Carcinoid Heart Disease: A Comprehensive Review and Update on Pathophysiology, Diagnosis, and Management

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Abstract: Carcinoid Heart Disease (CaHD) is a severe complication arising in patients with carcinoid syndrome, primarily impacting the heart's right side through valvular dysfunctions such as tricuspid regurgitation and pulmonary stenosis. The pathology is closely linked to serotonin-induced fibrosis, challenging both diagnosis and treatment. Advances in echocardiography and cardiac MRI have significantly improved the early detection and assessment of CaHD, while management strategies have evolved to include both medical treatments, like somatostatin analogues and novel pharmacotherapies, and surgical interventions, notably valve replacement surgeries. Despite progress, debates persist around the optimal timing for surgery and the choice between bioprosthetic and mechanical valves, given the distinct risks and benefits of each. This review synthesises the current understanding of CaHD, emphasising diagnostic advancements and the spectrum of treatment options, and advocates for ongoing research to refine therapeutic approaches..

Keywords: Carcinoid Heart Disease, Neuroendocrine Tumours, Pathophysiology, Diagnosis, Management, Serotonin, Multidisciplinary Care, Cardiac Imaging, Valve Replacement

Abbreviations: CaHD: Carcinoid Heart Disease, MRI: Magnetic Resonance Imaging, NET: Neuroendocrine Tumour, TVR: Tricuspid Valve Replacement, PVR: Pulmonary Valve Replacement, 5-HT: 5-Hydroxytryptamine (Serotonin), 5-HIAA: 5-Hydroxyindoleacetic Acid, NT-proBNP: N-terminal pro b-type Natriuretic Peptide, TTE: Transthoracic Echocardiography, TOE: Transesophageal Echocardiography, CT: Computed Tomography, ECG: Electrocardiogram, CXR: Chest X-Ray, NYHA: New York Heart Association, PRRT: Peptide Receptor Radionuclide Therapy, RHF: Right Heart Failure,

Introduction:

Carcinoid Heart Disease (CaHD) represents a challenging cardiac pathology, predominantly observed in patients with carcinoid syndrome. This syndrome primarily arises from neuroendocrine tumours that are most often located in the gastrointestinal tract or bronchopulmonary system.[1] Notably, up to 50% of patients with carcinoid tumours develop symptoms of the carcinoid syndrome, leading to CaHD, which significantly influences morbidity and mortality.[2] Historically, untreated CaHD has been associated with a 3-year survival rate as low as 31%, markedly lower than the 68% in patients without cardiac involvement. However, the

landscape of CaHD prognosis has considerably improved due to advancements in cardiac imaging, antitumor treatments, and surgical interventions.[1] A retrospective study highlighted that median survival rates have increased from 1.5 years in the 1980s to 4.4 years in the late 1990s, largely attributed to the rise in cardiac surgery rates among these patients.[3]

CaHD is characterised by its distinctive involvement of the right side of the heart, particularly affecting the tricuspid and pulmonary valves. The result is a spectrum of valvular dysfunctions, predominantly leading to conditions such as tricuspid regurgitation, pulmonary stenosis, and ultimately right-sided heart failure.[3] The pathophysiological processes underlying CaHD implicates various molecular pathways and cellular mechanisms. Most resources cite vasoactive substances, particularly serotonin, in stimulating fibroblast growth and fibrogenesis, contributing to the characteristic cardiac valvular fibrosis observed in CaHD.[1,3,4] Despite the progress in understanding the disease, many aspects of its pathophysiology remain elusive, prompting ongoing research to uncover the intricate mechanisms and potential therapeutic targets.

