Intraleaflet haemorrhage is associated with rapid progression of degenerative aortic valve stenosis

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Received 29 September 2010; revised 1 November 2010; accepted 8 November 2010; online publish-ahead-of-print 29 December 2010

Aims
The haemorrhage in the plaque (intraplaque haemorrhage) plays a critical role in the progression of atherosclerosis. The purpose of this study is to clarify whether the haemorrhage in the aortic valve leaflet (intraleaflet haemorrhage) accelerates the progression of aortic valve stenosis (AS).

Methods and results
We examined specimens of aortic valve leaflets obtained from 36 patients who had undergone aortic valve replacement for degenerative AS and in whom echocardiographic data were available just before the operation and at least 180 days before the last study. The stenotic valves were examined by immunohistochemistry to detect intraleaflet haemorrhage with antibody against glycophorin A, an erythrocyte-specific protein. The progression of AS was assessed by annualized change in the aortic valve area (ΔAVA: cm²/year). The patients were divided into two groups, namely the rapid progression group (ΔAVA ≥ 0.1 cm²/year) and the slow progression group (ΔAVA < 0.1 cm²/year), according to the reported average progression rate of AS. Intraleaflet haemorrhage was observed in 78% of the specimens. Intraleaflet haemorrhage was associated with neovascularization and macrophage infiltration. The areas of intraleaflet haemorrhage and macrophage infiltration were greater in the rapid progression group than in the slow progression group. Multivariate analysis has shown that the area of intraleaflet haemorrhage was the sole independent factor that positively correlated with ΔAVA.

Conclusions
Intraleaflet haemorrhage was frequently observed in the valve leaflets of degenerative AS and associated with a rapid progression of AS.

Keywords
Aortic stenosis • Glycophorin A • Intraleaflet haemorrhage • Neovascularization

Introduction
Degenerative aortic valve stenosis (AS) is common among the elderly and the most frequent cause of heart valve replacement in industrialized countries.¹–³ The incidence of degenerative AS has been increasing, and AS is associated with high morbidity and mortality.⁴,⁵ Many observations have suggested a link between the pathophysiology of AS and atherosclerotic disease. In cohort studies, many traditional atherosclerotic risk factors have been associated with an increased prevalence of AS.⁶–¹¹ In histological studies, AS and atherosclerosis of the arterial wall share several common features including lipid accumulation, calcification, infiltration of inflammatory cells, and neoangiogenesis.¹²–¹⁷

Recently, haemorrhage is a focus of attention as a mechanism of plaque progression and rupture in the atherosclerotic plaque (intraplaque haemorrhage).¹⁸,¹⁹ Intraplaque haemorrhages are likely to accelerate plaque progression and rupture in the carotid artery, coronary artery, and aorta.²⁰–²² In the histopathological studies of the coronary and carotid artery specimens, intraplaque haemorrhage has been shown to contribute to the accumulation of unesterified cholesterol, macrophage infiltration, enlargement of the necrotic core, and neutrophil protease enrichment.²³,²⁴
Although the heart is a vascular-rich organ, normal cardiac valves are avascular and oxygen is supplied via diffusion from the blood stream. In contrast, cardiac valves express angiogenic factors leading to neovascularization under such pathological conditions as rheumatic valvular disease and degenerative AS. Hence, we hypothesized that haemorrhage occurs in the process of degenerative AS to accelerate the decrease in aortic valve areas. The aim of this study is to demonstrate haemorrhage in the leaflet (intraleaflet haemorrhage) of human stenotic aortic valve and to clarify whether intraleaflet haemorrhage is related to the progression of the disease.

Methods

Tissue sampling

We examined specimens of the aortic valve leaflets obtained from 36 patients who had undergone aortic valve replacement for degenerative AS and in whom echocardiographic data were available just before the operation and at least 180 days before the last study. We excluded patients with congenitally abnormal valves and rheumatic valvular disease. Twenty-four patients underwent the operation because of isolated valve stenosis, and 12 patients underwent a combination of aortic valve replacement and coronary bypass grafting procedure. As controls, we collected specimens of the aortic valve leaflets obtained from 10 patients who had undergone aortic valve replacement for annulo-aortic ectasia. Tissue samples were collected in phosphate-buffered saline (PBS) and fixed in 4% paraformaldehyde in PBS within 4 h after surgery. Informed consent was obtained from each patient. The institutional Ethics Committee reviewed the protocol and approved this study.

