CASE REPORT

Assessment of Unicuspid Aortic Valve Stenosis Using Multimodality Imaging, X-ray Radiography and Raman Analysis

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Summary

Unicuspid aortic valve (UAV) is an extremely rare form of congenital cardiac malformation, leading to aortic stenosis (AS), aortic regurgitation (AR), or both.1) AS is characterized by thickening and calcification in different irregular areas of the aortic valves. The formation of AS is proposed via the 3 processes of lipid accumulation, inflammation, and calcification.2) It has been reported that approximately 60% of UAVs in adults are diagnosed after surgical resection or at autopsy, while only 20% are found on echocardiography.3) UAV has been categorized into two subtypes, pinhole-shaped acommissural UAV and slit-shaped unicommissural UAV.4,5) The pinhole-shaped UAV appears early in infancy with severe AS, while the slit-shaped UAV occurs much later in adulthood with a less aggressive clinical course. Although different imaging modalities have been applied to characterize UAV morphology,6) the comparative in vivo and in vitro morphological evolutions, as well as the calcification and composition of the calcified UAV, have been less examined. We herein report an adult case of slit-shaped unicommissural UAV with severe AS and mild AR by detecting with computed tomography (CT), transesophageal echocardiography (TEE), and transthoracic echocardiography (TTE). In addition, the degree of AV calcification and chemical compositions in this excised stenotic UAV were further examined by X-ray radiography and portable Raman spectroscopy.

Key words: Aortic stenosis (AS), Aortic regurgitation (AR)

Unicuspid aortic valve (UAV) is a rare congenital anomaly, which usually associates with aortic stenosis (AS), aortic regurgitation (AR), or both.1) AS is characterized by thickening and calcification in different irregular areas of the aortic valves. The formation of AS is proposed via the 3 processes of lipid accumulation, inflammation, and calcification.2) It has been reported that approximately 60% of UAVs in adults are diagnosed after surgical resection or at autopsy, while only 20% are found on echocardiography.3) UAV has been categorized into two subtypes, pinhole-shaped acommissural UAV and slit-shaped unicommissural UAV.4,5) The pinhole-shaped UAV appears early in infancy with severe AS, while the slit-shaped UAV occurs much later in adulthood with a less aggressive clinical course. Although different imaging modalities have been applied to characterize UAV morphology,6) the comparative in vivo and in vitro morphological evolutions, as well as the calcification and composition of the calcified UAV, have been less examined. We herein report an adult case of slit-shaped unicommissural UAV with severe AS and mild AR by detecting with computed tomography (CT), transesophageal echocardiography (TEE), and transthoracic echocardiography (TTE). In addition, the degree of AV calcification and chemical compositions in this excised stenotic UAV were further examined by X-ray radiography and portable Raman spectroscopy.

Case Report

A 55 year-old male patient was admitted to Taipei Veterans General Hospital (TVGH) for a health check-up due to intermittent chest tightness and short of breath that had started about 6 months previously. He was advised to visit a cardiologist for further examination and treatment. On cardiac auscultation, a loud high pitch diamond shaped systolic murmur (Grade IV/VI) over the aortic area was heard. On cardiac inspection, a visible apical impulse over the 5th intercostal space at the left lateral third of the clavicular line was also observed. Significant carotid shuddering was also palpated upon the carotid body of the carotid artery. Because the ascending aorta diameter was only 28 mm, we did not observe aneurysmal dilatation of the ascending aorta. Serial examinations were performed and an electrocardiogram (ECG) showed sinus rhythm without any abnormality but with a short PR interval and left ventricle hypertrophy (LVH), although there was no LV strain. LVH is thickening of the heart muscle of the left ventricle of the heart, which may be a major predictor of the development of cardiovascular events.7) The LVH was due to the fact that the sum of the S wave depth in lead V1 or V2 and R wave height in lead V5 or V6 was greater than > 35 mm, indicating that this LVH met Sokolow-Lyon voltage criteria.7)

