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Early and Late Results of Valvular Surgery for Carcinoid Heart Disease

To the Editor: Carcinoid tumors are rare, arising in 3 to 4 per 100,000 people per year (1). These tumors derive from enterochromaffin cells, particularly those located in the gastrointestinal tract and the bronchopulmonary system. At diagnosis, 20% to 30% of patients present with disseminated disease and consequent carcinoid syndrome, characterized by cutaneous flushing, gastrointestinal hypermotility, bronchospasm, and hypotension (2). The syndrome is associated with excess release of vasoactive substances of which serotonin is the most prominent. Valvular manifestations of the tumor typically consist of leaflet thickening and retraction of the right-sided valves and may cause severe valvular dysfunction requiring surgical correction. Herein we report our surgical experience in patients with carcinoid heart disease (CHD).

From 2001 through 2006, 10 patients underwent valvular surgery for CHD. A medical chart review was conducted to retrospectively collect demographic data and perioperative variables. Follow-up information was obtained through the patients' records and echocardiography reports from reference physicians. The study protocol was approved by our institutional review board. All patients underwent pre-operative evaluation including determination of urinary 5-hydroxyindoleacetic acid (HIAA) levels and other biological markers. Valvular morphology and function were assessed by echocardiography. Coronary angiography was also performed in all patients.

Pre-operatively, all patients were on octreotide (150 to 300 μg administered subcutaneously every 6 h or 20 to 30 mg of long-acting octreotide monthly). Intraoperatively, a loading dose of octreotide (50 μg/h) was started before anesthetic induction. During anesthetic induction, an additional bolus of 50 to 100 μg was given. The infusion of octreotide was increased to a maximum dose of 300 μg/h if required. Additionally, aprotinin was administered perioperatively in patients with preserved renal function at a loading dose of 2,000,000 kallikrein inhibitor units (KIU). Then, a maintenance dose of 500,000 KIU was given until the surgical procedure was finished. Post-

operatively, all patients returned to their octreotide routine on postoperative day (POD) 2.

Patient characteristics are summarized in Table 1. Mean age was 59 ± 9 (mean ± SD) years. Pre-operative cardiac medications included diuretics (n = 9) and angiotensin-converting enzyme inhibitors (n = 1). The mean urinary 5-HIAA level was 247 ± 18 mg/24 h. Mean serotonin, chromogranin A, and atrial natriuretic factor blood levels were 844 ± 248 ng/ml, 816 ± 315 ng/ml, and 215 ± 86 pg/ml, respectively.

Echocardiography revealed tricuspid valve restricted leaflet motion during diastole and systole in all patients (see panels A and B of the cover image from this issue of the *Journal*). Four patients had associated tricuspid stenosis (mean diastolic tricuspid valve gradient 5.3 ± 1.1 mm Hg). Six patients presented with severe right ventricular dysfunction. Intraoperative analysis confirmed leaflet thickening and retraction with severe subvalvular involvement (see panel C of the cover image from this issue of the *Journal*). Tricuspid leaflets were excised, and a bioprosthetic replacement was performed in all patients.

Combined pulmonary regurgitation and stenosis (average pulmonary valve peak gradient 14.2 ± 9.1 mm Hg) was noted by echocardiography in 9 patients. Operative analysis corroborated heavily thickened and immobile leaflets in the pulmonic position. Subsequently, a bioprosthetic replacement was performed in all cases. Six patients received an additional patch augmentation of the right ventricular outflow to accommodate the prosthetic valve.

Pre-operative echocardiography also revealed associated mitral valve dysfunction due to leaflet thickening and retraction in 3 patients. Mitral regurgitation was moderate to severe in all cases. None of the patients presented with mitral stenosis. On operative analysis, 2 patients had moderate thickening and retraction of the posterior leaflets, whereas the anterior leaflets had preserved mobility. The subvalvular apparatus was moderately thickened with chordal fusion. Therefore, several secondary chordae were

| Table 1 | Patient Characteristics and Echocardiographic Findings |

Patient #	Age/Gender	Tumor Location	5-HIAA mg/24 h*	NYHA Functional Class	Associated Comorbidities	LVEF (%)	Valve Involvement			
							TV	PV	MV	AV
1	56/F	Unknown	256	III	—	65	(+)	(+)	—	—
2	55/M	Ileum	254	IV	HTN, HF	55	(+)	(+)	—	—
3	64/F	Cecum	239	IV	—	60	(+)	(+)	—	—
4	66/M	Testicular	264	III	RF	40	(+)	(+)	—	—
5	68/M	Jejunum	229	IV	HTN, RF	55	(+)	(+)	—	—
6	42/M	Ileum	258	III	—	65	(+)	(+)	(+)	(+)
7	53/F	Cecum	241	III	—	60	(+)	(+)	—	—
8	73/M	Ileum	217	III	HF	70	(+)	—	—	—
9	60/F	Unknown	267	III	HTN, HF, PVD	70	(+)	(+)	(+)	—
10	49/M	Ileum	223	III	HTN	50	(+)	(+)	(+)	—

*Reference values 2 to 10 mg/24 h.

