

## **Outcomes of eight patients after surgical valve replacement for carcinoid heart disease**

Dharmesh RAMLUGUN<sup>1</sup>, MD ; Michel KINDO<sup>1</sup>, MD PhD; Jean-Philippe MAZZUCOTELLI<sup>1</sup>, MD PhD.

<sup>1</sup>Department of Cardiovascular Surgery, Strasbourg University Hospital, Strasbourg, France

Short running title : Carcinoid heart valve surgery

Correspondence to : Dharmesh RAMLUGUN, MD. Service de Chirurgie Cardiovasculaire, Nouvel Hôpital Civil, 1 Place de l'Hôpital, BP426-67091 Strasbourg Cedex, France. Tel : +33(0)6.79.48.54.45 / +33(0)3.69.55.15.41. Fax : +33(0)3.69.55.18.87. Email : dharmesh.ramlugun@chru-strasbourg.fr

No source of funding, no conflict of interest

Contributions : (I) Conception/Design/Data Collection/Drafting : D Ramlugun (II) Data analysis/interpretation : All authors, (III) Critical revision of article : JP Mazzucotelli (IV) Approval of article : All authors

## **INTRODUCTION**

Carcinoid tumor is a rare disease with an incidence of 2 cases and 0,7 case per 100,000 people in the United States and Europe respectively<sup>1</sup>. First described by Lubarsh in 1888, the carcinoid entity is due to high levels of circulating vasoactive mediators, mainly serotonin as described later in 1953 by Lembech<sup>2,3</sup>. Reduced hepatic metabolism due to liver metastasize allow these substances to reach the right side of the heart while generally sparing the left, mainly due to pulmonary metabolization of the vasoactive substances. This eventually leads to a carcinoid syndrome essentially characterized by flushing and diarrhea<sup>4,5</sup>.

As demonstrated by Page *et al.*, carcinoid tumors are accompanied by elevation of 5-hydroxy indole acetic acid (5-HIAA) which is itself a byproduct of serotonin metabolism and is commonly used to confirm the diagnosis<sup>1,6</sup>.

The first case of carcinoid heart disease (CHD) has been reported in 1954 by Thorson and Nordenfelt<sup>7</sup>. Right heart failure is common mainly due to tricuspid valve regurgitation. Though 20% of patients with carcinoid syndrome show signs of CHD at the time of diagnosis, cardiac involvement is present in about 60% of them<sup>4</sup>.

It is now well demonstrated that serotonin, mainly produced by the enterochromaffin (or Kulchitsky) cells, plays a major role in stimulating fibroblast growth and fibrogenesis. These lesions concern mostly the right side of the heart in about 90% of cases with the tricuspid valve being the main target; concomitant pulmonary valve lesion has been described as rare and the main mechanism is regurgitation rather than stenosis<sup>8,9</sup>. Upon histopathological assessment of the valve leaflets, valvular sub-apparatus and endocardium, it is common to find typical fibrous plaques and proliferating myofibroblasts in the extracellular matrix. In some cases, the intima of big vessels may be concerned<sup>8,10</sup>.

Without cardiac surgery, the overall survival of patients with CHD is reduced to 31% while only 10% survive during the next two years after falling into the category of New York Heart Association (NYHA) functional class  $> 2$ <sup>4,11</sup>. However, proper timing of surgery has improved 5-year survival from 30% in the 1980's to currently around 55%<sup>12</sup>. Furthermore, some studies show that this survival does not seem to be influenced by the number of valves replaced or the type of prosthesis being used, but the current literature about these statements is considered to be poor<sup>13-15</sup>.

In this study, we describe the clinical characteristics and present the early outcomes of 8 patients who underwent heart valve surgery after being diagnosed with CHD in our institution.

## **METHODS**

### **Study group**

Between April 2003 and January 2021, 8 patients underwent cardiac surgery for CHD at our institution. In each case, the diagnosis was initially made by a multidisciplinary committee based on clinical symptoms involving at least flushing in all patients, pathology specimens, 24 hour 5-HIAA urinary samples and thoraco-abdominal computed tomography. All patients had confirmed digestive lesions with at least hepatic metastasizes. The committee was comprised of internal medicine specialists, oncologists, general surgeons, pathologists, cardiologists and cardiac surgeons. Repeated echocardiograms performed by trained senior cardiologists confirmed cardiac involvement during carcinoid syndrome.