Histological analysis

One tissue sample from one leaflet was taken per aortic valve. After fixation, the thickest portion of the leaflet, mostly the mid-portion of the leaflet, was decalcified and embedded in paraffin, and 4 μm sections...
were cut for haematoxylin and eosin staining and immunohistochemistry. For immunohistochemical examination, one section for each antibody was treated for antigen activation, and non-specific binding sites were blocked by 3% hydrogen peroxide for 15 min. The slides were incubated with mouse monoclonal antibody against glycophorin A (an erythrocyte-specific protein that facilitates anion exchange) for detecting red blood cell remnant (1:200, DAKO M0819, Tokyo, Japan), rabbit polyclonal antibody against von Willebrand factor (vWF) for detecting vascular endothelial cells (1:1000, DAKO A0082, Tokyo, Japan), mouse monoclonal anti-CD68 antibody for detecting macrophage (1:100, DAKO M0814, Tokyo, Japan), or mouse monoclonal anti-4-hydroxy-2-nonenal (4-HNE) antibody for detecting major product of lipid peroxidation (1:100, Jalca MHN-020P, Fukuroi, Japan). A non-immune mouse polymer reagent (Mouse/HRP, DAKO) or non-immune rabbit polymer reagent (Rabbit/HRP, DAKO) served as a negative control. Antigen was activated as follows: water bath treatment at 95°C for 40 min for glycophorin A, proteinase K treatment at room temperature for 5 min for vWF, and microwave treatment at room temperature for 15 min for CD68.

**Quantitative methods**

The tissue area occupied by immunostained macrophages, glycophorin A, and 4-HNE was quantified using computer-aided planimetry and was expressed as a percentage of the total surface area of the tissue section. The grade of neoangiogenesis was assessed by counting the number of tube-like structures lined with vWF-positive endothelial cells in the entire tissue sections and was expressed as the number of blood vessels per squared millimetre of the tissue.

**Clinical data assessment**

We reviewed clinical data such as age, gender, blood pressure, and medications in patients’ charts. Reviewed laboratory data included serum levels of total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride,

![Figure 3](image-url)

**Figure 3** Relationship between intraleaflet haemorrhage and neoangiogenesis. Micrographs of an aortic valve leaflet obtained from a patient with degenerative aortic valve stenosis. (A) Immunostaining with anti-von Willebrand factor antibody. Many blood vessels were observed in the vicinity of calcified nodule (scale bar indicates 100 µm). (B) A high-power view of blood vessels stained with anti-von Willebrand factor antibody (scale bar indicates 50 µm). (C) The adjacent section to (B) stained with anti-glycophorin A antibody (scale bar indicates 50 µm). Immunoreactivity for glycophorin A was observed in red blood cells. (D) Immunostaining with anti-von Willebrand factor antibody in the vicinity of calcified nodule (scale bar indicates 100 µm). (E) The adjacent section to (D) stained with anti-glycophorin A antibody (scale bar indicates 100 µm). Immunoreactivity for glycophorin A was localized outside but adjacent to the blood vessels. (F) A graph showing that the glycophorin A-positive area was positively correlated with the number of blood vessels ($R = 0.28, P = 0.0009$).
creatinine, plasma glucose levels, and glycosylated haemoglobin A1C (HbA1C). Diabetes mellitus was defined as fasting plasma glucose $\geq 126$ mg/dL, HbA1C $\geq 6.5\%$, or receiving anti-diabetic medications. Hypertension was defined as systolic blood pressure $\geq 140$ mg/dL, diastolic blood pressure $\geq 90$ mg/dL, or receiving anti-hypertensive medications. Dyslipidaemia was defined as LDL $\geq 140$ mg/dL, HDL $< 40$ mg/dL, triglyceride $\geq 150$ mg/dL, or receiving anti-dyslipidaemic medications.

