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Carcinoid Heart Disease: A Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors TAM, RNDJ and IAMF wrote the draft of the manuscript. Authors TAM, RNDJ, IAMF and PGMBS managed the literature searches and contributed to the correction of the draft. Authors TAM, RNDJ, LGR, BBCL and MCS provided the cases, the figures and supervised the work. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Carcinoid tumors are rare malignancies able to spread and produce bioactive humoral products, mainly serotonin, which is responsible for the Carcinoid Syndrome (CS); its features are: flushing, diarrhea, bronchospasm and valvular heart disease. The Carcinoid Heart Disease (CHD) importantly worsens prognosis and it is found in up to 50% of patients with CS. After being produced by liver implants, serotonin finds its way straight into the right heart cavities, leading to valve tissue aggression and ventricular dysfunction. Early CHD diagnosis is still a challenge due to the asymptomatic initial stage, until right heart failure develops along with ascites, swelling and hepatomegaly. Echocardiography is still the main tool for diagnosis, especially due to its ability to appropriately evaluate ventricular and valve function, cardiac morphology and hemodynamics. Tricuspid regurgitation, pulmonic stenosis and dilated cardiomyopathy are the main impairments found in CHD. Magnetic resonance imaging has also developed well in this field, and it is now

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believed to be essential, due to accurate right cavities evaluation and fibrosis detection. For better prognosis, early diagnosis must be pursued, which has impact on clinical management and valve repair surgical decision.

Keywords: Carcinoid syndrome; carcinoid heart disease; neuroendocrine tumor.

1. INTRODUCTION

Carcinoid tumors (CT) are rare neuroendocrine neoplasms derived from the enterochromaffin cells which may appear anywhere on the human body, being located on 40 to 60% of cases in the gastrointestinal tract, and up to 25% in the bronchopulmonary system [1]. The World Health Organization updated the classification of neuroendocrine tumors based on tumor site of origin, clinical syndrome, and differentiation [2]. Carcinoid tumors and pancreatic neuroendocrine tumors are commonly divided by site of origin (eg foregut, midgut or hindgut). National Comprehensive Cancer Network guidelines recommend staging according to the 7th edition of the American Joint Committee on Cancer [3] for carcinoids of the stomach, duodenum/ampulla/jejunum/ileum, colon/rectum, and appendix, as well as adrenal gland tumors. Bronchopulmonary carcinoids are staged using the same system as for other pulmonary malignancies.

Incidence of CHD is estimated at around 1-2 cases per hundred thousand people in the general population, most common in the black population and in individuals between the fourth and fifth decades of life [4]. There is a slight prevalence of males, accounting for approximately 60% of cases [1]. Although rare, its incidence has increased due to improve diagnostic methods and clinical knowledge in recent decades [5,6] or a real increase in the incidence of neuroendocrine tumors. The term *carcinoid,* derived from the word "karzinoide", was first used in 1907 by Siegfried Oberndorfer in an attempt to distinguish this class of indolent course of malignant adenocarcinoma [7]. Due to its dragged course and the initial absence of symptoms it was mistakenly regarded as a benign tumor.

The most striking feature of CT is the ability to secrete humoral bioactive substances into the bloodstream, such as prostaglandins, histamine, bradykinin, substance P, neurokinin A and especially serotonin, among many others [1]. These substances are largely metabolized and inactivated in the liver, lung and brain, preventing its clinical expression [8]. A significant worsening of life quality and survival rates may occur concomitantly with the onset of symptoms, which has close relationship with the appearance of liver metastases.

The Carcinoid Syndrome (CS) is the classic clinical presentation of disseminated disease, consisting of episodes of flushing, secretive diarrhea, bronchospasm, hypotension and cardiac heart disease. CS is expressed when the bioactive substances are falling freely and directly into the hepatic vein and into the systemic circulation [5,8]. This set of findings occurs because there is production of these substances by hepatic metastases, which were initially secreted only by primary sites and had their inactivation in the liver, lungs and brain. It may also occur, but less commonly, in the absence of liver metastases when there is very high production from the primary site or in the case of primary ovarian CT, when the products bypass the hepatic circulation through the inferior vena cava, thus reaching directly the systemic circulation [8,9].