The mean age was  $60 \pm 9$  years (range 49-72) comprising of 5 men and 3 women.

### **Surgery**

1 patient had quadruple valve replacement, 3 patients had both tricuspid and pulmonary valve replacement while 4 patients had only tricuspid valve replacement. 3 patients had mechanical valve replacements.

All patients underwent aorto-bicaval cardiopulmonary bypass via sternotomy. Cross clamp was used in only 6 patients with myocardial protection done by antegrade and intermittent retrograde cold-blooded cardioplegia every 20 minutes. Central temperature was lowered to 33°C in those 6 patients while it was 36°C for the other 2 patients without cross clamp.

### **Follow-up**

All patients known by the multidisciplinary committee prior to surgery were monitored after heart valve surgery via latest medical records available. Peri-operative death was defined as occurring within 30 days after surgery or during the same hospital stay.

### **Consent**

All patients had given their oral consent for data retrieval and have been formal waivers during their follow-up.

## **RESULTS**

The clinical characteristics of all 8 patients are represented in table 1 including preoperative data.

Mean EuroSCORE II was 3,83% (range 1,22 – 16,03) ; the highest being 1 patient who had previous cardiac surgery (coronary artery bypass grafting) 11 years prior to the carcinoid diagnosis.

Patient	1	2	3	4	5	6	7	8
Age (years)	52	65	53	56	72	49	68	68
BMI (kg/m <sup>2</sup> )	21,6	23,3	23,6	25,1	21,1	31,5	17,5	22,8
Female gender	Yes	Yes	Yes	No	No	No	No	No
Hypertension	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Diabetes II	No	No	No	No	No	No	Yes	No
Dyslipidemia	No	No	Yes	No	Yes	No	Yes	No
Renal function (ml/min/m <sup>2</sup> )	91	91	56	90	54	77	87	37
Atrial fibrillation	No	No	No	No	Yes	No	No	No
NYHA								
Class I +	+			+				
Class II ++					++			
Class III +++		+++				+++	+++	+++
Class IV ++++			++++					
Tiffeneau index (%)	95	85	85	84	76	63	68	91
EuroSCORE II (%)	1,22	3,07	2,08	1,51	16,03	2,44	2,71	1,59
Primary tumor site	Unknown	Ileum	Rectum	Ileum	Ileum	Ileum	Ileum	Hepatic

**Table 1.** Preoperative clinical features of patients with carcinoid heart disease. Age is reported at time of operation. Data is expressed in mean values or percentage.  
*BMI : Body Mass Index, NYHA : New York Heart Association*

3 patients (37,5%) had renal impairment with creatinine clearance less than 60 ml/min/m<sup>2</sup> but none required dialysis before surgery.

The most common site for primary tumor localization was in the midgut with 62,5% being the ileum. In one patient, primary localization could not be found despite having subsequent abdominal surgery.

Tiffeneau index showed no pulmonary function impairment except for 1 patient with class 1 obesity.

Intra and postoperative data are represented in table 2; all patients had severe tricuspid regurgitation.

Mean ICU stay was 9,4 days (range 1-39) while mean hospital stay was 23,5 days (range 10-52).

Mean cardiopulmonary bypass time was 147 minutes (range 81-255) ; no patient required extracorporeal life support during the postoperative period.

Definite pacemakers were required in 2 patients out of which 1 required re-opening for bleeding.

2 out of the 3 patients with preoperative renal impairment needed dialysis during the postoperative phase out of which 1 had to be re-intubated.

