

- Weingarten TN, Abel MD, Connolly HM, Schroeder DR, Schaff HV. Intraoperative management of patients with carcinoid heart disease having valvular surgery: a review of one hundred consecutive cases. *Anesth Analg*. 2007;105:1192-9.
- Møller JE, Pellikka PA, Bernheim AM, Schaff HV, Rubin J, Connolly HM. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. *Circulation*. 2005;112:3320-7.
- Strosberg J, Weber J, Feldman M, Goldman J, Almanna K, Kvols L. Above-label doses of octreotide-LAR in patients with metastatic small intestinal carcinoid tumors. *Gastrointest Cancer Res*. 2013;6:81-5.
- Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut*. 2012;61:6-32.
- Killu AM, Newman DB, Miranda WR, Maleszewski JJ, Pellikka P, Schaff HV, et al. Carcinoid heart disease without severe tricuspid valve involvement. *Cardiology*. 2016;133:217-22.
- Connolly HM, Schaff HV, Mullany CJ, Abel MD, Pellikka PA. Carcinoid heart disease: impact of pulmonary valve replacement in right ventricular function and remodeling. *Circulation*. 2002;106(12 Suppl 1):I51-6.
- Whitlock RP, Sun JC, Frenes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e576S-600S.
- Castillo JG, Milla F, Adams DH. Surgical management of carcinoid heart valve disease. *Semin Thorac Cardiovasc Surg*. 2012;24:254-60.
- Kuntze T, Owais T, Secknus M-A, Kaemmerer D, Baum R, Girdauskas E. Results of contemporary valve surgery in patients with carcinoid heart disease. *J Heart Valve Dis*. 2016;25:356-63.
- Mokhles P, van Herwerden LA, de Jong PL, de Herder WW, Siregar S, Constantinescu AA, et al. Carcinoid heart disease: outcomes after surgical valve replacement. *Eur J Cardiothorac Surg*. 2012;41:1278-83.
- Rankin JS, He X, O'Brien SM, Jacobs JP, Welke KF, Filardo G, et al. The Society of Thoracic Surgeons risk model for operative mortality after multiple valve surgery. *Ann Thorac Surg*. 2013;95:1484-90.
- Bhattacharyya S, Raja SG, Toumanakis C, Caplin ME, Dreyfus GD, Davar J. Outcomes, risks and complications of cardiac surgery for carcinoid heart disease. *Eur J Cardiothorac Surg*. 2011;40:168-72.
- Chaowalit N, Connolly HM, Schaff HV, Webb MJ, Pellikka PA. Carcinoid heart disease associated with primary ovarian carcinoid tumor. *Am J Cardiol*. 2004;93:1314-5.
- Egbe AC, Connolly HM, Pellikka PA, Schaff HV, Hanna R, Maleszewski JJ, et al. Outcomes of warfarin therapy for bioprosthetic valve thrombosis of surgically implanted valves: a prospective study. *JACC Cardiovasc Interv*. 2017;10:379-87.
- Egbe A, Pislaru SV, Ali MA, Khan AR, Boler AN, Schaff HV, et al. Early prosthetic valve dysfunction due to bioprosthetic valve thrombosis: the role of echocardiography. *JACC Cardiovasc Imaging*. 2018;11:951-8.
- van Rijswijk JW, Vink A, van Herwerden LA, Kluijn J. Recurrent carcinoid involvement of a tricuspid bioprosthesis. *Eur J Cardiothorac Surg*. 2017;51:1015.

Key Words: carcinoid heart disease, tricuspid valve, surgery

Discussion



Dr Anita Nguyen (Rochester, Minn). Good morning. My name is Anita Nguyen, and I'm a research fellow at Mayo Clinic. Today I am presenting our study on improving outcomes of valve replacement for patients with carcinoid heart disease. We have no disclosures, but would like to acknowledge the very generous support of the Paul and Ruby Tsai family.

Carcinoid heart disease occurs in patients with carcinoid tumors, which are neuroendocrine malignancies secreting high levels of serotonin. This affects 20% to 50% of patients with carcinoid syndrome and can cause symptoms of right-sided heart failure and fibrosis, mainly affecting the tricuspid and pulmonary valves. In patients with right-sided heart failure symptoms, surgical valve replacement may be indicated. At the Mayo Clinic, we have operated on 240 patients with carcinoid heart disease over a 33-year period. The median age of patients was 63 years, and approximately half of our patients were male. Preoperatively, approximately 75% were in NYHA class III or IV.