Similarly, the diagnostic journey of CaHD has been revolutionised over the years, transitioning from a primarily echocardiography-based approach to a more comprehensive, multimodal strategy. Advanced imaging modalities, including cardiac magnetic resonance and speckle-tracking echocardiography, have enriched the diagnostic arsenal, allowing for more nuanced visualisation and assessment of the cardiac structures involved in CaHD.[5] These advancements have not only improved diagnostic precision but have also facilitated the early detection of CaHD, potentially altering the clinical course of the disease. Furthermore, the management of CaHD is inherently complex, demanding a comprehensive, multidisciplinary approach that encompasses medical and surgical strategies. Medical management focuses on controlling the systemic malignancy and managing the release of vasoactive substances, primarily through the use of somatostatin analogues. In cases where valvular disease progresses, surgical approaches, such as valve replacement surgeries, become paramount. These procedures have shown promise in alleviating cardiac symptoms and enhancing patient survival.[6] However, they are accompanied by their own set of challenges, including the careful selection of suitable candidates and the meticulous management of perioperative risks.

In this comprehensive review, we aim to synthesise our current understanding of CaHD, summarising its pathophysiology, the nuances of its diagnostic modalities, and the spectrum of its management strategies, while also exploring the frontier of emerging therapies and diagnostic tools that hold the promise of improving CaHD care.

Methodology:

This review evaluates the current understanding and management strategies of Carcinoid Heart Disease. The inclusion criteria for this review were limited to full-text articles written in English, covering the period from 2000 to 2023. This timeframe was selected to provide a comprehensive overview of the evolution of treatment protocols and diagnostic advancements in the field, capturing both longstanding practices and recent innovations.

Multiple databases were utilised for a thorough literature search, including PubMed, EMBASE, Google Scholar, the Cochrane Library, and Scopus. Key terms specifically related to Carcinoid Heart Disease were employed in the searches, such as “Carcinoid Heart Disease,” “Serotonin Heart Valve Disease,” “Neuroendocrine Tumours Cardiac Complications,” “Carcinoid Tumours Heart,” and “Right Heart Valve Dysfunction Carcinoid.” To broaden the search strategy, additional sources were identified through a manual examination of references listed in recent reviews focusing on CaHD and related cardiovascular complications. Strict exclusion criteria were applied, which involved omitting standalone abstracts, case reports, posters, and any unpublished or non-peer-reviewed material. This approach was aimed at maintaining the integrity of the review by ensuring the inclusion of only high-quality and scientifically robust evidence.

The scope of the review was not restricted to a specific number of studies, intending to encompass a comprehensive array of knowledge on Carcinoid Heart Disease. It included diverse study designs such as descriptive studies, animal-model studies, cohort studies, and observational studies. This inclusive approach ensured a wide-ranging understanding of Carcinoid Heart Disease, covering research conducted in both pre-clinical

and clinical settings. A summary of the methodology used is provided in Table 1, illustrating the depth and breadth of the literature search and selection process.

Methodology Steps	**Description**
Literature Search	PubMed, EMBASE, Google Scholar, the Cochrane Library, and Scopus
Inclusion Criteria	- Full-text articles published in English - Focus on applications in neurology and neurosurgery - Adult and paediatric populations
Exclusion Criteria	- Stand-alone abstracts - Case reports - Posters - Unpublished or non-peer-reviewed studies
Search Terms	Keywords and phrases such as "Carcinoid Heart Disease," "Serotonin Heart Valve Disease," "Neuroendocrine Tumours Cardiac Complications," "Carcinoid Tumours Heart," "Right Heart Valve Dysfunction Carcinoid," "Cardiac Complications," "Heart Valve Dysfunction," "Management of Carcinoid Heart Disease," and "Prognosis in Carcinoid Heart Disease."
Additional Search	- Manual examination of references cited in recent disease-specific reviews - Encompassing diverse study designs: * Descriptive studies * Animal-model studies * Cohort studies * Observational studies - Including investigations in both pre-clinical and clinical settings

Table 1: Summary of methodology for this review

Pathophysiology:

