Carcinoid Heart Disease: Diagnosis, Investigation, Progression and Management

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Declaration

I Sanjeev Bhattacharyya confirm that the work presented in this thesis is my own. Where information has been derived from other source, I confirm that this has been indicated in the thesis.

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September 2011

ABSTRACT

INTRODUCTION

Carcinoid heart disease is acquired form of valvular heart disease occurring in patients with carcinoid syndrome. We sought to identify the prevalence, predictive biomarkers, advanced echocardiographic features, risk factors for development and outcomes of cardiac surgery for carcinoid heart disease.

METHODS

A prospective, observational, cohort study of 252 patients with a history of carcinoid syndrome attending a neuroendocrine tumour clinic was undertaken. Patients underwent serial evaluation of symptoms (cardiac and neuroendocrine), functional status, biochemical markers, echocardiography, and tumour staging over a three year period.

RESULTS:

Carcinoid heart disease was initially identified in 20% of patients with carcinoid syndrome. The sensitivity and specificity of NT-proBNP, at a cut-off level of 260pg/ml, for detection of carcinoid heart disease was 0.92 and 0.91, respectively. Involvement of the tricuspid, pulmonary, mitral and aortic valves were found in 90%, 69%, 29% and 27% of patients respectively. Myocardial metastases were found in 3.8% of patients. 3D echocardiography provided more detailed anatomical assessment, particularly for tricuspid and pulmonary valves, than 2D techniques.

Independent predictors of the development or progression of carcinoid heart disease were a 5-HIAA greater than 300 μmol/24hr and greater than 3 episodes of flushing per day. Overall 30 day mortality of cardiac surgery was 18.2%. 2 year

survival was 44.4 %. Long term causes of death were related to advanced metastatic carcinoid tumour. No patient required re-operation for bio-prosthetic degeneration.

CONCLUSION

The prevalence of carcinoid heart disease is significantly less than reported in previous decades. The high negative predictive value of NT-proBNP may allow its use as a screening test for carcinoid heart disease. 3D echocardiography allows more detailed assessment of valvulopathy than 2D techniques. A 5-HIAA > 300 μmol/24hr and >3 episodes of flushing per day are predictors of the development and/or progression of carcinoid heart disease. Cardiac valve surgery is high risk but provides symptomatic relief.

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ABBREVIATIONS

New York Heart Association (NYHA)

5-hydroxytryptamine (5-HT)

5 hydroxyindoleacetic acid (5-HIAA)

N Terminal Brain Natriuretic Peptides (NT-proBNP)

Electrocardiograms (ECG)

Chromogranin (Cg A)

Two Dimensional (2D)

Three Dimensional (3D)

Transoesphageal Echocardiogram (TEE)

Transthoracic Echocardiogram (TTE)

Computed Tomography (CT)

Response Evaluation Criteria In Solid Tumour (RECIST)

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Bhattacharyya S, Toumpanakis C, Burke M, Taylor AM, Caplin M, Davar J. Features of Carcinoid Heart Disease Identified By Two- and Three- Dimensional Echocardiography and Cardiac Magnetic Resonance Imaging. ***Circulation: Cardiovascular Imaging*** 2010;3:103-111.

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Chapter 1: Introduction

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1.1 INTRODUCTION

Carcinoid tumours are relatively rare neuroendocrine malignancies most commonly originating from enterochromaffin cells in the gastrointestinal tract. The incidence is approximately 1 to 2 cases per 100,000 of the general population (1). They usually grow slowly over years, commonly causing no symptoms at all until large or they have metastasised. Carcinoid tumours of midgut origin may secrete large amounts of vasoactive substances including 5-HT, tachykinins and prostaglandins. These are largely inactivated by the liver. Carcinoid syndrome occurs when tumour cells metastasise to the liver as the vasoactive substances produced are able to reach the systemic circulation via the hepatic vein. Clinically this is characterised by flushing, diarrhoea and bronchospasm.

Over the past decade several new therapies for carcinoid tumours have emerged to reduce symptoms and cause tumour regression. Most notably the development of somatostatin analogues, which inhibit the release of various biogenic amines and peptides including serotonin, has resulted in a marked improvement in symptoms (2). These may also have contributed to increased survival although this has not been proven (2,3). Rarely, surgical resection is curative for non-metastatic disease. Otherwise, reduction of symptoms, improvement of quality of life and improvement in survival by inhibition of tumour hormones or reduction of tumour load are the main goals. Metastatic disease of the liver may be debulked either surgically or by hepatic artery embolization in selected patients. Interferon therapy and targeted radionuclide therapy may cause tumour stabilisation or regression. Chemotherapy is rarely an option except for pancreatic, bronchial and high grade neuroendocrine tumours.

Carcinoid heart disease was first reported in 1954 (4). Several series have reported carcinoid heart disease in up to 70% of cases of carcinoid syndrome (5,6). It is thought development is related to the vasoactive substances, secreted by the metastatic tumour cells in the liver, reaching the right heart. This is associated with deposition of fibrous tissue on the endocardial surfaces of the heart. The introduction of somatostatin analogues and other anti-tumour therapies designed to reduce the tumour load and the production of tumour secretory products may potentially reduce the prevalence of carcinoid heart disease(7). Exceptionally, carcinoid heart disease may present in carcinoid tumours without liver metastases or in primary ovarian carcinoid tumours where 5-HT is thought to reach systemic circulation directly, bypassing portal circulation and the liver (8,9).

1.2 CLINICAL PRESENTATIONS

Up to 20% of patients with carcinoid syndrome present with carcinoid heart disease at diagnosis. It is remarkably well tolerated initially. Patients may be in functional NYHA class I despite severe right sided valve lesions. Eventually the signs and symptoms of right heart failure including shortness of breath on exertion, peripheral oedema and fatigue develop as valvular dysfunction progresses. Case reports have demonstrated presentations due to pericardial effusions, restrictive cardiomyopathy (10), constrictive pericarditis (11) and patent foramen ovale presenting with cyanosis and hypoxia secondary to a combination of right heart disease and the inter-atrial shunts (12).

1.3 CLINICAL EXAMINATION

Initially, clinical examination reveals prominent CV waves of tricuspid regurgitation, a right ventricular heave can be palpated, auscultation reveals the pansystolic murmur of tricuspid regurgitation, early diastolic murmur of pulmonary regurgitation and systolic murmur of pulmonary stenosis at the left sternal edge. Murmurs may be difficult to detect as velocities in the right heart are low. Peripheral oedema, ascites and pulsatile hepatomegaly develop as disease progresses.

1.4 BIOCHEMICAL MARKERS AND PATHOGENESIS OF CARCINOID HEART DISEASE

The pathogenesis of the CHD and development of carcinoid plaques remains incompletely understood although a growing body of evidence points towards serotonin (5-hydroxytryptamine) playing a key role.

Evidence for 5-HT-induced valvulopathy has arisen from a variety of sources. The appetite suppressants, fenfluramine and phentermine, have been withdrawn because of development of valve pathology with similar changes to those seen in carcinoid patients (13). These drugs display a serotonergic action on human tissue (14).

Carcinoid heart valves demonstrate accumulation of tissue growth factor (TGF)-β latency associated peptide and latent binding protein (15). 5-HT has been shown to increase synthesis and up-regulate TGF-β as well as stimulating collagen synthesis by heart valve interstitial cells (16). These findings may contribute to the

pathophysiology of carcinoid heart valve involvement as 5-HT receptors are present in human heart valves.

In animal models both long term 5-HT administration and the deficiency of 5HT transporter gene can induce morphological and echocardiographic changes consistent with cardiac fibrosis and valvulopathy similar to those seen in human carcinoid heart disease (17,18).

5-HT is metabolised to urinary 5-HIAA by monoamine oxidases in the liver. 5-HIAA level has a high sensitivity (100%) but a very low specificity for development of carcinoid heart disease. Therefore it has been postulated that while 5-HT is important, other factors in combination with serotonin must be required of development of carcinoid heart disease (19). The tachykinins, neuropeptide K and substance P have been shown to be elevated in patients with carcinoid heart disease and may be an important part factor in the pathogenesis (6). In 2003, in a retrospective study, the Mayo Clinic analysed data from 71 patients with carcinoid heart disease (20). They identified peak 5-HIAA and those patients who received chemotherapy as risk factors for the progression of carcinoid heart disease. However the study was limited by retrospective analysis and possible selection bias as a large number of patients were excluded due to the lack of a follow up echocardiogram.

BNP is released by the atria and ventricles of the heart in response to wall stress (21). BNP is released in a variety of valvular lesions and ventricular dysfunction. Zuetenhorst and co-workers measured NT-proBNP in 32 patients with carcinoid tumours (7). Carcinoid heart disease was detected by echocardiography in 9 patients. Significantly greater median levels of NT-proBNP were found in patients with carcinoid heart disease than those without. The criterion for carcinoid heart disease was based on the presence of a thickened valve with grade III or greater

tricuspid regurgitation. Carcinoid heart disease is a heterogeneous disease affecting multiple valves. It remains to be established whether NT-proBNP is elevated in carcinoid patients with other valvular presentations.

1.5 MORPHOLOGICAL AND HISTOLOGICAL FEATURES OF CARCINOID HEART DISEASE

The carcinoid plaque, composed of smooth muscle cells, myofibroblasts and elastic tissue, forms a white fibrous layer lining the endocardial surface of cardiac valves superficial to normal valve tissue. Native, underlying valve morphology is unharmed (22). Roberts and Ross performed a necropsy study of 21 subjects with carcinoid heart disease and compared these to 15 patients with carcinoid syndrome but no heart disease. They found plaques developed on the endocardium of the right ventricle and atrium as well as on the valve leaflets and sub-valvular apparatus including chordae and papillary muscle. Deposition of plaques was also found in the vena cava, pulmonary artery, coronary sinus as well as coronary arteries. The tricuspid valve plaques have a preponderance to develop on the ventricular side of the leaflets causing adherence to mural endocardium creating a substrate for regurgitation of blood volume. Fibrous tissue at the valve annulus causes constriction at the ring resulting in a degree of valvular stenosis. For the pulmonary valve the predominant lesion is stenosis as plaques develop at the pulmonic root causing constriction of the root and diminishing an already small orifice (23,24).

1.6 INVESTIGATIONS

1.6.1 ELECTROCARDIOGRAM AND CHEST X-RAY

The ECG and Chest x-ray may provide clues in diagnosing carcinoid heart disease. The cardiothoracic ratio may be increased. The ECG in patients with carcinoid heart disease has a higher frequency of low voltage QRS complexes than in those without, however this finding has a low sensitivity (5,24).

1.6.2 ECHOCARDIOGRAPHY

The echocardiographic features of carcinoid heart disease are well described (5,25). Appearances are pathognomic in the absence of exposure to the appetite suppressants fenfluramine and phentermine, ergot derived dopamine agonists and ergot alkaloid agents such as methysergide and ergotamine (13,26).

Multiple views of each valve should be obtained for optimal evaluation of right sided heart valves. The tricuspid valve is visualised in parasternal long axis view of the right ventricular inflow tract, parasternal short axis view, apical four chamber view and the subcostal long axis view. The pulmonary valve is visualised in the parasternal long axis view of the right ventricular outflow tract, parasternal short axis view and subcostal short axis view (27).

In a seminal study, Pellikka and co-workers described the two dimensional echocardiographic features of carcinoid heart disease identified from the echocardiograms of 74 patients referred to their echocardiographic laboratory (5). 97% of patients had tricuspid valve involvement. Pulmonary valve was abnormal in

88% of cases. Both tricuspid and pulmonary valve leaflets and their corresponding sub-valvular apparatus were found to be thickened. Excursion of the leaflets was reduced. In some patients valve leaflets had become retracted, fixed with lack of co-aptation leading to the valve remaining in a semi-open position. Functionally, a combination of valvular regurgitation and stenosis occurred. A "dagger shaped" continuous wave Doppler profile, due to severe tricuspid regurgitation causing early peak pressure and rapid decline, representing equalisation of right atrial and ventricular pressures was seen in severe disease (Figure 1.2 and 1.2). The tricuspid valve, with or without pulmonary valve involvement, is involved in the majority of cases of CHD. Indeed, it is the combination of these which creates the most hemodynamic disturbance. Pulmonary stenosis is thought to make the severity of tricuspid regurgitation worse and conversely the severity of pulmonary stenosis may be underestimated because of low cardiac output and severe tricuspid regurgitation.

The right atrium and ventricle are typically enlarged. As the ventricle becomes volume overloaded, paradoxical motion of the interventricular septum occurs. Right ventricular function seemingly remains intact until quite late in the disease course. The increasing elevation in right ventricular pressure and increasing size of right atrium may lead to re-opening of patent foramen ovale in severe CHD (28).

Left sided lesions occur in up to 15% of all cases (5,29). Involvement is characterised by diffuse thickened of valve leaflets and is usually less severe than right sided valvular lesions. Serotonin is thought to be inactivated as it passes through lung parenchyma (30). Involvement of left sided valves is thought to be due to the presence of a patent foramen ovale with a right to left shunt, bronchial carcinoid or high levels of circulating vasoactive substances.

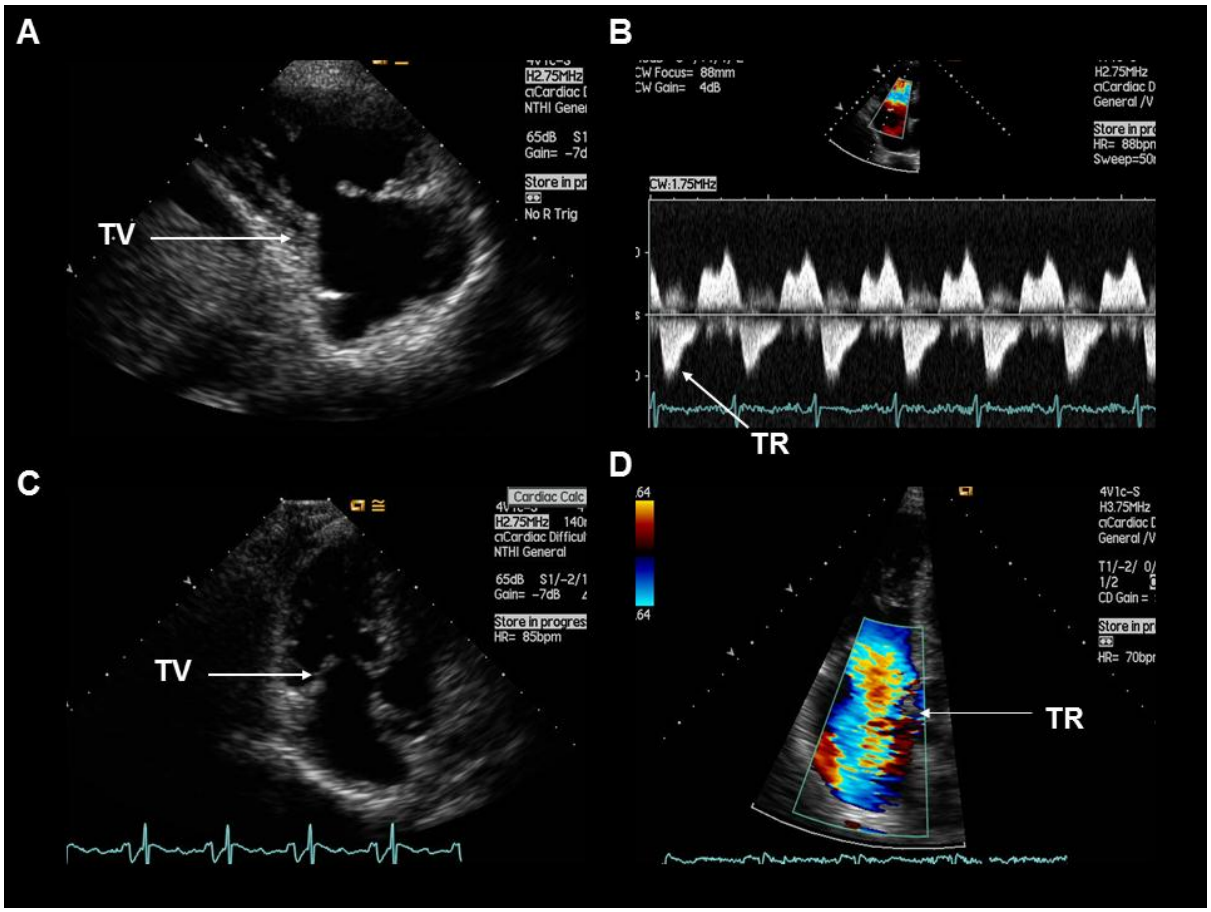


Figure 1.1 Carcinoid Involvement of Tricuspid Valve (TV) A. Right ventricular inflow view. Fixed, retracted and thickening of tricuspid valve leaflets and associated chordae. **B.** Continuous wave Doppler showing “dagger shaped” profile of tricuspid regurgitation (TR). **C.** Apical 4 chamber view showing dilated right ventricle with tricuspid valve leaflets failing to co-apt resulting in constant “semi-open” position. **D.** Colour Doppler demonstrating severe tricuspid regurgitation into a dilated right atrium.