**Transthoracic echo studies**

Echo studies were performed by experienced sonographers. All patients underwent a comprehensive examination including two-dimensional, M-mode, pulsed-wave Doppler, continuous-wave Doppler, and colour Doppler echocardiography. A particular care was taken to record the maximum aortic jet velocity. Aortic valve areas were calculated with the continuity equation. The progression of AS was assessed from serial echo studies separated by at least 180 days (mean 468 days, ranged from 180 to 1200 days). We also calculated the annualized changes in the aortic valve area ($\Delta$AVA, cm$^2$/year) by dividing the temporal changes in the parameters by the number of the days between the studies and, later, by multiplying 365. The patients were divided into two groups according to the reported average progression rate of AS ($0.1$ cm$^2$/year). The rapid progression group ($\Delta$AVA $\geq 0.1$ cm$^2$/year) consisted of 15 patients and the slow progression group ($\Delta$AVA $< 0.1$ cm$^2$/year) consisted of 21 patients.

**Statistical analysis**

All statistical analyses were performed using commercially available statistical software (Dr SPSS II for Windows, SPSS Japan Inc., Tokyo, Japan). Continuous variables are reported as mean values (± standard deviations) when normally distributed, or as medians (inter-quartile ranges) when not normally distributed. Analysis of normality of the continuous variables was performed using the Kolmogorov–Smirnov test. Differences in the continuous variables between groups were assessed with unpaired Student’s t-test for normal distributions or the Mann–Whitney U test for non-normal distributions. Categorical variables are reported as numbers and percentages and were compared using the Fisher’s exact test. Correlations were assessed with Spearman’s rank correlation coefficient. In addition, to examine the independent relationships between $\Delta$AVA, and factors influencing the progression of AS, we conducted multivariate analysis based on linear regression with $\Delta$AVA as a dependent variable and other measurements as independent variables. The independent variables with the P-value that is $< 0.10$ in a univariate analysis were included in the linear regression model. All tests were two-sided and the significance was accepted at $P < 0.05$.

**Results**

**Haemorrhage in aortic valves**

We often found brown stains on the section of aortic valve leaflets when they were obtained from patients who had undergone aortic valve replacements for degenerative AS, suggesting haemorrhage in the leaflets (Figure 1). Immunoreactivity of glycophorin A was observed in the aortic valve leaflets in 28 of the 36 patients.

**Figure 4** Relationship between intraleaflet haemorrhage and macrophage infiltration. Micrographs of an aortic valve leaflet obtained from a patient with degenerative aortic valve stenosis. (A) Immunostaining with anti-glycophorin A antibody (scale bar indicates 100 μm). (B) The adjacent section to (A) stained with CD68 (scale bar indicates 100 μm). CR68-positive macrophages were observed in the same area where immunoreactivity for glycophorin A was detected. (C) A graph showing that the percentage of the glycophorin A-positive area is positively correlated with the percentage of the CD68-positive area ($R = 0.78, P < 0.0001$).
with AS (78%) (Figure 2A, B, and E). Demographic profiles and cardiovascular risk factors of control patients (n = 10, age 65 ± 10 years, men/women: 7/3) were not different from those of patients with AS. Glycophorin A immunoreactivity was not observed in the aortic valve leaflet of any control patient (Figure 2C). There were vascular structures lined with vWF-positive endothelial cells in the aortic valve leaflets obtained from patients with degenerative AS (Figure 3A). There were no vascular structures in the aortic valve leaflet of any control patients. Few glycophorin A immunoreactivity was found on red blood cells in the vascular structure (Figure 3B and C). However, most glycophorin A immunoreactivity was localized outside the blood vessels, suggesting that haemorrhage occurred in the valve leaflet (Figure 3D and E). Haemorrhage was considered to occur before surgical procedure because glycophorin A immunoreactivity lost the shape of the red blood cells. Intra-leaflet haemorrhage was frequently identified in the vicinity of the calcified area, and, furthermore, intra-leaflet haemorrhage was mostly found in the area adjacent to neoangiogenesis (Figure 3D and E). The grade of glycophorin A immunoreactivity was positively correlated with the grade of neovascularization (Figure 3F). The aortic valve area of patients with intra-leaflet haemorrhage was not different from that without intra-leaflet haemorrhage [glycophorin A immunoreactivity-positive group vs. negative group: 0.70 (0.53–0.91) vs. 0.78 (0.70–0.98) cm², median (inter-quartile range), P = 0.193]. Patient characteristics and medications were not different between the patients with intra-leaflet haemorrhage and those without it.