Early diagnosis still is a challenge. Some cases of CT are nonfunctioning tumors, and a considerable portion of the secretive ones remain silent for up to a decade, being found when a routine examination is performed for other reasons [5]. It may acquire a malignant behavior and lead to death if not diagnosed and treated early and properly [1,4]. Studying 13,715 cases of carcinoid tumors along 5 decades, Modlin showed that 12.9% had metastases at diagnosis, with the liver being the main organ involved (80%). In this series, the presence of regional metastases was associated with worse prognosis, with a reduction of five years in survival rates [4].

The heart is rarely the primary site of the CT or its metastases. However, there may be direct cardiac consequences, especially after CS is installed. Changes in cardiac anatomy and physiology have been described since 1954 [10]. Carcinoid heart disease (CHD) occurs in 50 to 60% of patients with symptoms of CS [11], and its onset is significantly linked to unfavorable

clinical outcomes and reduction in survival rates [1].

The aim of this article is to describe the pathogenesis of CHD and its clinical behavior, highlighting the usefulness of diagnostic imaging methods.

2. CARCINOID HEAT DISEASE

2.1 Injury Mechanisms

The CHD pathogenesis has not been fully elucidated, despite numerous studies. After liver involvement there is local production of bioactive products, especially serotonin, which fall in the hepatic veins and are then taken directly to the right heart chambers. Serotonin remains in the bloodstream and returns to the liver, where it is metabolized into 5-hydroxyindoleacetic acid (5-HIAA) by hepatic monoamine oxidases, to be later excreted in urine, having an important diagnostic and prognostic value [6,8].

Animal models have demonstrated that serotonin stimulates the production of fibrous tissue by cardiac interstitial cells when exposed for long periods, leading to deposits in the form of plates over endocardial surfaces [5,12]. This is due to the presence of receptors for serotonin in the endocardial tissue, particularly in the valve tissue [8]. The right chambers are preferably affected because there is inactivation of humoral substances by lung parenchyma. There is also evidence that genetic predisposition and interaction of serotonin with other humoral factors play crucial roles in the development of CHD [1].

The fibrous plaques progressively form over normal valve surface after mitogenic stimulation mediated by serotonin, while keeping the underlying anatomical architecture intact, and lead to retraction and thickening of these structures [1]. They are composed of smooth muscle cells, myofibroblasts, extracellular matrix deposits, endocardial cells and elastic tissue, giving a whitish appearance when viewed in post-surgical anatomical pieces. But the affected structures are not only the valves: the atrial and ventricular endocardial right surfaces and all the subvalvular apparatus (papillary muscles, chordae) also are exposed to aggression [1,8]. Valve dysfunction is remarkable in CHD, and tricuspid insufficiency is the main finding (Fig. 1). There is retraction of its leaflets and subvalvular apparatus, with gradual reduction of mobility and increased coaptation defect during the cardiac cycle, until it reaches a stage where there is no more mobility: leaflets are paralyzed on a fixed semi-open position [6]. There is gradually moving from a mild regurgitation to a significant regurgitation, leading at a later stage to dilation of the cardiac chambers, right ventricular systolic dysfunction and development of signs and symptoms of right heart failure, such as lower extremity edema, jugular venous distension and ascites.

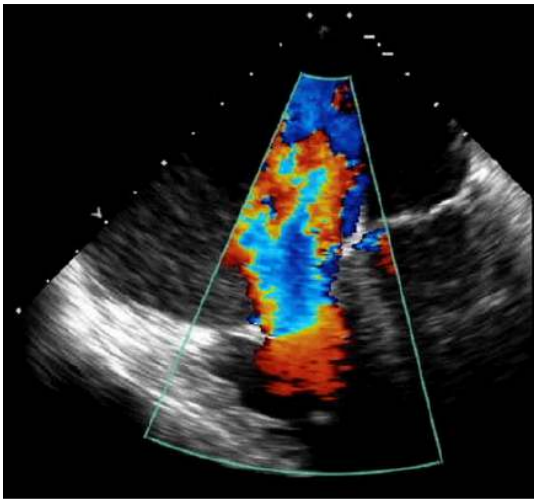

Fig. 1. Important tricuspid regurgitation seen on transesophageal echocardiography, using color Doppler method (Adapted from Castillo et al. [6])

When considering the PV, the most involved mechanism leads to the development of stenosis by constriction of the right ventricular outflow tract, thickening of the entire valve apparatus and fibrous tissue deposits in its annulus [1]. This event has significant hemodynamic effects, since pulmonary stenosis exacerbates an existing tricuspid insufficiency, as a barrier to the right ventricular ejection.