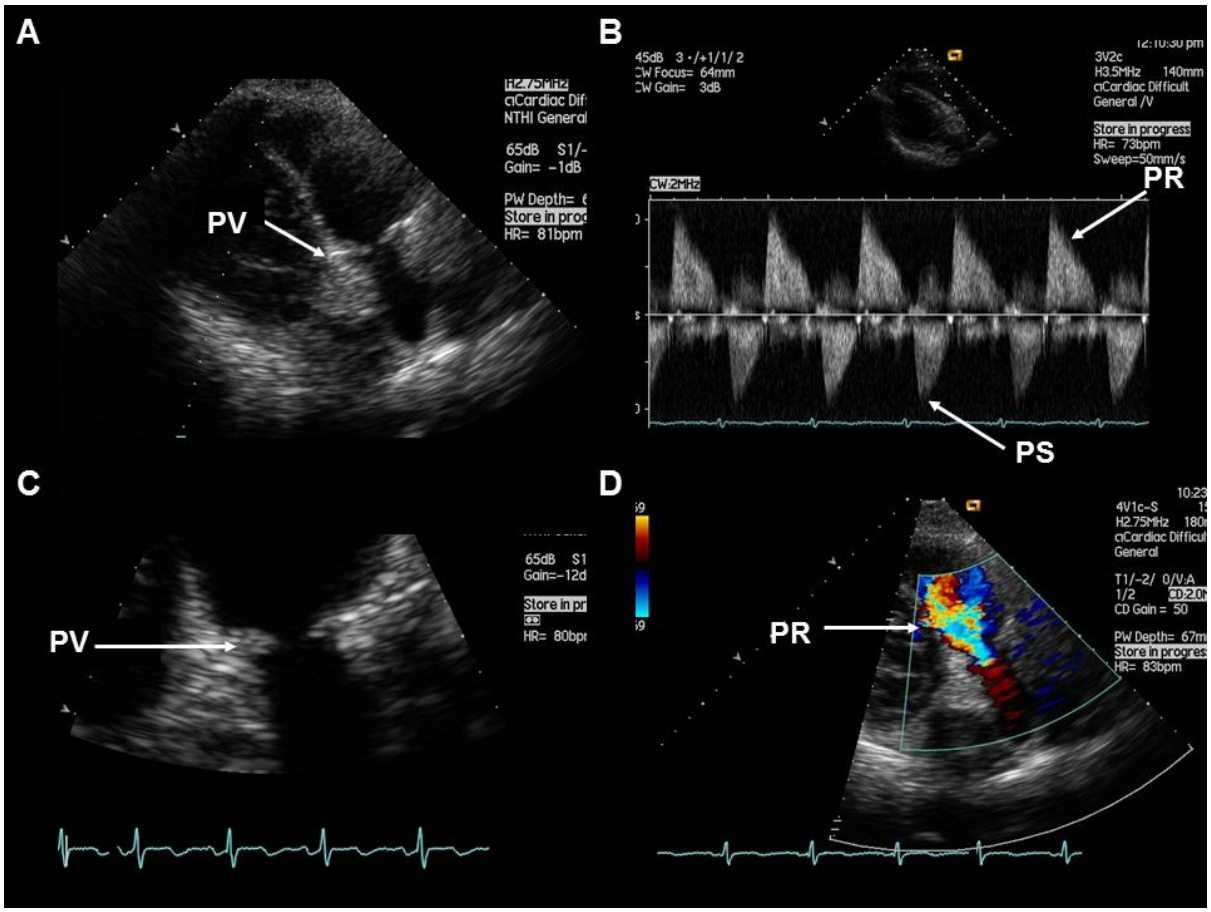


Figure 1.2 Carcinoid Involvement of Pulmonary Valve (PV) A. Right ventricular outflow tract. Thickened, fixed and retracted pulmonary valve leaflets that do not co-apt. **B.** Continuous Wave Doppler of pulmonary valve shows pulmonary regurgitation (PR) with short deceleration time and pulmonary stenosis (PS). **C.** Parasternal short axis view of pulmonary valve. Shortened and retracted valve leaflets. **D.** Colour Doppler in diastole demonstrates turbulent pulmonary regurgitant flow.

Small pericardial effusions are present in up to 10% of cases. Myocardial metastases are rare. The Mayo clinic reviewed the echocardiograms of patients diagnosed with metastatic carcinoid tumour to the heart (31). 11 patients were found to have cardiac metastases. In 8 patients the metastases could be identified on echocardiography. In five patients the metastases were only identified at autopsy. Metastases were found in the right ventricle in 40% of cases, left ventricle in 53% of cases and ventricular septum in 7% of cases. In the five patients with cardiac metastases found at autopsy but not seen with echocardiography the mean size was 0.35cm. The mean size of metastases identified by echocardiography was 2.4cm.This suggest that echocardiography is not able to detect small metastases.

Where transthoracic echocardiography cannot adequately visualise structures transoesophageal echocardiography should be undertaken (32). Over the past decade there have been significant advances in echocardiography, including the development of three dimensional transoesophageal and transthoracic echocardiography. These new technologies have not been evaluated in the assessment of carcinoid heart disease.

1.6.3 CARDIAC MAGNETIC RESONANCE IMAGING/ 64 SLICE COMPUTED TOMOGRAPHY

Cardiac magnetic resonance imaging has been shown to provide clear anatomic and functional information of both pulmonary and tricuspid valve in carcinoid heart disease. This can be of use, particularly in evaluating the pulmonary valve when it is difficult to visualise by echocardiography and limited ultrasound acoustic windows provide sparse echocardiographic data (33,34). Recently, 64 slice computed tomography coronary angiography has demonstrated similar anatomical

information (34). However the use of both modalities has been limited to isolated case reports.

1.7 MANAGEMENT

Without intervention patients with carcinoid heart disease patients may develop progressively worsening symptomatic right heart failure. Life expectancy is significantly reduced. The Mayo clinic showed a mean life expectancy of 1.6 years for those with cardiac disease compared to 4.6 years for those without cardiac disease in patients with metastatic midgut carcinoid tumours (5). Recent improvements in medical as well as surgical therapy, over the past decade, may have improved prognosis.

1.7.1 MEDICAL THERAPY

Treatment of carcinoid disease rarely achieves cure. However with modern anti-tumour therapy progression can be substantially slowed. Many patients survive for many years after resection of a primary carcinoid tumour or palliative treatment of metastatic disease. Therefore cardiac intervention should be considered in order to offer symptomatic palliation .

Medical management consists of relieving symptoms of right heart failure with a combination of loop and thiazide diuretic therapy. The use of digoxin may have a role to play but no convincing data for the right ventricle is available. Intuitively, optimising somatostatin analogue therapy should reduce circulating

vasoactive substances, reduce carcinoid syndrome and therefore may stabilise valvular lesions.

In patients not suitable for cardiac valve surgery the use of balloon valvuloplasty has been reported (35,36,37). Identification of suitable patients, with predominately stenotic valvular lesions, will be problematic as the majority of patients with CHD also have significant valvular regurgitation. Success of the procedure has been very limited. Although a couple of reports have shown some functional and haemodynamic benefit (36,37) others have noted either a lack of symptomatic benefit or a rapid relapse of symptoms and valvular stenosis where initial benefit did occur (35).

1.7.2 SURGICAL THERAPY

Cardiac surgery offers definitive therapy for symptoms. Data has been limited to small, retrospective US series. In a study of 26 patients with symptomatic carcinoid heart disease, Connolly and colleagues noted marked symptomatic improvement, of greater than one NYHA class, occurred post valve replacement for carcinoid heart disease. This was confirmed in a later series detailing the results of 11 patients undergoing surgery for left sided disease in addition to right sided valvular lesions. (29,38). Several series report high 30 day peri-operative mortality (38,39,40) In a limited database review of 8 patients undergoing tricuspid valve replacement at Duke Medical Center 5 patients (63%) died within 30 days (40). The results of a larger cohort series from the Mayo Clinic has noted a fall in peri-operative risk in their institution from over 20% in the 1980's to below 10% more

recently (41). The main peri-operative complications are bleeding and right ventricular failure.

In patients with pulmonary valve disease a small series has examined the effect of pulmonary valve replacement compared to pulmonary valvectomy. Connolly and colleagues compared the pre and post operative right ventricular diameter and function in 12 patients who underwent tricuspid and pulmonary valve replacement to 10 patients who underwent tricuspid valve replacement and pulmonary valvectomy, Right ventricular size decreased significantly post surgery in patients who underwent pulmonary valve replacement compared to patients with pulmonary valvectomy. Right ventricular dysfunction did not recover post operatively in either group (42). The optimal timing of surgery in relation to severity of valve dysfunction and symptoms has not been identified. However based on this data, cardiac surgery at the onset of either symptoms or right ventricular dysfunction, with pulmonary valve replacement in addition to replacement of the tricuspid valve, may be considered prudent.

More controversial is the choice of valve prostheses. There are no large series comparing the choice of valve prosthesis. Initial reports favoured the use of mechanical prosthesis based on the assumption of damage to a bioprosthetic valve with vasoactive substances. There have been several case reports of bioprosthetic valve degeneration (43,44,45). Carcinoid plaques have caused pulmonary valve allograft failure as early as three months after implantation (44) and tricuspid biological graft dysfunction after as little as four years (45). However the advent of somatostatin analogues and other anti –tumour therapies may theoretically protect the valve from deposition of further carcinoid plaques. Tissue valves have the advantage of not requiring anti-coagulation and consequently lower the risk of

bleeding in patients with hepatic dysfunction, reduce the risk of valve thrombosis (mechanical valve thrombosis is 4% per year) (46) and allows further procedures such as hepatic dearterilization to proceed at a later date. Therefore choice of prosthesis should be tailored to individual patient risk of bleeding, life expectancy and future interventions.

There have been several reports of patients presenting with dyspnoea and hypoxia and cyanosis. Inter-atrial shunts via patent foramen ovale associated with valvular disease were described. Surgical closure of a patent foramen ovale and percutaneous transcatheter closure devices in patients at high surgical risk have produced dramatic relief of symptoms (47,48) . Elevated right atrial pressure secondary to valvular disease may have contributed to stretching of the foramen ovale and development of a right to left shunt.

1.7.3 PERI-OPERATIVE ANAESTHETIC MANAGEMENT

Carcinoid crises characterised by hypotension, bronchospasm and flushing can be precipitated by surgery as well as drugs that release catecholamine and histamines. During the peri-operative period it can be difficult to differentiate between carcinoid crisis and hypotension secondary to myocardial dysfunction. Peri-operative octreotide, aimed at reducing serotonin release, is the most efficacious treatment for preventing crises during surgery and is the mainstay treatment of carcinoid crisis (49,50). Intravenous octreotide (50 – 100 micrograms per hour) should be started at least two hours prior to surgery. The infusion should continue for forty-eight hours post surgery. Patients may then require subcutaneous octreotide depending on previous somatostatin analogue requirements and current

control of carcinoid syndrome. Avoidance or minimising use of drugs known to precipitate mediator release such as opioids, the neuromuscular relaxants atracurioum and catecholamine producers such as dopamine and epinephrine, may reduce the risk of carcinoid crisis (50,51).

AIMS AND OBJECTIVES:

The aim of my thesis is to characterise the clinical manifestations of carcinoid heart disease. This will include 5 main areas of investigation:

1. Determine the prevalence and clinical features of carcinoid heart disease in a European cohort of patients in a contemporary era of medical management.

2. Determine the utility of biomarkers including N-Terminal pro Brain Natriuretic Peptide in the diagnosis of carcinoid heart disease.

3. Identify the echocardiographic features (including two and three dimensional imaging) of carcinoid heart disease.

4. Identify risk factors for the development and progression of carcinoid heart disease.

5. Investigate the role of cardiac surgery in the management of patients with carcinoid heart disease.

Chapter 2: Prevalence and Clinical Features of Carcinoid Heart Disease

2.1 Introduction

2.2 Methods

2.2.1 Patient Group

2.2.2 Echocardiography

2.2.3 Biochemical Markers

2.2.4 Functional Status

2.2.5 Statistical Analysis

2.3 Results

2.4 Discussion

2.5 Conclusion

2.1 INTRODUCTION

Carcinoid heart disease has been reported to develop in up to 70% of patients with carcinoid syndrome (5,6). Over the past two decades, new anti-tumour therapies for carcinoid syndrome including somatostatin analogues, interferon and targeted radionuclide therapy have emerged (2). These treatments result in inhibition of the production of tumour metabolites and may thereby alter the development and prevalence of carcinoid heart disease. Echocardiography remains the gold standard for diagnosis of carcinoid heart disease. Currently, in carcinoid patients, echocardiography is generally performed only if there is a clinical suspicion of valvular pathology due to symptoms or clinical signs. We aimed to establish the prevalence of carcinoid heart disease in an era of new treatment modalities and explore whether a screening programme needs to be established.

2.2 METHODS

2.21 Patient Group

One hundred and fifty consecutive patients with histologically confirmed carcinoid tumours of midgut origin and who had carcinoid syndrome were prospectively enrolled from April 2006. The Neuroendocrine Tumour Unit at the Royal Free Hospital is a large, tertiary referral centre for the management of neuroendocrine tumours. The Unit has more than 800 neuroendocrine tumour patients under active follow up. Ethical approval was obtained from the Royal Free Hospital Ethics Committee. Informed consent was obtained from all participants.

Diagnosis of carcinoid was based on histological examination of either primary tumour or liver metastases biopsy. Histology graded the tumour as high or low grade depending on differentiation and Ki-67 proliferation index.

Demographic data collected included information on patient age, sex, location of carcinoid tumour, tumour grade, duration of diagnosis of carcinoid tumour, current and previous anti-tumour therapies including treatment with somatostatin analogue.

2.2.2 Echocardiography

Comprehensive two dimensional transthoracic echocardiography was performed using Siemens Sequioa 512 (Siemens, USA). The echocardiogram was reviewed by 2 cardiologists blind to the clinical data. Multiple views of each cardiac valve were obtained.

The pulmonary valve was visualised from the high parasternal, long axis view of the right ventricular outflow tract and the parasternal short axis view. The tricuspid valve was visualised from the low parasternal long axis view of right ventricular inflow tract, short axis and apical four chamber views. The aortic and mitral valves were assessed from parasternal long axis, apical four, three and two chamber views.

Valvular regurgitation was assessed and graded according to The American Society of Echocardiography guidelines (52) . Valve stenosis was quantified according American College of Cardiology Guidelines (53). Pulmonary stenosis (peak gradient across valve)was graded as mild (<25mmHg), moderate (25-50mmHg) or severe(>50mmHg). Tricuspid stenosis (mean gradient across valve) was graded as mild (2- 5mmHg), moderate (5- 8mmHg) or severe(>8mmHg).

Contrast echocardiography was performed on all patients. 9mls of agitated saline was mixed with 0.5ml of the patients venous blood and 0.3mls of air. Boluses of 5mls of the agitated mixture were injected via a 20 gauge cannula inserted into a large vein in the left ante-cubital fossa. Cough and Valsalva manoeuvre were performed after introduction of the contrast. Either sub-costal, parasternal short axis or apical 4 chamber views were used depending on optimal visualisation of the atria.

Carcinoid heart disease was defined as the presence of characteristic thickening, reduced excursion or retraction of valvular leaflets (with associated evidence of valvular stenosis or regurgitation), or the presence of myocardial metastases, in the absence of other aetiologies. The presence of patent foramen ovale was defined as the passage of micro-bubbles from right atrium into the left atrium within 3 cardiac cycles of contrast visualisation in right atrium.

2.2.3 Biochemical Parameters

Twenty-four hour urine 5-HIAA samples were collected in bottles containing acetic acid. Samples were evaluated using reversed phase high performance liquid chromotography assay. Cg A samples were taken from antecubital fossa in a serum gel tube. Cg A was measured using DAKO Chromogranin A Enzyme-linked immunosorbent assay (DAKO A/S, Glostrup, Denmark).

2.2.4 Functional Status

Patients functional status was graded using NYHA classification. All patients had full examination of the cardiovascular system by a trained cardiologist.

2.2.5 Statistical Analysis

Comparison between continuous variables was measured using Mann-Whitney U Test and comparison between categorical variables was measured using the Chi Square Test or Fisher exact test where the number of variables was less than five. A value of $P < 0.05$ was considered to be of statistical significance. Analysis was undertaken using SPSS version 14, statistical software (SPSS, Chicago,USA).

2.3 RESULTS

One hundred and fifty patients were enrolled over the study period. No patient was excluded. Thirty (20%) patients with carcinoid syndrome were found to have carcinoid heart disease. There was no significant difference in age, sex, presence of liver metastases or tumour grade between those with carcinoid heart disease and those without carcinoid heart disease. The majority of patients in both groups were receiving somatostatin analogues. Very few patients received interferon therapy and no patient received a combination of somatostatin analogue and interferon therapy. There were significantly higher levels of Cg A and urinary 5-HIAA in the group with carcinoid heart disease compared to the group without carcinoid heart disease, $p<0.0001$ (table 2.1).

Table 2.1 Baseline characteristics of patients.

Variable		Carcinoid Heart Disease		P value
		Present N=30	Absent N=120	
Age (Years)		65(22-86)	65(30-87)	0.72
Sex (Female)		14 (47%)	55(46%)	0.93
Newly Diagnosed Patients		6(20%)	29(24%)	0.81
Time from diagnosis of carcinoid tumour (Years)		5(1-16)	4.5(0.4-20)	0.87
Presence of liver metastases		29(97%)	102(85%)	0.12
Therapy	Somatostatin Analogue	22 (73%)	86 (72%)	0.86
	Duration of Therapy (Months)	27(13.5-40)	24(12-40)	0.87
	Chemotherapy	0 (0%)	8 (7%)	0.16
	Targeted Radionuclide	6 (20%)	16 (13%)	0.25
	Interferon	0 (0%)	7 (6%)	0.32
	Duration of Therapy (Months)	0	4.5(3-12)	N/A
	^{123}I-metaiodobenzylguanidine	5 (3%)	15 (13%)	0.37
	Surgical Resection	14(47%)	70(58%)	0.25
Tumour Grade	Intermediate	2(7%)	5 (4%)	0.43
	Low	28(93%)	115 (96%)	0.43
Chromogranin A (pmol/L)		1000(56-1000)	238(37-1000)	<0.0001
Peak 5-hydroxyindolacetic acid (µMol/24 hours)		880(111-2228)	0 (0 -200)	<0.0001

Micromoles (uMol), picomoles per litre (pMol/L). Not applicable (N/A). Age is presented as mean and standard deviation. Chromogranin A, Urine 5-Hydroxyindolacetic acid and duration of carcinoid tumour and therapy are represented by median and interquartile range.

The majority of patients with carcinoid heart disease (53%, 16 patients)had only right sided valvular involvement. Fourteen (47%) of those with carcinoid heart disease were found to have both left and right sided valvular dysfunction.

Of those with only right sided carcinoid heart disease, isolated tricuspid valve lesions were most common in 9 (56%) cases and isolated pulmonary lesions were rare being present in 2 (13%) cases. Both pulmonary and tricuspid valve involvement was present in 5(31%) cases. Abnormalities of the tricuspid valve most commonly manifest as regurgitation of moderate to severe grade. Pulmonary valvular abnormalities manifest as regurgitation and stenosis of mild to moderate severity (table 2.2).

Table 2.2 Carcinoid Heart Disease – Functional Valvular Abnormalities

Echocardiographic Characteristic		Number	Echocardiographic Characteristic		Number
Tricuspid Stenosis	None	17(57%)	Tricuspid Regurgitation	None	3(10%)
	Mild	9 (30%)		Mild	5(17%)
	Moderate	4(13%)		Moderate	7(23%)
	Severe	0(0%)		Severe	15(50%)
Pulmonary Stenosis	None	16(53%)	Pulmonary Regurgitation	None	15(50%)
	Mild	8(27%)		Mild	10(33%)
	Moderate	6(20%)		Moderate	5(17%)
	Severe	1(3%)		Severe	0(0%)
Mitral Regurgitation	None	18(60%)	Aortic Regurgitation	None	21(70%)
	Mild	7(23%)		Mild	6(20%)
	Moderate	5(17%)		Moderate	3(10%)
	Severe	0(0%)		Severe	0(0%)

Of the left sided carcinoid heart disease, the mitral valve was most commonly involved in 5(36%) patients and the aortic valve was involved in 2 (14%) patients. Both aortic and mitral valves were involved in 7 (50 %) cases of left sided carcinoid heart disease. All patients with left sided carcinoid heart disease had a patent foramen ovale. Valvular regurgitation of mainly mild to moderate severity was seen. None of the patients had valvular stenosis (table 2.2).