**Intra-leaflet haemorrhage and macrophage infiltration**

Infiltration of CD68-positive macrophages was frequently observed in the area with intra-leaflet haemorrhage (Figure 4A and B), but not observed in the aortic valve leaflet of any control patients. The extent of intra-leaflet haemorrhage was positively correlated with the extent of macrophage infiltration (Figure 4C).

### Relationship between intra-leaflet haemorrhage and progression of AS

We assessed the association of the intra-leaflet haemorrhage with the progression of AS. The mean annualized change in the aortic valve area in our study population was 0.12 cm²/year, which was similar to the previously reported values.27–29 Patient characteristics did not differ between the rapid progression group and the slow progression group (Table 1). Medication also did not differ between the two groups (Table 2). In contrast, areas of glycophorin A and CD68 immunoreactivity were significantly larger in the rapid progression group than in the slow progression group (Figure 5). Moreover, the grades of intra-leaflet haemorrhage and macrophage infiltration in the aortic valve correlated positively with ΔAVA (Figure 6A and B). Regarding neoangiogenesis, the number of vessels was tended to be larger in the rapid progression group than in the slow progression group, but the difference did not reach statistical significance. According to these results, multivariate analysis based on linear regression was performed to assess the independent factors contributing to the progression of AS. ΔAVA was a dependent variable, and neoangiogenesis, glycophorin A staining, and CD68 staining were independent variables. Only intra-leaflet haemorrhage significantly contributed to the progression of AS (Table 3).

### Relationship between intra-leaflet haemorrhage and oxidative stress

We further investigated how intra-leaflet haemorrhage accelerated the progression of AS. The distribution of 4-HNE-positive area was quite similar to that of glycophorin A-positive area, suggesting the association of intra-leaflet haemorrhage and oxidative stress (Figure 7A and B). The extent of intra-leaflet haemorrhage was positively correlated with the extent of 4-HNE staining (Figure 7C).

### Discussion

Haemorrhage in the atherosclerotic lesion has been suggested to play critical roles in plaque progression and rupture in the...
carotid artery, coronary artery, and aorta.\textsuperscript{18–22} To our knowledge, the present study is the first to demonstrate that haemorrhage occurs in the leaflet of human aortic valve and that it is associated with the progression of degenerative AS. Intraleaflet haemorrhage appears to be extravasated from the vascular structures in the leaflet because intraleaflet haemorrhage was observed in the area adjacent to the area with angiogenesis and the grade of intraleaflet haemorrhage was correlated with the number of vascular structures.

Since intraleaflet haemorrhage was accompanied with the infiltration of macrophages, intraleaflet haemorrhage itself may convey circulating monocytes into the leaflet. Yunoki et al.\textsuperscript{30} have shown that the expression of haemoglobin scavenger receptor was enhanced in the accumulated macrophages of the culprit

![Figure 5](image)

**Figure 5** Differences between the slow progression group and the rapid progression group for histological findings. (A) A scatter graph showing that there is no significant difference between the two groups regarding neoangiogenesis. (B) A scatter graph showing that the percentage of the glycophorin A-positive area is larger in the rapid progression group than in the slow progression group. (C) A scatter graph showing that the percentage of the CD68-positive area is larger in the rapid progression group than in the slow progression group.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Medication of the patients</th>
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<td>Slow progression group (n = 21)</td>
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<tr>
<td>CCB</td>
<td>11 (52%)</td>
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<tr>
<td>ACE-I</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>ARB</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>Statin</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Insulin</td>
<td>1 (5%)</td>
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CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker. Results shown as numbers and percentages (%). P-value for differences between the slow progression group and the rapid progression group. Fisher’s test was used to compare the values between two groups.

