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RESEARCH PAPER

Clinical Significance of Angiographically Detectable Neovascularity in Patients with Cardiac Myxoma

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Abstract

Background: Myxomas are the most common primary cardiac tumors. Angiographically detectable neovascularity (ADN) of myxoma is increasingly being reported as a result of the use of coronary angiography (CAG) to detect coronary artery disease. However, the clinical significance of these findings is not fully understood.

Methods: We enrolled 59 patients with cardiac myxoma who also underwent CAG between January 2013 and October 2018. Patients were followed up for a mean of 28.9 months (range 1–69 months). The clinical features, echocardiography measurements, pathological examination findings, CAG results, and outcomes during follow-up were compared between patients with ADN and patients without ADN.

Results: ADN was found in 25 patients (42.4%). The arteries feeding the ADN included the right coronary artery ($n = 15$), the left circumflex coronary artery ($n = 7$), and both arteries ($n = 3$). The patients with ADN had a higher proportion of eosinophils (3.2% vs. 2.2%, P = 0.03) and higher low-density lipoprotein cholesterol level (2.7 mmol/L vs. 2.2 mmol/L, P = 0.02). Myxoma pedicles were more likely to be located in the interatrial septum in patients with ADN (96% vs. 73.5%, P = 0.02). No significant correlation was observed between the groups in clinical manifestations, atrial arrhythmia, myxoma size, cardiac chamber size, left ventricular ejection fraction, and the prevalence of complication with coronary artery disease [16% in the ADN group ($n = 4$) vs. 20.6% in the non-ADN group ($n = 7$), P = 0.66]. However, patients with ADN tended to have a lower incidence of major adverse cardiac and cerebrovascular events on long-term follow-up (0% vs. 14.7%, P = 0.07).

Conclusion: CAG-detected ADN in patients with cardiac myxoma is associated with a borderline lower rate of major adverse cardiac and cerebrovascular events.

Keywords: Cardiac myxomas; coronary angiography; angiographically detectable neovascularity; major adverse cardiac and cerebrovascular events

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All authors are responsible for the reliability of and freedom from bias of the data presented and their discussed interpretation.

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Introduction

Primary heart tumors are quite rare, with an estimated incidence of approximately 0.03% in the general population. Three-quarters of these tumors are benign, and nearly half of them are myxomas [1]. The classic triad of symptoms in patients with myxoma includes obstructive symptoms, constitutional symptoms, and embolic events [2–4]. Echocardiography, computed tomography, and magnetic resonance imaging are the usual diagnostic tools for cardiac myxoma [5–7]. Coronary angiography (CAG) is also indicated for patients with myxoma before surgical excision to confirm or exclude the presence of coexisting coronary artery disease (CAD) [8–10]. Consequently, angiographically detectable neovascularity (ADN) is increasingly being reported, and some reports have suggested that ADN might cause a "coronary steal phenomenon," which might be responsible for the pathogenesis of ischemic symptoms in patients with myxoma [11, 12]. The clinical significance, particularly the effects of ADN on the long-term outcomes of patients with myxoma, remains largely unknown. The aim of this study was to determine the prevalence of ADN among patients with cardiac myxoma who undergo CAG and the clinical significance of the findings, particularly the effects of ADN on the long-term outcomes of patients with myxoma after myxoma excision surgery.

Patients and Methods

Clinical data, including clinical features, laboratory test results, echocardiography measurements, coronary artery abnormality, and pathological features, from 408 patients with diagnosed cardiac myxomas between January 2013 and October 2018 in our center were reviewed. Among these patients, 59 underwent CAG and were enrolled in this study. ADN was found in 25 of the 59 patients (42.4%). The typical angiographic features of ADN are shown in Figure 1. All 59 patients underwent myxoma excision surgery, and histological sections were reviewed in all cases by the same pathologist. ADN was defined as abnormal clusters of small and tortuous vessels arising from the coronary arteries and supplying the myxoma. CAD was defined as the presence of at least 70% stenosis in the left anterior descending artery, left circumflex artery, or right coronary artery, or at least 50% stenosis in the left main coronary artery. CAG was assessed by two experienced interventional cardiologists. Patients were followed up for a mean of 28.9 months. Follow-up information was obtained by our contacting the patients with a standardized questionnaire. The primary clinical end point was a composite of major adverse cardiac and cerebrovascular events (MACCE) including all-cause death, cerebral infarction, and myocardial infarction. The secondary end point was tumor recurrence.

