Carcinoid Heart Disease
A Review

Aimee R. Hayes, BSc (Med), MMed (Clin Epi), FRACP[a], Joseph Davar, MRCP, MD, PhD[b], Martyn E. Caplin, DM, FRCP[a,*]

KEYWORDS

• Carcinoid heart disease • Carcinoid syndrome • Neuroendocrine tumor

KEY POINTS

- Carcinoid heart disease remains a major cause of morbidity and mortality among patients with carcinoid syndrome and metastatic neuroendocrine tumours.
- Screening of all patients with NT-proBNP and transthoracic echocardiogram is critical for early detection as early symptoms and signs have low sensitivity for the disease.
- Cardiac surgery, in appropriate cases, is the only definitive therapy for advanced carcinoid heart disease and it improves patient symptoms and survival.
- Management of carcinoid heart disease is complex and multidisciplinary assessment of cardiac status, hormonal syndrome and tumour burden is critical in guiding optimal timing of surgery.

INTRODUCTION

Although progress in the medical and surgical management of patients with metastatic neuroendocrine tumors (NETs) has resulted in improved symptoms and survival, carcinoid heart disease (CHD) remains a major cause of morbidity and mortality among patients with carcinoid syndrome. CHD has been previously described in up to 50% of patients with carcinoid syndrome,[1,2] although recent studies suggest the prevalence has fallen to approximately 20%,[3,4] perhaps secondary to the more widespread use of somatostatin analog therapy. It is reported to occur most frequently in patients with primary small bowel NETs (72%), followed by NETs arising from the lung, large bowel, pancreas, appendix, and ovaries.[1] A slight male predominance has been reported (approximately 60%), with a mean age at diagnosis 59 (± 11) years.[1]

Disclosure: The authors maintain they have no conflicts of interest for this article. No external funding or grants were used.
[a] Neuroendocrine Tumour Unit, Royal Free Hospital, Pond Street, London NW3 2QG, UK; [b] Carcinoid Heart Disease Clinic, Department of Cardiology, Royal Free Hospital, Pond Street, London NW3 2QG, UK
* Corresponding author.
E-mail address: m.caplin@ucl.ac.uk

Endocrinol Metab Clin N Am 47 (2018) 671–682
https://doi.org/10.1016/j.ecl.2018.04.012
0889-8529/18/

Without treatment, the prognosis of CHD is poor, with 3-year survival as low as 31% (compared with 68% in patients with NETs but without CHD).[1] CHD with advanced symptoms (New York Heart Association [NYHA] functional class III or IV) carries a particularly poor prognosis, with median survival only 11 months.[5] Over the past few decades, however, the prognosis of patients with CHD has improved. In a retrospective series of 200 patients with carcinoid syndrome and CHD,[6] the median survival improved from 1.5 years in the 1980s to 4.4 years in the late 1990s, with the data suggesting this improvement is related to increased rates of cardiac surgery and the use of somatostatin analogs.

PATHOPHYSIOLOGY

The pathogenesis of CHD is thought to be multifactorial and is not completely understood. A variety of vasoactive substances secreted by the tumor, including serotonin, prostaglandins, histamine, bradykinin, and other substances with fibroblast proliferative properties, such as tachykinins (substance P, neurokinin A, neuropeptide K) or transforming growth factor-beta, are thought to be involved in the disease pathogenesis.[7]

The Role of Serotonin

There is a growing body of evidence that suggests serotonin plays a major role in the pathogenesis of CHD. It is well known that urinary 5-hydroxyindoleacetic acid (5-HIAA), the serotonin metabolite, is significantly higher in patients with CHD compared with those without cardiac involvement.[1,2,8,9] Other support for the pathophysiological role of serotonin arises from the observation that serotoninergic drugs, such as the ergot-alkaloid derivatives (eg, ergotamine and methysergide used for treatment of migraine; pergolide and cabergoline used for treatment of Parkinson disease) or the anorectic drugs (eg, fenfluramine, alone or in combination with phentermine, and dexfenfluramine), cause valvular fibrosis similar to that seen in CHD.[10,11] These agents are full or partial 5-HT2B receptor agonists, suggesting that activation of this receptor is involved in the pathologic process that leads to plaque development.[12,13] Furthermore, in cell culture studies, serotonin has been shown to promote cell proliferation in valvular subendocardial cells,[14] and human heart valves have been demonstrated to express the serotonin receptors 5-HT1B, 1D, 2A, and 2B.[13,15] In addition, preliminary animal studies, using Sprague-Dawley rats and cynomolgus monkeys, have demonstrated that long-term exposure to elevated levels of serotonin induces carcinoid-like plaques on cardiac valves, as well as echocardiogram findings similar to those seen in humans with CHD.[16–18] Furthermore, the concomitant administration of the ergoline terguride (transdihydrolisuride), a 5-HT2B/2C receptor antagonist, inhibited these changes.[19] Nevertheless, despite the growing evidence that serotonin plays a major role in the development of CHD, it is likely that other biochemical mediators are also significant and may act as cofactors in the fibrotic process.[20–22]

Pathologic Findings

CHD is characterized by plaque-like deposits on the endocardium of valvular cusps, leaflets, chordae, and papillary muscles and cardiac chambers, and occasionally within the intima of the pulmonary arteries or aorta.[23–25] The deposits are composed of myofibroblasts and smooth muscle cells surrounded by extracellular matrix components (collagen and myxoid matrix) and covered by an endothelial cell layer.[23,26] The valves and endocardium of the right side of the heart are most frequently affected and this is usually due to the presence of hepatic metastases that secrete large quantities