The pathophysiology of CaHD is multifactorial, with serotonin being a major contributor. Serotonin, a monoamine neurotransmitter, originates from enterochromaffin cells within the gastrointestinal tract and plays roles in regulating intestinal movement and central nervous system functions like mood and sleep. Serotonin stimulates fibroblast growth and fibrogenesis, leading to cardiac valvular fibrosis.[7] These changes mirror those induced by ergot-alkaloid derivative or fenfluramine, implicating serotonin in the fibrotic process.[8] Consequently, the disease is characterised by plaque-like deposition of fibrous tissue on valvular cusps (leaflets), papillary muscles, chordae tendineae and the ventricular walls, predominantly affecting the right heart valves by causing tricuspid and pulmonary regurgitation and, less frequently, stenosis of these valves.[2] This specificity arises because the lung vasculature enzymatically deactivates serotonin, preventing its effects on the left. Resultantly, left-sided CaHD is uncommon and usually linked with right-to-left intracardiac shunts or, in rare instances, bronchopulmonary carcinoid disease or uncontrolled carcinoid syndrome, leading to elevated serotonin levels.[9]

The presence of serotonin receptors, notably the 5-HT2B subtype, on heart valves also facilitates collagen synthesis by valvular interstitial cells, further contributing to the disease pathology. Upon binding with serotonin, the 5-HT2B receptor undergoes a conformational change that activates its associated G proteins. One of the immediate downstream effects of 5-HT2B receptor activation is the stimulation of phospholipase C (PLC) and phospholipase A2 (PLA2).[2,10]PLC catalyses the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol (DAG), leading to increased intracellular calcium levels and activation of protein kinase C (PKC).[2] PLA2, on the other hand, releases

arachidonic acid from membrane phospholipids, serving as a precursor for various eicosanoids that can further modulate cellular responses. Not only this but the 5-HT2B receptor signalling also involves the activation of nitric oxide synthase (NOS), leading to the production of nitric oxide (NO).[11] NO acts as a signalling molecule that can induce vasodilation and influence various cellular functions, including cell proliferation and apoptosis.

Activation of the 5-HT2B receptor initiates a series of interconnected events that play a crucial role in the development of cardiac fibrosis, a key feature of CaHD. Initially, this receptor's activation has a mitogenic effect, stimulating cell division and proliferation, notably within cardiac fibroblasts. This increased proliferation is critical for the fibrotic remodelling of heart valves, as it leads to the accumulation of fibrous tissue. The activation of the 5-HT2B receptor further amplifies this process by triggering a signalling cascade that increases the secretion of inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α).[1,11] These cytokines exacerbate tissue inflammation and fibrosis, worsening the condition. Additionally, the receptor activates the MAPK pathway, involving a series of phosphorylation events that culminate in the activation of extracellular signal-regulated kinases (ERK1/2).[6] The activation of ERK1/2 is pivotal for regulating gene expression, cell growth, and differentiation, all of which contribute to the pathological remodelling observed in CaHD.

Compounding these effects, 5-HT2B receptor signalling also leads to the overexpression of transforming growth factor-beta 1 (TGF-β1), a key cytokine that drives fibrosis by promoting the synthesis of extracellular matrix proteins.[12] TGF-β1 is central to the development of cardiac fibrosis, facilitating the excessive deposition of collagen and other matrix components that characterise CaHD.[12] The result of this enhanced fibrogenic activity is the formation of fibrous plaques on the valves and endocardial surfaces. Composed of myofibroblasts, smooth muscle cells, and a collagen-rich extracellular matrix, these plaques are initially intended for tissue repair and remodelling.[13] However, they ultimately lead to pathological thickening and stiffening of the valves, compromising their function and exemplifying the detrimental effects of unchecked 5-HT2B receptor activation in cardiac health.