AV = aortic valve; HF = hepatic failure; HTN = systemic hypertension; LVEF = left ventricular ejection fraction; MV = mitral valve; NYHA = New York Heart Association; PV = pulmonic valve; PVD = peripheral vascular disease; RF = renal failure; SRVD = severe right ventricular dysfunction; TV = tricuspid valve.

| Table 2 | Operative Procedures and Outcome |

	Surgical Procedure								Patient Follow-Up		Follow-Up Echocardiography			
Patient #	TV	PV	MV	AV	PFO Closure	Major Complications	LOS (Days)	Discharge Status	Status (Months)	EF (%)	TR	PR	MR	AR
1	R	R	—	—	—	—	7	Alive	Alive (75)	68	Mild	Mild	—	—
2	R	R	—	—	+	—	6	Alive	Alive (60)	55	None	Trace	—	—
3	R	R	—	—	—	—	11	Alive	Alive (50)	55	Mild	Mod	—	—
4	R	R	—	—	—	DIC, MSOF	17	Death	—	—	—	—	—	—
5	R	R	—	—	—	RSF	26	Alive	Alive (34)	55	Mild	Mild	—	—
6	R	R	P	P	—	—	11	Alive	Alive (21)	50	Mod	Mod	Mild	Mild
7	R	R	—	—	—	—	7	Alive	Alive (23)	55	Mild	Trace	—	—
8	R	—	—	—	+	Rectorragia	15	Alive	Alive (19)	65	Mod	—	—	—
9	R	R	P	—	—	HITT, MSOF	10	Death	—	—	—	—	—	—
10	R	R	R	—	+	—	9	Alive	Alive (6)	53	None	Trace	Mild	—

AR = aortic regurgitation; DIC = disseminated intravascular coagulation; EF = ejection fraction; HITT = heparin-induced thrombocytopenia; LOS = length of stay; Mod = moderate; MSOF = multisystemic organ failure; MV = mitral valve; P = repair; PFO = patent foramen ovale; PR = pulmonic regurgitation; R = replacement; RSF = respiratory failure; TR = tricuspid regurgitation; other abbreviations as in Table 1.

resected to increase the mobility of the posterior leaflet, and a remodeling annuloplasty was performed in both patients. The third patient underwent a bioprosthetic valve replacement for advanced lesions. Only 1 patient presented with additional moderate aortic valve regurgitation on pre-operative echocardiography. In this case, operative analysis showed localized moderate thickening of the right coronary cusp at the commissural area that was surgically treated with a comissuroplasty. A patent foramen ovale (PFO) closure was concomitantly performed in 3 patients (1 of 3 had left-sided valve involvement). Surgical details are summarized in Table 2.

After valve replacement, valvular samples were processed and stained with hematoxylin-eosin and Masson's trichrome stain. Microscopically, the presence of fibrocellular plaques with hypercellularity and collagenous matrix was observed in all specimens (see panel D of the cover image from this issue of the *Journal*).

Surgical outcome is detailed in Table 2. There were 2 (20%) operative deaths. One patient developed low cardiac output syndrome due to right heart failure and subsequent multiorgan system failure and expired on POD 17. The second patient presented with severe post-operative hypotension due to vasoplegia and developed hepato-renal syndrome. He expired on POD 10. The median length of hospital stay was 11 days (interquartile range 7 to 14 days).

All 8 discharged patients were alive at a mean follow-up of 37 months (range 6 to 75). There were no cases of endocarditis, thromboembolic events, or structural valve deterioration. Five patients were in New York Heart Association functional class I and 3 patients were in class II (Fig. 1). Patients' medications included beta-blockers (n = 5), diuretics (n = 5), angiotensin-converting enzyme inhibitors (n = 2), and calcium-channel inhibitors (n = 1). All patients were on octreotide (30 to 60 mg monthly, n = 6; 1,000 μg daily, n = 2). Echocardiographic findings at follow-up are reported in Table 2.

Advances in medical and oncologic therapies have resulted in better control of carcinoid symptoms and potentially improved survival. Consequently, right-sided valvular disease has become a major source of morbidity and mortality. In 1995, Robiolio et al. (3) published a series of patients undergoing right-sided valve replacement with an operative mortality as high as 63%. More recently, Møller et al. (4) updated the Mayo Clinic experience and showed that despite high post-operative mortality (16%), a trend toward improved surgical outcome was achieved. In our series, we

report 2 (20%) operative deaths, both of which highlight the challenges (vasoplegia and right heart failure) associated with cardiac surgery in this patient population.