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation; Student's *t* test was used to compare continuous variables. Non-normally distributed parameters are expressed as the median and the range; the Mann-Whitney *U* test was used to compare non-normally distributed parameters. Fisher's exact test was used as required. $P < 0.05$ was considered statistically significant. Data analysis was performed with SPSS Statistics version 21.0 (IBM, Armonk, NY, USA).

Results

Clinical Characteristics

The clinical characteristics of patients with ADN and patients without ADN are listed in Table 1. The general clinical characteristics of patients with ADN and patients without ADN were similar. The most common symptom was dyspnea (68% vs. 79.4%, $P = 0.41$), followed by palpitation (20% vs. 17.7%, $P = 0.96$), chest pain (4% vs. 11.8%, $P = 0.64$), and syncope (8% vs. 0%, $P = 0.18$). Only four patients were asymptomatic at admission (16% vs. 11.8%, $P = 0.71$) in each group. Limb dysfunction was found in two patients with ADN (2/25, 8%). In addition, the prevalence of atrial fibrillation/atrial flutter (AF/AFL) during hospitalization was similar between patients with ADN and patients without ADN (12% vs. 26.5%, $P = 0.18$).

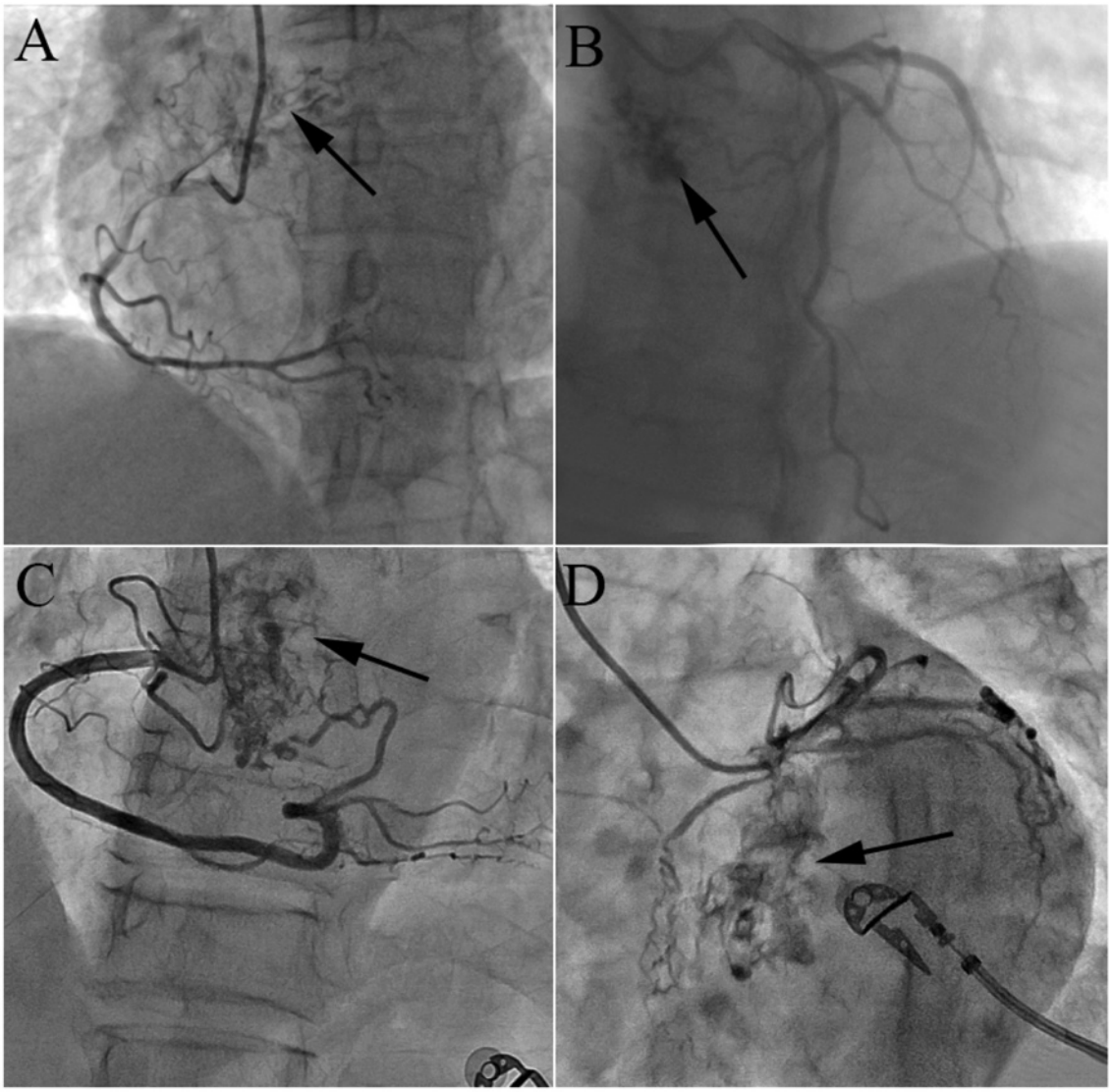

Figure 1 Typical Angiographically Detectable Neovascularity in Patients with Myxoma.
(A) Neovascularity supplied by the right coronary artery found in a patient with left atrium myxoma. (B) Neovascularity supplied by the left circumflex coronary artery, found in a patient with left atrium myxoma. (C, D) Neovascularity supplied by both the left circumflex coronary artery and the right coronary artery, found in a patient with left atrium myxoma.

Laboratory Tests