Preoperative imaging diagnosis of this patient was...
performed using cardiac CT, and 2-dimensional (2D) or 3-dimensional (3D) TTE or TEE. A CT scan revealed that a normal heart size with aortic valve (AV) calcification was observed from the coronal plane of the heart (Figure 1A). Calcareous deposits on the AV were clearly seen from the cross section, 4 mm above the annular basal plane (Figure 1B). A unicommissure was also observed between the left and non-coronary cusps (LCC and NCC). The thickness of two calcified areas observed from the coronal plane of the heart was markedly increased (Figure 1C). Cardiac CT can detect as well as quantify the extent of AV calcification.\textsuperscript{10,11} Calcium scoring of AV calcification in this AV stenosis was calculated by a CT scanner with non-enhanced study. A calcified plaque calculated from a cardiac CT scan was about 421.31 Agatston units in this cross-sectional slice (Figure 1D). This non-enhanced image showed fairly large calcified lesions of the AV leaflets scored with a threshold of 1150 HU. In addition, the total Agatston score from all slices of the whole calcified plaque was approximately 4083.05 Agatston units. After the TEE and TTE echocardiographic examinations, a UAV with severe AS and mild AR was found (Figure 2). The blood volume in the end-diastolic phase was eccentrically ejected from a small outlet (arrow head) into the aorta during systole, leading to the occurrence of turbulent blood flow (Figure 2A). A reflux of blood through a small opening (arrow head) in the diastolic stage also occurred due to the heavy AV calcification (Figure 2B).

Color Doppler echocardiographic image displays showed that this patient had a maximum velocity ($V_{\text{max}}$) of 507 cm/s, mean velocity ($V_{\text{mean}}$) of 370 cm/s, maximum pressure gradient (Max PG) of 103 mmHg, and mean pressure gradient (Mean PG) of 61 mmHg (Figure 2C), suggesting that the severe AS caused a significant amount of turbulent blood flow in both systole and diastole with high shear forces. In addition, the left ventricular ejection fraction (LVEF) was 57% and aortic valve area (AVA) was 0.50–0.72 cm$^2$ while his AVA index was 0.30–0.43 cm$^2$/m$^2$. Moreover, real-time 3D TEE revealed a characteristic, teardrop-shaped eccentric valve orifice with a unicommissural UAV (Figure 2D). During a surgical AV replacement (AVR) operation, a slit-shaped unicommissural UAV in the absence of cusp separation was directly observed from the intraoperative inspection (Figure 3A). Only a single AV commissure was attached to the aortic wall at the level of the valve orifice. This unicommissural UAV was present between the LCC and NCC, as schematically illustrated in Figure 3B according to Figure 3A.
Two raphes were respectively located between the right coronary cusp (RCC) and LCC positions, and between the RCC and NCC positions, respectively. After the AVR operation, the excised surgical specimen of the UAV revealed a slit-shaped structure with heavy calcification. By visualizing this UAV from the aortic and ventricular views, the valve leaflet morphology along with severe fibrotic thickening and prominent calcified nodules were observed (Figure 3C and D).

This patient agreed to undergo cardiac surgery at TVGH. The pre-operative survey did not find any other comorbidity. Although his family history of cardiovascular disease was unknown, coronary angiography also indicated no congenital abnormality or stenosis of the coronary arteries. After admission, traditional surgical AVR was performed with a 21 mm bovine prosthetic valve and the whole hospitalization course was uneventful. The patient was discharged home 2 weeks later. The patient provided informed consent before entering the study and agreed to allow us to survey his clinical data and examine his excised UAV. The protocol was approved by the Institutional Review Board of TVGH.

