abstracted from the medical record. Echocardiograms, including pre-operative and most recent (if different) were reviewed for features indicative of cardiac amyloidosis.

Results

Patient characteristics are presented in Table 1. Half (52%) of the resected AVs contained CR+ deposits. Patients with CR+ deposits were older ($p=0.003$), and more commonly men ($p=0.047$). Though non-specific sequelae of systemic amyloidosis were more common in this population (erectile dysfunction, $p=0.029$; carpal tunnel syndrome, $p<0.0001$), no significant difference was apparent on echocardiography and no patients were diagnosed with cardiac amyloid during the follow-up period. CR+ deposits were directly associated with calcium deposition ($p<0.0001$) and usually adjacent to it (65%), with 5 (10%) valves containing exclusively nodular deposits away from calcium, and 13 (25%) showing both morphologies. Proteomic analysis was performed on microdissected CR+ deposits from 9 cases, all revealing a universal amyloid protein signature. Pericalcific deposits show a non-specific proteome, while nodular deposits have a profile more typical of ATTR (transthyretin) amyloidosis. Ultrastructural and additional LC-MS/MS analysis is ongoing.

Table 1.

	Congo red-positive (n=52)	Congo red-negative (n=48)	p-value
Patient Characteristics			
Age (years), median (IQR)	67 (63, 74)	64 (51, 71)	0.0032
Sex, M (%)	37 (71)	31 (65)	0.0465
Follow up interval (days), median (IQR)	386 (195, 475)	471 (364, 580)	0.051
Erectile dysfunction (men), n (%)	14 (38)	8 (29)	0.0285
Carpal tunnel syndrome, n (%)	12 (24)	5 (11)	<0.0001
Valve Properties			
<i>Valve status</i>			
Stenotic	43 (86)	25 (53)	
Regurgitant	1 (2)	21 (45)	
NOS	6 (12)	1 (2)	
<i>Histopathologic Diagnosis</i>			
Degenerative fibrocalcific	28 (54)	18 (38)	
Congenitally bicuspid	22 (43)	17 (35)	
Post-inflammatory	2 (4)	2 (4)	
Annular dilatation	-	11 (23)	
Calcium*, mean	2.42	1.19	<0.0001
Chronic inflammation*, mean	0.94	0.44	0.0001
Echocardiography			
Properties			
Septal wall thickness (mm), median (IQR)	13 (11, 14)	11 (10, 14)	0.3665
Posterior wall thickness (mm), median (IQR)	11.5 (10, 13)	11 (9.5, 12)	0.1915

*semi-quantitative: 0=none, 1=mild, 2=moderate, 3=marked

IQR= interquartile range; n=number

Conclusion

CR+ deposits are relatively common in AVs, specifically those in which there is concomitant fibrocalcific degeneration, and are associated with degree of calcification, older age, and male sex, in keeping with prior literature. However, morphologic differences are present, requiring correlation with proteomic and ultrastructural studies, as well as clinical outcome, to further characterize the nature of these deposits.