Patient	1	2	3	4	5	6	7	8
LVEF , %	58	60	71	56	55	55	65	69
Regurgitation								S
Tricuspid	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe
Pulmonary	Mild	-	Severe	-	-	Severe	Mild	Moderate
Mitral	-	-	Mild	-	-	-	-	-
Aortic	-	-	Mild	-	-	-	-	-
Stenosis								
Tricuspid	Moderate	-	Severe	Moderate	Mild	Mild	Moderate	Moderate
Pulmonary	-	-	Moderate	-	-	-	-	-
Mitral	-	-	-	-	-	-	-	-
Aortic	-	-	-	-	-	-	-	-
Duration of cardiac symptoms before surgery (months)	6	6	12	60	12	1	12	24
Valve and size (mm)								
Tricuspid	Bio 29	Bio 31	Mec 29	Mec 29	Bio 33	Mec 33	Bio 31	Bio 31
Pulmonary			Mec 19			Mec 23	Bio 21	Bio 25
Mitral			Med 21					
Aortic			Med 29					
Bypass (mins)	90	81	255	118	159	173	146	156
X-clamp (mins)	74	53	210	102	0	145	0	129
Extubation (hours)	24	5	168, R	8	23	5	15	28
ICU stay (days)	5	3	39	1	6	3	9	9
NYHA post-op	1	1	1	1	1	1	1	1
Pacemaker	-	-	Post-op	-	-	-	Post-op	-
Dialysis	-	-	+	-	-	-	-	+
Hospital stay (days)	12	13	47	10	20	17	17	52
Follow up (months)	84	48 (D)	43 days (D)	54	77 days (D)	36	12	2

**Table 2.** Perioperative data of carcinoid heart disease patients who underwent heart valve surgery.

Data is expressed in mean values or percentage.

*LVEF : Left Ventricle Ejection Fraction, Bio : Bioprosthesis, Mec : Mechanical prosthesis, X-clamp : Cross clamp, Extubation, R : Re-intubated, Post-op : postoperative event, Follow up (D) : death during follow up*

The mean time delay from carcinoid heart disease diagnosis to valve surgery was 16,6 months (range 1-60).

Postoperative functional status showed NYHA class 1 in all patients. No case of valvular complications (thrombus, leak or infection) was reported till the last date of follow-up.

Current follow-up status accounts a perioperative survival rate of 75%. A total of 3 deaths was recorded : 2 during the perioperative period which were secondary to nosocomial pulmonary infections and 1 distant death due to the carcinoid tumor evolution.

All 5 remaining patients showed NYHA functional class 1 while being uneventful upon their last medical visit ; one patient has had a 7-year spell as such, but follow-up has since been lost due to overseas migration.

All pathological findings of excised valves were pathognomonic of CHD with fibrosis being the predominant aspect in both the leaflets and sub apparatus.

## **DISCUSSION**

It is now well established that heart valve surgery is the only definite way to ensure that patients with carcinoid heart disease find symptomatic relief with Moller *et al.* reporting a postoperative median survival up to 11 years<sup>14</sup>. Despite our small number of patients, we share common findings concerning preoperative functional NYHA class with over 30% in class III and 10% in class IV<sup>12</sup>.

If pulmonary stenosis can worsen tricuspid regurgitation, low cardiac output might underestimate the former. Elevated right heart pression or dilated chambers may lead to stretching and reopening of patent foramen ovale in severe CHD, but we had no such event. Even though the use of somatostatin analogues since 1986 has significantly changed the way to handle carcinoid syndrome, no consensus has been reached so far concerning the optimal surgical timing<sup>5</sup>.

Our findings clearly display this fundamental problem in carcinoid patients with disparate time lapse from diagnosis to surgery. Moreover, if surgery is not considered for end-stage metastatic disease or poorly controlled carcinoid syndrome, it is a clinical challenge to distinguish it from right heart failure. In such cases, only postoperative clinical status eventually helps for confirmation but it may be at the cost of having straight away decreased survival due to intrinsic cancer related morbidity issues<sup>15-17</sup>.

Clinical findings show that 20% of patients with carcinoid syndrome present valve lesions at the time of diagnosis. Cases have been reported where patients had severe valvular lesions despite being NYHA I<sup>14</sup>.

Hence, we believe it is wise in this current era to encourage early surgery which shows acceptable short-term mortality<sup>18,19</sup>. In addition, more frequent cardiac and biological screening should be done in CHD patients without excluding the possibility of new biomarkers else than urinary 5-HIAA and N-terminal pro-Brain-Type Natriuretic Peptide (NT-pro-BNP)<sup>5,20</sup>.

The choice of a mechanical or biological prosthesis stays a highly controversial subject as literature is limited. Thorburn & *al.* showed in 1983 that survival was neither linked to the number of heart valves being replaced nor to the type of

prosthesis used<sup>13</sup>. Other authors showed that freedom from reintervention was not related to prosthesis type<sup>15</sup>.