Clinical Presentation:

Clinical presentation of CaHD spans a spectrum from subtle early manifestations to overt signs of advanced cardiac involvement, reflecting the disease's progressive nature. The initial stages of CaHD may be marked by nonspecific symptoms such as fatigue and dyspnea, particularly on exertion, which can be attributed to the involvement of the tricuspid and pulmonary valves.[11,14] These early signs are often challenging to detect due to the low-pressure system of the pulmonary circulation, where even significant valvular disease might be tolerated for extended periods without clear clinical manifestations. The interval between symptom onset to the diagnosis of CaHD can range widely, averaging 24-48 months but potentially extending up to five years.[15] Remarkably, patients can maintain a functional status within the New York Heart Association (NYHA) class I, indicating no limitation of physical activity, despite having severe right-sided valvular lesions.[1,15] This initial tolerance showcases the insidious nature of CaHD, where the structural heart changes can be substantial before significant clinical symptoms emerge.

As the disease progresses, paralleled by tumour growth and increased serotonin levels, symptoms of right-sided heart failure become more pronounced. This progression is characterised by worsening dyspnea, anasarca (generalised swelling), and cardiac cachexia (severe muscle and weight loss), indicating advancing cardiac impairment.[16] The excessive vasoactive substances, with serotonin at the forefront, trigger symptoms such as flushing, diarrhoea and bronchospasm.[15,16] The onset of CaHD-specific symptoms, typically between the ages of 50 and 70, starts subtly but can escalate to include signs of right-sided heart failure such as edema, pleural effusions, and ascites.[17] In the same token, uncommon presentations of CaHD have also been reported, including cases where patients exhibit pure right-sided heart failure without the hallmark symptoms of CaHD, and even more rare instances of right heart failure secondary to constrictive pericarditis rather than direct valvular dysfunction. Arrhythmias, another rare presentation of CaHD, merit consideration due to serotonin's potential to enhance cardiac excitation and sympathetic discharge, leading to tachyarrhythmias.[16,17] This is supported by experimental evidence linking sudden serotonin release with

episodes of ventricular tachycardias and atrial arrhythmias. Interestingly, a subset of patients may not exhibit overt symptoms or signs pointing directly to CaHD, necessitating a high degree of clinical suspicion to prompt timely diagnosis.

Physical examination findings in CaHD typically include elevated jugular venous pressure and a palpable right ventricular impulse, hallmarks of increased right heart strain. Auscultation may reveal murmurs indicative of tricuspid and pulmonary valve regurgitation, although murmurs associated with pulmonary stenosis or tricuspid stenosis are less commonly observed.[18] Blood pressure variability, marked by episodes of significant hypotension or hypertension, can also be observed in some CaHD cases, reflecting the fluctuating levels of circulating vasoactive substances. Eventually, as valve disease advances, peripheral edema, ascites, and pulsatile hepatomegaly may develop, underscoring the progression to severe valvular dysfunction and right-sided heart failure.[19]

In assessing the clinical progression of CaHD, *Table 2* delineates the evolution of symptoms and signs from early manifestations, such as fatigue and exertional dyspnea, through to the advanced stages characterised by significant right heart failure and valvular dysfunction, offering clinicians a structured guide for early identification and monitoring of disease progression.

Clinical Feature	**Early Stage ()**	**Progressive Stage ()**	**Advanced Stage**
Fatigue			
Dyspnea, especially on exertion			
Anasarca (generalised swelling)			
Cardiac cachexia (muscle and weight loss)			
Flushing, diarrhoea, bronchospasm			
Edema, pleural effusions, ascites			
Right-sided heart failure without typical CaHD symptoms			
Constrictive pericarditis			
Tachyarrhythmias due to serotonin			
Elevated jugular venous pressure			
Palpable right ventricular impulse			
Murmurs (tricuspid/pulmonary regurgitation, stenosis)			
Blood pressure variability			
Peripheral edema, ascites, pulsatile hepatomegaly			

Table 2: Checklist for Clinical Presentation and Progression of Carcinoid Heart Disease.

