Outcomes of surgery for functional cardiac paragangliomas: A single-center experience of 17 patients

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ABSTRACT

Objective: Cardiac paragangliomas are rare neuroendocrine tumors. Early surgical treatment improves clinical symptoms and prolongs survival. We review our experience in 17 patients who underwent surgical resection for functional cardiac paraganglioma.

Methods: Seventeen patients underwent surgery for functional cardiac paraganglioma from 2004 to 2017 were identified. Clinical data and long-term outcomes were extracted and analyzed.

Results: All 17 patients with cardiac paraganglioma (11 males) with a median age of 35 years (range, 11 to 51 years) were hormonally functional and underwent operations. A 24-hour urine catecholamine assay documented elevation of norepinephrine, epinephrine, and dopamine. Tumors were determined with octreotide scintiscan in all 17 patients and metaiodoben-zylguanidine scintigraphy in 10 of 15 patients. Tumor sites were right atrioventricular groove in 4 patients, between the main arteries in 10 patients, and interatrial groove in 4 patients. All patients underwent complete resection. Concomitant surgeries were: structural reconstruction in 16 patients (94%) and coronary artery bypass graft in 8 patients (47%). One patient had a history of incomplete resection of an intra-atrial tumor. One patient died postoperatively. Operative mortality is 5.8%. During follow-up (mean, 6.5 years; range, 1.5 to 14.2 years), 16 patients are alive in functional class I or II. Two patients developed tumor recurrence and 14 remained symptom-free with normal urinary catecholamines.

Conclusions: With a multidisciplinary treatment, early diagnosis, complete resection for the tumor along with complex reconstruction is achievable for most patients, and it offers promising long-term survival. (J Thorac Cardiovasc Surg 2019;157:1556-64)

Distribution of 18 functional cardiac paragangliomas (red discs) on the heart.

Central Message

Complete surgical resection and reconstruction is possible for most functional cardiac paraganglioma patients. Satisfactory postoperative survival and long-term outcome are expectable.

Perspective

As a single institutional study of functional cardiac paraganglioma, we review our single-center experience of surgical treatment of 17 patients and demonstrate its common complications and outcomes. With high postoperative survival and good long-term outcome, we recommend to considering complete tumor resection and reconstruction as the first choice.

See Commentary on page 1565.

Cardiac paraganglioma is defined as a specific neuroendocrine tumor arising from heart. Not all paragangliomas can secrete catecholamine.¹ Functional cardiac paraganglioma was defined when the measured catecholamine or metanephrine concentration was greater than the reference

range.² The diagnosis is difficult and often delayed. Surgery for functional cardiac paraganglioma is more challenging because of vascular supply from coronary arteries and close anatomic proximity to the heart and main vessels.³ Between April 2004 and December 2017, 17 symptomatic patients had a diagnosis of functional cardiac paraganglioma and underwent surgical resection, several has been reported previously.^{4,5} We now review these cases, including clinical

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Abbreviations and Acronyms

Ao	= ascending aorta
AVG	= atrioventricular groove
CPB	= cardiopulmonary bypass
ECMO	= extracorporeal membrane oxygenator
IABP	= intra-aortic balloon pump
IAG	= interatrial groove
ICU	= intensive care unit
MIBG	= metaiodoben-zylguanidine scintigraphy
MPA	= main pulmonary artery
OCT	= octreotide scintiscan

presentation, diagnosis, surgical management, and outcome.

MATERIALS AND METHODS

Approval for retrospective review was obtained from our institutional review board. Seventeen patients underwent operations for functional cardiac paragangliomas at the department of cardiac surgery of Peking Union Medical College Hospital between 2004 and 2017 were identified. Clinical data including demographic information, clinical manifestations, results of assays and radiographies, perioperative information, and follow-up data, including postoperative survival and current catecholamine level, were extracted from all available medical records. Preoperative medical therapy using α -receptor blockers, β -receptor blockers, and calcium channel blockers was recorded. Intraoperatively, size and location of the tumor, procedure, duration of surgery, intraoperative hemodynamic information, postoperative inotropic agents, vasopressors, and mechanical support

with an intra-aortic balloon pump (IABP), and extracorporeal membrane oxygenator (ECMO) were also recorded. Length of intensive care unit (ICU) stay, follow-up time, and current catecholamine level of all survival patients are also collected.