Thirteen (43%) of the patients with carcinoid heart disease were in NYHA Class I. Twelve (40%), four (13%) and one (3%) of the patients with carcinoid heart disease were in functional NYHA classes II, III and IV respectively . Overall 17 patients (57%) with moderate to severe tricuspid regurgitation were in NYHA class I – II (table 2.3).

Table 2.3 Severity Of Tricuspid Regurgitation In Relation To New York Heart Association Class

New York Heart Association Class	Severity of Tricuspid Regurgitation			
	None/Trivial	Mild	Moderate	Severe
I	2 (7%)	3 (10%)	5 (17%)	3 (10%)
II	1 (3%)	2 (7%)	2 (7%)	7 (23%)
III	0 (0%)	0 (0%)	0 (0%)	4 (13%)
IV	0 (0%)	0 (0%)	0 (0%)	1 (3%)

Eleven (37%) of the patients with carcinoid heart disease had no clinical signs of cardiac abnormalities on physical examination. 10 (33%) did not have raised jugular venous pressure, 15(50%) did not have a cardiac murmur and 8(27%) did not have ankle oedema.

2.4 DISCUSSION

The prevalence of carcinoid heart disease in this study (20%) is lower than that reported in previous decades (50 – 70%) (5,6). There may be several reasons for the differences reported. Previous studies may be subject to referral bias as they included patient referred for echocardiography due to a clinical suspicion of carcinoid heart disease rather than screening all patients with carcinoid syndrome. Secondly, the characteristics of patients seen at different institutions may differ. Thirdly, over the past decade new anti-tumour therapies which have been shown to cause significant reduction in the production of tumour metabolites have been introduced. Most notable of these therapies are somatostatin analogues. These analogues control symptoms of carcinoid syndrome and also result in a reduction of 5-HIAA, a urinary metabolite of serotonin, in up to 70% of patients (54).

In our cohort of patients the majority of carcinoid patients were receiving somatostatin analogues. In our group with carcinoid heart disease, the majority were also receiving somatostatin analogues yet had significantly higher urinary 5-HIAA and Cg A levels than the group without carcinoid heart disease. This may represent a lack of biological and biochemical response to these analogues. 5-HT is thought to be important in the pathogenesis and progression of carcinoid heart disease having a high sensitivity although low specificity (19,20). Therefore further research to delineate whether aggressive medical therapy with higher dose or higher affinity somatostatin analogues to prevent the development of carcinoid heart disease is needed.

Pellikka et al (5) reported 90% of tricuspid regurgitation being of moderate to severe degree. In our study only 73% of tricuspid regurgitation was of moderate to

severe degree and 27% was of trivial or mild degree. The higher incidence of mild valvular involvement in our cohort may be in part due to the prospective nature of this study allowing diagnosis of early disease in asymptomatic individuals and significant advances in echocardiography techniques over the past two decades may have allowed better visualisation of valves and quantification of valvular regurgitation.

A substantial proportion of patients with carcinoid heart disease are asymptomatic. This group included a spectrum of severe to mild disease. Patients with early stage disease and mild functional valvular abnormalities would be expected to have little by signs or symptoms. However it is important to diagnose early stage disease as an early diagnosis would allow monitoring and potentially a chance to retard progression of their carcinoid heart disease by reduction of circulating 5-HT levels. It is equally important to diagnose asymptomatic but advanced carcinoid heart disease (57% of our patients) as it will allow timely surgical intervention prior to the development of right ventricular failure.

A substantial proportion of patients did not display signs of valvular disease. This is not surprising as previous studies have shown auscultatory and clinical examination is not an accurate predictor of the presence of tricuspid regurgitation (55). Our results differ from previous reports where the majority of patients with carcinoid heart disease had cardiac murmurs present (5,56). Whereas these studies included patients referred for echocardiography or with clinical suspicion of carcinoid heart disease our study prospectively screened consecutive patients with carcinoid syndrome regardless of clinical suspicion. Secondly, in our cohort the proportion of patients with mild involvement of valvular structures is greater than previously stated.

Intuitively auscultation would be less likely to detect cardiac murmurs in these patients.

Including only new referrals with a diagnosis of carcinoid will not establish the true incidence of carcinoid heart disease as a substantial proportion of patients will have had a carcinoid tumour for several years before a diagnosis is made and autopsy studies of carcinoid tumours show many are never diagnosed whilst alive even though they may have had symptoms of carcinoid syndrome. Therefore we decided to screen our patient population. This would indicate the total number of patients with carcinoid heart disease representing the prevalence and burden of disease in the patient group.

CONCLUSION

In conclusion the prevalence of carcinoid has reduced from previous decades. This is likely to be due to the introduction of modern anti-tumour therapies. A screening programme for carcinoid heart disease in this patient group is warranted as a substantial number of patients are functionally asymptomatic and do not have signs of carcinoid heart disease.

Chapter 3: N-Terminal Brain Natriuretic Peptide As A Biomarker Of The Presence Of Carcinoid Heart Disease

3.1 Introduction

3.2 Methods

3.2.1 Patient Group

3.2.2 Echocardiography

3.3.3 Biochemical Markers

3.2.4 Statistical Analysis

3.3 Results

3.4 Discussion

3.5 Conclusion

3.1 INTRODUCTION

Carcinoid heart disease is characterised by the deposition of fibrotic plaques on endocardial surfaces of the heart, resulting in the development of a complex combination of predominantly right-sided valvular lesions (5). Many patients are initially asymptomatic despite severe disease. Early detection and timely intervention is essential as development of right ventricular dysfunction heralds a poorer prognosis and does not recover post cardiac valve replacement (29,42) .

Patients with carcinoid syndrome are already subject to an intensive regimen of investigations and therapies necessary for monitoring and treatment of their tumour. Within this setting, routine echocardiography for the detection of carcinoid heart disease may be time- consuming and expensive .

BNP are neurohormones released by the ventricle in response to an increase in ventricular wall stress due to both volume and pressure overload (58,59,60). BNP is synthesised as a pre-hormone (proBNP) comprising 108 amino acids. Upon release into the circulation, it is cleaved in equal proportions into the biologically active 32 amino acid BNP, which represents the C-terminal fragment, and the biologically inactive 76 amino acid N-terminal fragment (NT-proBNP). BNP is stable in whole blood at room temperature for 24 hours, whereas NT-proBNP is stable for at least 72 hours. We sought to investigate whether NT-proBNP could be used as a biomarker of the presence of carcinoid heart disease and thereby be used to select which patients should be further evaluated by echocardiography.

3.2 METHODS

3.2.1 PATIENT GROUP

Two hundred and four patients diagnosed with carcinoid tumours of midgut origin and a history of carcinoid syndrome were consecutively and prospectively enrolled from April 2006.

Diagnosis of carcinoid was based on histological examination of either primary tumour or liver metastases biopsy. Histology graded the tumour as high or low grade depending on differentiation and Ki-67 proliferation index.

The following demographic data was collected: age, sex, duration of carcinoid symptoms, duration of diagnosis of carcinoid tumour and the presence of liver metastases. The functional status of patients was assessed by NYHA Class.

All patients underwent comprehensive two-dimensional echocardiography. Blood samples for NT-proBNP, Cg A, serum creatinine and a 24 hour urinary sample for 5-HIAA were collected.

Patients were excluded from the study if suitable echocardiographic windows to allow adequate visualisation of cardiac structures were not obtainable or if creatinine clearance was less than 60 millilitres per minute.

The study was approved by the ethical review committee of the institution and all patients gave written informed consent.

3.2.2 Echocardiography

Two dimensional transthoracic echocardiography was performed using Acuson Sequoia C512 (Siemens Medical Systems, USA). All studies were reported

by two cardiologists blinded to patient's symptom status, clinical and biochemical data.

Diagnosis of carcinoid heart disease was based on echocardiographic criteria. Carcinoid heart disease was defined as the presence of characteristic thickening, reduced excursion or retraction of valvular leaflets (with associated evidence of valvular stenosis or regurgitation), or the presence of myocardial metastases, in the absence of other aetiologies. Left sided CHD was only diagnosed in the presence of right sided CHD.

Echocardiograms of patients diagnosed with carcinoid heart disease were scored in order to obtain an objective description of the severity of carcinoid heart disease. Each affected valve was scored individually (table 3.1). The total score of all affected valves and the right ventricle assessment was combined to produce a final score. The score will assess valve leaflet thickness, mobility, shortening/retraction and ability to co-apt together with the degree of regurgitation or stenosis and ventricular dilatation and function.

Table 3.1 Valvular Abnormalities Score

	Score			
	0	1	2	3
Leaflet Thickness	< 3mm	3-4mm	4-5mm	>5 mm
Leaflet Mobility	Normal	Leaflet excursion <75% of normal	Leaflet excursion <50% of normal	Leaflet excursion <25% of normal or fixed
Leaflet Retraction	Normal	Mild	Moderate	Severe
Valve Stenosis	Normal	Mild	Moderate	Severe
Valve Regurgitation	Normal	Mild	Moderate	Severe

Twenty-five percent of patients found to have carcinoid heart disease were scored by two readers to assess inter-observer variability.

Valve morphology and function was evaluated in several views. Pulmonary valve was visualised from high parasternal, long axis view of right ventricular outflow

tract and parasternal short axis view. Tricuspid valve was visualised from low parasternal long axis view of right ventricular inflow tract, short axis and apical four chamber view. Aortic and mitral valves were assessed from parasternal long axis, short axis, apical four, three and two chamber views. Valve regurgitation severity and quantification were assessed and graded according to The American Society of Echocardiography guidelines (52). Valve stenosis was quantified according American College of Cardiology Guidelines (53). Pulmonary stenosis was graded (according to peak gradient across valve) as mild (<25mmHG), moderate (25-50mmHg) or severe(>50mmHG).Tricuspid stenosis was graded (mean gradient across valve) as mild (2 -5mmHg), moderate (5- 8mmHg) or severe(>8mmHg).

Right and left ventricular function and sizes were assessed and calculated according to American Society of Echocardiography guidelines. Right ventricular function was measured using right ventricular fractional shortening change. The right ventricular diameter was measured in the apical four chamber view at the level of tricuspid valve leaflet tips in diastole. Left ventricular ejection fraction was calculated by the modified Simpson's method from apical four and two chamber views (61).

3.2.3 Biochemical Markers

NT-proBNP samples were taken, immediately prior to echocardiography, from the left antecubital fossa at room temperature in a serum gel tubes. Analysis was undertaken immediately, after being centrifuged, by Roche Modular Analytics E-170 immunoassay analyser using electrochemilunescence detection. 24 hour urine 5-HIAA samples were collected in bottles containing acetic acid. Samples were evaluated using reversed phase high performance liquid chromatography assay. Cg

A samples were taken from antecubital fossa in a serum gel tube. CgA was measured using DAKO Chromogranin A Enzyme-linked immunosorbent assay (DAKO A/S, Glostrup, Denmark). Creatinine clearance was calculated from the Cockcroft-Gault Formula.

3.2.4 Statistical Analysis

The Mann-Whitney U test was used to compare differences between continuous variables. The Chi squared test was used to compare categorical variables. When the number of categorical variables was less than five the Fisher exact test was used. Kruskal Wallis Test was used to compare differences in NT-proBNP levels of subjects grouped according to NYHA class. Receiver operating characteristic plot analysis was used to determine the sensitivity and specificity of NT-proBNP for diagnosis of carcinoid heart disease. The cut-off for NT-proBNP was determined retrospectively by ROC coordinated for a maximum sensitivity of > 90% and minimal loss of specificity. Spearman Rank Correlation Co-efficient (r) was used to compare the association of NT-proBNP level to carcinoid heart disease score. Inter-observer concordance was expressed as exact agreement and by the Kappa (κ) statistic. Poor agreement was indicated by a κ value of <0.2, fair agreement indicated by a κ value of 0.21 – 0.4, moderate agreement was indicated by a κ value of 0.41 - 0.6, good agreement was indicated by a κ value 0.61 – 0.8 and excellent agreement by a κ value > 0.81.The number of patients screened with echocardiography needed to diagnose one case of carcinoid heart disease was defined as the ratio of the total number of patients to the number of patients with echocardiograms confirming carcinoid heart disease. A P-value of <0.05 was

considered statistically significant. Statistical analysis was performed using StatsDirect Version 2.5.7 (StatsDirect, United Kingdom).

3.3 RESULTS

Two hundred and four patients were enrolled in the study. After initial assessment four patients were excluded; suitable echocardiographic windows were not obtainable in one patient and in three patients creatinine clearance was below the entry criteria. Two hundred patients were included in the analysis.

Carcinoid heart disease was present in 39 (19.5%) of patients. There was no significant difference in age, sex, duration of carcinoid tumour, presence of liver metastases or tumour grade between those with or without carcinoid heart disease. There were significantly greater levels of Cg A and urinary 5-HIAA in the carcinoid heart disease group compared to the group without carcinoid heart disease. This, as might be expected, probably represents greater disease activity and tumour burden in the group with carcinoid heart disease (table 3.2). The sensitivity and specificity of urinary 5-HIAA for a diagnosis of carcinoid heart disease at a cut-off level of 57µmol/24 hours was 0.93 and 0.52 respectively.

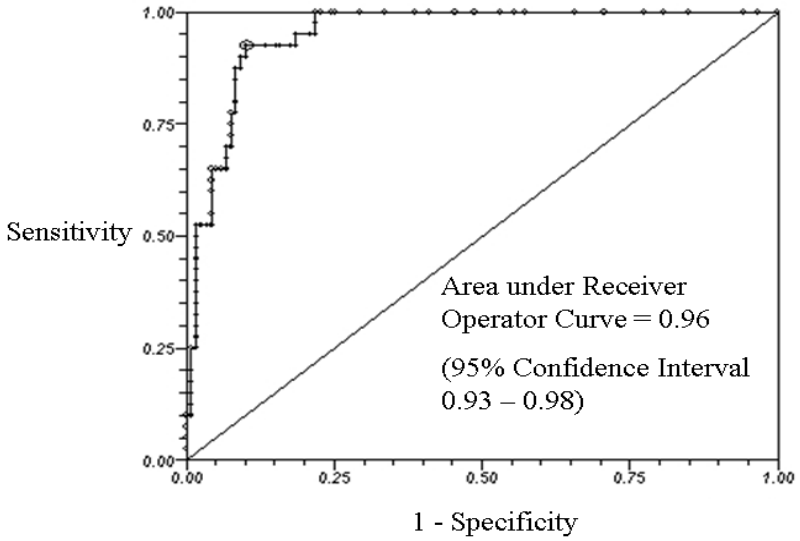
Median NT-proBNP was significantly higher in those with carcinoid heart disease (median 1149pg/ml (interquartile range 404 - 1601)) than in those without (median 101pg/ml (interquartile range 50 – 169)), $p<0.001$. The sensitivity and specificity for carcinoid heart disease, at a cut-off level of 260pg/ml, was 0.92 (92%) and 0.91 (91%) respectively. Area under receiver operator curve was 0.96 (95% Confidence Interval 0.93 – 0.98). The negative and positive predictive value were 0.98 and 0.71 respectively (figure 3.1).

Table 3.2 Baseline characteristics

			Carcinoid Heart Disease (n=39)	No Carcinoid Heart Disease (n=161)	P value
Age			63 ± 12.2	65 ± 11.0	0.39
Sex (Females)			18 (46%)	78 (48%)	0.93
Duration of carcinoid tumour (years)			4 (2 - 5.5)	5 (3 -7)	0.40
Presence of liver metastases			37 (95%)	130 (81%)	0.06
Therapy	**Somatostatin Analogue**		31(80%)	120(75%)	0.67
	Interferon		1(3%)	8(5%)	0.99
	^{123}I-metaiodobenzylguanidine		6(15%)	23(14%)	0.80
	Targeted Radionuclide		10(26%)	22(14%)	0.11
	Chemotherapy		1(3%)	10(1%)	0.70
	Surgical Resection		19(49%)	96(60%)	0.29
Tumour Grade		**Medium**	2 (5%)	6(4%)	0.66
		Low	37 (95%)	155(96%)	0.66
Cg A (pmol/L)			1000 (928-1000)	224(62-561)	<0.0001
Peak 5-HIAA (µMol / 24 hours)			880 (458-1659)	25(0-217)	<0.0001
NYHA	**I**		16(41%)	96 (60%)	0.05
	II		15(38%)	55(34%)	0.71
	III		6(15%)	10(6%)	0.09
	IV		2(5%)	0(0%)	0.04

Chromogranin A (Cg A), 24 hour urinary 5-hydroxyindolacetic acid (5-HIAA), New York Heart Association Functional Class (NHYA), Picomoles per litre (pMol/L), Micromoles (uMol) Entries are number (%). Mean and standard deviation is used for age. Median and interquartile range is used for duration of carcinoid tumour, Cg A and 24 hour urinary 5-HIAA.

Figure 3.1 Receiver Operator Curve of N Terminal Brain Natriuretic Peptide (NT-proBNP) for diagnosis of Carcinoid Heart Disease.



Median Carcinoid Score for those with carcinoid heart disease was 18 (interquartile range 11 to 26). Left ventricular function was preserved in all patients. The range of functional valvular abnormalities is described in table 3.3 . The score correlated positively with NT-proBNP. Spearman Rank Correlation co-efficient (r) was 0.81 (95% confidence interval 0.67 - 0.89), $p<0.0001$ (figure 3.2).