Diagnosis:

5.1. Imaging Modalities

Initial non-specific investigations such as ECG (electrocardiogram) and CXR (chest x-ray) serve as preliminary tools in the diagnostic workup of CaHD. The ECG might reveal low-voltage QRS complexes more frequently in CaHD patients than in those without the disease, alongside non-specific ST-T changes, PR prolongation and sinus tachycardia, hinting at the underlying cardiac involvement.[20] Conversely, CXR may show an enlarged cardiothoracic ratio, indicative of cardiomegaly, primarily due to right-sided chamber enlargement, although these findings are not sensitive or specific to CaHD.[21]

Ultimately, transthoracic echocardiography is most commonly used in the diagnosis of CaHD, offering more tangible insights into the valvular and subvalvular apparatus affected by the disease. Echocardiographic hallmarks of CaHD include thickening and reduced mobility of the tricuspid and pulmonary valve leaflets, leading to regurgitation and stenosis.[22] A distinctive "dagger-shaped" continuous-wave Doppler profile is emblematic of severe tricuspid regurgitation, illustrating the equalisation of right atrial and ventricular pressures[23]. Such echocardiographic features are pathognomonic, especially in the absence of exposure

to appetite suppressants or ergot-derived agents that could mimic similar valvular abnormalities. The echocardiographic evaluation should encompass multiple views of each valve, especially the tricuspid valve visualised through various echocardiographic windows, to ensure a comprehensive assessment.[16] The right atrium and ventricle typically exhibit enlargement due to volume overload, with paradoxical motion of the interventricular septum observable in advanced stages.[15] Despite these significant structural changes, right ventricular function often remains preserved until the late disease phase.

TOE (Transoesophageal echocardiography) is subsequently recommended if transthoracic echocardiography fails to provide adequate visualisation of the cardiac structures, offering superior images of the valve leaflets and subvalvular apparatus.[2] Similarly, cardiac magnetic resonance imaging (MRI) and 64-slice computed tomography (CT) are also used as critical adjuncts, particularly for evaluating the pulmonary valve when echocardiographic visualisation is challenging.[24] These modalities excel in providing clear anatomic and functional information, facilitating the assessment of right ventricular function and aiding in the evaluation of myocardial metastases, which although rare, can present as homogenous well-circumscribed masses. *Table 3* summarises the advantages, disadvantages, and key notes of primary and secondary imaging modalities employed in diagnosing CaHD.

Imaging Modality	**Advantages**
2D TTE	Affordable, widely accessible, assesses valvular apparatus and RV strain analysis.
3D TTE	Enhances visualisation of valve leaflets and subvalvular apparatus, aids in operative planning.
TOE	Improved visualisation of the pulmonic valve and valves with suboptimal windows.
Cardiac CT	Facilitates operative planning, visualises coronary arteries, assesses RV dimensions and valvular dam
Cardiac MRI	Improved visualisation of valves, accurate measurement of regurgitant volumes and chamber sizes, id
ECG	Can indicate sinus tachycardia and nonspecific ST and T-wave changes.
CXR	Can show right heart chamber prominence and pleural effusions in severe right-sided valve disease.
PET	Highly sensitive and specific for myocardial metastasis detection.

Table 3: Comparative Overview of Imaging Modalities in Carcinoid Heart Disease Diagnosis

5.2. Biochemical Diagnostics

As outlined before, serotonin (5-HT), produced by NETs, plays a pivotal role in the pathogenesis of CaHD. Consequently, patients with CaHD exhibit serum platelet, serotonin, and urinary 5-Hydroxyindoleacetic acid (5-HIAA) levels that are 2 to 4 times higher than those without CaHD. The urinary 5-HIAA levels, in particular, have been correlated with CaHD progression and worsening echocardiographic findings.[25] As the end metabolite of serotonin, 5-HIAA's measurement in 24-hour urine samples is a reliable initial diagnostic approach for carcinoid syndrome, closely linked to the presence of carcinoid tumours. A level exceeding 300 mmol/24 h is indicative of a heightened risk for CaHD, highlighting the need for holistic patient evaluation.[11,26] However, dietary factors and certain medications may influence 5-HIAA levels, necessitating dietary restrictions prior to testing to avoid false-positive results. Moreover, the prognostic value of posttreatment 5-HIAA levels, particularly a threshold of 100 mg/24 h, significantly aids in predicting CaHD progression, as confirmed through serial echocardiographic assessments.[27]