RESULTS

Preoperative Characters

Average age at admission was 35 years (range, 11 to 51 years), 11 of 17 patients (65%) were male. 3 patients (18%) were confirmed to have a family history of paraganglioma. At admission, 16 patients (94%) complained paroxysmal hypertension, 11 patients (65%) complained palpation, 9 patients (53%) complained of headache, and 7 patients (41%) complained of perspiration. Two patients (12%) also complained of chest pain. Length of symptom ranged from 2 to 25 years (mean, 9.5 years). Under a 24-hour urine catecholamine assay, urinary norepinephrine was elevated in 15 patients (88%), epinephrine was elevated in 5 patients (29%), and dopamine was elevated in 8 patients (47%; Table 1).

All patients were hormonally functional and were prepared for surgery using α -receptor blockers, β -receptor blockers, and calcium channel blockers for 10 to 14 days following the guidelines for paraganglioma.⁶

Value of Different Imaging Methods

Multiple imaging techniques were used to determine and locate the tumor. OCT (Figure 1) were adopted in all cases, all of which were positive. Among 15 patients who underwent

TABLE 1. Preoperative characteristics

Patient number	Sex	Age (years)	Family history	Presentation	Urine catecholamine	Syndrome length (years)	Medical prepare
1	Male	11	None	Perspiration, palpation, HTN	NE, DoA	9	α , β
2	Male	34	Yes	Palpation, chest pain, HTN	NE	1	α , β
3	Male	13	None	Perspiration, HTN	NE, E, DoA	5	α , β
4	Male	19	None	Perspiration, palpation, headache, HTN	NE, E, DoA	N/A	α
5	Female	23	None	Perspiration, palpation, headache, HTN	NE, DoA	4	α
6	Male	48	None	Perspiration, palpation, headache, HTN	NE, E	15	α
7	Female	50	None	Palpation, HTN	None	10	α
8	Male	50	None	Palpation, headache, HTN	NE, DoA	2	α , β
9	Male	44	Yes	Palpation, HTN	DoA	20	α
10	Female	35	None	Perspiration, headache, HTN	NE, E, DoA	3	α
11	Male	51	None	Perspiration, palpation, headache, HTN	NE	16	α
12	Female	21	None	Palpation, headache, chest pain, HTN	NE	2	α , β
13	Female	48	None	HTN	NE	6	α , β , CCB
14	Male	17	None	Headache, HTN	NE, E	13	α , β
15	Female	48	None	Perspiration, headache, HTN	NE, DoA	25	α
16	Male	37	None	Perspiration, palpation, headache, HTN	NE	N/A	α
17	Male	45	Yes	Palpation, headache	NE, E	12	α , β , CCB

HTN, Hypertension; NE, norepinephrine; DoA, dopamine; α , α -receptor blocker; β , β -receptor blocker; E, epinephrine; CCB, calcium channel blocker.

FIGURE 1. Otide scintiscan showed a focus of intense uptake on right side of the heart silhouette, indicating the location of the left atrium.

metaiodoben-zylguanidine scintigraphy (MIBG; [Figure 2](#)), 10 patients (67%) had positive results. Tumors were located under multiple imaging tests ([Figure 3](#)). To elucidate the blood supply of the tumor, coronary arteriography was adopted in all cases ([Video 1](#)). Blood supply of all 18 tumors of 17 patients were from the coronary artery ([Figure 4](#)). Twelve tumors (67%) were fed by the left coronary system, 11 tumors (61%) were fed by right coronary system, and 5 tumors (28%) had dual supply from left and right coronary circulation.