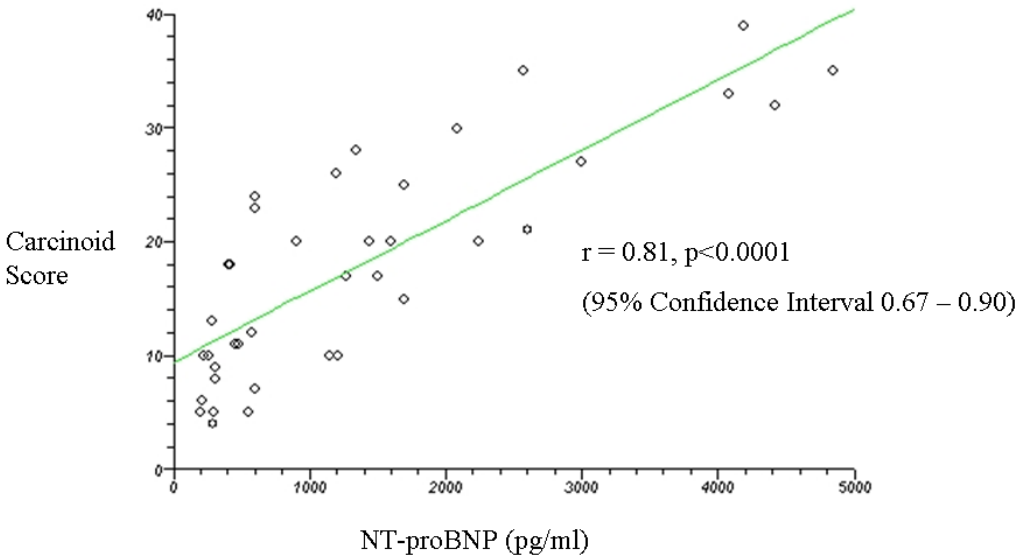
Table 3.3 Echocardiographic Features of Carcinoid Heart Disease

Echocardiographic Characteristic		Number(%)	Echocardiographic Characteristic		Number %)
Tricuspid	**None**	24(62%)	**Tricuspid**	**None**	3(8%)
Stenosis	**Mild**	11(28%)	**Regurgitation**	**Mild**	6(15%)
	Moderate	4(10%)		**Moderate**	9(23%)
	Severe	0(0%)		**Severe**	21(54%)
Pulmonary	**None**	20(51%)	**Pulmonary**	**None**	18(46%)
Stenosis	**Mild**	10(26%)	**Regurgitation**	**Mild**	15(38%)
	Moderate	8(21%)		**Moderate**	6(15%)
	Severe	1(3%)		**Severe**	0(0%)
Mitral	**None**	26(67%)	**Aortic**	**None**	25(64%)
Regurgitation	**Mild**	9(23%)	**Regurgitation**	**Mild**	9(23%)
	Moderate	4(10%)		**Moderate**	4(10%)
	Severe	0(0%)		**Severe**	1(3%)
Mitral Stenosis	**None**	39(100%)	**Aortic Stenosis**	**None**	39(100%)
RV Diameter Diastole (cm)		3.9 (3.5 – 4.1)			
Right Atrial Area (cm^2)		19.8 (16.2 - 24.8)			
Left Ventricle Ejection Fraction (%)		62% (±6.2)			

Right Ventricular Function	**Normal**	**Mildly Reduced**	**Moderately Reduced**	**Severe Reduced**
	35 (90%)	3 (8%)	1(3%)	0 (0%)

Median and range are given for right atrial area and right ventricular diameter. Mean and standard deviation are given for left ventricular ejection fraction.

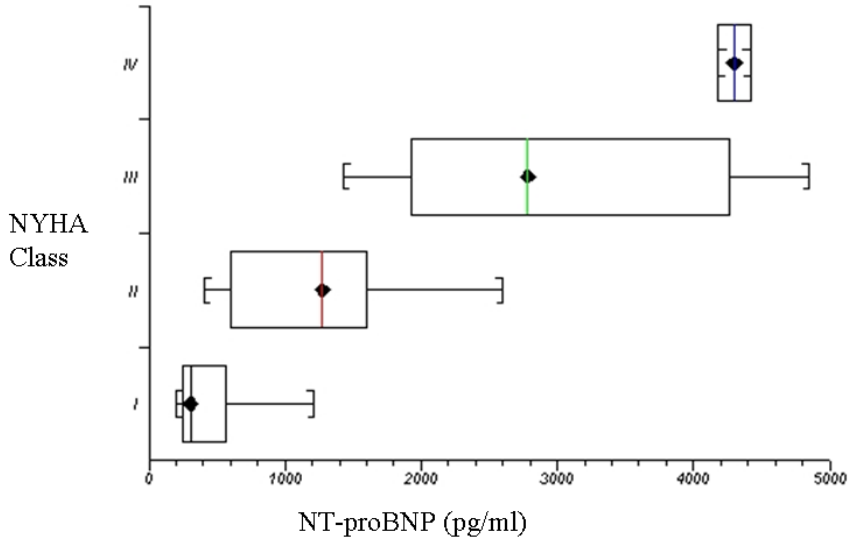
Figure 3.2 Correlation of N Terminal Brain Natriuretic Peptide (NT-proBNP) and Carcinoid Heart Disease Score.



Of the 10 studies scored by both readers, exact inter-observer agreement was present in 6(60%) of patients. Three patients scores differed by 2 points and 1 patients score differed by one point. A corresponding κ value of 0.89 confirmed overall excellent agreement.

NT-proBNP was significantly related to symptomatic status increasing with higher functional NYHA class (Median NT-proBNP: NYHA Class I 304pg/ml, NYHA Class II 1271pg/ml, NYHA Class III 2783pg/ml, NYHA Class IV 4300pg/ml, P<0.001, figure 3.3).

Figure 3.3 Box plot of N Terminal Brain Natriuretic Peptide (NT-proBNP) levels according to New York Heart Association (NYHA) functional class in patients with carcinoid heart disease. (The box defines interquartile range and median represented by crossbar. The error bars depict range).



Of the 39 patients found to have echocardiographic evidence of carcinoid heart disease, 16 (41%) patients were functionally asymptomatic (NYHA Class I). Fourteen (88%) of these patients had an NT-proBNP level greater than the threshold of 260pg/ml.

NT-proBNP was elevated in 15 patients without echocardiographic evidence of carcinoid heart disease (false positives). Two patients were found to have aortic regurgitation, 3 patients had aortic stenosis, 2 patients had mitral regurgitation and left ventricular dysfunction was present in 8 patients.

If patients with carcinoid tumours of mid-gut origin are screened for carcinoid heart disease using echocardiography alone 5.1 patients will need to be screened in

order to detect 1 patient with carcinoid heart disease. If NT-proBNP is used as a screening test and only those with a level of greater than 260pg/ml underwent echocardiography 1.4 patients will need to undergo echocardiography in order to detect 1 patient with carcinoid heart disease.

3.5 DISCUSSION

This is the first large prospective trial to assess whether NT-proBNP can be used as a biomarker of the presence of carcinoid heart disease encompassing the full range of valvular abnormalities seen in this condition. Median NT-proBNP is significantly higher in patients with carcinoid heart disease than those patients without. The sensitivity and specificity of NT-proBNP at a cut-off value of 260pg/ml were 0.92 and 0.91 respectively. A high negative predictive value of 0.98, at this cut off level, may allow this biomarker to be used to exclude carcinoid heart disease. Secondly, the level of NT-proBNP correlates with the severity of carcinoid heart disease (carcinoid heart score) and higher NYHA functional classes have greater median NT-proBNP levels than lower NYHA classes although there is overlap between the ranges.

Currently, the incidence of carcinoid tumours is increasing. The overall 5 year survival for small bowel carcinoid tumours in the present decade is over 60% (3,57). The development of an array of modern anti-tumour therapies, most notably somatostatin analogues, over the past 2 decades has led to an increased ability to provide relief of the symptoms of carcinoid syndrome and stabilise carcinoid tumours (62,63,64). In this era, more emphasis will be placed on the detection and management of carcinoid heart disease where valve replacement can provide

considerable symptomatic relief of cardiac symptoms and may improve prognosis(38,41).

Assessment, monitoring and management of this complex form of valvular heart disease requires expert and experienced assessment. The relative rarity of carcinoid heart disease may lead to assessment of these patients, by echocardiography, in centres that are not familiar particularly with the early changes of carcinoid heart disease. Secondly, evaluation by echocardiography, in addition to the intensive regimen of investigations and therapies already imposed on the carcinoid patient, is expensive, time consuming and in some areas timely availability is limited. Thirdly, at present, screening for carcinoid heart disease is not routine and usually only occurs when clinical suspicion exists. A large proportion of our patients were functionally asymptomatic despite the presence of carcinoid heart disease. A biomarker which is not operator dependent, quick, reliable and relatively inexpensive would be advantageous in order to identify and select patients who may require further expert evaluation.

An early diagnosis of carcinoid heart disease is essential for management and therapy decisions regarding the carcinoid tumour itself and for timely cardiac surgical intervention prior to the development of right ventricular dysfunction. Right ventricular dysfunction may not recover post cardiac valve replacement, increases operative risk of cardiac surgery and leads to the development of signs and symptoms associated with right heart failure. We have shown the use of NT-proBNP can be used as an accurate marker of the presence cardiac involvement. This marker is able to detect both early stage disease and those with advanced disease and subsequent right ventricular dysfunction.

5-HT is an important factor in the pathogenesis and progression of carcinoid heart disease (17,19,20). Our results confirm urinary 5-HIAA has a high sensitivity but very low specificity for the development of carcinoid heart disease (17). Therefore it is not clinically useful as a screening tool.

The present study does not provide sufficient evidence for the use of NT-proBNP as a tool for monitoring progression of carcinoid heart disease. Further long term follow up studies combining serial echocardiograms and parallel measurements of NT-proBNP are required to evaluate whether NT-proBNP may provide a modality for monitoring patients with carcinoid heart disease.

The carcinoid score we developed was based on our experience of assessing and reviewing the echocardiograms of over 200 carcinoid patients. Some of the components of the score relied on semi-quantative assessments. This was because components such as degree of excursion of valve leaflets can be difficult to quantify. Despite this limitation, inter-observer agreement was good.

The presence of left sided carcinoid heart disease could be difficult to distinguish from rheumatic or degenerative/age related valve disease. The characteristic features of left sided carcinoid heart disease include diffuse valve thickening with reduced excursion, retraction and valvular regurgitation. They do not include fusion of commissures or significant valvular stenosis characteristic of rheumatic disease. Secondly, the median age of the patient cohort is relatively young and the degree of valvular thickening seen is much greater than would be expected for age related changes. Thirdly, left sided carcinoid heart disease was only included in the carcinoid score in the presence of right sided valvular lesions as isolated left sided carcinoid heart disease only occurs in the presence of primary bronchial carcinoid.

There is intra-individual variation in NT-proBNP levels. Some studies have noted differences of up to 20% between readings (65,66).This is unlikely to make a difference to the diagnostic ability of NT-proBNP in the majority of patients as they are either substantially above or below the cut-off value. This is most likely to be a problem in patients very near the cut-off level for carcinoid heart disease. In the three patients with carcinoid heart disease but false negative NT-proBNP (below the cut-off level) the values were very close to 260pg/ml. These patients had very mild disease with little functional consequences. The possible options available to the clinician are either to perform echocardiography on all patients near the cut-off line or repeat the measurement in these patients at a later date.

3.6 Conclusion

In conclusion, NT-proBNP is an excellent biomarker of the presence and severity of carcinoid heart disease in patients with carcinoid syndrome. A high negative predictive value may allow its use as a screening test for carcinoid heart disease allowing a targeted approach to the use of echocardiography and further expert evaluation in carcinoid heart disease.

Chapter 4. Features of Carcinoid Heart Disease Identified By Two- and Three- Dimensional Echocardiography and Cardiac Magnetic Resonance Imaging.

4.1 Background

4.2 Methods

4.2.1 Patient Group

4.2.2 Two Dimensional Echocardiography

4.2.3 Three Dimensional Echocardiography

4.2.4 Three Dimensional Transoesphageal Echocardiography

4.2.5 Cardiac Magnetic Resonance Imaging

4.2.6 Statistical Analysis

4.3 Results

4.3.1 Right Ventricle, Atrium and Tricuspid Valve

4.3.2 Pulmonary Valve

4.3.3 Left Sided Heart Valves and Foramen Ovale

4.3.4 Aortic Valve

4.3.5 Mitral Valve

4.3.6 Cardiac Metastases

4.3.6 Cardiac Magnetic Resonance Imaging

4.4 Discussion

4.5 Conclusion

4.1 BACKGROUND

Carcinoid tumours occur in between 1 to 2 cases per 100,000 of the population. Carcinoid syndrome is thought to occur when the tumour metastases to the liver allowing high levels of 5-HT to reach the systemic circulation. Manifestations of the syndrome include flushing, diarrhoea, bronchospasm and the development of carcinoid heart disease (67).

5-HT is thought to promote deposition of plaques composed of myofibroblasts onto the endocardial surfaces of the heart. Cardiac involvement is commonly manifested by the development of right sided valvular dysfunction. Characteristic changes include thickening of valve leaflets/cusps which become retracted and eventually immobile, resulting in a combination of valvular regurgitation and stenosis (5, 6).

Significant advances in echocardiography, including the development of 3D echocardiography, have allowed greater understanding and assessment of valve pathology (68). Secondly, newer imaging modalities such as cardiac magnetic resonance imaging have emerged which may allow complimentary assessment of cardiac pathology (69).

The purpose of this study is to describe the echocardiographic features of carcinoid heart disease identifying features of both early and advanced disease and to ascertain the value of advanced echocardiographic techniques and other imaging modalities.

4.2 METHODS

4.2.1 PATIENTS

Patients with carcinoid syndrome were consecutively and prospectively enrolled from April 2006. The diagnosis of carcinoid tumour was based on histological examination of either primary tumour or liver metastases biopsy. The protocol was approved by the institution's ethics committee. All patients gave written, informed consent.

All patients underwent comprehensive 2D TTE. Additional 3D TTE was performed after the 2D study from 2008 onwards. 3D TEE was performed where transthoracic windows were not suitable for full evaluation of heart valves and there was clinical suspicion of valvular heart disease or as part of pre-operative assessment prior to valve surgery.

4.2.2. TWO- DIMENSIONAL ECHOCARDIOGRAPHY

2D TTE were performed in all patients using commercially available echocardiography machines (Siemens Acuson C512 and Philips iE33). Valve morphology and function was evaluated in several views. Valve regurgitation severity and quantification were assessed and graded according to The American Society of Echocardiography guidelines (52). Valve stenosis was quantified according American College of Cardiology Guidelines (53). Pulmonary stenosis was graded (according to peak gradient across valve) as mild (<25mmHg), moderate (25 - 50mmHg) or severe (>50mmHg).Tricuspid stenosis was graded (mean gradient

across valve) as mild (2 - 5mmHg), moderate (5 - 8mmHg) or severe (>8mmHg). Right and left ventricular function and sizes were assessed and calculated according to American Society of Echocardiography guidelines(61).

All echocardiograms were reviewed by two cardiologists experienced in echocardiography. The abnormalities described are based on the consensus of the two reviewers. Carcinoid heart disease was defined as the presence of characteristic thickening, reduced excursion or retraction of valvular leaflets (with associated evidence of valvular stenosis or regurgitation), or the presence of myocardial metastases, in the absence of other aetiologies.

All patients were assessed for the presence of a patent foramen ovale using “microbubble” contrast at rest and with cough and Valsalva manoeuvre. The presence of patent foramen ovale was defined as the presence of at least 3 microbubbles in the left atrium within 3 cardiac cycles of contrast visualisation in right atrium. The degree of shunting was classified as mild if 3-9 microbubbles appeared, moderate if 10 to 30 microbubbles appeared and large if more than 30 microbubbles appeared (70).

4.2.3 THREE-DIMENSIONAL TRANSTHORACIC ECHOCARDIOGRAPHY

3D TTE was performed using Phillips iE33 equipped with X3-1 transducer (Philips Medical Systems, Andover, Massachusetts) after 2D examination was complete. Full volume, 3D zoom and live datasets were obtained from parasternal, apical views and subcostal views. Full volume acquisition was performed over 5 cardiac cycles with breath hold. Image rendering was performed after the procedure. Pyramidal datasets were cropped along x,y,z axes or manually using the cropping

plane of choice. Gain settings, smoothing and brightness were adjusted to optimise visualisation of valve and valvular apparatus.

4.2.4 THREE DIMENSIONAL TRANSOESPHEAGEAL ECHOCARDIOGRAPHY

TEE was performed using Phillips iE33 equipped with a X7-2t transducer. Multi-plane 2D TEE evaluation was completed followed by acquisition of a 3D dataset. A live 3D zoom and full volume dataset was obtained. Images were rendered in the same way as for transthoracic echocardiography.

4.2.5 CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance imaging was undertaken using commercially available 1.5 Tesla MR scanners. Steady state free precession and gradient echo pulse sequences were used to assess valve morphology, ventricular function and to detect valvular regurgitation. By using phase contrast sequences, the forward and regurgitant volumes were calculated from phase-encoded velocity maps. Delayed enhancement gadolinium images were acquired to assess myocardial involvement.

4.2.6 STATISTICAL ANALYSIS

Data are expressed as either median and (first – to – third quartile) or number and percentage. The Mann-Whitney U test was used to compare continuous variables between groups. The Chi squared test was used to compare groups regarding categorical variables; when a cell frequency was less than five, the Fisher

exact test was used. All tests of significance were two sided. A probability value (p) of <0.05 was considered statistically significant. Statistical analysis was performed using StatsDirect Version 2.5.7 (StatsDirect, United Kingdom).

4.3 RESULTS

Two hundred and fifty-two patients were recruited over the study period and underwent 2D TTE. Fifty-two patients were found to have abnormalities consistent with carcinoid heart disease. 100 patients (40 patients with carcinoid heart disease) underwent additional 3D TTE. Twenty-two patients with carcinoid heart disease underwent 3D TEE and 10 patients with carcinoid heart disease had a CMR study.

There were no significant differences in age, sex, tumour characteristics or treatments received between those patients with or without carcinoid heart disease. Significantly higher levels of urinary 5-hydroxyindolacetic acid and plasma Chromogranin A were found in patients with carcinoid heart disease (Table 4.1).

Table 4.1 Baseline Demographics

		Carcinoid Heart Disease		**P value**
		Present (n = 52)	Absent (n = 200)	
Age (years)		64 (55 - 69)	64 (58 - 71)	0.4
Sex (female)		28 (54%)	98 (49%)	0.6
Duration of diagnosis (months)		5 (1 – 6)	4 (3 - 6)	0.42
Tumour Grade	Low	48 (92%)	194 (97%)	0.25
	Intermediate	4 (8%)	6 (3%)	0.25
Presence of Liver Metastases		50 (96%)	171 (86%)	0.06
Chromogranin A (pMol/L)		1000 (655 - 1000)	140 (56 - 484)	<0.0001
Urinary 5-hydroxyindolacetic acid (ųMol/24 hours)		800 (399 - 1490)	42 (0 – 205)	<0.0001
Therapies	Somatostatin Analogue	48 (92%)	161 (81%)	0.07
	Interferon	2 (4%)	8 (4%)	0.99
	Chemotherapy	6 (12%)	13 (7%)	0.24
	Surgery	19 (37%)	98 (49%)	0.15
	Targeted Radionuclide	18 (35%)	52 (26%)	0.21

Data are expressed as median and interquartile range or number (%). Picomoles per litre (pMol/L), Micromoles (ųMol).