NT-proBNP, a neurohormone released in response to increased cardiac wall stress, serves as an antifibrotic agent in the myocardium. Its levels are markedly elevated in CaHD patients compared to those without CaHD, making it an extremely useful biomarker for evaluating CaHD severity and prognosis. The high sensitivity and specificity of NT-proBNP in predicting CaHD underscore its utility in the clinical setting, particularly as a screening tool recommended by the UK and Ireland NET Society guidelines.[28] This correlation is substantiated by echocardiographic evaluations, advocating for regular 6- to 12-month clinical assessments of NT-pro-BNP levels to monitor for valvular disease or heart failure signs.[15] Moreover, plasma activin A levels are significantly higher in NET patients with CaHD, serving as an independent predictor for CaHD presence. Activin A stands out as an independent predictor for CaHD, demonstrating an 87%

sensitivity and 57% specificity at plasma levels of [?]0.34 ng/ml.[29] This marker's elevation across both early and advanced stages of CaHD positions it as a critical indicator for early disease detection, offering a distinct advantage over traditional markers such as neuropeptide K, substance P, and atrial natriuretic peptide, which are typically associated with later stages of CaHD.[30] Unlike NT-proBNP, elevated activin A levels are also found in CaHD patients without right heart dilatation, offering a broader diagnostic scope. Elevated levels of Connective Tissue Growth Factor (CTGF) have also been associated with reduced right ventricular function in NET patients with CaHD, providing another layer of diagnostic and prognostic information.[31] Lastly, despite Chromogranin A's broad application as a biomarker for NETs and CaHD, its utility in CaHD screening is limited by lower sensitivity and specificity. Nonetheless, it emerges as a vital follow-up tool for detecting carcinoid recurrence, boasting a sensitivity of 100% for CaHD.[26]

Treatment:

6.1 Medical Management

Management of CaHD presents several challenges, with most of these predicated on balancing the control of the neuroendocrine tumour (NET) and its cardiac manifestations. This task necessitates a multidisciplinary team (MDT) effort, involving cardiologists, cardiac surgeons, NET specialists, anesthesiologists, and radiologists.[32] The primary goal is to tailor a management plan that addresses both the cardiac complications and the underlying NET, ensuring a comprehensive care strategy for patients.

With respect to managing heart failure symptoms in CaHD, this revolves around vigilant monitoring and the judicious use of diuretics.[19] For asymptomatic patients, a watchful waiting strategy is employed until symptoms manifest. The development of right-sided heart failure symptoms, particularly peripheral edema, necessitates the introduction of loop or thiazide diuretics and aldosterone antagonists.[19] Despite their efficacy, the potential for intravascular volume depletion and reduced cardiac output warrants cautious use. Other pharmacological agents like digoxin and angiotensin-converting enzyme inhibitors have been explored, though their specific efficacy in CaHD remains to be fully established.[32]

Understandably, reducing 5-HT secretion from the NET is crucial, employing both medical and interventional strategies. Somatostatin analogues like octreotide and lanreotide have been instrumental in this regard.[33] Notably, the PROMID and CLARINET studies expanded treatment criteria to include asymptomatic patients, demonstrating these drugs' anti-proliferative potential and positive effects on progression-free survival.[34,35] Octreotide LAR and lanreotide AG, for instance, are administered in doses up to 30 mg and 120 mg every four weeks, respectively, with potential dose adjustments for refractory cases.[26] At the same time, peptide receptor radionuclide therapy (PRRT), particularly with yttrium 90Y-edotreotide and Lutetium-DOTATATE, targets advanced NETs with somatostatin receptor-positive lesions.[36] A prospective study highlighted that while only 4% of patients showed objective response, 70% exhibited no disease progression for a median of 18 months.[36] Additionally, symptom improvement was reported in a majority of patients, underscoring PRRT's role in managing CaHD, albeit with considerations for amino-acid and fluid infusions during treatment.