Intraoperative Findings

Among 18 tumors in 17 patients, 10 tumors (56%) were located at the root of the ascending aorta (Ao) or the main pulmonary artery (MPA), 4 tumors (22%) were located in the right atrioventricular groove (AVG), and 4 tumors (22%) were located in the interatrial groove (IAG), respectively ([Figure 5](#)). The average size of tumors was 60×48 mm (range, 30×30 mm to 100×80 mm). Local invasion of the tumor was found intraoperatively in 8 patients (47%). In the other 9 patients, tumors were found to have continued capsules. All patients underwent complete tumor resection under cardiopulmonary bypass (CPB). A variety of autologous, allogeneic and synthetic vascular grafts were used for concomitant reconstruction in 16 patients (94%). Coronary artery bypass grafting was adopted in 8 patients (47%). Average duration of CPB was 160 minutes (range, 42 to 328 minutes). Average duration of Ao cross-clamp was 105 minutes (range, 17 to

137 minutes). No heart transplantation was committed. Histologic and immunohistochemical examinations in all patients showed large polygonal cells with ample amphophilic cytoplasm and moderate nuclear pleomorphism. Chromogranin A immunohistochemistry showed positive staining in the tumor cells, representing cardiac paragangliomas ([Table 2](#)).

Complications and Follow-up Information

Perioperative hemorrhage was a common complication. In our 17 patients, the average amount of intraoperative blood transfusion was 4 U (range, 0 to 8 U). Low cardiac output syndrome and vasoplegia were the next most common complications. Three patients (17%) required ECMO support because of recalcitrant hypotension and subsequently presented tamponade that required emergent bedside thoracotomy and daily debridement. One patient died of bleeding complication 40 hours after ECMO implantation, and the other 2 patients recovered after 5 and 16 days of ECMO support, respectively. Among the 16 survival patients, average ICU stay was 6 days (range, 1 to 20 days). Average follow-up was 6.5 years (range, 1.3 to 14.2 years). Three patients (18%) presented late endocrinal relapse at 3, 10, 12 years, respectively, of whom 2 were diagnosed as recurrence of cardiac tumor, whereas the other was attributed to the residual of the adrenal pheochromocytoma. Fourteen of the patients (82%) are free of symptoms and have normal 24-hour urinate catecholamine level currently ([Table 3](#)).

FIGURE 2. Metaiodoben-zylguanidine scintigraphy showed a focus of intense uptake on the right side of heart silhouette.

DISCUSSION

Characters and Diagnosis

Cardiac paraganglioma has an average age of onset of 39.7 years (range, 12 to 85 years) and a balanced M-F ratio.⁷ One third to half of paragangliomas were reported to be one of the symptoms of a genetic syndrome.⁸ A retrospective study including 14 patients of mediastinal paraganglioma found that 21% of patients had a family history,⁹ whereas 18% of patients in our study had a confirmed family history.

Headache, palpation, and perspiration are characteristic symptoms of functional paraganglioma because of high catecholamine secretion.⁹ Wang and colleagues⁷ also reported symptoms of chest pain in cardiac paraganglioma. Twelve percent of patients in our study complained of chest pain. However, in our series of patients, the average length of symptom before diagnosis is 9.5 years, indicating that the diagnosis of functional paraganglioma is difficult and often delayed, which is in accordance with the literature.² Actually, the diagnosis can be improved with the help of urine catecholamine assays and multiple imaging techniques. Urine catecholamine levels are high in 31% of patients

with paraganglioma, but in functional paragangliomas, norepinephrine elevates most frequently.¹⁰ In our study, all 18 cardiac paragangliomas were hormonally functional, which we considered the result of referral bias. The Mayo study reported no elevation of urinate epinephrine.⁹ In our study, functional cardiac paragangliomas could secrete all types of catecholamines, even 2 or 3 types at the same time. High norepinephrine level was detected most frequently. The value of MIBG has been emphasized since 1995, when Jeevanandam and colleagues¹¹ reported its significance in the determination of cardiac paraganglioma. According to our data, MIBG seems not to be as sensitive as OCT (67% vs 100%), although not statistically significant because of the poor sample size. The advantage of MIBG is its high specificity, and it should be significant for final qualitative diagnosis. Therefore, we consider urine catecholamine assay, combined with multiple imaging techniques, as sufficient measures for differentiation between functional cardiac paragangliomas and other primary cardiac tumors. Furthermore, experience with preoperative coronary angiography to detect tumor blood supply has

FIGURE 3. Tumors can be located under multiple imaging tests including (A) contrast-enhanced computed tomography, (B) magnetic resonance imaging, and (C) transthoracic echocardiography.

been reported in several studies.³ In our study, all 18 tumors were fed by the coronary artery, and nearly half of patients underwent CABG, which made preoperative coronary angiography even more significant.