Others have reported perioperative coagulopathy as a major source of mortality and morbidity (5). This complication, mostly present in elderly patients with an abnormal liver profile, was not observed in our series. We believe that the reduction of post-operative bleeding we observed may have been, in part, related to the use of perioperative aprotinin in these patients.

In patients with right-sided CHD, valvular lesions are often too advanced and not amenable to reconstructive surgery. Although the choice of valve prostheses remains unresolved and may require individual selection, limited data suggest that bioprosthetic valve replacement is preferable in these patients, who commonly present with multiple liver metastases and associated coagulopathies (6). Furthermore, mechanical prostheses may not be ideal for patients with CHD, as subsequent surgical tumor resections are
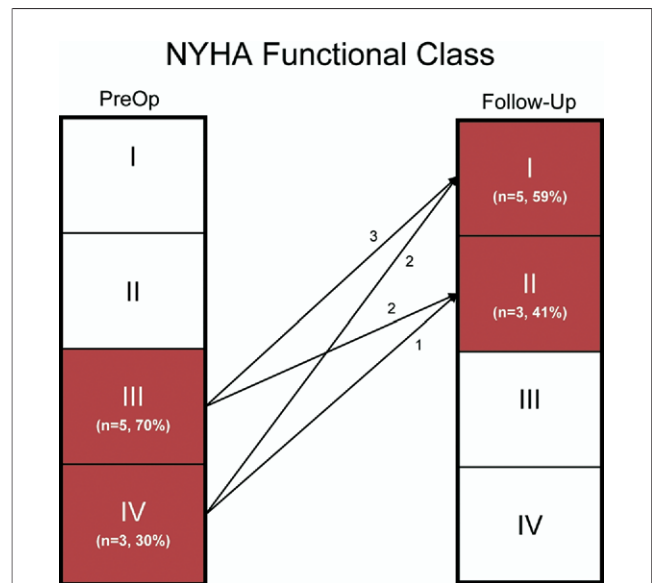

| Figure 1 | PreOp and Follow-Up NYHA Functional Class for Patients Who Survive to the Surgical Procedure |

NYHA = New York Heart Association; PreOp = pre-operative.

often required and are complicated by the use of anticoagulation. Accordingly, all patients in this series underwent pericardial bioprosthetic valve replacement in the tricuspid and pulmonic positions.

Involvement of left-sided valves is rare and has been associated with the presence of an intracardiac shunt, endobronchial tumor localization, or a high tumor activity. Connolly et al. (7), in the only published series specifically focused on left-sided CHD, noted the absence of a PFO in 6 of 11 patients. Among these patients, the authors reported higher levels of 5-HIAA. We observed a PFO in one-third of patients with left-sided valve involvement. Interestingly, both patients without a PFO presented with the highest urinary 5-HIAA levels, potentially suggesting major tumor activity. In contrast to right-sided CHD, the optimal surgical approach for left-sided valvular disease remains debatable. Our experience suggests that left-sided lesions may be less advanced compared with those on the right side. In these patients with moderate left-sided valvular lesions, we elected to perform reconstructive surgery. Late echocardiography has shown only mild valvular regurgitation, indicating that in selected cases these techniques can be performed safely with good midterm results.

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Letters to the Editor

Usefulness of ⁹⁹ᵐTc-DPD Scintigraphy in Cardiac Amyloidosis

In their useful state-of-the-art paper on the evaluation and management of cardiac amyloidosis, Selvanayagam et al. (1) rightly dedicate much space to noninvasive evaluation but make no mention of a relevant imaging tool: ^{99m}Tc-3,3-diphosphono-1,2-propano-dicarboxylic acid (^{99m}Tc-DPD) scintigraphy. The authors do discuss radiolabeled serum amyloid P component (SAP) scintigraphy, which can provide valuable information on the distribution and extent of amyloid deposition in the body as a whole, but (as the authors point out) cannot adequately image amyloid in the heart. Unlike the SAP technique, ^{99m}Tc-DPD scintigraphy is capable of imaging amyloid deposition in the myocardium of patients with transthyretin-related (TTR) amyloidosis (i.e., hereditary systemic amyloidosis and senile systemic amyloidosis) (2–5). This specific imaging characteristic may facilitate differential diagnosis between TTR and AL cardiac amyloidosis in routine practice—a clinically relevant distinction (5). Because ^{99m}Tc-DPD scintigraphy is a standardized technique that uses a widely available tracer, we think that this noninvasive examination should be known to all clinicians involved in the diagnosis and management of systemic amyloidosis.

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