Emerging treatments like telotristat ethyl and everolimus present new avenues for managing CaHD. Telotristat ethyl, in particular, has shown promise in phase II and III trials, with significant reductions in bowel movement frequency and serotonin levels in patients inadequately responding to somatostatin analogues.[37] For instance, a phase III trial reported that 44% and 42% of patients on telotristat etiprate experienced a durable response, compared to only 20% on placebo.[38] Everolimus, studied in the RADIANT-2 trial, while not primarily focused on CaHD, demonstrated a significant reduction in 5-HIAA levels, offering an indirect benefit in managing the disease.[26] However, its use demands caution due to potential side effects and considerations around surgical interventions.

6.2. Surgical Management

Valve replacement surgery is the most effective treatment for managing symptomatic CaHD, significantly improving patient outcomes. The criteria and optimal timing for such surgery, however, remain subjects of debate. Consensus says that the indications for valve replacement surgery are symptomatic right heart fail-

ure, in conjunction with either progressive right ventricular enlargement or a decline in right ventricular systolic function, irrespective of the presence of symptoms.[26]The decision-making process for valve replacement should be predicated upon a thorough evaluation by a multidisciplinary team, taking into account comprehensive operability, the oncological status, and cardiac functionality. Surgical interventions have shown not only to alleviate symptoms of RHF but also to reverse right ventricular remodelling. Studies highlight the postoperative symptomatic improvement and survival benefits. For instance, a study by Mokhles et al. involving 19 patients showed a significant improvement in functional capacity one year post-valve replacement, with survival rates at 1- and 5-year follow-ups standing at 71% and 43%, respectively.[39]

Predominant surgical interventions include tricuspid valve replacement (TVR) and, less frequently, pulmonary valve replacement (PVR). Survival outcomes post-combined TVR and PVR surpass those of surgeries excluding PVR, thus advocating for the former as the preferred surgical intervention for the majority of patients (unless there is significant pulmonary valve involvement).[40] In cases requiring intervention on both the tricuspid and pulmonary valves, combined valve replacement has been successfully performed, with reported median survival times extending from six to eleven years post-operation.[1] Additionally, although balloon valvuloplasty has been attempted in patients deemed unsuitable for surgery, its utility is limited due to the high recurrence rate of valvular disease and the potential for concurrent TV and PV regurgitation.[15]

The selection of the valve prosthesis type remains a subject of debate, with no large comparative studies available. Initial preferences leaned towards mechanical prostheses to avoid the presumed risk of damage to bioprosthetic valves from vasoactive substances.[1]However, the protective potential of somatostatin analogs and other antitumor therapies against carcinoid plaque deposition on tissue valves has been recognized, shifting some opinion in favour of bioprosthetic valves. While bioprosthetic valves are susceptible to early degeneration from carcinoid-related fibrosis, this risk can be mitigated with effective postoperative control of neuroendocrine activity. Therefore, despite the potential for thrombosis, bioprosthetic valves generally do not require lifelong anticoagulation—typically, a three to six-month course suffices.[26] Conversely, mechanical valves offer durability but necessitate lifelong anticoagulation, increasing the risk of bleeding and potentially complicating future interventions. In instances of bioprosthetic valve deterioration, Transcatheter Valve Implantation emerges as a logical subsequent treatment step.[15]

As often is the case with most surgical interventions, they are not devoid of risks. In the perioperative phase, the anaesthetist confronts challenges specific to CaHD, including the risk of carcinoid crisis, bleeding, and the potential onset of low cardiac output syndrome attributed to right ventricular (RV) failure.[41] To mitigate these potential complications, an infusion of short-acting octreotide is initiated 12-24 hours prior to surgery and maintained throughout the perioperative period for three days, supplemented, if necessary, by the administration of catecholamines and histamine-releasing drugs.[41] The paramount importance of bleeding management mandates that surgeons and anesthesiologists meticulously assess and refine surgical techniques, implement autologous blood recovery systems, and focus on the optimization of postoperative coagulation.[40] Notably, the operative risk has decreased from 20% in the 1980s to 10% in more recent years, marking a significant advancement.[15]