Tumor Location

Although fewer than 160 cases have been reported in the literature, a wide variety of the tumor sites could be found. According to the review by Wang and colleagues,⁷ cardiac paraganglioma mostly originated from the epicardium and the root of great vessels. In our study, most tumors were located near the root of Ao and MPA, whereas others were located in the right atrioventricular groove and interatrial groove, similar to the distribution of the cardiac plexus (Figure 5). It can be explained by the embryonic origin of paraganglioma.¹²

Preoperative Medical Treatment

Preoperative medical preparation for functional paraganglioma was recommended by the guidelines⁶ to prevent perioperative hemodynamic fluctuation. Several studies hold the opinion that preoperative medical treatment is not necessary for tumor resection,^{13,14} whereas no randomized controlled studies provide reliable evidence. Therefore, we continued the preoperative medical treatment for our patients, the same as the newest report from the Mayo Clinic.¹ However, the specific regimen should be negotiated with endocrinologists.

Malignancy of the Tumor

The 2004 World Health Organization Classification of Tumors considered that the one and only criterion of malignancy of paraganglioma was metastasis.¹⁵ Diagnosis of

VIDEO 1. Preoperative coronary arteriography for patient 5 demonstrated a large oval-shaped tumor with rich blood supply from the right coronary artery and branches. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32512-1/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32512-1/fulltext).

malignant paraganglioma requires evidence of metastases at nonchromaffin sites distant from the primary tumor, such as the lymph nodes, bones, or liver. Unfortunately, we recorded no distant metastasis in our series of patients. Although we have found local invasion of the tumor in 8 patients, it does not predict malignancy potential according to the literature.¹⁶

FIGURE 4. Coronary arteriography demonstrates a large oval-shaped tumor with a rich blood supply from the right coronary artery and branches.

Surgical Procedure and Complications

Inherent to this particular organ, surgery for functional cardiac paraganglioma usually poses more challenges including exposure, complete resection, and the need for complex reconstruction to preserve function. Because of the blood supply from coronary arteries, embolization is considered unwise. We routinely performed operations under CPB. Depending on tumor localization, extension to surrounding structure, and the presence of coronary artery involvement, surgical therapy includes complete tumor and involved cardiac tissue or vessels resection, and complex reconstruction using a variety of autologous, allogeneic, and synthetic vascular patches or grafts. Experience taught us that, because of the rich blood supply, resecting a few millimeters alongside the tumor edge caused less blood loss than clinging to the edge. Atrium injured can be easily patched using pericardium or other grafts. Usually, the feeding vessels from coronary arteries can be coagulated or clipped. When a main coronary artery was involved by tumor or incidentally injured, coronary artery bypass grafting was performed using either arterial or venous grafts (Video 2). Latest research stated that a 3-dimensional printing model would be helpful for familiarization with the anatomic interrelationship of tumor positioning within vascular structures.¹ We noticed that most functional cardiac paragangliomas could be completely resected in their primary surgery. Redo surgery for tumor recurrence remains challenging, and we have only one experience with a patient with a history of previous incomplete resection of atrial septal tumor (patient 11). During the patient's second operation, we completely resected the residual paraganglioma involving interatrial groove and reconstructed both atria, coronary sinus and grafted the inferior vena cava (IVC).