Discussion

The congenital malformations of AVs commonly present as a unicuspid, bicuspid, or quadricuspid AV (UAV, BAV, or QAV), in which an estimated prevalence of each above abnormality was 0.02~5% for UAV, 0.9~2.0% for BAV, or 0.013~0.043% for QAV, respectively.12,13) UAV has been described as an important morphologic subset of BAV, and it has been shown that UAV patients presented with predominantly AS at a younger age than other BAV patients.14,15) Due to the failure of valve leaflet division during embryonic development, the adjacent 3 aortic cusps failed to separate, resulting in the development of UAV.13,14) The first UAV case was reported more than 60 years ago and it is more common in males than females (4:1).13-15)

Since the diagnosis of cardiac structure and function performed with TEE displays clearer images that are more accurate than those obtained by TTE, aortic plaques can be easily seen on TEE.14,16) However, TEE is not always reliable, particularly in patients with heavy calcifications.17) Here, TEE not only evidenced the calcified UAV with severe AS and mild AR (Figure 2A and B), but also showed a thickened mitral valve with mild AR.

Although normal LVEF (57%) was observed, the values of intracardiac hemodynamic parameters such as Vmax, Max PG, Mean PG, AVA, and AVA index were significantly over the cut-off values of the severe AS grade in the AS quantification (Figure 2C).18) In addition, 3D TEE showed a unique eccentric valve orifice with a unicommissural UAV (Figure 2D). This UAV was covered with the consolidated, heavily calcified masses, leading to the formation of severe AS.

This excised UAV exhibited an eccentric “teardrop” opening with a single and unfused commissural structure, which was qualitatively similar to the echocardiographic criteria for identifying UAV reported by Ewen, et al.19) Ewen, et al. had currently defined 3 major echo criteria for the echocardiographic diagnosis of UAV morphology.
Figure 3. Intraoperative surgical photograph showing a single and slit-shape UAV (A), a schematic illustration according to photo in A (B), and optical photographs of surgically excised UAV observed from aortic and ventricular views (C, D). CA indicates coronary artery; LCC, left coronary cusp; RCC, right coronary cusp; and NCC, non-coronary cusp.

Based on a preoperative baseline examination as follows: (1) single commissural attachment zone, (2) rounded, leaflet-free edge on the opposite side of the commissural attachment zone, and (3) eccentric valvular orifice during systole. In our case, the echocardiographic feature of this UAV was characterized to be a unicommissural valve with a single commissural zone of attachment. Moreover, an eccentric valvular orifice during systole was also observed in the present case, since the excised UAV exhibited an eccentric “teardrop” opening with a slit-shaped unicommissural structure. This UAV was found to be a rigid, thickened, and stenotic body.

The degree of AV calcification in this excised UAV before and after detection using an X-ray machine is shown in Figure 4A and B. The white regions related to calcification on the excised UAV were clearly visualized from the X-ray radiograph (Figure 4B), in which the calcified deposits were not evenly distributed within the UAV. Calcification is generally associated with cusp fibrosis, leading to gradual fibrotic thickening of this UAV. When the images of calcified deposits on the X-ray radiograph were captured using a special camera and scored using cellSens digital imaging software after optimal setting of region of interest (ROI) in an image, the calcified areas (red color) in this UAV were quantified, as shown in Figure 4C. The degree of AV calcification in each defined cusp of this excised UAV indicated that the NCC had the largest dimension of the calcified areas and the mean value of the calcified plaques deposited in this UAV was about 37.28%, leading to severe involvement of AS.

Since many calcified nodules and thickened parts were clearly observed from the aortic and ventricular surfaces in Figure 3C and D, Raman spectral analysis was applied to exactly examine the compositional components in this calcified UAV. Raman spectra of the excised UAV for this patient are illustrated in Figure 5. After 52 randomized Raman spectral determinations from this excised UAV, 3 different Raman spectral patterns (I—III) were obtained. Type I Raman spectrum (blue line) consisted mainly of one predominate band at 959 cm⁻¹ and several minor bands at 1071, 1035, 581, and 420 cm⁻¹, which were assigned to the calcium hydroxyapatite and type-B carbonate apatite. A weak Raman band was ob-
Figure 4. Photographs of the excised UAV before (A) and after detection by X-rays (B), as well as scoring result based on cellSens digital imaging software and its data of calcified area in each leaflet (C). Table shows the degree of AV calcification in each defined curop of this excised UAV.