Loop diuretic therapy was necessary in approximately half of our patients, and the majority of patients required somatostatin analogue therapy. Hepatic metastases are common in patients with carcinoid heart disease, but despite this, our patients had normal renal and liver function. This table shows the operative details. The majority of patients underwent tricuspid valve replacement, and 84% had tissue valves. Left-sided heart valves are less commonly affected by carcinoid heart disease, and 16% required operation on the aortic or mitral valve. Concomitant atrial septal defect or patent foramen ovale closure was necessary in 24% of patients. We excised cardiac tumors, which were a rare complication of carcinoid heart disease in 6 patients.

After surgery, early mortality, which we defined as death within 30 days of operation, occurred in 9% of patients. Before 2000, our early operative mortality was 17%, and after 2000, this decreased to 6%. On univariate analysis, higher NYHA class and older age was predictive of early mortality. Higher aspartate transaminase levels, which are associated with liver dysfunction, were somewhat predictive. This graph shows the overall survival of our study population. Of note, most of the late deaths occurred as the result of tumor progression. We grouped our patients by NYHA class and noticed that patients with NYHA class 1 or 2 had significantly better survival.

We then conducted univariate and multivariable analyses and noticed that older age and higher NYHA class were independently predictive of overall mortality. These graphs show the association between log relative hazard and age and NYHA class. The association was linear for both age and NYHA, which means that the higher the age or the higher the NYHA class, the higher the risk of overall mortality. Twenty patients required cardiac reintervention, and 16 patients required valve reintervention at a mean follow-up of 6 years. Only 3 patients required valve reintervention because of recurrence of carcinoid heart disease, and pericardiectomy for constrictive pericarditis was necessary in 4 patients. This graph shows patients alive without reintervention in dark blue and the cumulative incidence of reintervention in light blue. We assessed functional outcomes at 1 year in 107 patients and noticed that preoperatively, more than 65% were in NYHA class 3 or 4, and

postoperatively, this number decreased to less than 15%.

Patients with carcinoid heart disease who undergo valve surgery have improved early mortality, late survival is limited by tumor progression, the majority of patients experience symptomatic improvement, carcinoid involvement of bioprosthesis is rare, and earlier operation may decrease operative mortality and increase overall survival.

Questioner. Can you tell us how many patients still had tumor burden after the surgery and whether they ever received complete resection of the primary?

Dr Nguyen. The primary indication for performing the surgery was that most patients already had hepatic metastases at presentation, and we operated on the valves in view of future resection of the metastases, but it's rare for patients who are disease free to be completely disease free. This is only something that occurs with certain types of carcinoid tumors, such as ovarian cancers.

Questioner. What is your valve of choice, and if it's a bioprosthesis, is there any special novel therapy that you're doing to try to prevent carcinoid to involve a bioprosthetic valve?

Dr Nguyen. The valve of choice in this series was a bioprosthesis, and 84% of patients had a bioprosthesis. There is nothing specific that we can recommend to decrease the risk of carcinoid heart involvement in the future; however, the risk in this series was small, 3 of 240 patients.

Questioner. When you compare your historical mortality, that is pre-2000, it is 17% versus 6%. What other things did you change and do you think that might reflect just better management of the right ventricle? As I reflect upon this, I would have to assume that age and NYHA class are robust risk factor predictors, but perhaps it was better management of right ventricular dysfunction perioperatively that led to the better results. Is this true?

Dr Nguyen. Yes, we tried to ascertain the causes of the decrease in early mortality, and it was difficult for us to really pinpoint what exactly was causing the decrease in early mortality. We think it's a combination of better patient selection and improvement in general management of carcinoid heart disease with newer medical therapies.



Dr Joseph Cleveland (*Aurora, Colo.*)

Are you using valve-in-valve transcatheter aortic valve replacement technology to salvage some of the recurrent disease in the right-sided heart valves?

Dr Nguyen. We performed 2 percutaneous right-sided reinterventions.

Dr Cleveland. Hartzell?



Dr Hartzell Schaff (*Rochester, Minn.*)

Just to clarify a point that Anita made about the treatment of patients afterward with bioprosthesis. We don't know for certain but would advise continued use of somatostatins that might have an influence on reducing the risk of carcinoid development on the bioprosthesis.

The perioperative deaths are not related necessarily to right heart failure, and in fact, that's an uncommon cause of death. Most of the deaths are due to hepatic and renal failure, and liver function tests don't really predict who's going to have hepatic insufficiency after operation, so that's a challenge. Your last question had to do with how many of these patients were disease free. All of the patients had hepatic metastases except for 2 or 3 patients who had ovarian carcinoid tumors, who have serotonin going directly into the heart. So all of the patients had metastatic disease at the time we operated on them and afterward.