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Editorial

Contemporary Evaluation and Management of Carcinoid Heart Disease

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Introduction and Clinical Perspectives

Carcinoid heart disease (CHD) is a common (up to 50%) and serious complication of the rare carcinoid syndrome (1–2/100,000 population), which arises from metastatic neuroendocrine tumors, typically originating in the gastrointestinal tract or lungs. These tumors secrete bioactive substances like serotonin and other vasoactive peptides, which can cause fibrosis of the heart valves, leading to restrictive cardiomyopathy and right-sided heart failure [1,2]. The hallmark of CHD is the fibrotic thickening of the tricuspid and pulmonary valves, resulting in valve dysfunction and ultimately impaired cardiac function [3]. It predominantly affects the right side of the heart, including the tricuspid and pulmonary valves, due to the effects of serotonin and other metabolites primarily passing through the right side of the heart, only affecting the left side of the heart in the presence of an intracardiac defect and shunt [2,4]. The main clinical features are therefore exertional dyspnea, fatigue, edema and ascites, which mimic right-sided heart failure. Other cardiac manifestations include pericardial effusion, paroxysmal atrial or ventricular tachycardias and cardiac metastases [5].

Evaluation

A diagnosis of CHD involves measuring urinary 5 hydroxyindoleacetic acid and N terminal prohormone of brain natriuretic peptide with elevated levels indicating carcinoid syndrome and CHD progression risk [1–3]. An electrocardiogram with nonspecific findings such as ST-T wave abnormalities, sinus tachycardia, and a prolonged PR interval. A chest radiograph often shows normal results, but may reveal cardiomegaly with prominence of the right-sided cardiac chambers, mild pulmonary congestion, and, in advanced cases, pleural effusions and metastatic pleural plaque formation [1].

Echocardiography is the first line and cornerstone imaging modality to identify right-sided heart fibrosis with fixed limited moment, resulting in tricuspid and pulmonary valve stenosis and regurgitation (Fig. 1), and over time right-sided heart dilation and dysfunction. Cardiac magnetic resonance imaging (MRI) is increasingly utilized as the reference standard for right-sided heart chamber quantification, assessing valvular regurgitation and stenosis [3,6]. Computed tomography (CT) imaging has a separate role in assessing systemic carcinoid syndrome involvement, along with pre-operative coronary and thoracic anatomy and disease evaluation [6].

Non-Surgical Management

The medical management of CHD focuses on controlling the underlying carcinoid syndrome, alleviating symptoms, and preventing disease progression. The primary medical strategies include the use of somatostatin analogs, targeted therapies, and supportive treatment for heart failure. Somatostatin analogs, such as octreotide and lanreotide, are the mainstay treatment options for controlling the symptoms of carcinoid syndrome, including flushing, diarrhea, and wheezing [2]. Interferon-alpha may be considered for patients with a more aggressive disease. It has antiproliferative effects on carcinoid tumors and can help reduce the size of tumors, potentially lowering the secretion of vasoactive substances [3,7,8]. Patients with CHD frequently develop right-sided heart failure due to valve fibrosis and pulmonary hypertension. Standard right heart failure treatments such as diuretics are used to manage symptoms, although they do not address the underlying cause of the heart disease. Other advanced medical therapies for refractory symptoms include telotristat, systemic chemotherapy, radiotherapy and antidiarrheals [9,10].

Surgical Management

The first step in managing CHD is controlling the underlying carcinoid syndrome, which can help reduce the progression of heart disease. Surgical resection of the primary tumor, if localized and accessible, or debulking of liver metastases, which are common in carcinoid tumors, can reduce the release of serotonin and other vasoactive substances [11]. The general approach is to prioritize the