The involvement of the left chambers, as well as of their valves (mitral and aortic), is much less frequent (up to 15% of cases) and generally milder, rarely of hemodynamic significance. As there is inactivation of humoral substances by the lung parenchyma, the presence of disease on the left side is only possible if there is production of these substances in a concentration exceeding the capacity of pulmonary metabolism [6], or the presence of any communication (shunts) between left and right chambers. The main associated shunt is

persistent foramen ovale, which should be pursued in such cases [1,8]. When the CHD is only expressed on the left, the main hypothesis is that there are metastatic carcinoid sites implanted directly into the bronchopulmonary system.

The direct involvement of the myocardium by carcinoid metastases is even more unusual, occurring in less than 4% [13]. By 2010 there were only 45 reported cases, 28 of which being associated with CS, and univentricular in 21 cases (eleven of them in the right ventricle). This type of implant, which penetrates the ventricular wall and conduction tissue, predisposes to other complications such as malignant arrhythmias, cardiogenic shock and atrioventricular conduction blocks, thus worsening the prognosis [5]. Predisposing factors for myocardial metastases are still not known, except the fact that they are mostly associated to midgut carcinoid tumors [13].

2.2 Clinical Presentation

The suspicion of its presence should be raised in all patients who present the classic stigmata of the carcinoid syndrome: flushing, diarrhea and bronchospasm, triggering early diagnostic procedures that will impact over treatment beginning and the choice of treatment for each individual case, and thus survival rates. The patient may remain asymptomatic at early stage which may delay the diagnosis for several months [14]. The average time between symptoms onset and the diagnosis is around one to two years, reflecting the diagnostic difficulty in the early stages of the disease [15].

Symptoms of ventricular dysfunction secondary to valve lesions are the most common clinical setting. They start insidiously and take a progressive course, worsening with the advancement of ventricular dysfunction. Even advanced valve lesions can be well tolerated. Right heart failure begins with fatigue, which decreases its threshold gradually over time. Lower extremity edema, painful pulsatile hepatomegaly (due to distension of its capsule) and ascites appear and are of high morbidity [1].

Pericardial involvement is not frequent (less than 10% of cases) and is manifested by effusions of small volume, the vast majority without clinical expression [8]. The occurrence of malignant arrhythmias, atrioventricular blocks, coronary spasms, acute myocardial infarction, pericarditis, myocarditis and restrictive cardiomyopathy granulomatous is also unusual [1,5,16].

2.3 CHD Risk Factors and Prognosis

Currently, the role of urinary 5-HIAA in the progression of CHD has been one of the main study interests. For more than a decade now it is believed that its maximum value is closely associated with this event [17]. A recent study prospectively assessed 252 patients with CS for 29 months and suggested that urinary 5-HIAA levels exceeding 300 µmol/24h and a number greater than three flushing episodes a day increased in five times the risk of CHD progression [18]. It is suggested that the reduction of tumor burden and its circulating levels of active metabolites, through resection of liver metastases for example, could reduce the progression of the disease [19], but this is still controversial [1].

CHD onset is the main factor for poor prognosis of the carcinoid disease and after its emergence survival is reduced dramatically for less than four years [20]. This scenario is further aggravated after ventricular functional loss, with decreased survival reaching one year after onset of symptoms compatible with heart failure class III / IV(New York Heart Association Heart Failure Classification) [16]. The degree of tricuspid regurgitation [20], the presence of multiple regional and distant metastases [4], and late diagnosis [15] are also associated with a worse prognosis.