An early study¹¹ noted that intraoperative hemorrhage was the fiercest complication, and the authors recommended heart transplantation as a potential therapeutic strategy for paragangliomas invading the atrioventricular groove or directly invading the coronary artery. We agree that intraoperative hemorrhage remains a devastating complication of surgical resection. However, in our study, major bleeding is avoidable with meticulous reconstruction. Myocardial ischemia owing to coronary artery injury is usually reversible after a successful grafting. However, adrenergic receptor downregulation owing to preoperative catecholamine hypersecretion led to occurrence of recalcitrant hypotension where inotropic agents and vasopressors are required.¹ Some patients developed vasoplegia; in this situation, ECMO support was absolutely needed. We had 3 patients using ECMO; 2 patients survived and 1 patient died of bleeding complication.

On some level, we absolutely agree that heart transplantation is an option for complete removal of cardiac tumors;

FIGURE 5. Distribution of tumors (*red discs*) on the heart in (A) frontal and (B) axial view. Each disc has the similar size, shape, and position of a corresponding tumor. Deeper color means that tumors invaded this spot more frequently. Tumors were primarily located between the ascending aorta and the main pulmonary artery, in the interatrial groove, and in the atrioventricular groove, similar to the distribution of cardiac plexus (*green line*).

however, considering its unsatisfactory long-term results,¹⁷ we would not recommend transplantation as the first choice. We observed that operative mortality was comparable with previous reports. Although tumor

recurrence occurred in 2 of our 16 surviving patients (patients 4 and 14), all survivors reported functional improvement, and 82% of patients had normal catecholamine levels during follow-up.

TABLE 2. Intraoperative findings

Patient number	Tumor location	Tumor size (mm)	Intraoperative blood pressure (mm Hg)*	Local invasion	Concomitant surgery	CPB/Ao X clamp (minutes)
1	Root of Ao	74 × 61	160-50/70-30	No	Rec of Ao and LA	90/57
2	Root of Ao and MPA	55 × 34	210-30/120-30	Yes	Rec of VS, MPA and RPA, CABG	285/222
3	Root of Ao and MPA	100 × 80	180-90/80-60	No	Rec of RVOT and MPA, CABG	170/193
4	Right AVG	67 × 55	170-50/100-30	Yes	Rec of RVOT and Ao, CABG	93/50
5	Right AVG	75 × 65	140-60/90-30	No	Rec of RVOT, CABG	171/92
6	Root of MPA	40 × 30	170-50/100-40	No	None	42/17
7	Root of Ao and MPA	75 × 64	150-70/80-20	Yes	Rec of LA and VS, CABG	265/199
8	IAG	40 × 32	140-40/100-20	No	Rec of LA, RA and RSPV, CABG	139/105
9	Root of Ao and MPA/Right AVG	80 × 55, 60 × 40	150-80/80-40	Yes	Rec of Ao and MPA, CABG	134/91
10	IAG	67 × 55	170-40/130-20	No	Rec of LA	70/40
11	IAG	64 × 60	190-50/100-30	Yes	Rec of LA, RA, CS, IAS and IVC	252/172
12	Right AVG	40 × 30	160-60/110-50	No	Rec of RA	50/32
13	Root of Ao and MPA	50 × 40	160-50/90-30	Yes	Rec of Ao, CABG	328/137
14	Root of Ao and MPA	59 × 46	140-40/60-30	Yes	Rec of Ao, MPA and RVOT	143/90
15	Root of Ao and MPA	30 × 30	150-60/110-40	Yes	Rec of Ao and RPA	127/82
16	Root of Ao and MPA	50 × 47	160-60/80-20	No	Rec of LA and RPA	108/82
17	IAG	60 × 45	140-40/110-30	No	Rec of RA, IAS and IVC	145/118

CBP, Cardiopulmonary bypass; Ao X clamp, aortic cross clamp; Ao, aorta; Rec, reconstruction; LA, left atrium; MPA, main pulmonary artery; VS, Valsalva sinus; RPA, right pulmonary artery; CABG, coronary artery bypass grafting; RVOT, right ventricular outflow tract; AVG, atrioventricular groove; IAG, interatrial groove; RSPV, right superior pulmonary vein; RA, right atrium; CS, coronary sinus; IAS, intra-articular septum; IVC, inferior vena cava. *Presented as systolic pressure over diastolic pressure with ranges.