Early degeneration in bioprosthesis and anticoagulation in mechanical valves are the two main relevant issues with respect to the population's survival chances and the need for adjuvant treatment with high bleeding risks<sup>4</sup>. Thrombus can occur in both types with around 4% per annum in mechanical tricuspid valves and it is also the main reason for bioprosthesis dysfunction<sup>9,15</sup>.

Circulating vasoactive substances have been thought to be the reason for early bioprosthesis degeneration via plaque extension and fibrosis but these observations have been uncommon in explanted bioprostheses whereby thrombus was the main cause of dysfunction. As a matter of fact, octreotide therapy and liver dearterialization following cardiac surgery can be very effective. These CHD patients often have subsequent surgical procedures and chemotherapy hence making the use of mechanical valves with vitamin K antagonists difficult to handle without additional risks. Moreover, since life expectancy rarely exceeds bioprosthesis durability, short-term outcomes are better when using them<sup>21,22</sup>.

That is why current literature shows a tendency towards the preferred use of bioprosthesis ; some authors authorize 3 months of anticoagulation during the postoperative period with frequent postoperative echocardiogram monitoring<sup>15</sup>.

While it is common to find pure tricuspid regurgitation in CHD, the pulmonary valve shows both stenosis and regurgitation. Knowing that postoperative mortality is mainly due to the carcinoid disease itself and not as a complication of the surgery, it is legitimate to consider pulmonary valve replacement<sup>23</sup>. This can avoid late deaths as shown by Yong & *al.* thus improving long-term and overall outcomes<sup>24</sup>. Due to obvious known reasons of calcification and thickening, pulmonary homografts are generally avoided. However, transcatheter pulmonary valve may be considered in high-risk patients

Univariate and multivariate analysis in the literature show that CHD patients with advanced NYHA functional class have a lower rate of survival either in long term or during the perioperative period. However, this survival rate can increase when valve surgery includes treatment of coexistent left heart valvular disorders<sup>25</sup>. Multiple valve replacements should hence be carried out upon the situation as the outcomes seem to be independent from the number of valves replaced or types of prostheses being used while showing good mid-term survival rates<sup>16</sup>.

In our study, the same argument seems to be valid since we had a 75% perioperative survival rate with acceptable short and mid-term results as compared to larger series whereby median survival ranges from 6 to 11 years after cardiac surgery<sup>4,22</sup>. Furthermore, we did not find any valve-related complications; the 2 perioperative deaths at 43 and 77 days and a midterm one at 4 years were not related to surgical issues.

Nevertheless, all the patients showed significant improvement in their NYHA functional class after surgery. Even those described as preoperative NYHA class

1 stated a different state of well-being. This could be a very subjective issue since data was obtained from medical records kept by different physicians at different times of the clinical evolution of patients<sup>26</sup>. Moreover NYHA functional class in itself seems to be less performing during the clinical evaluation of mildly symptomatic or asymptomatic patients ; the addition of another tool for evaluating NYHA 1 or 2 CHD patients could help to overcome this heterogeneity<sup>27</sup>.

## **CONCLUSION**

In our study, we confirm that single or multiple valve replacements in CHD is feasible and acceptable with good outcomes in the current era provided that an experienced multidisciplinary committee ensures well controlled carcinoid symptoms prior to surgery. Prosthesis choice should be done singularly considering each patient's data. Regular cardiac screening can help to consider early valve replacement, prior to symptoms of right and/or left heart failure, thus increasing survival rates with low perioperative morbidity.

## **LIMITS**

Our main limitation is in the fact that this study is based on a single center experience at a teaching hospital with a small sample size. Data prior to year 2000 was unavailable in the archives as well as those from a non-teaching hospital with cardiac surgery activity in the same geographical zone. Follow-up of patients were mainly based on latest available medical records which we assume to be the last date of information.