4.3.1 RIGHT VENTRICLE, ATRIUM AND TRICUSPID VALVE

Abnormalities of the tricuspid valve were found in 47 (90%) patients with carcinoid heart disease. The mildest changes were thickening of the valve leaflets and subvalvular apparatus. The normal concave curvature of the leaflets was diminished causing them to become straightened. The dynamic motion of the leaflet during diastole was altered. The leaflets moved in a stiff “board like” fashion rather than the normal undulating motion. Only trivial or mild centrally directed tricuspid regurgitation was noted.

Thickening of the valve leaflets was associated with thickening of the chordae and papillary muscles. Chordae may become fused and shortened. This was associated with greater degrees of retraction and reduction excursion of the valve cusps. The extent to which each leaflet and subvalvular apparatus was affected was variable and produced several patterns of disease (Figure 4.1).

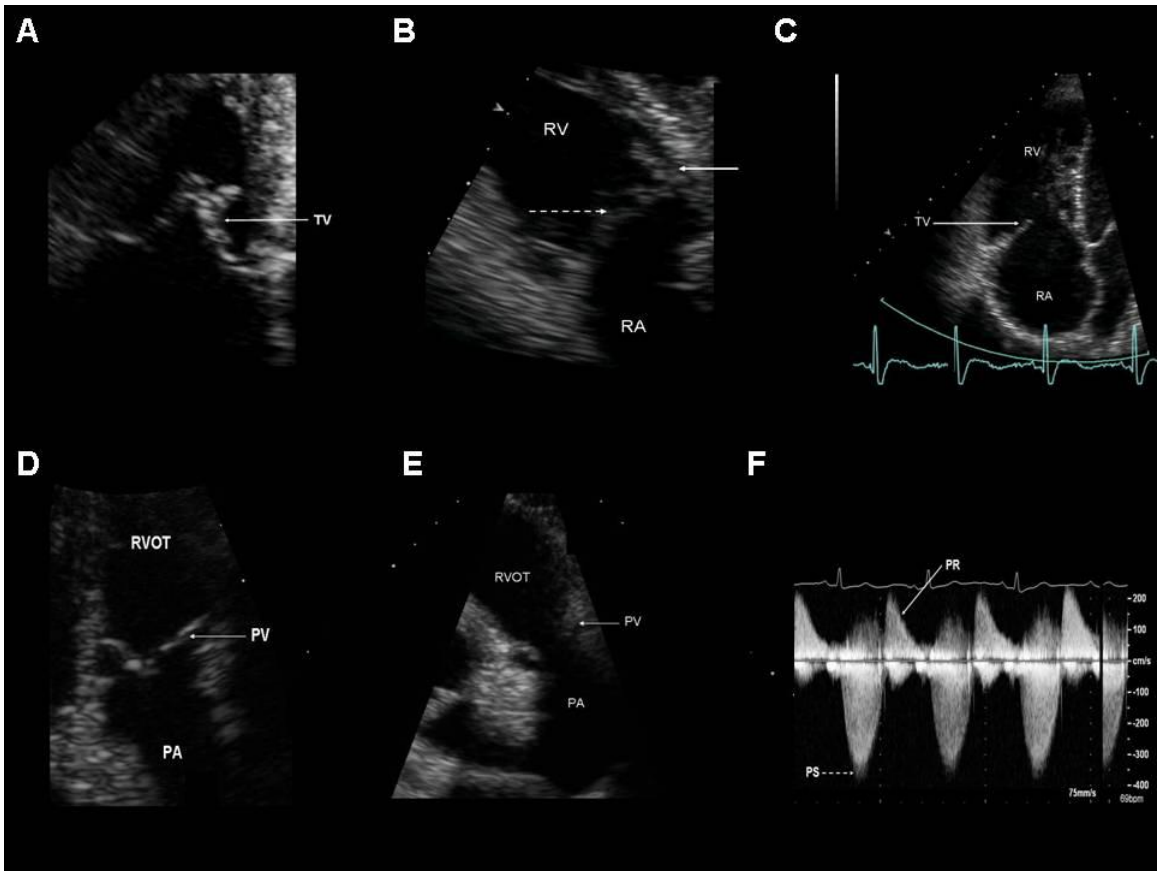


Figure 4.1 Two dimensional transthoracic echocardiogram. Right atrium (RA),right ventricle (RV), right ventricular outflow tract (RVOT), pulmonary artery (PA).
A. Diffuse thickening of septal and anterior tricuspid valve (TV) leaflets (arrow) and chordae. Leaflets are "stiffened" and "board like" and lose their normal curvature. Good excursion of the leaflets was present. Trivial/mild tricuspid regurgitation was present.
B. Fixed, thickened septal leaflet of tricuspid valve tethered to ventricular endocardium (arrow). Anterior leaflet, although thickened had good excursion (dashed arrow). The tip of anterior leaflet meets body of septal leaflet in diastole causing an eccentric jet of moderate tricuspid regurgitation.
C. Tricuspid valve (TV) leaflets (arrow) are thickened, fixed and retracted. This patient had "free flowing" severe tricuspid regurgitation. Both right atrium and right ventricle are dilated.
D. Mild thickening of pulmonary valve cusps. The cusps are "straightened" and lose their normal curvature.
E. Grossly thickened, fixed, and retracted pulmonary valve (PV) cusps (arrow) which do not co-apt.
F. Continuous wave Doppler demonstrating pulmonary stenosis (PS) with a peak gradient of 58 mmHG and peak velocity of 3.8 metres per second and the steep deceleration slope of severe pulmonary regurgitation (PR).

In the most severe cases leaflets were fixed, retracted and did not co-apt. This was associated with severe tricuspid regurgitation with a characteristic “Dagger shaped Doppler” profile and mild or moderate tricuspid stenosis (median gradient 3.5mmHg (interquartile range 2.9mmHg – 4.3mmHG). RV was dilated in 28 (93%) patients with severe tricuspid regurgitation (median 3.9cm (interquartile range 3.6cm – 4.2cm). The right atrium was enlarged in all patients with severe tricuspid regurgitation (median 26cm^2 (interquartile range 22cm^2 – 27cm^2) (Figure 4.1).

Three dimensional TTE visualisation of the tricuspid valve allowed an en-face view of the valve from either atrial or ventricular side to be obtained. In 22 patients, all three leaflets were thickened and fixed in a semi-open position. This caused a large area of non-coaptation. Detailed delineation of sub-valvular structures was obtained. Gross thickening, shortening and fusion of chordae together with papillary muscles was observed (Figure 4.2). The ability to visualise all three leaflets simultaneously allowed comparison between leaflets. Three patients had involvement of an isolated septal leaflet. This leaflet was thickened, retracted and fixed with preservation of mobility of anterior and posterior leaflets. This caused mal-coaptation of the cusps. Typically the tip of unaffected leaflet met the body of the affected leaflet. This was associated with a moderate, eccentrically directed jet of tricuspid regurgitation.

2D and 3D TEE assessment of the tricuspid valve allowed visualisation of valve leaflets in all patients who had poor transthoracic windows. Eighteen (90%) of patients with carcinoid heart disease who underwent TEE had thickened right ventricular endocardium with probable deposition of carcinoid plaque (Figure 4.2).

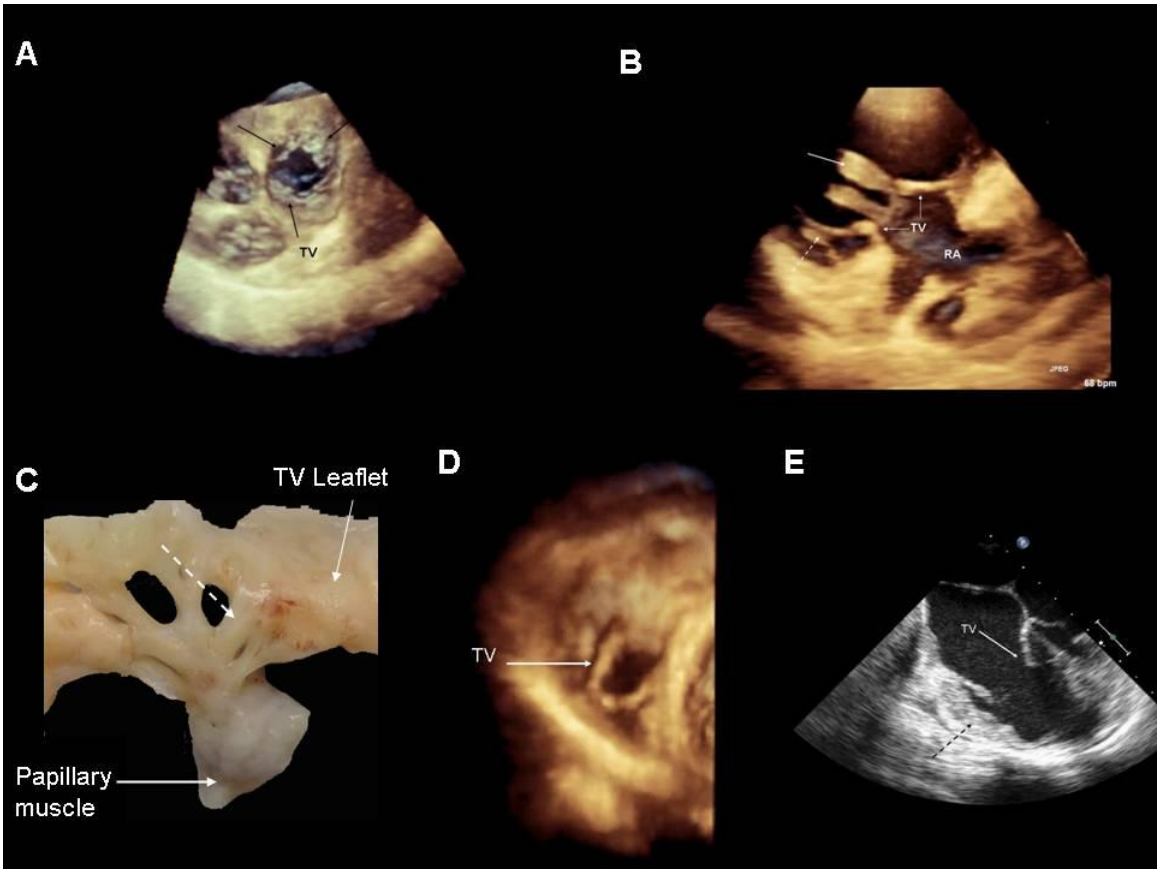


Figure 4.2 Three dimensional Transthoracic Echocardiogram.
A. View from the right atrium. Visualisation of anterior, septal and posterior tricuspid valve (TV) leaflets (arrow). Thickened tricuspid valve leaflets fixed and retracted towards ventricular walls.
B. Thickening, shortening and fusion of chordae tendinae (dashed arrow) and grossly thickened papillary muscles (arrow).
C. Resected tricuspid valve of patient in panel B. Papillary muscle encased in carcinoid "plaque". Thickening and fusion of chordae tendinae. Histology confirmed plaque composed of myofibroblasts.
D. View from the right ventricle apex. Thickened tricuspid valve (TV) leaflets (arrow) fixed in a semi-open position. Large area of non-coaptation.
E. Transoesphageal echocardiogram demonstrating carcinoid involvement of tricuspid valve (TV) (arrow). Thickened endocardial surface of the right ventricle with carcinoid plaque deposition (black dashed arrow).

4.3.2 PULMONARY VALVE

Abnormalities of the pulmonary valve were found in 36 (69%) of patients with carcinoid heart disease. Changes in valve morphology were similar to the tricuspid valve. With mild involvement, valve cusps were diffusely thickened which caused them to become straightened. With more severe disease varying degrees of retraction and reduction in excursion of valve cusps was seen. In severe cases valve cusps were fixed, retracted and thickened with severe pulmonary regurgitation. The characteristic sharp deceleration slope of severe pulmonary regurgitation was seen. The peak velocity through the pulmonary valve ranged from 1.6 to 3.8 metres per second (Figure 4.1).

3D TTE allowed identification of all three pulmonary valve cusps simultaneously. In two patients 3D TTE demonstrated marked thickening of a single cusp of the pulmonary valve (demonstrating probable carcinoid plaque deposition) with the other two cusps unaffected (Figure 4.3). These abnormalities were not on identified on 2D images. Additionally 3D TTE allowed the anatomical relationship between all three leaflets and endocardial surfaces as well as the degree of coaptation of the cusps to be assessed. In patients with severe disease 3D TTE demonstrated constriction of the pulmonary valve annulus with thickened, partially retracted and fixed pulmonary cusps causing non-coaptation of the cusps and significant stenosis. Post-stenotic dilatation of the pulmonary artery was seen. In three patients the arterial surfaces of the pulmonary valve cusps were grossly thickened to the extent they completely filled the valve sinus. This made it difficult to demarcate the valve cusps from underlying endocardium (Figure 4.3).

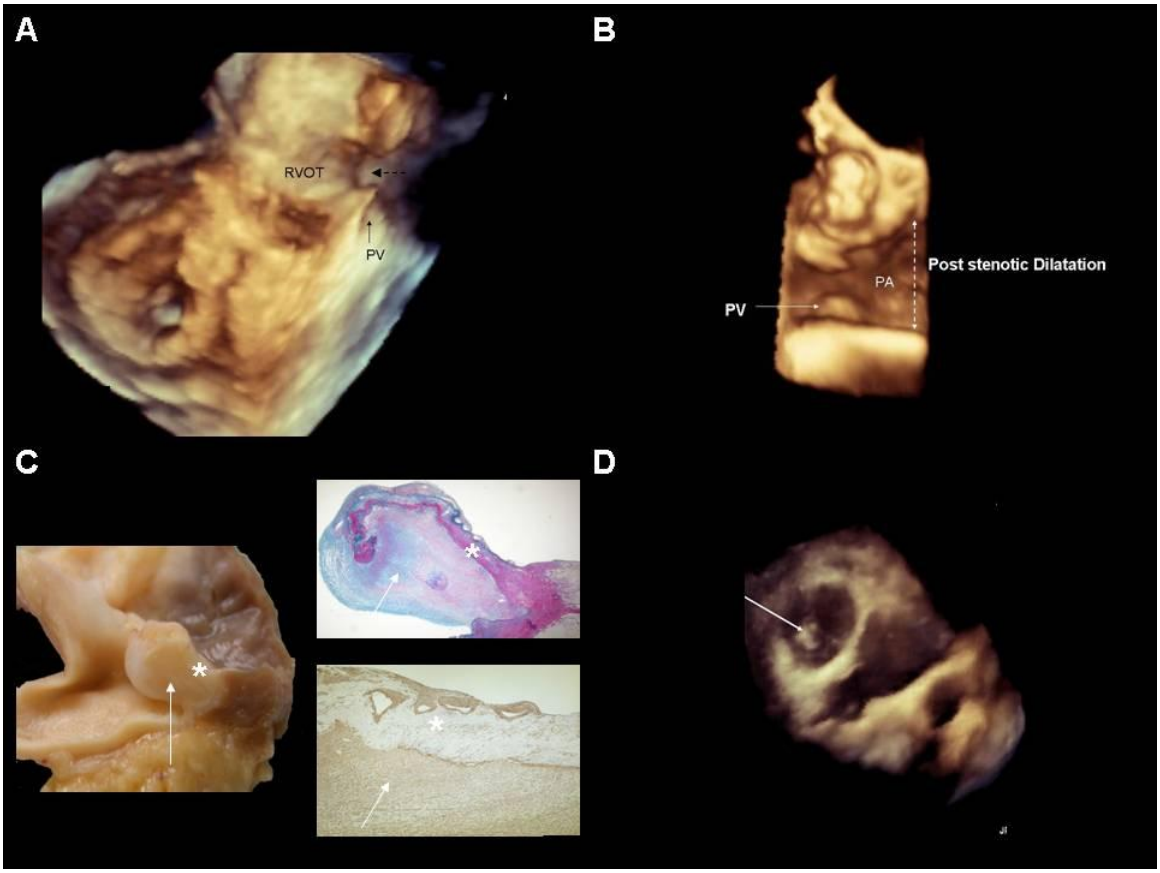


Figure 4.3 Three dimensional echocardiography of pulmonary valve. Right ventricular outflow tract (RVOT), pulmonary artery (PA).
A. Thickened, fixed and retracted pulmonary valve (PV) cusps (arrow) coupled with constriction of pulmonary valve annulus causing severe pulmonary stenosis. Pulmonary valve (PV) cusps do not co-apt leading to a large area of non-coaptation (dashed arrow).
B. Post stenotic dilatation of the pulmonary artery (dashed arrow) in a patient with carcinoid involvement of the pulmonary valve (PV) and severe pulmonary stenosis. Pulmonary valve sinus obliterated and fused with valve cusp (arrow).
C. Resected pulmonary valve of patient in panel B. Gross, nodular thickening of valve cusp causing obliteration of valve sinus (arrow). The normal cusp (*****) just being discernable on the ventricular surface of the nodule. Inset upper right. Histopathological examination. Thickening of valve cusp is due almost entirely to deposition of myxoid tissue on the arterial surface of the cusp (arrow) which has otherwise retained its normal structure and shape (*) (Alcian Blue – Elastic Van Gieson). Inset lower right. Myxoid tissue is due to proliferation of myofibroblasts, shown here as brown-staining spindle cells with an antibody to smooth muscle actin (arrow). The cusp itself (*) does not stain with this antibody (Streptavidin-biotin, SMA mab @ dilution 1:100, Dako Ltd).
D. Carcinoid plaque deposition on anterior cusp of pulmonary valve (PV) (arrow) with preserved mobility. Other two cusps unaffected.

3D TEE provided anatomic information regarding relationship of the all three pulmonary valve cusps including the relationship of cusps to the ventricular walls, mobility and thickness as well as allowing assessment of pulmonary valve annulus constriction and visualisation of right ventricular outflow tract and pulmonary artery.

4.3.4 LEFT SIDED HEART VALVES AND FORAMEN OVALE

Fifteen (29%) patients had left sided valvular involvement. Thirteen (87%) of these were associated with a patent foramen ovale. The two patients with left sided disease but without patent foramen ovale both had multiple bronchial carcinoid metastases. Three patients with a severe degree of shunting on their bubble contrast had severe mitral and/or aortic valve regurgitation. The remaining 10 patients with mild or moderate degree of shunting had mild or moderate mitral or aortic regurgitation.