![Figure 6](image)

**Figure 6** Relationship between progression of aortic valve stenosis and intraleaflet haemorrhage or macrophage infiltration. (A) A graph showing that the percentage of the glycophorin A-positive area is positively correlated with change in the aortic valve area ($R = 0.58$, $P < 0.0001$). (B) A graph showing that the percentage of the CD68-positive area is positively correlated with change in the aortic valve area ($R = 0.52$, $P < 0.0001$).
lesions in patients with acute coronary syndrome. Therefore, macrophages may have infiltrated into the valve leaflet in order to scavenge haemoglobin.

We also examined the role of the intraleaflet haemorrhage in the progression of AS by assessing the changes in the aortic valve area before operation. Interestingly, intraplaque haemorrhage was associated with a rapid progression of AS. Haemorrhage in the lesion is likely to play a critical role in accelerating the progression of AS as observed in the atherosclerosis of the coronary artery, carotid artery, and aorta. The accumulation of haemoglobin may induce iron overload and oxidative stress in the atherosclerotic plaque. In this study, intraleaflet haemorrhage was positively correlated with 4-HNE staining. This finding suggests that intraleaflet haemorrhage induces oxidative tissue damage and contribute to the progression of AS. Oxidative modification of LDL in the stenotic valve may be accelerated by haemoglobin and iron. The accumulation of haemoglobin can also activate the pro-inflammatory transcription factor leading to inflammation and angiogenesis. Thus, intraleaflet haemorrhage may accelerate the progression of AS. On the contrary, the rapid progression of AS may cause severe hypoxia in the leaflet, which could induce neoangiogenesis and intraleaflet haemorrhage. Since intraleaflet haemorrhage was not evaluated until specimens were available after the surgery, it cannot be determined whether intraleaflet haemorrhage is a cause, a result, or, both, of the rapid progression of AS in the present study. Further studies are necessary to elucidate the roles of intraleaflet haemorrhage on the progression of AS.

These days, there is a rapid increase in the number of patients with degenerative AS, and the patients with severe AS are indicated for surgical treatment even at an advanced age. If the progression of AS could be retarded even a little, the patients may be free from the operation and also from AS-related major cardiovascular events. According to the results of recent clinical trials, the effects of statins and cholesterol absorption inhibitor have been examined but gave mixed results in preventing the progression of AS. Hence, new strategies are necessary for retarding the progression of AS. The future research should explore whether preventing intraleaflet haemorrhage could retard the progression of AS.

<table>
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<th>Table 3</th>
<th>Multivariate analysis based on linear regression model of annualized change in aortic valve area (ΔAVA) in patients with aortic stenosis</th>
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<tbody>
<tr>
<td>Independent factor</td>
<td>Standardized coefficient</td>
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<td>Neoangiogenesis</td>
<td>0.259</td>
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<tr>
<td>Glycophorin A staining</td>
<td>0.677</td>
</tr>
<tr>
<td>CD68 staining</td>
<td>−0.060</td>
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Figure 7 Relationship between intraleaflet haemorrhage and oxidative stress. Micrographs of an aortic valve leaflet obtained from a patient with degenerative aortic valve stenosis. (A) Immunostaining with anti-glycophorin A antibody (scale bar indicates 500 μm). (B) The adjacent section to (A) stained with 4-hydroxy-2-nonenal (scale bar indicates 500 μm). 4-Hydroxy-2-nonenal-positive area was observed in the almost same area where immunoreactivity for glycophorin A was detected. (C) A graph showing that the percentage of the glycophorin A-positive area is positively correlated with the percentage of the 4-hydroxy-2-nonenal-positive area (R = 0.843, P < 0.0001).
Study limitations
First, the number of samples was small in the present study. As the sample size of this study is quite small, our univariate or multivariate analyses may be underpowered; therefore, we could not detect important variables as statistically significant. Especially, because most of the variables evaluated were categorical, the ability to detect a difference was insufficient. Moreover, we employed multivariate analysis based on linear regression model to explore the relationships between ΔAVA, and factors influencing the progression of AS. Since the use of the linear regression model assumes the normality of the error or dependent variable distribution, we should have applied the data transformation such as inverse, logarithmic, square and cube root, Box-Cox to ΔAVA, neangiogenesis, glycophrin A, and CD68 staining. However, such data transformation was not applicable to our study, as these variables had some zero values. Because of small sample size, it was also quite difficult to identify the shape of the data distribution, and in such a situation, inappropriate transformation could lead to wrong results. Thus, we performed a usual linear regression analysis. Analyses of larger number of samples are necessary to confirm our conclusion. Secondly, intraleaflet haemorrhage was evaluated in only one slice for each patient. It is uncertain whether one slice from the thickest portion of one leaflet could represent the three aortic valve leaflets. More precise evaluation of the whole leaflet is necessary to validate our hypothesis. Thirdly, time intervals between two echocardiograms were diverse. To assess ΔAVA accurately, uniform time intervals are desirable.