<table>
<thead>
<tr>
<th>Leaflets</th>
<th>Total Area (mm²)</th>
<th>Calcified area occupied (mm²)*</th>
<th>Ratio of Calcified area (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCC</td>
<td>259.13</td>
<td>95.3</td>
<td>36.78</td>
</tr>
<tr>
<td>RCC</td>
<td>75.76</td>
<td>24.41</td>
<td>32.22</td>
</tr>
<tr>
<td>NCC</td>
<td>208.11</td>
<td>89.15</td>
<td>42.84</td>
</tr>
</tbody>
</table>

*Red area in C. ROI > 100 (scored by using the cellSens digital imaging software)

Figure 5. Three Raman spectral patterns (I–III) summed up from all Raman spectra of the excised UAV leaflet after 52 randomized determinations. I: calcium hydroxyapatite-rich part (blue points and blue line); II: calcium hydroxyapatite and lipid part (red points and red line); and III: lipid-rich part (green points and green line).

Served at 1004 cm⁻¹ due to phenylalanine residues of proteins/collagens,²⁰,²¹ implying that proteins/collagens were not abundant on the surface of this UAV. A type II Raman spectrum (red line) was constructed by 3 major Raman spectral peaks at 1667, 1446, and 960 cm⁻¹. The former two peaks were attributed to the saturated and unsaturated lipid-related spectral bands,²³,²⁴ while the latter peak at 960 cm⁻¹ corresponded to the calcium hydroxyapatite and type-B carbonate apatite. Two small peaks at 699 and 607 cm⁻¹ corresponded to the cholesterol.²⁵,²⁶ On the other hand, a type III Raman spectrum (green line) was dominantly composed of saturated and unsaturated lipids, due to two main Raman peaks that appeared at 1667 and 1445 cm⁻¹ and small amounts of cholesterol (699 and 607 cm⁻¹).
1516 cm\(^{-1}\) were found in all Raman spectra, which corresponded to the \(\beta\)-carotene.\(^{17,18}\)

From the Raman spectra in Figure 5, the calcified UAV leaflet of this AS patient was mainly constructed by uneven random distribution of 3 portions: a calcium hydroxyapatite-rich part (55.8%), calcium hydroxyapatite and lipid part (15.4%), and lipid-rich part (28.8%). The calcium hydroxyapatite-rich part was randomly distributed over 50% on the surface of UAV, confirming that this was a unicommissural UAV with severe calcification. Furthermore, the Raman spectral results clearly indicate that there was no evidence of a progressive calcification step in this UAV, as compared with the progressive calcification in the tricuspid aortic valve (TAV).\(^{19}\) This might be due to this slit-shaped UAV which typically presents relatively later in adults with a less aggressive course.\(^{12}\)

In this case study, we report the case of a 55-year-old man who presented with left anterior chest pain due to severe AS and mild AR secondary to a unicommissural UAV. The calcified UAV with associated AR can be commonly diagnosed by various diagnostic modalities such as 2D or 3D TTE or TEE, cardiac CT, or cardiac magnetic resonance imaging, as described in other reports.\(^{14,30,31}\) To the best of our knowledge, however, this is the first study to determine the compositional components in a calcified UAV by Raman spectral analysis.

Conclusion

A case of unicommissural UAV presenting in the form of severe AS and mild AR has been reported in which the diagnosis was eventually confirmed before surgery by using CT, 2D TEE, and TTE, as well as 3D TEE. The large dimensions of the calcified areas were detected in this excised UAV, indicating severe involvement of AS. The Raman spectroscopic results also revealed that this calcified UAV was mainly constructed by 3 unevenly distributed components, in which the calcium hydroxyapatite-rich part over 50% of the surface of the UAV might strongly confirm the severe AS that developed in this UAV.

Disclosures

Conflicts of interest: There are no conflicts of interest to declare.

References

9. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J 1949; 57: 161-86.