3. DIAGNOSIS

As mentioned above, the initial stage presents with insidious course and has a delayed diagnosis in most cases, requiring high level of clinical suspicion [6]. Careful anamnesis and physical examination are important at that time, and finding a heart murmur (which is present in up to 90% of patients at diagnosis) in the left sternal border is a valuable clue [6]. Symptoms compatible with CS and right ventricular failure are other clues.

Electrocardiogram and chest radiography are the initial tools and should be performed in all patients, but unfortunately some findings are nonspecific and may even be normal in many patients (50%), requiring complementation with other methods [1,21].

This disease has a wide diagnostic imaging arsenal, which can be used in multiple

combinations depending on each individual case. Echocardiography has a central diagnostic role, closely followed by Magnetic Resonance [22]. These methods have been receiving important technological advances that allowed more accurate studies and growing contribution to the knowledge of CHD and its peculiarities.

3.1 Echocardiography

It is currently the diagnostic imaging method most frequently used. It has the advantage of being noninvasive, safe, of low cost and does not use ionizing radiation or nephrotoxic contrast. Moreover, it is highly available in most of the medical centers, already validated and widely studied in valve assessment and ventricular function. It is the preferred test to be performed after a CHD suspicion, being important not only in diagnosis but also as a follow up tool.

Transthoracic two-dimensional echocardiography (Echo) allows accurate qualitative and quantitative assessment of valve dysfunction, as well as impairments over right cavities (dilation and systolic contractile dysfunction). The tricuspid valve is dysfunctional in 90% of patients [1,22], showing thickening of the leaflets and subvalvular apparatus in varying degrees, resulting in shrinkage, mobility changes, varying degrees of failure and elevated right atrial pressure [6]. Assessment by color Doppler method demonstrates a dagger-shaped feature curve, related to significant regurgitation (Fig. 2). Functionally, the presence of stenosis is frequently associated to CHD. The 3D Echo adds useful information, since it allows simultaneous viewing of the three cusps and side by side comparison, seen in their atrial or ventricular surface [22].

The alterations in the pulmonary valve seen through Echo are similar to those found in the tricuspid valve, except that this valve is somewhat less affected (approximately 60% of cases) and it has stenosis as the main dysfunction mechanism due to thickening and retraction of the valve annulus (Fig. 3). During the examination, mitral and aortic valves can also be evaluated, but only about 30% of cases present injury (rarely stenosis), reflecting left cardiac involvement [1,6]. When this is present, one patent foramen ovale should be investigated, as it may be present in up to 80% of these patients [1].

The progression of valve dysfunction results in overload of the right heart chambers, with right atrial dilation and ventricular contractile dysfunction [6]. Ventricular function is preserved until advanced stages of heart disease are reached [1,8]. Echo has several techniques to quantify the ventricular ejection fraction and it is well established for this purpose. However, the right ventricle has complex semi-lunar shape and undergoes remodeling due to pressure and volume overload, reducing the accuracy of the volumetric estimates by 2D Echo. The 3D Echo may help mitigate this problem [24].

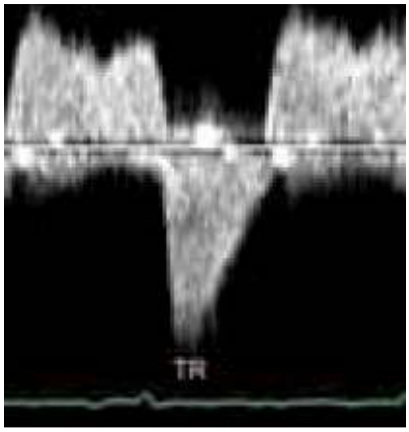

Fig. 2. Characteristic dagger-shaped curve indicating significant tricuspid regurgitation (adapted from Klobučić et al. [23])

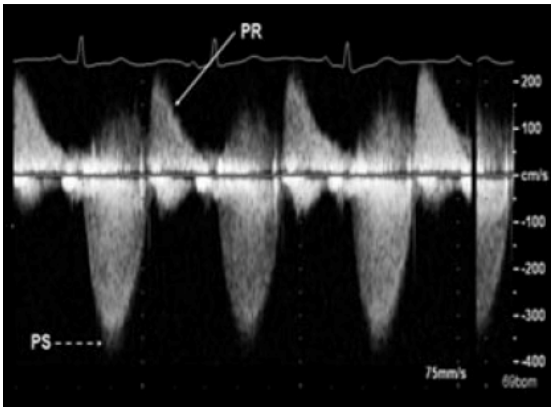

Fig. 3. Pulmonary stenosis (PS) and pulmonary regurgitation (PR) seen on transthoracic echocardiography, color Doppler method (Adapted from Bhattacharyya et al. [22])