4.3.5 AORTIC VALVE

Aortic valve involvement was seen in 14(27%) cases of carcinoid heart disease. Diffuse thickening of valve cusps was identified together with mild aortic regurgitation. One patient had gross thickening of the non coronary cusp with mild thickening of right coronary cusp. Two patients had severe aortic regurgitation. Visualisation of the valve cusps was poor on 2D TTE but they were clearly thickened. On 2D TEE gross thickening, retraction of all three leaflets which were almost fixed leading to non-coaptation of the leaflets was found (Figure 4.4).

4.3.6 MITRAL VALVE

Mitral valve involvement was seen in 15 (29%) patients with carcinoid heart disease. Similar to the aortic valve, patients had diffuse thickening of both leaflets although one patient had a nodular like involvement. Trivial or mild mitral regurgitation was present. Three patients had grossly thickened papillary muscles and shortened chordae. This caused tenting of the mitral valve leaflets and associated severe mitral regurgitation. Although leaflet mobility was restricted no significant stenosis was seen. 2D and 3D TEE enabled detailed assessment of the sub-valvular apparatus and visualise valve anatomy.

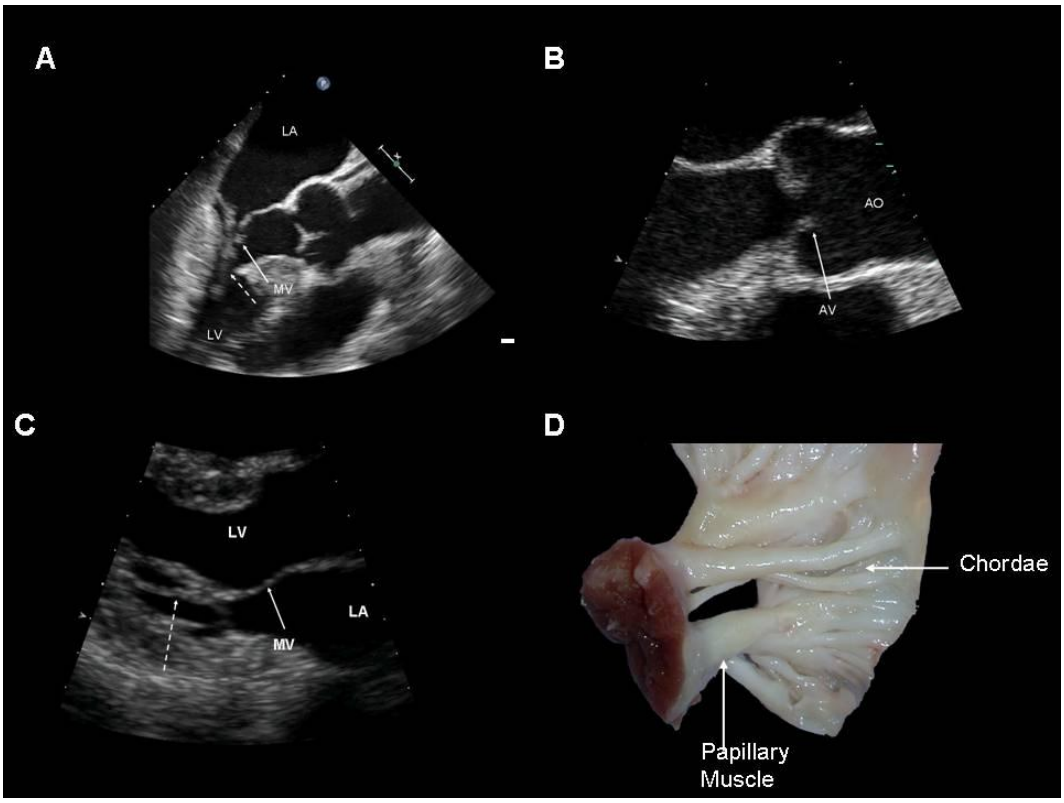


Figure 4.4 Left sided Carcinoid Heart Disease. Left ventricle (LV), left atrium (LA), aorta (Ao), right atrium (RA), right ventricle (RV).

A. Two dimensional tranoesphageal echocardiogram demonstrating diffusely thickened mitral valve (MV) (arrow) and sub-valvular involvement of mitral valve chordae (dashed arrow).

B. Two dimensional transoesphageal echocardiogram demonstrating fixed, thickened and retracted aortic valve (AV) cusps (arrow). This was associated with severe aortic regurgitation.

C. Two dimensional transthoracic echocardiogram. Diffusely thickened mitral valve leaflets, chordae and papillary muscles. Minimal mitral regurgitation was noted.

D. Resected mitral valve of patient in panel C. Papillary muscle encased in white “carcinoid plaque”. Thickened and partially fused chordae tendinae. Histology confirmed plaque composed of myofibroblasts.

4.3.7 MYOCARDIAL METASTASES

Metastases were detected in 2 (3.8%) of patients with carcinoid heart disease. One patient with valvular involvement had a 1.2cm X 10mm metastasis in the right atrium and one patient without valvular involvement had multiple metastases in the inferior (3.3cm X 2.2cm) and anterior walls (4.1cm X 2.9cm and 3.4cm X 5.6cm) as well as basal septum of the left ventricle. Two dimensional TTE and TEE allowed visualisation of the cardiac masses. However only an estimate of their diameter could be obtained as it was difficult to demarcate the mass from surrounding myocardium.

3D TTE demonstrated better delineation of the mass to adjacent structures. CMR allowed identification of location, number, size and relationship of cardiac metastases to surrounding structures. Gallium-68 octreotate positron emission tomography demonstrated avid focal uptake in the two masses suggesting metastatic spread (figure 4.5).

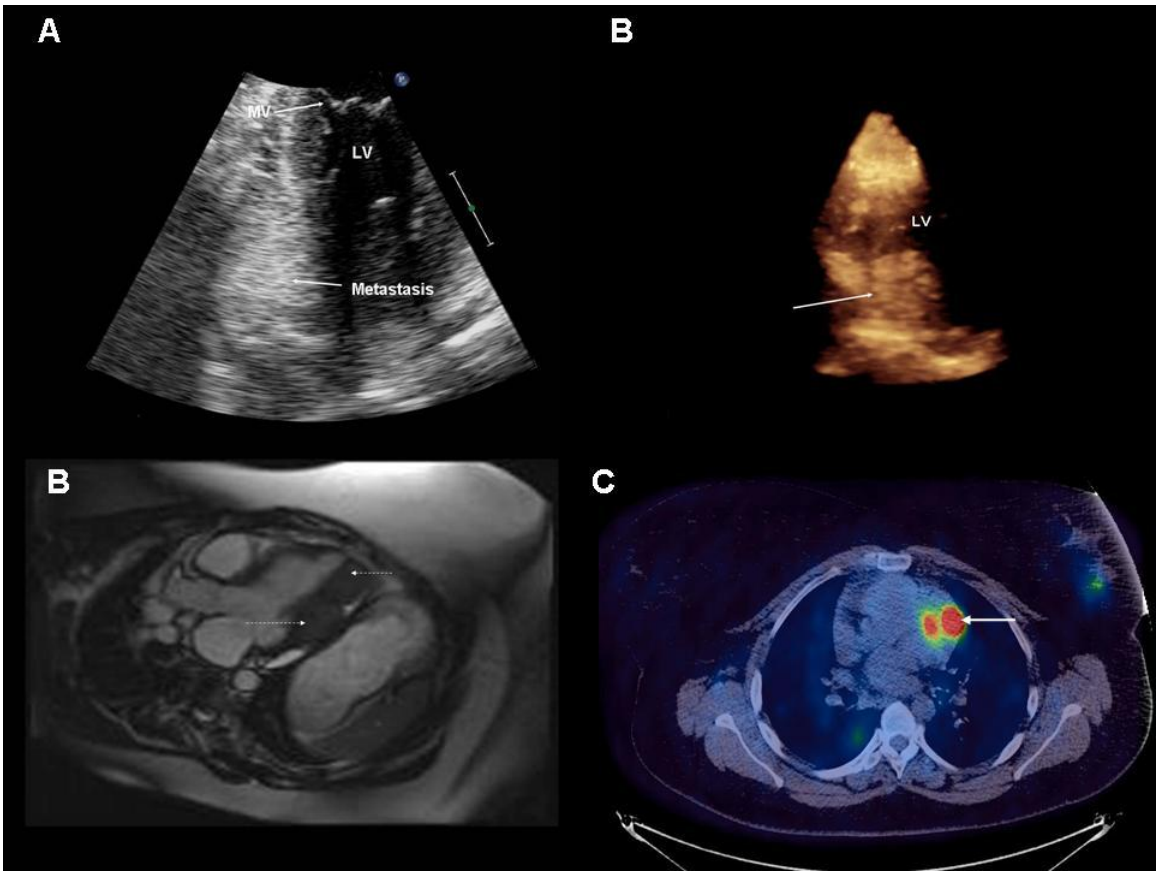


Figure 4.5

A. Tranoesphageal echocardiogram demonstrating large mass in mid to distal inferior wall of the left ventricle (arrow).

B. Three dimensional transthoracic echocardiogram showing well demarcated, rounded mass (arrow) in the posterior wall of left ventricle (LV).

C. Cardiac Magnetic Resonance demonstrating two well demarcated masses in the mid infero-lateral wall extending to the apex (dashed arrow). Masses are limited to myocardium with no extra cardiac extension.

D. Gallium 68 Octreotate PET demonstrating focal avid uptake of tracer in the region of the two masses (arrow) suggesting metastatic carcinoid tumour.

4.3.8 CARDIAC MAGNETIC RESONANCE IMAGING

Ten patients with carcinoid heart disease underwent cardiac magnetic resonance imaging (Figure 4.6). Eight patients had dilated right ventricles and 2 patients had impaired right ventricular function. Thick, fixed and retracted tricuspid valve leaflets which did not co-apt were demonstrated in all 10 patients. Quantification of tricuspid regurgitation was severe in all cases. One patient had mild tricuspid stenosis.

Eight out of ten patients had thickened pulmonary valve cusps with restricted motion. All of these patients had either mild or moderate pulmonary stenosis. Five of these patients had mild pulmonary regurgitation and three had moderate pulmonary regurgitation. No patient demonstrated myocardial involvement on late gadolinium enhancement imaging.

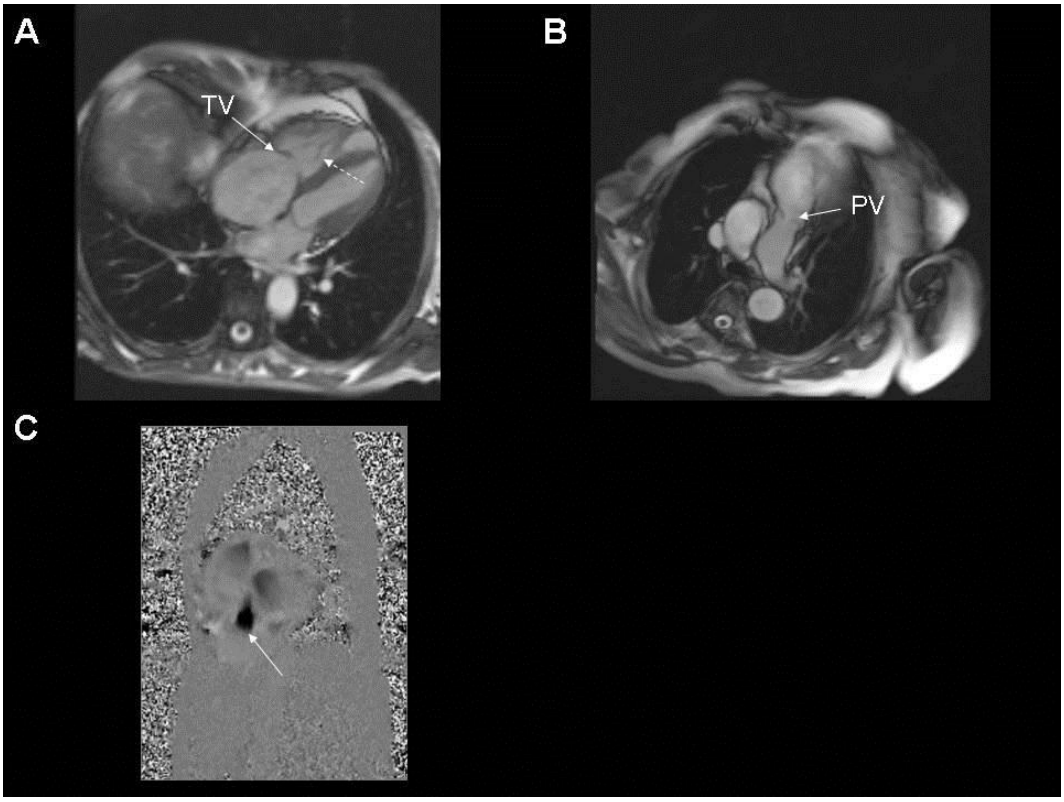


Figure 4.6 Cine Cardiac Magnetic Resonance Imaging.

A. 4 Chamber View (Systole). Dilated right atrium and ventricle. Thickened, fixed and retracted tricuspid valve leaflets (arrow) with associated subvalvular involvement (dashed arrow).

B. Thickening, retraction and reduced excursion of the pulmonary valve leaflets (arrow).

C. Phase contrast flow map (short axis view in systole). Severe tricuspid regurgitation demonstrated by black retrograde jet (arrow).

4.3.9 Pathological Correlation

Twenty-one patients with carcinoid heart disease underwent cardiac valve replacement surgery. Gross morphological and histological examination of the excised valves was performed in all patients. The identification of carcinoid heart disease in individual valves by echocardiography correlated with findings at pathological examination.

In one patient with severe right sided valvular dysfunction, echocardiography demonstrated diffuse thickening of mitral valve leaflets and chordae with trivial regurgitation (Figure 4C +D). At the time of surgery, visual inspection identified features of carcinoid heart disease in this valve, therefore mitral valve replacement was performed in addition to tricuspid and pulmonary valve replacement. Histological examination confirmed the diagnosis. In one patient (with bronchial in addition to liver metastases) with severe left sided valvular dysfunction, echocardiography demonstrated mild thickening and retraction of pulmonary and tricuspid valves. This was associated with mild pulmonary stenosis and moderate tricuspid regurgitation. The patient underwent replacement of all 4 valves. Histological examination confirmed carcinoid involvement of all valves.

4.6 DISCUSSION

This study describes the features of carcinoid heart disease encompassing the spectrum of disease from early to advanced disease and encompassing both 2D and 3D echocardiography as well as cardiac magnetic resonance imaging and positron emission tomography imaging.

Echocardiography remains pivotal in the investigation of patients with carcinoid syndrome and suspected carcinoid heart disease. The classical features of advanced carcinoid heart disease typically involving the tricuspid valve and pulmonary valve have been well-described (5, 25, 71). However the spectrum of disease is wide.

In this study we have identified several patients with diffuse thickening of valve leaflets or isolated thickening of a single valve leaflet without significant reduction in leaflet mobility or the development of valvular regurgitation. Histological examination in two of these patients demonstrated changes typical of carcinoid heart disease. Therefore, these findings may represent the early stages of carcinoid heart disease.

We have demonstrated greater involvement of the sub-valvular apparatus and valve leaflets can lead to a wide heterogeneous array of appearances and functional consequences. These findings are in keeping with previous necropsy studies (24), where the location, extent and pattern of “plaque” deposition on valvular and sub-valvular structures is highly variable with both focal and diffuse patterns of plaque deposition described.

Advanced techniques such as 3D TTE or 3D TEE are helpful in identifying and assessing valve pathology, particularly in the pulmonary and tricuspid valve, as all leaflets may not be visualised on 2D echocardiography. The ability to crop images and change the plane of view allowed detailed assessment of the sub-valvular apparatus and delineation of the relationship between valve leaflets to each other and surrounding structures and the endocardium.

Cardiac magnetic resonance imaging can be a valuable adjunct in the investigation of these patients particularly where echocardiographic windows are

poor or structures such as the pulmonary value are difficult to visualise. Morphological features of severe carcinoid heart disease can be delineated with assessment of valvular regurgitation, stenosis and quantification of ventricular volumes. The technique enables measurement of size of metastases and is able to offer information regarding extension into extra cardiac structures which is not available on echocardiographic techniques.

Cardiac metastases from carcinoid tumour are rare. In this study 4% of patents had cardiac metastases. Although echocardiographic and cardiac magnetic imaging techniques may be able to accurately identify and characterise the mass they are not able to elucidate whether it is a carcinoid metastases or another primary cardiac tumour. Carcinoid tumours express several somatostatin receptors, particularly receptors 2 and 5. Gallium-68 octreotate positron emission tomography utilises a somatostatin analogue labelled with gallium-68 tracer. Neuroendocrine tumour cells will take up the somatostatin analogue and this will be visible on positron emission tomography as it is labelled with Gallium-68. Recent data suggest greater than 97% sensitivity and 92% specificity of Gallium-68 octreotate positron emission tomography for metastatic deposits in patients with neuroendocrine tumours (72).

A limitation of the present study is pathological correlation was not available in all patients. This was because patients with mild abnormalities or those with progressive carcinoid tumour would not undergo valve replacement surgery. The number of patients studies may seem relatively small, however, given the relative rarity of the condition this represents one of the largest cohorts of carcinoid patients studied and a full range of pathology has been described.

4.7 CONCLUSIONS

Carcinoid heart disease is a heterogeneous disease with a wide spectrum of echocardiographic findings. An integrated approach using multiple modalities should be adopted in patients at risk of developing carcinoid heart disease in order to identify pathology and assess severity of disease.

CHAPTER 5: RISK FACTORS FOR THE DEVELOPMENT AND PROGRESSION OF CARCINOID HEART DISEASE

5.1 INTRODUCTION

5.2 METHODS

5.2.1 CLINICAL EVALUATION

5.2.2 BIOCHEMICAL MARKERS

5.2.3 ECHOCARDIOGRAPHY

5.2.4 QUANTIFICATION OF CARCINOID HEART DISEASE

5.2.5 RADIOLOGICAL ASSESSMENT

5.2.6 STATISTICAL ANALYSIS

5.3 RESULTS

5.3.1 CHANGES IN CLINICAL, BIOCHEMICAL AND RADIOLOGICAL PARAMETERS

5.3.2 RISK FACTORS FOR THE PROGRESSION AND DEVELOPMENT OF CARCINOID HEART DISEASE

5.3.3 RATE OF DEVELOPMENT AND PROGRESSION OF VALVULAR ABNORMALITIES

5.4 DISCUSSION

5.5 CONCLUSION

5.1 INTRODUCTION

Gastrointestinal carcinoid tumours are relatively rare, usually slow growing malignancies. Carcinoid syndrome occurs when the tumour metastasises to the liver and vasoactive amines and peptides secreted by the tumour, including 5-HT, are able to reach the systemic circulation. Manifestations of carcinoid syndrome include symptoms of flushing, diarrhoea and wheeze (67,73).

