

Carcinoid Heart Valve Disease. Still a Puzzle and a Challenge

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Carcinoid tumor is a rare tumor in neuroendocrine cell line, which occurs in 1.2 to 2.1 per 100,000 people per year. At diagnosis, 20% to 30% of patients have the disease disseminated and subsequent heart disease, which affects 40% of patients causing high morbidity and mortality in the carcinoid syndrome. Primary cardiac carcinoid tumors were not reported and, rarely, metastatic tumor masses were found in the myocardium, usually in conjunction with valvular involvement. It is believed that cardiac involvement occurs when serotonin and other active substances are released from liver metastases or primary ovarian carcinoid tumors, bypassing the metabolism in the liver. Carcinoid heart disease typically involves the tricuspid and pulmonary valves, causing right heart failure. Involvement of the left valve is rarely reported (<10% of patients). Thus, the mitral and aortic carcinoid disease may occur more frequently in patients with atrial septal defect or patent foramen ovale with diversion of blood from right to left. However, cardiac involvement may also occur in the absence of this diversion due to an association with bronchopulmonary carcinoid or with high levels of circulating serotonin¹⁻³.

Three-year survival is 31% compared to the percentage of 68% for individuals without echocardiographic evidence of cardiac involvement³. Recent analysis of 200 cases of carcinoid heart disease showed an increase in median survival of 1.5 years to 4.4 years over the past two decades⁴. This improvement in survival may result a better overall result and more frequent use of valvular surgery. The prognosis has further improved as a consequence of cytoreduction surgery, ablative therapy of liver metastases and the use of somatostatin, but there is no robust evidence of such correlations. However, many points still need solid evidence to establish a consensus of that surgical approach: 1) What is the time of surgical indication? 2) What is the surgical risk? 3) What is the evolution of patients operated? 4) Valvular plasties, bioprosthesis or mechanical prosthesis? 5) What is the role of serotonin inhibitors after surgery?

The first heart valve surgery for carcinoid heart disease was conducted in 1963⁵. Despite initial evidence of prolonged palliation, the mortality rate was considered unacceptably

high (20%-50%). In later series, the reduction in perioperative mortality to less than 10% and marked improvement of symptoms increased the enthusiasm for the surgery. In two decades (1980-2000), a retrospective analysis of 87 patients with carcinoid heart disease treated at a single institution revealed that perioperative mortality was reduced by 25% in the 1980s to 9% in the last five years of the study⁴. During the same period, the percentage of patients undergoing surgery increased from 18% to 64%. Therefore, the surgery that used to be performed only in severely symptomatic patients, is now proposed for those who are only mildly symptomatic, as it is evident that the progression of heart failure increases perioperative mortality even further. The number of patients operated is still very small for the establishment of evidence as to the time of surgery, including the proposal of surgical treatment for asymptomatic patients with the aim of changing the natural history of the disease. Because the disease is relatively rare, it is possible that imaging tests and biomarkers will play an important role in this scenario⁶.

The surgical risk, though declining, is still larger than the surgical risk of rheumatic valve diseases and degenerative diseases. From this perspective, there is already evidence on the use of serotonin inhibitors, in the case of occurrence of intraoperative and perioperative carcinoid crisis, as well as the security of interaction with vasoactive drugs. In the case of liver involvement, the incidence of major bleeding may be a factor with some incriminating evidence of the beneficial effect of aprotinin by inhibition of kallikrein-kinin system⁷.

The replacement of heart valve and/or "compensation" for carcinoid heart disease is increasingly accepted. Nevertheless, the results are not always favorable. In a previous report from the Mayo Clinic, 9 out of 26 patients died in the early perioperative period and nine other people, within about 19 months after surgery. Although mortality was higher, the long-term survival (8 out of 26 patients) resulted in a considerable reduction (2 patients) or elimination (6 patients) of symptoms⁸. A later report from the same institution presents the results in 11 patients with carcinoid heart disease who underwent surgery for the left and right valves¹. The tricuspid valve was replaced in all of the 11 patients; the pulmonary valve, in 3 (valvectomy, 7); the mitral valve in 6 (plasty in 1); and aortic valve in 4 (plasty in 2). There were two perioperative deaths and four additional deaths over an average period of 41 months. All but one surgical survivor improve functional class by ≥ 1 ⁹.

Replacing damaged valves for mechanical prostheses was previously recommended by virtue of fear of premature degeneration of bioprosthesis. In recent years, the use of

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prostheses have become more accepted and in many cases, preferably, probably due to lower life expectancy than the duration of the bioprosthesis. A mechanical prosthesis would not have any risk of carcinoid hormone-induced degeneration. However, the mandatory anticoagulation represents considerable risk for bleeding during hepatic artery embolization or citoreducer surgical procedures performed to achieve hormonal control⁶. The “never ending story” about the choice of prosthesis is strongly present in the treatment of carcinoid valvulopathy. Some considerations, though speculative, deserve a mental exercise. The use of biological prostheses was apparently more logical based on three main points: a) no need for anticoagulation in patients with a chance of liver disease; b) European experience shows that the degeneration of bioprostheses was not significant, suggesting no influence of carcinoid disease in the process of degeneration; c) the life expectancy of patients, even the young ones, was lower than the durability of the bioprosthesis. As for the isolated plasties, also apparently, these would not be a logical choice as they would keep the valve tissue ill. There are few reports of exchanges of the four heart valves, the largest experience reported by the Mayo Clinic¹⁰. There is no consensus on the choice of the prosthesis, although the apparent logic of the choice of bioprostheses requires an individualized therapy.

Why a puzzle and a challenge? Some puzzling data would be: 1) the unknown role of serotonin in valvular disease; 2) against the hypothesis of atrial septal defect as a condition for the left valve diseases, there are reported cases of left valve diseases in the absence of such septal defect; 3) the natural history of the disease is still unclear and the disease could be underestimated. Some “challenging”

highlights would be: 1) early diagnosis grounded on imaging and more accurate biomarkers, 2) which is the optimal timing for surgery? 3) although there is preference for bioprostheses, there would be potential treatments that reversed the binomial prosthesis/patient survival? 3) does it make sense to associate plasties with valve exchanges? Finally, these questions have encouraged this article, pointing out that the increasing number of publications on the carcinoid heart disease can assign it the characteristic of an emerging disease deserving greater attention from basic scientists, clinicians and surgeons.

Searches with broad indicators (carcinoid and Brazil), using the databases MEDLINE, SciELO and LILACS, revealed only 29 Brazilian publications on the digestive and respiratory systems without mention of heart involvement. Thus, either the problem does not exist in Brazil or it is being underestimated, a question that has encouraged this “Point of View.”

Potential Conflict of Interest

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