The results of laboratory tests are listed in Table 2. The eosinophil proportion (3.2% vs. 2.2%, P = 0.03) and the low-density lipoprotein cholesterol level (2.7 mmol/L vs. 2.2 mmol/L, P = 0.02) were significantly higher in patients with ADN than in patients without ADN.

Echocardiography Measurements

Echocardiography measurements are listed in Table 3. The cardiac myxomas were located in the right atrium in eight patients and in the left atrium in 51 patients. There was no statistical difference in myxoma size (P = 0.83), left ventricular end-diastolic diameter (P = 0.31), left atrial end-systolic diameter (P = 0.46), right ventricular end-diastolic diameter (P = 0.50), right atrial end-systolic diameter (P = 0.71), left ventricular ejection fraction (P = 0.73), prevalence of mitral regurgitation (P = 0.06), and prevalence of tricuspid regurgitation (P = 0.72) between groups.

CAG Abnormalities

CAD was found in 11 patients with myxoma [18.6%; four in the ADN group and seven in the non-ADN

Table 1 Clinical Characteristics of Patients with Myxoma who Underwent Coronary Angiography.

	With ADN (*n* = 25)	Without ADN (*n* = 34)	P-value
Male	6 (24%)	11 (32.4%)	0.48
Age (years)	62.6 ± 5.0	63.4 ± 6.1	0.64
Smoker	4 (16%)	6 (17.6%)	0.87
Diabetes	4 (16%)	3 (8.8%)	0.40
SBP (mmHg)	121.9 ± 17.6	122.9 ± 18.7	0.83
DBP (mmHg)	74.1 ± 11.0	74.9 ± 12.2	0.78
HR (bpm)	85.8 ± 13.6	84.7 ± 21.7	0.82
Tumor history	1 (4%)	0 (0%)	0.24
BMI (kg/m^2)	22.6 ± 3.0	23.4 ± 2.7	0.28
NYHA class			
I	0 (0%)	3 (8.8%)	0.26
II	6 (24%)	14 (41.2%)	0.17
III	18 (72%)	17 (50%)	0.09
IV	1 (4%)	0 (0%)	0.42
Main symptoms			
Dyspnea	17 (68%)	27 (79.4%)	0.41
Palpitation	5 (20%)	6 (17.7%)	0.96
Chest pain	1 (4%)	4 (11.8%)	0.64
Syncope	2 (8%)	0 (0%)	0.18
Limb dysfunction	2 (8%)	0 (0%)	0.18
Asymptomatic	4 (16%)	4 (11.8%)	0.71
Other symptoms	2 (8%)	4 (11.8%)	0.75
AF/AFL	3 (12%)	9 (26.5%)	0.18
Stroke history	2 (8%)	5 (14.7%)	0.44