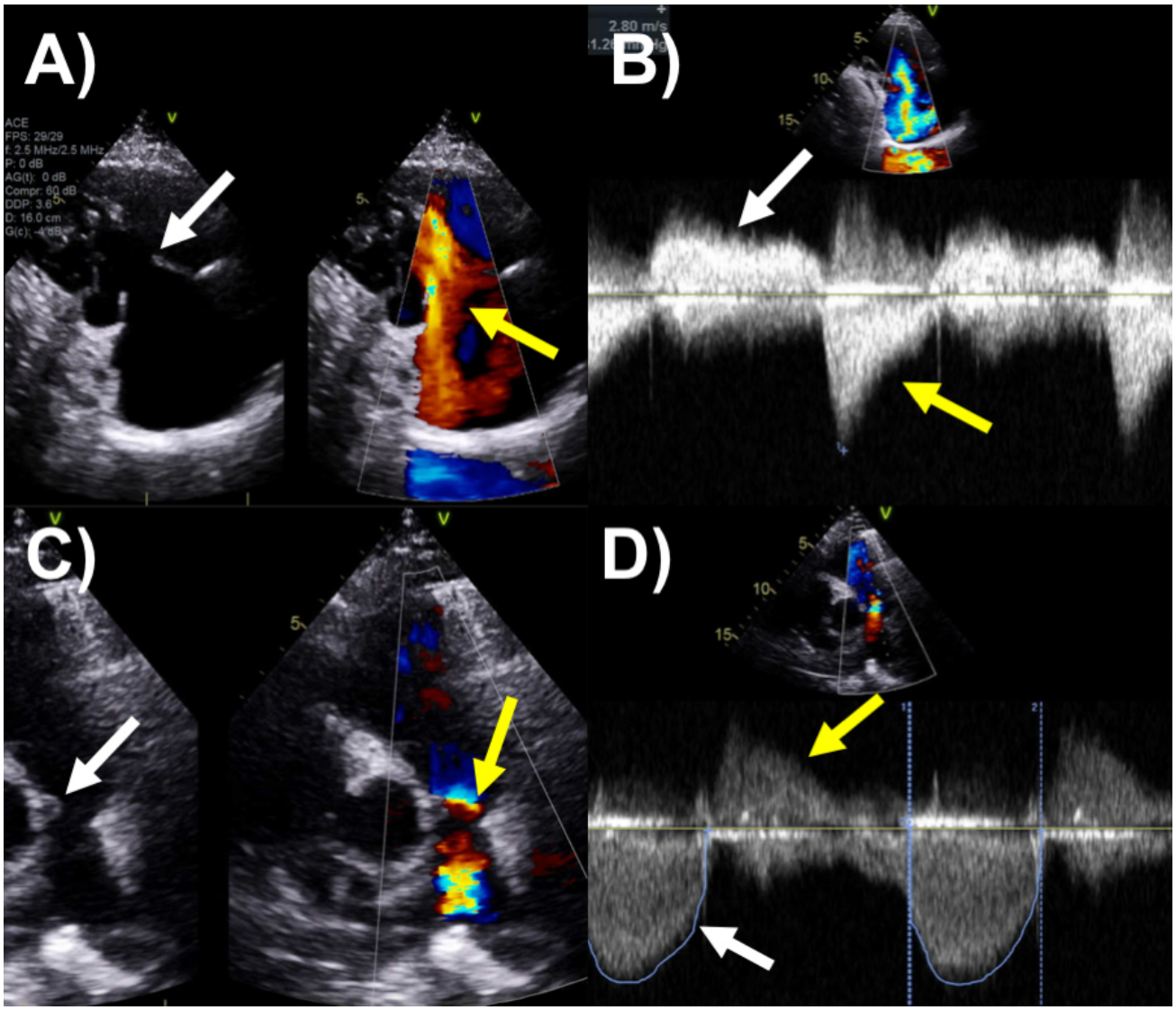

Fig. 1. Transthoracic echocardiography case carcinoid tricuspid and pulmonary valve heart disease. (A) Parasternal tricuspid valve inflow view showing fixed thickened tricuspid valves (white arrow) with flow acceleration indicating stenosis on color-Doppler (yellow arrow). (B) Continuous wave Doppler of tricuspid valve showing severe tricuspid stenosis inflow (white arrow) and regurgitation (yellow arrow). (C) Pulmonary artery and valve view showing thickened pulmonic valve leaflets (white arrow) with flow acceleration indicating stenosis on color-Doppler (yellow arrow). (D) Continuous wave Doppler of pulmonic valve showing significant pulmonic stenosis inflow (white arrow) and regurgitation (yellow arrow).

treatment of the primary tumor (such as in the liver or bowel) first, before addressing the heart. This may slow the progression of valvular damage in some patients. Liver transplant or somatostatin analogs like octreotide are also considered adjuncts in patients with extensive liver metastases to control hormone secretion. Once the tumor has been managed, cardiac surgery is often necessary to address the valvular damage caused by CHD.

Tricuspid and/or pulmonary valve surgeries are indicated for severe valve stenosis and/or regurgitation, especially in the presence of associated right heart failure symptoms and signs and/or progressive right ventricular dilation and dysfunction [12,13]. Nguyen *et al*. [14] analyzed the data of 240 patients who underwent surgery for CHD at the Mayo Clinic between 1985 and 2018. Their findings revealed that valve replacement for CHD is a safe procedure with a continually improving short-term mortality rate. They also emphasized that earlier intervention might contribute to better long-term survival outcomes. Macfie *et al*. [15] conducted a study on 282 patients. CHD patients (n = 40) had lower survival rates compared to non-CHD patients (n = 242). CHD patients without valve replacement (VR) had poorer survival rates, while those with VR had survival rates similar to non-CHD patients. Pulmonary valve replacements are usually performed with bioprosthetic valves, and in select cases, with homografts or

tissue-engineered valves, and combined surgeries may have superior survival over isolated tricuspid valve surgery [16]. Prophylactic octreotide is generally recommended, and additional, fluids and vasopressors may be necessary in those who become hemodynamically unstable during surgery. In cases of refractory disease or severe heart failure, surgical resection of the carcinoid tumor may be considered, although it is often not curative. Surgical management of the heart valves may be required in advanced cases to improve cardiac output and quality of life, and transcatheter interventions are now available in selected high-risk patients, as prognosis is poor in those medically managed patients with heart failure [4,17,18].

Conclusion

Advances in medical and surgical therapies have improved outcomes in patients with carcinoid syndrome and CHD. Early detection of CHD and multidisciplinary team efforts in identifying patients who might benefit from cardiac interventions remain the cornerstone of management.

Author Contributions

AA, EH and TW all contributed to planning, writing, critical revision and approval of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This editorial is based on previously published studies and does not involve any new human or animal research conducted by the authors. Therefore, ethical approval and informed consent are not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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