1. Schnirer II, Yao JC, Ajani JA. Carcinoid: A Comprehensive Review. *Acta Oncol (Madr)*. 2003;42(7):672-692.
2. Lubarsch O. Ueber den primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberculose. *Arch für Pathol Anat und Physiol und für Klin Med*. 1888.
3. Lembeck F. 5-Hydroxytryptamine in a Carcinoid Tumour. *Nature*. 1953;172(4385):910-911.
4. Ram P, Penalver JL, Lo KBU, Rangaswami J, Pressman GS. Carcinoid heart disease: Review of current knowledge. *Texas Hear Inst J*. 2019;46(1):21-27.
5. Bhattacharyya S, Davar J, Dreyfus G, Caplin ME. Carcinoid Heart Disease. *Circulation*. 2007;116(24):2860-2865.
6. Page IH, Corcoran AC, Udenfriend S, Szoedsma A, Weissbach H. Argentaffinoma as endocrine tumour. *Lancet*. 1955.
7. Thorson A, Nordenfelt. Development of valvular lesions in metastatic carcinoid disease. *Br Heart J*. 1959;21(2):243-248.
8. Grozinsky-Glasberg S, Grossman AB, Gross DJ. Carcinoid Heart Disease: From Pathophysiology to Treatment - "Something in the Way It Moves." *Neuroendocrinology*. 2015;101(4):263-273.
9. Voigt PG, Braun J, Teng OY, et al. Double bioprosthetic valve replacement in right-sided carcinoid heart disease. *Ann Thorac Surg*. 2005;79(6):2147-2149.
10. Mota JM, Sousa LG, Riechelmann RP. Complications from carcinoid syndrome: Review of the current evidence. *Ecancermedicalscience*. 2016;10:1-17.
11. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation*. 1993;87(4):1188-1196.
12. Ito T, Lee L, Jensen RT, et al. Carcinoid Syndrome 1. 2019:1-26.
13. Thorburn CW, Morgan JJ, Shanahan MX, Chang VP. Long-term results of tricuspid valve replacement and the problem of prosthetic valve thrombosis. *Am J Cardiol*. 1983.
14. Møller JE, Pellikka PA, Bernheim AM, Schaff H V, Rubin J, Connolly HM. Prognosis of carcinoid heart disease: Analysis of 200 cases over two decades. *Circulation*. 2005;112(21):3320-3327.
15. Connolly HM, Schaff H V, Abel MD, et al. Early and late outcomes of surgical treatment in carcinoid heart disease. *J Am Coll Cardiol*. 2015;66(20):2189-2196.
16. Mujtaba SS, Clark S. Quadruple valve replacement for carcinoid heart disease. *Brazilian J Cardiovasc Surg*. 2018;33(4):398-403.
17. Yuan S-M. Valvular Disorders in Carcinoid Heart Disease. *Brazilian J Cardiovasc Surg*. 2016;31(5):400-405.
18. Hart EA, Meijs TA, Meijer RCA, et al. Carcinoid heart disease: A guide for screening and timing of surgical intervention. *Netherlands Hear J*. 2017;25(9):471-478.
19. Nguyen A, Schaff H V, Abel MD, et al. Improving outcome of valve replacement for carcinoid heart disease. *J Thorac Cardiovasc Surg*. 2019.
20. Davar J, Connolly HM, Caplin ME, et al. Diagnosing and Managing Carcinoid Heart Disease in Patients With Neuroendocrine Tumors: An Expert Statement. *J Am Coll Cardiol*. 2017;69(10):1288-1304.
21. Warner RRP, Castillo JG. Carcinoid heart disease: The challenge of the unknown known. *J Am Coll Cardiol*. 2015.
22. Mabvuure N, Cumberworth A, Hindocha S. In patients with carcinoid syndrome undergoing valve replacement: Will a biological valve have acceptable durability? *Interact Cardiovasc Thorac Surg*. 2012;15(3):467-471.
23. Manoly I, McAnelly SL, Sriskandarajah S, McLaughlin KE. Prognosis of patients with carcinoid heart disease after valvular surgery. *Interact Cardiovasc Thorac Surg*.

- 2014;19(2):302-305.
24. Yong MS, Kong G, Ludhani P, et al. Early Outcomes of Surgery for Carcinoid Heart Disease. *Hear Lung Circ.* 2019.
  25. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease : executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:2440-2492.
  26. Goode KM, Nabb S, Cleland JGF, Clark AL. A Comparison of Patient and Physician-Rated New York Heart Association Class in a Community-Based Heart Failure Clinic. *J Card Fail.* 2008.
  27. Yap J, Lim FY, Gao F, Teo LL, Lam CSP, Yeo KK. Correlation of the New York Heart Association Classification and the 6-Minute Walk Distance : A Systematic Review. *Clin Cardiol.* 2015;38(10):621-628.