ADN, angiographically detectable neovascularity; AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association; SBP, systolic blood pressure.

group (16% vs. 20.6%, P = 0.66)]. In the 25 patients with ADN, the myxoma was supplied by coronary artery branches arising from the right coronary artery in 15 patients (60%), from the left circumflex artery in seven patients (28%), and from both the right coronary artery and the left circumflex artery in three patients (12%). Detailed information on the 25 patients with myxoma and ADN is provided in Table 4 according to the timing sequence.

Surgical Operation and Pathological Data

All 59 patients with myxoma were referred for cardiac surgery, and pathological evaluation was performed on excised myxomas. Surgical operation and pathological data are shown in Table 5. There was no significant difference in operation time (165.0 min vs. 171.0 min, P = 0.31) and cardiopulmonary bypass time (48.0 min vs. 51.0 min, P = 0.69) between patients with ADN and patients without ADN. In patients with ADN, 24 myxomas (96%) were attached to the interatrial septum, three myxomas (12%) were attached to the atrial wall, and two myxomas were attached to both the atrial wall and the interatrial septum. In patients without ADN, 25 myxomas (73.5%) were attached to the interatrial septum, seven myxomas (20.6%) were attached to the atrial wall, three myxomas (8.8%) were attached to the annulus, and one myxoma was attached to both the atrial wall and the interatrial septum. The prevalence of myxomas attached to the interatrial septum was significantly higher in patients with ADN than in patients without ADN (96% vs. 73.5%, P = 0.02). The pathological examination results were similar between groups (all P > 0.05).

Table 2 Laboratory Test Results for Patients with Myxoma who Underwent Coronary Angiography.

	With ADN (*n* = 25)	Without ADN(*n* = 34)	P-value
WBCs (10^9/L)	6.6 ± 2.5	6.2 ± 2.3	0.54
Hemoglobin (g/L)	121.8 ± 13.7	118.3 ± 15.3	0.38
Platelets (10^9/L)	234.9 ± 78.0	226.9 ± 101.1	0.64
Neutrophils (%)	63.2 ± 8.3	62.4 ± 9.4	0.74
Lymphocytes (%)	26.5 ± 7.0	28.4 ± 9.1	0.88
Eosinophils (%)	3.2 ± 2.1	2.2 ± 1.3	0.03*
Basophils (%)	0.5 ± 0.3	0.4 ± 0.2	0.52
BUN (mmol/L)	5.6 ± 1.7	5.6 ± 1.4	0.63
Creatinine (μmol/L)	68.6 (37.7–229.6)	66.4 (43.8–103.5)	0.55
UA (μmol/L)	323.6 ± 99.1	316.8 ± 105.1	0.81
ALT (U/L)	13.4 (4.4–52.9)	13.6 (6.5–45.7)	0.46
AST (U/L)	18.3 (10.1–63.5)	18.3 (12.3–68.8)	0.45
Albumin (g/L)	36.9 (30.2–67.0)	36.6 (24.1–60.1)	0.64
Globulin (g/L)	20.6 ± 5.7	29.6 ± 6.5	0.59
TG (mmol/L)	1.1 (0.6–3.8)	1.0 (0.4–4.4)	0.48
LDL-C (mmol/L)	2.7 ± 0.9	2.2 ± 0.7	0.02*
HDL-C (mmol/L)	1.1 (0.7–1.9)	1.1 (0.5–2.0)	0.85
PT	12.1 (10.6–17.9)	12.5 (10.4–35.6)	0.90
APTT	36.4 ± 6.1	36.6 ± 8.4	0.94
Fibrinogen (g/L)	3.5 (2.4–6.8)	4.0 (2.6–7.7)	0.14
BNP (pg/mL)	126.0 (25.4–1053.0)	130.5 (5.0–278.0)	0.75

ADN, angiographically detectable neovascularity; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PT, prothrombin time; TG, triglycerides; UA, uric acid; WBCs, white blood cells. *Significant difference.