Conclusions
Intraleaflet haemorrhage occurs in the stenotic aortic valve leaflets and is associated with the rapid progression of AS.

Acknowledgement
We thank all the staff of Department of Cardiovascular Surgery, Hyogo College of Medicine, for supporting the collection of samples. We thank Akari Furuse, Division of English, Hyogo College of Medicine, for her critical reading of the manuscript.

Funding
This study was supported by grants from the Ministry of Health, Labour and Welfare (Tokyo, Japan) (H-19 Junkankitou-Seishuu-Ippan-015).

Conflict of interest: none declared.

References

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Survived sudden cardiac death in a patient with a huge sinus of Valsalva aneurysm

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A 75-year-old man was admitted to the hospital with acute coronary syndrome after strenuous physical activity, associated with ventricular fibrillation and successful defibrillation (Panel A). Echocardiographic study (Panel B) and multidetector computed tomography (Panel C) demonstrated a giant unruptured isolated aneurysm of the left sinus of Valsalva (SVA). Cardiac catheterization confirmed the diagnosis of a large SVA (6 × 6 cm), compressing the left main coronary artery, the proximal parts of both the left anterior descending (LAD) and the circumflex coronary arteries (Panel D 1). Due to the severe haemodynamic instability, rescue percutaneous coronary intervention with implantation of two bare-metal stents and good immediate angiographic result was performed (Panel D 2). The patient had full recovery and was scheduled for aortic root and aortic valve replacement in combination with internal mammary artery bypass grafting to the LAD. At 6 months follow-up, the patient had no complaints and a negative treadmill exercise test.

Sinus of Valsalva aneurysm is a rare cardiac anomaly especially when the left coronary sinus is involved. The prevalence was 0.09% in a large autopsy series and associated anomalies are common. The malformation consists of a separation, or lack of fusion, between the media of the aorta and the annulus fibrosis of the aortic valve.

Unruptured SVAs are usually asymptomatic, although rupture of the dilated sinus may lead to intracardiac shunting. Pressure on the intracardiac conduction system may cause complete AV block. Rarely, myocardial ischaemia may be caused by coronary arterial compression, as described in our case.

Panel A. Electrocardiogram: ventricular fibrillation, terminated with a biphasic 360 J shock.
Panel B. Transoesophageal echocardiography, demonstrating the connection of the sinus of Valsalva aneurysm (AN) to the aorta (AO) and the aortic valve (AV).
Panel C. Multidetector computed tomography: showing the large sinus of Valsalva aneurysm (asterisk) and its relationship to the aorta (AO), pulmonary artery (PA), and the left ventricle (LV), respectively.
Panel D. Cardiac catheterization; (D 1) compression of both the left anterior descending (LAD, black arrow) and of the circumflex arteries (CX, white arrow). (D 2) LAD and CX after implantation of two bare metal stents.

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