Myocardial metastases are rare and can be identified by Echo as cardiac masses in up to 4% of patients, circumferential aspect, wrapped in normal myocardium [6]. There is a limitation in the delimitation of its edges, thus providing only

an estimate of its actual size. A previous study of a case series with 11 patients showed that the average size of lesions identified by Echo was 2.4 cm, while many which were smaller than 0.5 cm were seen only in autopsies. Thus, small lesions have a high chance of not being diagnosed by the method [13].

Other Echo limitations are the presence of reduced field of view due to unfavorable "echocardiographic window", the inability of an accurate evaluation of the right chambers in some patients [6], and the high interobserver variability (15±13%) in the measurement of left ventricular ejection fraction, demonstrating low reproducibility [16]. These negative aspects of Echo evaluation led to the increasing use of Magnetic Resonance Imaging in that situation, which is now established as a method of great importance.

3.2 Magnetic Resonance Imaging (MRI)

The MRI is another noninvasive method that does not use ionizing radiation. It is mainly useful in the morphological and functional cardiac assessment, overcoming on the last decade most limitations presented by Echo [23]. However, it is very expensive and thus less available, and needs intravenous contrast (Gadolinium based) when fibrosis is to be searched.

One of its main advantages is its accurate reproducibility: there is low inter observer variability in the evaluation of ejection fraction of the right ventricle [16]. Also important is the fact that there is no limitation of the visual field of view by inadequate windows, allowing excellent visualization of the four heart chambers, particularly the right chambers [1], providing clear anatomical and functional information [8]. It is considered the gold standard method for volumes and ejection fraction quantification [25].

Valve morphological evaluation is done together with functional evaluation for the presence of stenosis or regurgitation, providing information of the regurgitant volume, trans valvular flow velocities and pressure gradients. The most commonly used sequence for this purpose is the Velocity Encoded Phase Contrast, a very accurate assessment method of valve dysfunction when compared to Doppler Echo [21]. It is noteworthy that the pulmonary valve is often difficult to assess through Echo, and MRI is valuable in these cases [22] (Fig. 4).

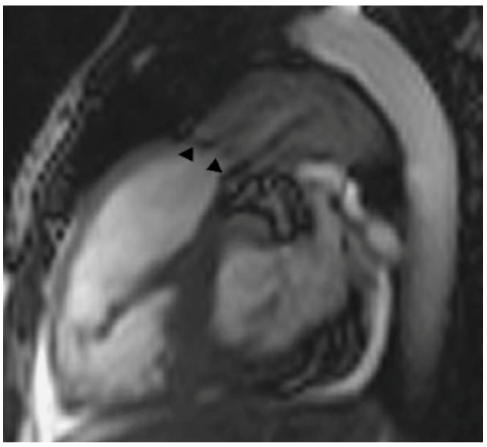

Fig. 4. MRI cine image of the right ventricular outflow tract showing shrinkage and pulmonary valve stenosis (arrows), and the systolic turbulence jet (Adapted fromBastarrika et al. [21])

Myocardial metastases can be identified and characterized in location, number, size and appearance. Their well-defined borders, as well as the degree of infiltration in tissue, can also be evaluated [5,6] (Fig. 5).