Table 3 Echocardiography Measurements of Patients with Myxoma who Underwent Coronary Angiography.

	With ADN (*n* = 25)	Without ADN (*n* = 34)	P-value
LVEDd (mm)	45.2 ± 4.9	46.8 ± 6.5	0.31
LAESd (mm)	35.4 ± 4.5	36.5 ± 5.8	0.46
RVEDd (mm)	33.0 ± 5.3	33.0 ± 3.4	0.50
RAESd (mm)	35.3 ± 9.0	33.3 ± 3.8	0.71
LVEF (%)	67.4 ± 6.6	66.8 ± 5.9	0.73
Mitral regurgitation	20 (80%)	19 (55.9%)	0.06
Tricuspid regurgitation	7 (28%)	11 (32.4%)	0.72
Right atrium myxoma	2 (8%)	6 (17.6%)	0.29
Myxoma size (cm^2)	12.1 ± 7.6	12.5± 6.8	0.83

ADN, angiographically detectable neovascularity; LAESd, left atrial end-systolic diameter; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction RAESd, right atrial end-systolic diameter; RVEDd, right ventricular end-diastolic diameter.

Follow-up Findings

Follow-up information is shown in Table 6. All 59 patients with myxoma were successfully followed up, with a mean follow-up period of 28.9 months (range 1–69 months). No adverse events were observed in patients with ADN, whereas cerebral infarction occurred in three patients without ADN. Moreover, two deaths occurred in patients without ADN. The incidence of MACCE

Table 4 Characteristics of Patients with Myxoma and Angiographically Detectable Neovascularity According to the Timing Sequence.

Patient no.	Sex	Age (years)	Symptom 1	Symptom 2	Symptom 3	AA	SH	CAD	Pedicle location	Feeding artery
1	M	75	Dyspnea			+			Septum	LCX
2	F	61	Dyspnea						Septum	RCA
3	F	63	Dyspnea						Septum	RCA
4	F	68	Dyspnea	Syncope					Septum	LCX
5	F	64	Asymptomatic			+			Septum	RCA
6	F	62	Dyspnea	Palpitation					Septum	LCX
7	F	59	Dizziness		Limb dysfunction				Septum	RCA
8	F	62	Dyspnea	Palpitation					Septum	LCX
9	F	67	Asymptomatic				+		Septum	RCA
10	F	68	Dyspnea			+			Septum	RCA
11	M	62	Dyspnea						Septum	RCA
12	M	52	Dyspnea					+++	Septum	RCA
13	F	62	Syncope						Septum	RCA
14	F	59	Dyspnea	Palpitation					Septum	LCX
15	M	57	Dyspnea				+		Wall	RCA
16	F	60	Dizziness						Septum	LCX + RCA
17	F	68	Asymptomatic						Septum	LCX + RCA
18	F	62	Palpitation	Dyspnea					Septum	RCA
19	F	65	Dyspnea		Limb dysfunction				Septum	RCA
20	F	65	chest pain					+	Septum	RCA
21	M	63	Dyspnea					+++	Septum + wall	LCX
22	F	51	Dyspnea						Septum + wall	LCX
23	F	66	Dyspnea	Palpitation					Septum	RCA
24	M	62	Asymptomatic					+	Septum	RCA
25	F	63	Dyspnea						Septum	RCA + LCX

AA, atrial arrhythmia; CAD, coronary artery disease; F, female; LCX, left circumflex coronary artery; M, male; RCA, right coronary artery; SH, stroke history.
+, with the diseases history; +++, serious coronary heart disease needing revascularization.