Furthermore, partial hepatic resection and tumour debulking are generally reserved for patients with metastatic disease localised to a specific hepatic lobe.[42] Indeed, liver resection is correlated with a diminished risk of CaHD cardiac progression, underscoring its critical role in the surgical management of CaHD.[43] In select scenarios of metastatic carcinoid disease confined to the liver, patients might also be eligible for liver transplantation and the excision of the primary tumour.

Future Prospects/Recommendations:

As the healthcare field advances its understanding of CaHD, the trajectory for future management and research is set towards improving patient outcomes with a focus on innovation and personalised care. Advances in diagnostic modalities promise a new era where early detection and precise characterization of CaHD become the norm. The development of advanced imaging techniques such as 3D echocardiography and cardiac MRI, alongside specific biomarkers for early disease detection, are anticipated to revolutionise the diagnostic

landscape of CaHD, enabling earlier and more targeted interventions.[24,31]

The exploration into the genetic and molecular bases of CaHD holds the potential to identify novel therapeutic targets. Uncovering the mechanisms behind serotonin-mediated valvular disease could pave the way for therapies that prevent or significantly reduce valvular fibrosis, moving beyond the current pharmacological approaches that primarily manage symptoms.[1] In tandem with molecular research, the quest for innovative therapeutic agents that specifically address the pathophysiological processes of CaHD is critical. This includes not only drugs that effectively manage serotonin levels but also those that can inhibit fibrosis or offer cardioprotective effects without the drawbacks of existing treatments.

Surgical treatment of CaHD is also poised for advancement, with a focus on developing new valve prostheses and exploring minimally invasive and transcatheter interventions. The design of valve prostheses that are resistant to serotonin-induced fibrosis or mechanical valves that minimise thrombosis risk could significantly improve patient prognosis.[7] Additionally, minimally invasive techniques could offer viable alternatives for high-risk patients, reducing perioperative complications and broadening treatment options.[45] Furthermore, personalised treatment strategies are imperative for the future of CaHD management, advocating for treatments tailored to individual genetic profiles, disease severity, and therapeutic responses. This approach necessitates the creation of comprehensive databases and the application of advanced analytics, ensuring treatments are both effective and minimised for side effects. Integral to this personalised approach is the reinforcement of multidisciplinary care models, emphasising coordinated, patient-centred management across specialties to optimise treatment timing and patient care.

In addition, the establishment of patient registries and the commitment to long-term follow-up will provide critical insights into disease progression, treatment efficacy, and quality of life. These registries are essential for facilitating large-scale studies and validating new management strategies. International collaboration and the development of consensus guidelines based on the latest evidence will also play a pivotal role in advancing global standards of care for CaHD, ensuring patients everywhere have access to the best possible outcomes.[45] Although the ideal scenario would involve a multicenter, randomised survival study, the rarity of CaHD and logistical challenges render this prospect unlikely.

Conclusion:

CaHD presents significant challenges in cardiac pathology associated with neuroendocrine tumours, characterised by valvular dysfunction due to serotonin-induced fibrosis. Central to its management are advancements in diagnostic modalities such as echocardiography and cardiac MRI, which have significantly enhanced the ability to diagnose the disease early and accurately. The management strategy for CaHD has evolved into a comprehensive approach, incorporating both medical and surgical treatments. Medical therapies, including somatostatin analogues and newer pharmacological options, aim to control symptoms and slow disease progression. However, surgical valve replacement remains a well-researched option for those with advanced symptomatic disease, offering symptomatic relief and improved survival. Ultimately, the goal in managing CaHD is to improve both survival and the quality of life of affected patients through early decision, tailored treatment strategies and ongoing research to refine and discover new therapeutic options.

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