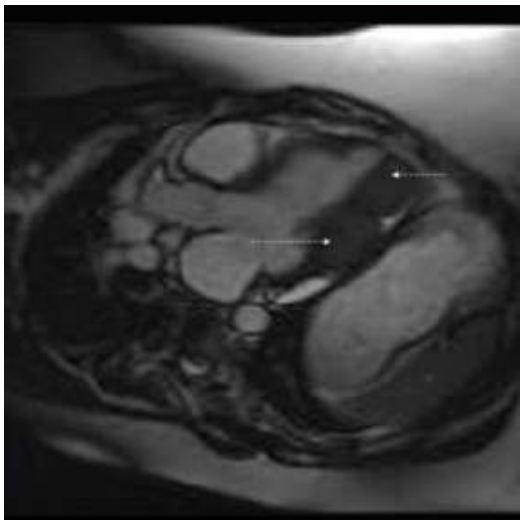

Fig. 5. MRI cine image of the left ventricular outflow tract showing two well-defined masses (arrows) in the medium inferolateral segment extending to the cardiac apex (Adapted from Bhattacharyya et al. [22])

Sequences of late enhancement (LGE) performed after the injection of the extracellular contrast Gadolinium, capable of identifying tissue fibrosis, have been highlighted in the evaluation of these patients. Some case reports have

emerged in literature in recent years, in which endocardial enhancement of the right chambers, tricuspid valve, valve annulus and subvalvular apparatus could be observed, corresponding to the histological aspects of fibrous carcinoid plaques in these topographies [23,26,27].

3.3 Other Diagnostic Imaging Methods

Multi Detector Computed Tomography (MDCT) has a high spatial resolution, allowing a detailed morphological evaluation of cardiac valve structures and cavities. Among other advantages is the possibility of assessing the coronary arteries, useful in the perioperative period, and pulmonary involvement [28]. Late enhancement on the tricuspid valve annulus five minutes after injection of iodinated contrast media has been reported in literature [27]. Its main disadvantage is the use of ionizing radiation and iodinated intravenous contrast for acquisition of the images, and is now considered an alternative method when patients do not tolerate MRI and do not have satisfactory results in Echo [6].

Positron emission tomography (PET) can be currently used as a diagnostic method for this disease due to the expression of neuroendocrine receptors on the surface of carcinoid tumors, especially for somatostatin, enabling the use of specific radiotracers marked for their identification [1]. It is mainly useful for the identification of metastatic sites, especially those with smaller size, reaching over 97% of sensitivity and 92% of specificity whenGallium-68 octreotide [5,29] is used (Fig. 6). Thus it enables early diagnosis of cardiac metastases, even when they are smaller than half an inch. The disadvantages to the wider use of this method are the high cost and low availability, in addition to using ionizing radiation.

3.4 NT- proBNP

The NT-proBNP (Nterminal pro-brain natriuretic peptide) is released from cardiac myocytes after myocardial stretch and elevated levels reflect increased wall tension and pressure, making its a useful biomarker for diagnosis and prognosis in the cardiac involvement in CHD [30,31]. Cut-off levels greater than 260 pg/ml were predicted for CHD in patients with carcinoid syndrome with a sensitivity and specificity of 92% and 91%, respectively [32]. Levels of NT-proBNP in patients with CHD are significantly higher than in those without CHD and independently associated with the presence of CHD whereas age, gender and creatinine did not offer additional information to discriminate patients with or without CHD [33]. Likewise, NT-proBNP levels also are correlated with dilatation of the right atrium and ventricle as well as thickening of the tricuspid valve and degree of regurgitation [31]. The high negative value of the NT-proBNP may allow it to provide a good screening test for CHD [32] and is a reliable biomarker to make a rapid and accurate differentiation between patients with and without CHD [31].

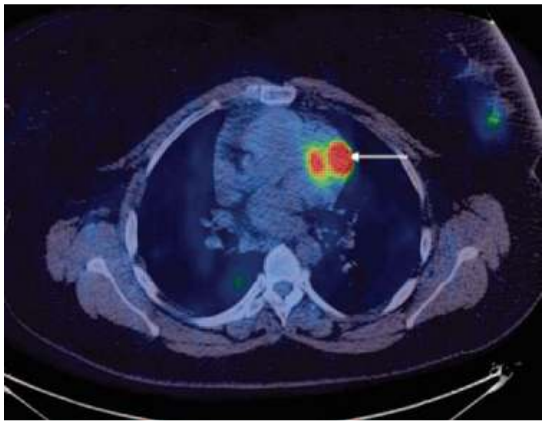

Fig. 6. PET CT with Gallium-68 showing intense radiotracer uptake suggesting metastatic carcinoid tumors (Adapted from Bhattacharyya et al. [22])