The development of valvular heart disease in these patients, commonly termed carcinoid heart disease, is classically characterised by the deposition of carcinoid plaque on the endocardium of the right side of the heart. Subsequent thickening, retraction and fixation of right sided heart valve leaflets causes a combination of valvular regurgitation and stenosis (5). Progression of valvular dysfunction eventually leads to right heart failure and significantly impairs survival (5,74,).

The mechanisms for the development of valvular dysfunction are incompletely understood. Elevated levels of 5-HT are thought to be a key mediator in the development of carcinoid heart disease (19,20). However, Robiolo et al (19) noted more than 50% of patients with elevated 5-HT did not develop carcinoid heart disease. Therefore other co-factors may also be involved.

The identification of potentially modifiable risk factors for the development of carcinoid heart disease is desirable. The purpose of the present study was to prospectively identify clinical, metabolic, and tumour characteristics which predict patients with carcinoid syndrome who are at risk of developing or progression of carcinoid heart disease.

5.2 METHODS

We conducted an observational cohort study. Patients with histologically proven metastatic carcinoid tumour of mid-gut origin and carcinoid syndrome were consecutively and prospectively recruited from the neuroendocrine tumour clinic at the Royal Free Hospital, London, UK from April 2006. All patients gave written, informed consent for the study. The study was approved by the institution's local ethics committee.

5.2.1 Clinical Evaluation

All patients were evaluated at 4 to 6 monthly intervals in the neuroendocrine tumour clinic. Symptoms of carcinoid syndrome were assessed during these visits on the basis of a symptom score. This included the number of flushing episodes and bowel movement over each 24 hour period for the last 7 days. Patients were classified as having symptomatic progression if there was a greater than 50% increase in the median daily number of flushing episodes or bowel motions compared to either last clinic visit or baseline (i.e the first study) visit.

5.2.2 Biochemical Tumour Markers

5-HIAA and plasma CgA were measured at baseline and at each clinical evaluation (4-6 month intervals). 24 hour urine 5-HIAA samples were collected in bottles containing acetic acid. Samples were evaluated using reversed phase high performance liquid chromatography assay. CgA was measured using DAKO

Chromogranin A Enzyme-linked immunosorbent assay (DAKO A/S, Glostrup, Denmark). All samples were analysed at the Peptide Laboratory, Hammersmith Hospital, London, UK. Patients were classified as having biochemical progression if there was a 50% increase of biochemical markers compared to either previous clinic visit or the baseline value.

5.2.3 Echocardiography

A baseline comprehensive two dimensional transthoracic echocardiogram was performed. Repeat echocardiograms were performed at 6 monthly intervals or sooner if clinically indicated. Valve morphology and function was evaluated in several views including the use of pulse, continuous wave and colour Doppler. Pulmonary valve was visualised from high parasternal, long axis view of right ventricular outflow tract and parasternal short axis view. Tricuspid valve was visualised from low parasternal long axis view of right ventricular inflow tract, short axis and apical four chamber view. Aortic and mitral valves were assessed from parasternal long axis, short axis, apical four, three and two chamber views.

Valvular regurgitation was quantified into grades on the basis of an integrated approach including valve morphology, semi-quantitative parameters (colour flow jet area/width) and quantitative parameters (vena contracta, proximal isovelocity surface area) together with supportive signs in accordance with American Society of Echocardiography guidelines (52). Valve stenosis was quantified into grades based on parameters recommended by American Society of Echocardiography guidelines (53). Tricuspid stenosis was graded (mean gradient across valve) as mild (2 - 5mmHg), moderate (5 - 8mmHg) or severe (>8mmHg). Right and left ventricular

function and sizes were assessed and calculated according to American Society of Echocardiography guidelines. Right ventricular diameter was measured at the mid-cavity of the right ventricle in the apical four chamber view. Right ventricular function was measured using fractional area change. Left ventricular ejection fraction was calculated by the modified Simpson's method from apical four and two chamber view (61).

5.2.4 Quantification of carcinoid heart disease

Carcinoid heart disease was defined as the presence of characteristic thickening, reduced excursion and retraction of valvular leaflets (with associated evidence of valvular stenosis or regurgitation) in the absence of other aetiologies.

Quantification of severity was performed by scoring each valve individually. The score incorporated leaflet thickness, mobility, retraction and valvular regurgitation and stenosis (Table 5.1). Right ventricular size and function were graded according to American Society of Echocardiography guidelines. Scores of 0, 1, 2 and 3 were assigned to normal, mild, moderate and severe right ventricular dilatation and dysfunction respectively. The sum of the scores for each valve together with the right ventricle score produced a total score.

All echocardiograms were reviewed and scored by a reader blinded to clinical, biochemical and radiological data. A second reader reviewed and scored a sample of 25 (10%) patients to calculate inter-observer variability. A sample of 10 echocardiograms was re-read to calculate intra-observer variability. Patients were defined as having progression of carcinoid heart disease if their score increased by

25% or more. Patients were defined as having developed carcinoid heart disease if features of carcinoid heart disease was not present on previous echocardiogram.

Table 5.1 Valvular Abnormalities Score

	Score			
	0	1	2	3
Leaflet Thickness	< 3mm	≥3mm to <4mm	≥4mm to <5mm	≥5 mm
Leaflet Mobility	Normal	Leaflet excursion ≤75% but >50% of normal	Leaflet excursion ≤50% but >25% of normal	Leaflet excursion ≤25% of normal or fixed
Leaflet Retraction	Normal	Mild	Moderate	Severe
Valve Stenosis	Normal	Mild	Moderate	Severe
Valve Regurgitation	Normal	Mild	Moderate	Severe

5.2.5 Radiological Assessment

A baseline triple phase CT of the thorax, abdomen and pelvis was undertaken. Re-staging CT scan was performed at 4-6 monthly intervals. All CT scans were reported by radiologists with expertise in neuroendocrine tumours. Radiological assessment was based on the RECIST criteria (75). Patients were classified as being progression free if a less than 20% increase or 30% decrease in tumour size occurred. Patients were classified as having progressive disease if there was a greater than 20% increase in size of tumour lesions or the development of new lesions. Patients were classified as having an objective (partial) response if tumour size decreased by 30% or more. CT scans were compared both to the previous scan and the baseline CT scan.

5.2.6 Statistical Analysis

Descriptive statistics were used for patients and tumour characteristics at study entry. Data are expressed as either median and interquartile range or number and percentage. The Mann-Whitney U test was used to compare differences between continuous variables and the Chi squared test was used to compare categorical variables. When the expected number in any cell was less than five the Fisher exact test was used. For comparison of paired variables the Wilcoxon test was used. Due to the relatively rare incidence of carcinoid tumours, sample size was based on identification of all eligible patients within our cohort of patients and not on statistical considerations.

A time to event analysis was undertaken using a Poisson regression model (rather than a survival analysis as there was no natural time zero). Univariate Poisson regression analysis was performed to identify risk factors for the progression of carcinoid heart disease. The following variables were included in the analysis: age, sex (female), progression of biochemical markers (5-HIAA and CgA), progression of clinical symptoms (diarrhoea and flushing), progression of liver metastases and treatment with chemotherapy, somatostatin analogue, targeted therapy and surgical resection. The following continuous variables were dichotomized (a priori) for the analysis: CgA (<500pmol/L and ≥500pmol/L), number of liver metastases (<5 and ≥ 5), number of flushes over 24 hours (<3 and ≥3) and number of episodes of diarrhoea over 24 hours (<5 and ≥ 5). 5-HIAA was split into 4 groups <300 μmol/24 hour, ≥300 to 599 μmol/24 hour, ≥600 to 899 μmol/24 hour and ≥900μmol/24 hour. Multivariate Poisson analysis was performed to identify independent predictors of the progression of carcinoid heart disease. To account for

changes in variables during the study period the following variables were considered as time updated variables: 5-HIAA, CgA, episodes of diarrhoea and flushing. Therefore the effect of the most recent level of the variable on the outcome was considered. Inter-observer agreement between echocardiography readers was expressed as the percentage with exact agreement. All tests of significance were two sided. A probability value (p) of <0.05 was considered statistically significant. Statistical analysis was performed using StatsDirect Version 2.5.7 (StatsDirect, United Kingdom).

5.3 RESULTS

Two hundred and fifty-two patients were recruited. Median follow up was 29 months (interquartile range, 24-36). At baseline 41 patients had carcinoid heart disease. 44 patients either developed carcinoid heart disease during the study period or had progression of existing carcinoid heart disease (15 patients developed and 29 patients progressed). 34 patients died during the study period (13 patients had carcinoid heart disease). 5 patients were lost to follow up during the study period.

Baseline demographics are reported in table 5.2. There were no significant differences between those with progression of carcinoid heart disease and those without progression in terms of baseline age, sex, follow-up, duration of diagnosis of carcinoid tumour, presence of liver metastases or treatment modalities received. There were significantly greater baseline levels of 5-HIAA and Chromogranin in those patients with progression of carcinoid heart disease.

Table 5.2 Baseline Demographics

		Progression of Carcinoid Heart Disease (n = 44)	No Progression of Carcinoid Heart Disease (n = 208)	P value
Age (years)		60 (55-67)	63 (55-69)	0.35
Sex (Female)		22 (50%)	110 (52.9%)	0.86
No of Echocardiograms		5 (3.5 – 6)	5 (3 – 6)	0.09
Follow up (Months)		32 (24-36)	29 (24-34)	0.10
Duration of diagnosis of carcinoid tumour(Months)		5 (3-6)	4 (3- 7)	0.67
Tumour Grade	Intermediate	4 (9.1%)	11 (5.3%)	0.31
	Low	40 (90.9%)	197 (94.7%)	0.31
Presence of Liver Metastases		42 (95.5%)	186 (89.4%)	0.27
Therapy	Somatostatin Analgoue	42 (95.5%)	178 (85.6%)	0.08
	Duration of somatostatin therapy (months)	29.5 (18- 44)	27 (18 – 41)	0.85
	Interferon	4 (9.1%)	10 (4.8%)	0.28
	Chemotherapy	4 (9.1%)	12 (5.8%)	0.49
	Targeted Radionuclide	17 (38.6%)	56 (27%)	0.14
	Surgical Resection	15 (34.1%)	100 (48.3%)	0.10
5-Hydroxyindolacetic Acid (µMol/24 hours)		465 (244 -1324)	46.5 (0-205)	<0.001
Chromogranin A (pMol/L)		990 (323-1000)	206 (72 – 529)	<0.001

Data are expressed as median and interquartile range or number (%). Picomoles per litre (pMol/L), Micromoles (µMol).

5.3.1 Changes in Clinical, Biochemical and Radiological Parameters

In patients with development or progression of carcinoid heart disease there was a significant increase in levels of 5-HIAA (median 791μmol/24hr (interquartile range, 581 to1084)) and episodes of flushing (median 4.5 episodes per 24hours (interquartile range, 4 to 6)) at the time of progression compared to the previous 6 months (median 5HIAA 460.5 μmol/24hr (interquartile range, 309 to 948.5) and median flushing episodes per 24 hours, 2 (interquartile range 1 to 3)). There were no significant changes in median levels of CgA or episodes of diarrhoea during the same period (Table 5.3). Nineteen of the 44 patients (43%) with progression of carcinoid heart disease had an increase in the size of liver metastases (progressive disease by RECIST criteria on CT).

In patients without development or progression of carcinoid heart disease there was no significant change in median levels (baseline compared to peak) of 5-HIAA, CgA or episodes of either diarrhoea or flushing during the study period (Table 3). Twenty-five out of 208 patients (12%) without progression of carcinoid heart disease had an increase in the size of liver metastases (progressive disease by RECIST criteria on CT)

Table 5.3 Changes in clinical, biochemical parameters during the study period

	Progressive Carcinoid Heart Disease (n=44)		
	At Time of Progression	Previous 6 Months	Significance
5-Hydroxyindolacetic Acid (µMol/24 hours)	791 (581-1084.5)	460.5(309-948.5)	0.001
Chromogranin A (pMol/L)	1000(428.5-1000)	976.5(323-1000)	0.17
Episodes of flushing per 24 hours	4.5 (4-6)	2.0 (1-3)	<0.001
Episodes of diarrhoea per 24 hours	2 (2-3)	3 (2-4.5)	0.09
	No progression of Carcinoid Heart Disease (n=208)		
	Baseline	Peak	Significance
5-Hydroxyindolacetic Acid (µMol/24 hours)	52.5(0-205)	55(0-205)	0.09
Chromogranin A (pMol/L)	206(72-520)	209.5(68.5-561.5)	0.08
Episodes of flushing per 24 hours	1(0-1)	1(0-1)	0.45
Episodes of diarrhoea per 24 hours	2(1-3)	2(0.5-3)	0.45

Data are expressed as median and interquartile range. Picomoles per litre (pMol/L), Micromoles (µMol).

5.3.2 Risk factors for the progression and development of carcinoid heart disease

Incidence Rate ratio (IRR) for the development or progression of carcinoid heart disease are displayed in table 5.4. Flushing of greater than 3 episodes over 24 hours, progressive symptoms (flushing), 5-HIAA levels of ≥300 to 599 µmol/24hr, 5HIAA ≥600 to 899 µmol/24hr, 5HIAA ≥900µmol/24hr, progression of 5-HIAA, the presence of more than 5 liver metastases and progression of liver metastases were associated with progression of carcinoid heart disease.

In a multi-variate model (table 5.5) independent predictors of the development or progression of carcinoid heart disease were flushing of greater than 3 episodes per 24 hours and 5-HIAA levels of ≥300. There was stepwise increase in the risk of progression of carcinoid heart disease as levels of 5-HIAA increased. Compared to those patients with a 5HIAA <300 µmol/24 hour, those who had 5HIAA levels of ≥300 to 599, 600-899 and >900 µmol/24 hour had 2.74, 3.16 and 3.40 times the risk of progression of carcinoid heart disease, respectively.

Table 5.4 Univariate Analysis of Risk Factors For The Development and Progression of Carcinoid Heart Disease

Parameter		Incidence rate ratio	95% Confidence Interval	Significance
Age		0.99	0.97-1.02	0.49
Sex (Female)		0.87	0.48-1.57	0.64
Diarrhoea >5 stools/24 hours		1.95	0.94- 4.05	0.08
Progressive Symptoms (Diarrhoea)		1.27	0.53 – 3.01	0.58
Flushing > 3 episodes/24 hours		26.87	10.59 – 68.18	<0.001
Progressive Symptoms (Flushing)		21.46	9.98 – 46.20	<0.001
5-Hydroxyindolacetic Acid (µMol/24hours)	<300	0.01	0.00 – 0.09	<0.001
	300 – 599	3.26	1.76 – 6.02	<0.001
	600 – 899	4.51	2.36 – 8.61	<0.001
	>900	5.17	2.71 – 9.89	<0.001
Progressive Biochemical Markers (5-HIAA)		10.07	5.56 – 18.23	<0.001
Chromogranin A > 500 pMol/L		1.73	0.95 – 3.15	0.07
Progressive Biochemical Markers (CgA)		1.82	0.84 – 3.91	0.13
>5 Liver Metastases		4.19	1.95 – 9.01	<0.001
Progressive Disease (Radiological)		2.85	1.57 – 5.17	<0.001
Tumour Grade - Intermediate		0.55	0.20 – 1.55	0.26
Therapy	Chemotherapy	1.39	0.50 – 3.89	0.53
	Somatostatin Analogue	1.75	0.54 – 5.63	0.35
	Targeted Therapy	1.63	0.90 – 2.96	0.11
	Interferon	0.98	0.30 – 3.16	0.97
	Surgical Resection	0.54	0.29 – 1.03	0.06

Picomoles per litre (pMol/L), Micromoles (µMol).

Table 5.5 Multi-variate Analysis of Risk Factors For The Development and Progression of Carcinoid Heart Disease

Factor		Incidence Rate Ratio	95% Confidence Interval	Significance
Flushing > 3 episodes per 24 hours		5.20	1.33 – 20.40	0.02
Progressive Symptoms (Flushing)		2.72	0.87 – 8.50	0.08
5-Hydroxyindolacetic Acid (µMol/24hours)	300 – 599	2.74	1.13 – 6.65	0.03
	600 – 899	3.16	1.07 – 9.36	0.04
	>900	3.40	1.42 – 8.17	0.01
Progressive Biochemical Markers (5-Hydroxyindolacetic acid		1.45	0.69 – 3.03	0.33
> 5 Liver Metastases		0.88	0.38 – 2.04	0.77
Progressive Tumour (Radiological)		1.23	0.64 – 2.37	0.53

Picomoles per litre (pMol/L), Micromoles (µMol).

