JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 20, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.05.086

EDITORIAL COMMENT

Carcinoid Heart Disease

The Challenge of the Unknown Known*

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Carcinoid tumors are rare (2.5 to 5.0 cases per 100,000 of the population per year), slow-growing neuroendocrine malignancies with significant potential to produce hepatic metastases and release excessive amounts of vasoactive amines into the systemic circulation (1). As a consequence, up to 15% of patients may develop carcinoid syndrome, with cutaneous flushing, gastrointestinal hypermotility, and cardiac involvement. Cardiac manifestations, also known as carcinoid heart disease (CaHD), are caused by endocardial deposition of pearly fibrotic plaques (notable for absence of elastic fibers) that generally extend to the right-sided valves, leading to multiple patterns of severe valve dysfunction. Plaque formation causes annular constriction, leaflet thickening, and fusion of the subvalvular apparatus. Marked degeneration of the leaflet architecture leads to severe retraction and noncoaptation of the valve, which remains fixed in a semiopen position (2). In this setting, valve replacement is the only definitive treatment to potentially mitigate symptoms, provide survival benefit, and improve quality of life.

Cardiac surgery for CaHD traditionally has been reserved for patients with symptomatic right ventricular (RV) failure because of its inherent prohibitive perioperative mortality; however, recent series have documented a significant trend toward improved outcomes, which consequently has triggered a more liberal surgical referral (3). Poor functional class and RV failure are independently associated with adverse outcomes, so much so that surgery is currently indicated unless an imminent demise is anticipated, especially if liver metastases are amenable to surgical resection. In this context, perioperative management of patients with CaHD may pose 2 challenges: the potential acute onset of a carcinoid crisis (vasodilation, cardiac arrhythmias, bronchospasm, and facial hyperemia) and the identification and management of low cardiac output syndrome (hemodynamically significant RV failure vs. profound hypotension secondary to severe systemic vasodilation vs. terminal metastatic disease).

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In this issue of the *Journal*, Connolly et al. (4) introduce the largest series to date of surgical patients with CaHD. The authors, academically proficient in this complex field, update the Mayo Clinic experience after scrutinizing the medical records of 195 consecutive patients who underwent multivalve surgery during a 27-year period (1985 to 2012). This retrospective study analyzed medical and surgical trends, perioperative outcomes, long-term follow up, and referral patterns. From a critical point of view, there are 3 major points that deserve further attention, because they will potentially become decision-making tenets: 1) the surgical management of right-sided CaHD should routinely consist of valve replacement and subsequent enlargement of the RV outflow tract; 2) there is a clear trend toward significantly improved perioperative outcomes and survival, which will probably impact management and referral patterns in the very near future; and 3) a comprehensive multidisciplinary assessment of tumor burden and cardiac status (introduction of new imaging tools and more accurate biomarkers) is critical in guiding optimal timing of surgery in patients with carcinoid syndrome and CaHD.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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The most common primary site of carcinoid tumors is the gastrointestinal tract (60%); one-third of them (34%) arise in the small intestine, and up to 75% of these may metastasize to the liver (5). Resection of the primary carcinoid tumor and the hepatic metastases when feasible is routinely recommended in all patients with carcinoid syndrome. However, in the setting of CaHD, severe tricuspid regurgitation may lead to hepatic venous outflow obstruction, significant elevation of post-sinusoidal pressures, visceral engorgement, and pulsatile liver. In this scenario, identification of resectable hepatic metastases in patients with severe CaHD should prioritize and prompt cardiac surgery over any hepatic intervention.

As described in the paper by Connolly et al. (4), valve replacement should be the procedure of choice to treat right-sided lesions, mainly on the basis of 2 axioms: 1) the presence of severe leaflet fibrosis and thickening, as well as fusion of the subvalvular apparatus, makes repair either unfeasible or not durable; and 2) the potential impossibility of effectively eliminating or at least reducing the levels of circulating vasoactive amines (disease progression in patients with uncontrolled or refractory disease) favors valve replacement. Although tricuspid valve replacement has been habitually accepted by most authors, the need for pulmonary valve replacement has remained debatable. In this regard, although many patients may certainly tolerate some degree of pulmonary regurgitation (as reported, pulmonary valvectomy was once preferred over replacement), Connolly et al. (4) observed incomplete RV remodeling in patients with long-standing overload. In addition, a more uneventful post-operative recovery has been seen among those patients undergoing concomitant pulmonary valve replacement. Therefore, the authors recommend pulmonary valve replacement and concomitant enlargement of the RV outflow tract to accommodate a larger prosthesis. This has been our institutional routine at Mount Sinai; however, some European institutions still advocate the use of homografts in the pulmonary position. According to the data described by Connolly et al. (4) and per our own experience, the use of homografts may not be optimal for several reasons: 1) constriction of the homograft may lead to early valve dysfunction; 2) homograft calcification and subsequent stiffening may exclude patients from having future percutaneous interventions with a consequent risk of potential rupture after balloon inflation; and 3) homografts might be more amenable to plaque deposition and recurrent CaHD (6).

The most incendiary debate among carcinoid experts is the choice of prosthesis at the time of valve replacement. Historical series have favored the use of mechanical prostheses on the basis of likely early structural valve deterioration caused by high levels of vasoactive substances and the relatively young age of patients. However, as emphasized in the paper by Connolly et al. (4), the literature has progressively supported the use of bioprostheses based on multiple key points: 1) patients receiving bioprostheses have better short-term outcomes; 2) survival rarely exceeds current valve durability (69%, 35%, and 24% at 1, 5, and 10 years, respectively); 3) patients with CaHD often present with abnormal liver profiles and secondary coagulopathies; 4) long-term or chronic use of vitamin K antagonists may represent an additional risk in patients who will surely undergo multiple subsequent procedures or receive chemotherapy; and 5) pathology review of explanted bioprostheses has proved that carcinoid involvement of the bioprosthesis is uncommon (only found in a single explanted valve vs. valve thrombosis in the rest). Regarding the latter point, the present report advocates the use of post-operative vitamin K antagonists 3 months after surgery and then periodic echocardiographic surveillance (the authors noted the reversal of bioprosthetic dysfunction after initiation of anticoagulation). We also adopted this protocol 1 year ago and have experienced similar results. Yet unpublished data have suggested some degree of bioprosthetic dysfunction in approximately 20% of patients (unclear pathogenesis, recurrent carcinoid vs. thrombosis).

The first report on the surgical management of CaHD was published in 1963, but it was not until the early 1990s that the first surgical series were published. In 1995, an analysis of the Duke Carcinoid Database observed an operative mortality rate as high as 63% (7). That same year, Connolly et al. (8) reported the initial Mayo Clinic experience, with an overall operative mortality rate of 35%. A decade later, Møller et al. (9) updated the Mayo Clinic experience and demonstrated a more important decline in perioperative mortality (16% in a series of 87 patients). Since then, several European series have shown 30-day mortality rates below 20%, with optimistic short-term outcomes (10,11). In the present study, Connolly et al. (4) observed an overall operative mortality rate of 10%. Interestingly, this rate was much lower when patients were divided according to different study periods (17% before 2000 vs. 6% after 2000). In our own experience with 32 patients, the mortality rate also dropped, from 20% to 9%, if analyzed according to different study periods (12). We strongly believe that as with every complex surgical procedure, knowledge about the disease and volume highly impact outcomes (**Figure 1**).