4. TREATMENT

Therapeutic options for CHD include drugs used to control symptoms of right heart failure and somatostatin analogues. The first-line treatment for patients with unresectable disease includes somatostatin analogs, such as octreotide or lanreotide, both approved by the US Food and Drug Administration [34]. Somatostatin analogs (SA) can improve diarrhea/flushing episodes in over 80 percent [35] of patients with metastatic carcinoid tumors and chemotherapy may also have a selective role, particularly in pancreatic neuroendocrine tumors. SA act by binding to somatostatin receptors, witch are expressed in nearly 80 percent [36] of the carcinoid tumors. Both octreotide and lanreotide are effective for inhibiting the release amines and well tolerated. Octreotide should be administered intramuscularly at a dose of 20 to 30 mg every four weeks and gradual increase dose may be necessary for symptoms not controlled [37]. Lanreotide as a long-acting agent is administrated every four weeks (60-120 mg) [38] and has similar clinical efficacy as octreotide [39]. It remains uncertain whether somatostatin analog therapy can inhibit or reverse progression

of existing carcinoid heart disease. Antidiarrheal agents such as loperamide and diphenoxylate/atropine and opiates agents can be useful for control refractory diarrhea. Ondansetron, a serotonin receptor antagonist, can relieve diarrhea in patients who do not improve with SA [40].

In association with clinical treatment, surgical approach could be considered, especially in patients with symptomatic valvular dysfunction or with cardiac metastasis with compressive effect. Hepatic resection is considered for resectable liver metastases in the absence of diffuse involvement or widespread extrahepatic metastases. Long-term disease-free survival is reported in up to 20 percent of patients. Preoperative and interoperative octreotide therapy is essential to protect against carcinoid crises that can arise from anaesthesia and/or tumor manipulation.

Localized approaches, including cytoreductive surgery, hepatic arterial embolization, and ablative therapies, may be used for palliative treatment in patients with liver metastases. Well-differentiated carcinoid tumors may be refractory to conventional citotoxic agents and cytotoxic chemotherapy in general is not helpful for control of symptoms. Its use is indicated primarily to poorly-differentiated carcinomas, although rare association with carcinoid syndrome.

Since there is a trend for improved survival rates when there is early surgical intervention in dysfunctional valves [15], each case is assessed individually and followed to decide the optimal time for specific approaches. Considering the higher perioperative mortality (20%) [41], intervention should be performed early, so before the development of severe myocardial dysfunction, ventricular volume overload or valve dysfunction [23].

Cardiac surgery is an important approach for symptomatic patients. Improvement on New York Heart Association class has occurred after valve replacement [42]; however, concerning the severity of valve dysfunction and symptoms, the optimal timing of surgery has not been identified. Although a reduction of the perioperative mortality have been reported from 1980 [43], currently the main perioperative complications are bleeding and right ventricular failure, which cannot be recognized postoperatively [44]. Pulmonary valve replacement in addition to tricuspid valve replacement has shown to reduce right ventricular size after surgery compared with patients with isolated tricuspid valve replacement, even in patients with mild pulmonary valve disease. Although the choice of prosthesis is controversial, initial reports favor the use of mechanical prosthesis based on possible damage to a bioprosthetic valve by vasoactive substances [45] affecting pulmonary and tricuspid valves allografts on average 3 months [46] and 4 years [47] after implantation, respectively. Thus, the choice of prosthesis should be guided by life expectancy, risk of bleeding and future interventions.

5. CONCLUSION

Carcinoid heart disease is an important cause of cardiac involvement and early diagnosis is important to improve the prognosis. Efforts should be made to achieve a reduction on morbidity of this disease and increase survival rate of these patients. Echocardiography has a central diagnostic role, closely followed by Magnetic Resonance. Clinical treatment and cardiac surgery should be considered regarding symptoms and the presence of metastases, individualizing to each clinical feature. New future studies are expected to clarify the controversial aspects that are still unclear.

CONSENT

It is not aplicable.

ETHICAL APPROVAL

It is not aplicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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