TABLE 3. Complications and follow-up information

Patient number	Intraoperative transfusion (U)	Perioperative complications	ICU stay (days)	Postoperative vasopressors	Follow-up time (years)	Current urinate CA
1	2	IABP	3	NE	5.2	—
2	4	LCOS, IABP, ECMO (16 d), hemorrhage (PT)	20	NE, E	3.5	+
3	4	None	6	NE, V	2.3	—
4	2	None	5	NE	12.5	+
5	2	LCOS, IABP, ECMO (5 d), hemorrhage (PT)	16	NE, E, DoA, V	5.9	—
6	0	None	1	NE, E	2.4	—
7	4	IABP	8	NE, E, DoA	2.9	—
8	4	None	2	NE, E, DoA	8.9	—
9	2	None	4	NE, DoA	10.9	—
10	8	None	6	NE, DoA	13.7	—
11	4	None	5	NE, E	2.75	—
12	8	None	7	NE, E	2	—
13	8	LCOS, IABP, ECMO (1 d), hemorrhage (dead*)	1	NE, E, DoA, V	N/A	N/A
14	4	None	4	NE, E, DoA	14.2	+
15	2	None	8	NE, E	8.75	—
16	0	None	2	NE, E	7.3	—
17	2	None	2	NE, E	6.2	—

ICU, Intensive care unit; CA, catecholamine; LCOS, Low Cardiac Output Syndrome; IABP, Intra-aortic Balloon Pumping; ECMO, Extracorporeal Membrane Oxygenation; PT, Pericardial Tamponade; NE, norepinephrine; E, epinephrine; V, vasopressin; DoA, dopamine. *This patient died postoperatively.

CONCLUSIONS

Functional cardiac paragangliomas are rare neuroendocrine tumors with catecholamine-secreting potential and close anatomic proximity to the heart and main vessels. Because of the neuroendocrine properties and risky

anatomic location, multidisciplinary treatment including the department of endocrinology, cardiac surgery, and ICU is necessary (Figure 6). Patients should undergo preoperative medical preparation under the guidance of endocrinologists. Despite the risk of intraoperative bleeding, complete resection for the tumor along with complex reconstruction is achievable. Postoperative low cardiac output syndrome and bleeding complication of ECMO are 2 main fatal complications. With the help of a professional heart team, good postoperative survival and long-term outcomes are expectable. However, because of the potential of recurrence, we recommend lifelong surveillance.

Study Strengths and Limitations

This retrospective study of 17 patients with functional cardiac paraganglioma is, to our knowledge, the largest single institutional study of functional cardiac paraganglioma to date. Although, the sample size of our study is limited, all of our patients received diagnoses, underwent operations, and received critical care from our multidisciplinary treatment team at Peking Union Medical College Hospital. None of our patients got a tumor extending to the left ventricle, where orthotopic transplantation may be a choice.¹¹ We have not performed orthotopic transplantation for cardiac paraganglioma patients; therefore, we cannot assess the potential benefit. Besides, it is a retrospective study lacking a designed control group and rigorous contrast analysis, we can only compare our results with

VIDEO 2. In patient 5, tumor was found in the right atrioventricular groove and invaded into the myocardium. The right coronary artery (RCA) was involved by the tumor and injured during surgery. After complete resection of the tumor, ligation of the stumps of the RCA and venous grafting were performed. The large structural defect was reconstructed with pericardial patch to prevent bleeding. Video available at: [https://www.jtcvs.com/article/S0022-5223\(18\)32512-1/fulltext](https://www.jtcvs.com/article/S0022-5223(18)32512-1/fulltext).

FIGURE 6. The process of diagnosis and treatment concluded from our 13 years of experience at Peking Union Medical College (PUMC). *PREOP*, Pre-operative; *INTRAOP*, intraoperative; *POSTOP*, postoperative; *MIBG*, metaiodoben-zylguanidine scintigraphy; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *CABG*, coronary artery bypass grafting; *IABP*, intra-aortic balloon pumping; *ECMO*, extracorporeal membrane oxygenator.

former studies of other institutions years ago. All these factors can reduce the credibility and affect the extrapolation of our conclusions.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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