Table 5 Surgical Operation and Pathological Characteristics.

	With ADN (*n* = 25)	Without ADN (*n* = 34)	P-value
Myxoma calcification	1 (4%)	0 (0%)	0.42
Interstitial hemorrhage	9 (36%)	7 (20.6%)	0.13
Myxoma necrosis	0 (0%)	2 (5.9%)	0.22
Active proliferation	5 (20%)	4 (11.8%)	0.34
Myxoma pedicle adhesion			
Interatrial septum	24 (96%)	25 (73.5%)	0.02*
Atrial wall	3 (12%)	7 (20.6%)	0.49
Annulus	0 (0%)	3 (8.8%)	0.26
Operation time (min)	165.0 (91.0–322.0)	171.0 (120.0–355.0)	0.31
Cardiopulmonary bypass time (min)	48.0 (31.0–144.0)	51.0 (17.0–176.0)	0.69

ADN, angiographically detectable neovascularity.
*Significant difference.

Table 6 Follow-Up of Patients with Myxoma.

	With ADN (*n* = 25)	Without ADN (*n* = 34)	P-value
MACCE	0 (0%)	5 (14.7%)	0.07
All-cause death	0 (0%)	2 (9.5%)	0.50
MI	0 (0%)	0 (0%)	1.00
CI	0 (0%)	3 (14.%3)	0.26
Tumor recurrence	0 (0%)	0 (0%)	1.00

ADN, angiographically detectable neovascularity; CI, cerebral infarction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

Table 7 Clinical Features of Patients with Myxoma with no Angiographically Detectable Neovascularity, with or without Major Adverse Cardiac and Cerebrovascular Events (MACCE).

	MACCE group (*n* = 5)	Non-MACCE group (*n* = 29)	P-value
Age (years)	61.4 ± 3.7	63.7 ± 6.5	0.45
Male	2 (40%)	9 (31.0%)	1.00
AF/AFL	4 (80%)	5 (17.2%)	0.01*
Eosinophils (%)	1.8 ± 1.1	2.2 ± 1.3	0.55
LDL-C (mmol/L)	2.2 ± 0.2	2.2 ± 0.7	0.88
Myxoma size (cm^2)	16.1 ± 3.5	12.0 ± 7.0	0.27
Myxoma adhered to interatrial septum	4 (80%)	21 (72.4%)	1.00
Operation time (min)	151.4 ± 15.6	198.3 ± 67.8	0.14
Cardiopulmonary bypass time (min)	50.0 (40.0–51.0)	55.0 (17.0–176.0)	0.21
CAD	2 (40%)	5 (17.3%)	0.27

AF, atrial fibrillation; AFL, atrial flutter; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol.
*Significant difference.

tended to be lower in patients with ADN than in patients without ADN (0% vs. 14.7%, P = 0.07). We further compared the clinical features of five patients with myxoma and MACCE with those of 29 patients with myxoma in the non-ADN group, and found that the former had a higher incidence of atrial arrhythmia (80% vs. 17.2%, P = 0.01) (Table 7).

Discussion

The primary aim of this study was to assess the prevalence and clinical significance of ADN in patients with cardiac myxoma, focusing on the relationship between ADN and clinical outcomes observed during follow-up. The major finding of this study was that the prevalence of MACCE was lower in patients with ADN than in patients without ADN (0% vs. 14.7%, P = 0.07) during follow-up for a mean period of 28.9 months.

Although ADN is increasingly reported in patients with cardiac myxoma, the effects of ADN on the clinical presentation have not been fully described because of the small number of ADN cases. The clinical presentation of patients with myxoma depends largely on the appearance, location, size, and mobility of the myxoma [3, 10–13]. Symptoms such as dyspnea, chest pain, and syncope are most likely to be due to the obstruction of atrioventricular valvar flow and may mimic valvar stenosis. Previous studies showed that dyspnea is the most common clinical symptom of cardiac myxoma, owing to the obstruction of ventricular inflow or outflow tracts, and is followed by chest pain and syncope, in agreement with our present findings [6]. Cardiac myxoma vascularity consists of clusters of small and tortuous vessels arising from the coronary arteries, which may be visualized by CAG in some patients and are called "angiographically detectable neovascularity" (ADN). Our results demonstrated that the presence of ADN is not associated with differences in clinical presentation. According to previous studies, ADN is found in 33.3–55.6% of patients with myxoma [9, 14–17]. Similarly to findings from prior studies, ADN was observed in 25 of 59 patients (42.4%) in this clinical report. Some studies have postulated that massive blood leak from the coronary artery into giant cardiac myxomas might give rise to a "coronary steal phenomenon" and subsequent nonspecific symptoms in patients [11, 12]. Suh et al. [18] described the case of a myxoma with the formation of an unusual fistula in the left atrial cavity and the development of "intra-atrial steal." Other studies have recommended individual ligation or percutaneous closure with coiling of the neovascularity in cases of myxoma with large feeding branches to relieve patient symptoms [19, 20]. In our study, we did not find negative effects of ADN on the clinical manifestations in patients with myxoma. Therefore, our findings in this patient cohort do not support the hypothesis of a coronary steal phenomenon caused by ADN in patients with myxoma.

To the best of our knowledge, this is the first report with a relatively large sample size describing the long-term outcomes of patients with myxoma with or without ADN after myxoma excision surgery. We found that patients with myxoma with ADN had borderline better outcomes than patients without ADN. The underlying reasons remain elusive. The following factors might be associated with our findings. Despite the similar clinical features between patients with ADN and patients without ADN, we observed a higher prevalence of AF/AFL in patients without ADN (26.5% vs. 12%, P = 0.18). Subgroup analysis showed that among patients with no ADN, the prevalence of AF/AFL was significantly higher in patients with MACCE than in patients without MACCE (Table 7). Moreover, 96% of the atrial myxomas were attached to the interatrial septum (typical adhesion location) in patients with ADN (Table 5), a proportion significantly higher than that in the patients without ADN (P = 0.02). Thus, myxomas without ADN were more likely to be attached to an atypical location. According to previous studies, atypical myxoma pedicle adhesion is associated with a higher risk of embolism [21]. During cardiac surgery, myxomas that attach to the atrial wall or annulus require additional repair of the atrial wall or annulus. Therefore, we speculated that myxomas at atypical locations in patients without ADN have greater adverse effects on outcomes after surgery. The myxoma was located on the interatrial septum in four of the five non-ADN patients who developed MACCE; thus, the outcome was not associated with the myxoma's location. Low-density lipoprotein cholesterol levels and eosinophil proportions differed between ADN patients and non-ADN patients, but were similar between non-ADN patients with MACCE and non-ADN patients without MACCE (Table 7). Moreover, the prevalence of CAD was also similar in non-ADN patients with MACCE and non-ADN patients without MACCE (Table 7).

Patients with myxoma with ADN showed borderline better outcomes than patients with myxoma without ADN, a finding potentially attributable to rapid repair of the cardiac tissue around the incision with rich vasa vasorum. Surgeons should potentially

pay more attention to bleeding and hemostasis at the incision if the vasa vasorum in patients with ADN is sufficiently thick (usually more than 5 mm), as shown by CAG.

The limitations of this study include that only 59 patients underwent CAG, thus limiting our ability to evaluate the true prevalence of CAD in patients with myxoma. Moreover, the cohort was relatively small for evaluating the prognosis of patients with myxoma with or without ADN. Future clinical studies with larger cohorts are warranted to validate the findings derived from this study.

Conclusions

The presence of ADN in patients with myxoma does not affect clinical manifestations but may be associated with better clinical outcomes after myxoma excision surgery during long-term follow-up. AF/AFL is an important risk factor for MACCE in non-ADN patients with myxoma after myxoma excision surgery. Therefore, intensive medical intervention is needed for non-ADN patients with myxoma with AF/AFL after myxoma excision surgery.

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Conflicts of Interest

None.

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