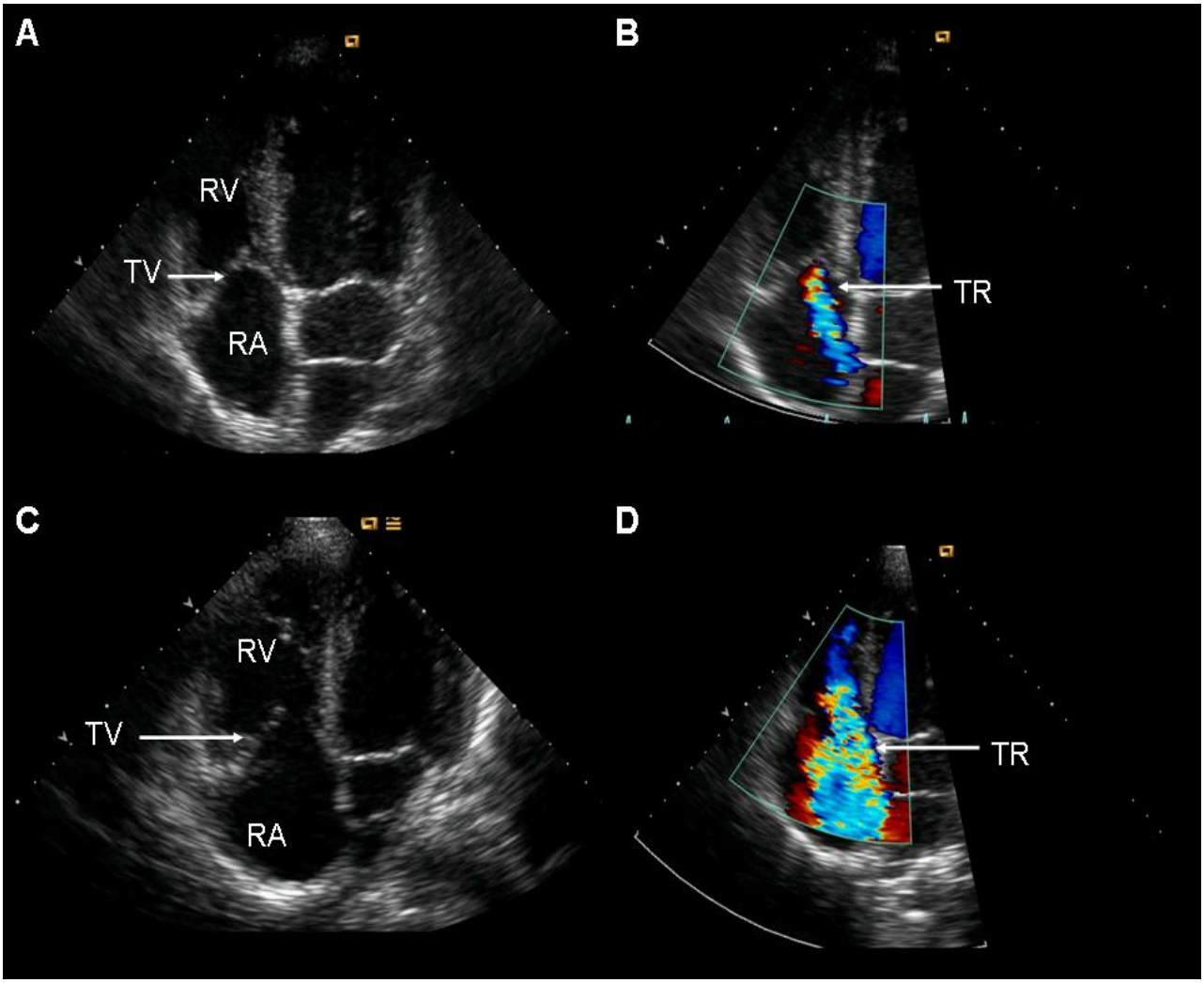
5.3.3 Rate of development and progression of valvular abnormalities

The overall rate of the development or progression of carcinoid heart disease was 7.4 events per 100 person-years. Fifteen patients developed carcinoid heart disease during the study (median score 15 (interquartile range, 8 to 20)). Nine of these had involvement of both tricuspid and pulmonary valves. One patient had isolated pulmonary valve involvement and 5 patients had isolated tricuspid valve involvement. Seven of the 14 patients with tricuspid valve involvement had severe tricuspid regurgitation and 4 of the 10 patients with pulmonary valve involvement had either severe pulmonary regurgitation or stenosis.

Twenty-nine patients had progression of existing carcinoid heart disease (baseline median score 9 (interquartile range, 7 to 12) and post progression median score 22 (interquartile range, 13 to 26)). All patients had worsening of valvular stenosis or regurgitation by more than 1 grade. Nineteen of the twenty nine had worsening of valvular stenosis or regurgitation by two grades. 5 patients had worsening of valvular stenosis or regurgitation by more than 3 grades. Six of the 29 patients developed new left sided valvular lesions. In 4 of these patients a patent foramen ovale was present and bronchial metastases were present in 2 patients. An example of a patient whose carcinoid heart disease progressed is given in figure 5.1. No patient showed regression of carcinoid heart disease.

Of the 25 studies scored by both readers, exact inter-observer agreement was present in 20 (80%) patients. Three patients scores differed by 1 points and 2 patients score differed by two points. Exact intra-observer variability was present in 9 out of the 10 studies reviewed.

Figure 5.1 Baseline and follow-up echocardiogram demonstrating progression of carcinoid heart disease



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A. Baseline echocardiogram. Right atrium (RA), Right Ventricle (RV). Thickened tricuspid valve (TV) leaflets. The leaflets have normal excursion although there is mal-coaptation at the leaflet tips.
B. There is mild tricuspid regurgitation (TR).
C. After 9 months the patient symptoms of carcinoid syndrome deteriorate. She experiences 5 to 6 flushing episodes per day. Her 5-HIAA is elevated at 790µMol/24hours. The right ventricle and atrium are now dilated. The tricuspid valve leaflets are now fixed, retracted and do not co-apt.
D. There is now severe tricuspid regurgitation.

5.4 Discussion

The development of carcinoid heart disease and subsequent development of right sided heart failure is a major cause of morbidity in patients with carcinoid syndrome. The risk factors for development and progression of carcinoid heart disease are poorly defined.

In this study independent predictors of the development and progression of carcinoid heart disease were a 5-HIAA greater than 300 μmol/24hr or symptomatic flushing of greater than 3 episodes per day. Based on unadjusted univariate analysis, progression of liver metastases and those patients with more than five metastases were predictors of the development of carcinoid heart disease. However they were no longer significant in the multi-variate model. This suggest only where the progression of liver metastases lead to high levels of hormone production are they significant for development of carcinoid heart disease.

Moller et al (20) found elevated levels of 5-HIAA and the use of chemotherapy to be associated with progression of carcinoid heart disease. However the study was limited due to a retrospective design and possible selection bias as over 50% of the sample population were excluded as serial echocardiograms were not available. Denney et al (76) performed a prospective study however only 23 patients with carcinoid syndrome were studied. This study is a large, prospective, longitudinal study with serial measurements of echocardiographic, clinical, biochemical and radiological parameters.

Current treatment objectives in these patients are the improvement of symptoms of carcinoid syndrome and also the control of tumour growth (73). The mainstay of therapy is the administration of long acting somatostatin analogues

which have been shown to produce a biochemical response in up to 60% of patients and symptomatic response in between 40 - 80 % of patients (77). However at present there are no recommended targets for reduction in biochemical markers or clinical symptoms. A 5-HIAA level above 300 µmol/24hr confers a two to three fold increase in risk in developing carcinoid heart disease and having greater than 3 flushing episodes a day confers a five-fold risk. Therefore a therapeutic strategy to reduce development of carcinoid heart disease may be to aim to reduce 5-HIAA and flushing episodes below these levels.

The majority of patients who developed carcinoid heart disease were already receiving somatostatin analogues. Although a strategy of dose escalation of somatostatin analogue may be used initially, eventually patients may become refractory to somatostatin analogues (78). Both hepatic artery embolisation with or without intra-arterial chemotherapy (79,80,81) and alpha-interferon (82) have been shown to be effective in reducing symptoms and biochemical markers in appropriately selected patients with carcinoid syndrome who become refractory to somatostatin analogues. Evidence for the use targeted radionuclide therapies in this context is slowly emerging (83).

5-HT is thought to be a major mediator in the development of valvular dysfunction in patients with carcinoid syndrome. 5-HT has been shown to up-regulate TGF-β and stimulate collagen synthesis in human aortic interstitial cells (15,16). In animal models long term administration of 5-HT has been shown to induce development of subendocardial plaque composed of myofibroblasts within a collagen matrix on heart valves (17). These histopathological changes are similar to those found in carcinoid heart disease.

Robiolio et al (19) noted 5-HIAA has a very high sensitivity but low specificity as a marker of valvular dysfunction in patients with carcinoid syndrome. This suggests other co-factors may be necessary for the development of pathology. Our study suggests high levels of daily flushing is also a marker of development and progression. The aetiology of the carcinoid flush is not fully characterised. However it is thought a range of vasoactive substances including 5-HT, tachykinins as well as prostaglandins are responsible (84). Indeed Lundin et al (6) noted elevated levels of the tachykinins (substance P and neurokinin A) in patients with valvular dysfunction and carcinoid syndrome. Both these markers are also known to stimulate fibroblast proliferation (85). Therefore it is likely the combination of hormones is required for development of valvular heart disease in patients with carcinoid syndrome.

The lower prevalence of valvular dysfunction and rate of development of valvular dysfunction in this study contrasts with echocardiographic screening studies from over two decades ago where nearly 60% of patients with carcinoid syndrome had evidence of valvular dysfunction (5,56). This may be partly explained by the use of somatostatin analogue being substantially greater in our cohort (90.5%) compared series from the 1980s where either limited (57%) or no somatostatin analogue was used (5,56). In 65% of patients with progression of valvular dysfunction the grade of valvular stenosis or regurgitation increased by more than 2 grades in less than 6 months. In 17% of patients this increased by more than 3 grades in this time frame. Although classically carcinoid tumours have been thought of slow growing the effects of high hormone load on the cardiac structure and the development of valvular dysfunction may be rapid.

A possible limitation of the study is there are no standardised criteria for quantifying the progression of carcinoid heart disease. Similar to previous studies

(20) we used an echocardiographic score and chose a cut-off valve of 25% increase in the score for our definition of the progression of carcinoid heart disease. Using this score there was a good inter and intra observer agreement.

This study has identified predictors of the development and progression of valvular heart disease in these patients. Clinical trials would be needed to test the hypothesis that modulation of these risk factors may attenuate the development of valvular heart disease in patients with carcinoid syndrome.

5.5 CONCLUSION

In conclusion elevated 5-HIAA > 300 μmol/24hr and daily flushing episodes greater than 3 are predictors of the development and progression of carcinoid heart disease. The development of valvular dysfunction may be rapid with severe dysfunction occurring within a short time period.

CHAPTER 6: OUTCOMES AND COMPLICATIONS OF CARDIAC SURGERY FOR CARCINOID HEART DISEASE

6.1 BACKGROUND

6.2 METHODS

6.2.1 PATIENT GROUP

6.2.2 ECHOCARDIOGRAPHY

6.2.3 BIOCHEMICAL TESTING

6.2.4 CARDIAC CATHETERISATION

6.2.5 ANAESTHETIC MANAGEMENT

6.2.6 CARDIAC SURGERY

6.2.7 STATISTICAL ANALYSIS

6.3 RESULTS

6.4 DISCUSSION

6.5 CONCLUSION

6.1BACKGROUND

Gastrointestinal carcinoid tumours are relatively rare slow growing malignancies. A proportion will develop carcinoid syndrome which is the result of the release of a range of vasoactive peptides and hormones that reach the systemic circulation, without being metabolised by the liver. Symptoms of “carcinoid syndrome” include flushing, diarrhoea, bronchoconstriction as well as the development of carcinoid heart disease (2).

Carcinoid heart disease develops in between 20 and 60% of cases of carcinoid syndrome (5). Deposition of fibrotic plaque on endocardial surfaces is thought to be mediated by high levels of 5-HT (86). Characteristically valvular dysfunction involves the tricuspid and pulmonary valve although left sided valvular dysfunction may also occur (87).

The prognosis of patients with carcinoid heart disease treated medically is poor (5). Cardiac valve replacement surgery for patients with carcinoid heart disease has been advocated in patients with symptomatic carcinoid heart disease. An improvement in functional class post operatively has been observed (38). Surgical mortality is high with case series reporting 30 day mortality rate of between 10% up to 60% (38,39,40). Reported peri-operative complications include right ventricular failure, renal dysfunction, sepsis and carcinoid crises.

Due to the relative rarity of the disease experience in the field of valve surgery for carcinoid is limited. Most data is limited to patients operated on over a decade ago in US series (38,40). We sought to investigate outcomes, complications and predictors of survival of cardiac surgery in a contemporary cohort of patients in Europe.

6.2 METHODS

6.2.1 PATIENT GROUP

All patients referred to the neuroendocrine tumour unit with carcinoid tumour of mid-gut origin and carcinoid syndrome were screened for the presence of carcinoid heart disease. Serial follow-up echocardiograms were performed in all patients. Patients with carcinoid heart disease were followed in a specialist valvular heart disease clinic at 6 monthly intervals. Patients were referred for valve surgery if they met the following criteria: (1) stable carcinoid tumour (2) severe valvular dysfunction (3) symptomatic and (4) had no other significant co-morbidities. The study was approved by the institutional ethics committee and all patients gave written informed consent.

6.2.2 Echocardiography

All patients underwent comprehensive two dimensional echocardiograms to assess each valve for the presence of carcinoid involvement and the severity of valvular dysfunction. Valve morphology and function was evaluated in several views. Pulmonary valve was visualised from high parasternal, long axis view of right ventricular outflow tract and parasternal short axis view. Tricuspid valve was visualised from low parasternal long axis view of right ventricular inflow tract, short axis and apical four chamber view. Aortic and mitral valves were assessed from parasternal long axis, short axis, apical four, three and two chamber views. Valvular regurgitation and stenosis were assessed and graded according to The American

Society of Echocardiography guidelines (52,53). Pulmonary stenosis was graded (according to peak gradient across valve) as mild (<25mmHG), moderate (25-50mmHg) or severe(>50mmHG).Tricuspid stenosis was graded (mean gradient across valve) as mild (2 - 5mmHg), moderate (5- 8mmHg) or severe(>8mmHg).

A contrast echocardiogram was performed to detect the presence of a patent foramen ovale using “microbubble” contrast at rest and with cough and Valsalva manoeuvre. The presence of patent foramen ovale was defined as the presence of at least 3 “microbubbles” in the left atrium within 3 cardiac cycles of contrast visualisation in right atrium.

6.2.3 Biochemical Testing

Urinary 5-HIAA, plasma CgA and NT-proBNP were measured. 24 hour urine 5-HIAA samples were collected in bottles containing acetic acid. Samples were evaluated using reversed phase high performance liquid chromatography assay. Cg A samples were taken from antecubital fossa in a serum gel tube. CgA was measured using DAKO Chromogranin A Enzyme-linked immunosorbent assay (DAKO A/S, Glostrup, Denmark). NT-proBNP samples were taken from the left antecubital fossa at room temperature in a serum gel tubes. Analysis was undertaken immediately, after being centrifuged, by Roche Modular Analytics E-170 immunoassay analyser using an electrochemilunescence detection.

6.2.4 Cardiac Catheterisation

All patients underwent cardiac catheterisation and coronary angiography to assess the presence or absence of coronary artery disease.

6.2.5 Anaesthetic Management

All patients were started on an Octreotide infusion of 50mcg/hour 12 hours prior to surgery and for 48 hours post-surgery. After this period they were started on subcutaneous Octreotide 200mcg three times a day for the next 14 days. Thereafter they were recommenced on their long acting somatostatin analogue.

6.2.6 Cardiac Surgery

Surgery was performed on aorto-bicaval cardiopulmonary bypass through a midline sternotomy. Systemic temperature was lowered to 32°C. Myocardial protection was achieved through antegrade as well as retrograde cold blood cardioplegia. Details of individual operations are summarised in table 1. Tricuspid, mitral and aortic valves were replaced with pericardial tissue valves. The pulmonary valves was replaced with a cryopreserved pulmonary homograft. If a patent foramen ovale was present this was closed with a simple prolene suture. If the patient had documented atrial fibrillation a Cox Maze procedure was carried out. Intra-operative transoesphageal echocardiograms were performed routinely.

6.2.7 Statistical Analysis

Patient characteristics are reported as median and inter-quartile range or number and percentage. Kaplan Meier survival analysis curves were formulated to demonstrate overall survival. Survival curves were formulated to compare the following groups of patients: NYHA I/II vs NYHA III/IV, NT-proBNP above median level for the cohort (> 1245pg/ml vs NT-proBNP <1245 pg/ml) and mild/moderate right ventricular dysfunction versus severe dysfunction. Differences in survival between stratified groups was analysed by Peto's log rank test. All tests of significance were two sided. A probability value (p) of <0.05 was considered statistically significant. Statistical analysis was performed using StatsDirect Version 2.5.7 (StatsDirect, United Kingdom).

6.3 RESULTS

Two hundred and fifty-two patients were screened during the study period. 52 patients had carcinoid heart disease. 40 patients developed severe valvular dysfunction during the study period. Of these 22 (55%) patients underwent cardiac valve surgery during the study period. Reasons for not being referred for valve replacement surgery included: severe right ventricular dysfunction in 3 patients, poorly controlled symptoms of carcinoid syndrome in 3 patients, progressive increase in tumour size in 8 patients, patient choice in 3 patients and being asymptomatic in 1 patient.

Demographics of the group are in table 6.1.The median age of patients was 60. The majority of patients were in NYHA Class II (50%) and III (36.4%) prior to

surgery. The medical management consisted of loop diuretics (90.9%) and aldosterone antagonists (50.1%). NT-proBNP. 5-HIAA and CgA were elevated in all patients.

The operative procedures performed are summarised in table 6.2. Three patients underwent tricuspid valve replacement alone, 15 patients underwent tricuspid and pulmonary valve replacement, 1 patients underwent tricuspid, pulmonary and mitral valve replacement and 2 patients underwent replacement of all 4 cardiac valve. Patent foramen ovale was closed in all patients with left sided carcinoid heart disease. One Patient underwent concurrent coronary artery bypass grafting in addition to tricuspid and pulmonary valve replacement. Cox Maze procedure was performed in 2 patients.

Table 6.1 Baseline Demographics

Characteristic		Number (%)
Age		60 (50-65)
Sex (Female)		11 (50%)
Duration of Diagnosis		4 (3-6)
Presence of Liver Metastases		22 (100%)
Chromogranin A (pmol/L)		1000 (688-1000)
5-Hydroxyindolacetic Acid (µmols/24hours)		787.5(340-979)
N-Terminal Brain Natriuretic Peptide (pg/ml)		1245 (381-2083)
Glomerular Filtration Rate (mls/min)		70 (60 – 79)
Hypertension		4 (18.2%)
Diabetes		3 (13.6)
Previous Cardiac Valve Surgery		1 (4.5%)
New York Heart Association Class	I	1 (4.5%
	II	11 (50%)
	III	8 (36.4%)
	IV	2 (9.1%)
Medication	Loop Diuretics	20 (90.9%)
	Aldosterone Antagonists	13 (59.1%)
	Angiotensin Converting Enzyme Inhibitors	2 (9.1%)
Signs of right heart failure	Ascites	2 (9.1%)
	Leg Oedema	15 (68%)

Table 6.2 Operative Procedures Performed

Procedure	Number (%)
Tricuspid Valve Replacement	22 (100%)
Pulmonary Valve Replacement	15 (68.2%)
Mitral Valve Replacement	3 (13.6%)
Aortic Valve Replacement	2 (9.1%)
Closure of Patent Foramen Ovale	9 (40.9%)
Cox Maze Procedure	2 (9.1%)
Coronary Artery By-Pass Grafting	1 (4.5%)
Excision of Cardiac Metastases	1 (4.5%)

Overall 30 day peri-operative mortality was 18.2% (4 patients). Causes of death were right ventricular dysfunction in 2 patients and stroke with aspiration pneumonia in 1 patient and carcinoid crisis in 1 patient. Median length of hospital stay was 10 days. Complications occurring within the immediate 7 day post-operative period were: persistent complete heart block requiring permanent pacemaker implantation in 4 patients, sustained ventricular tachycardia requiring cardioversion in one patient, carcinoid crisis in 1 patient and acute renal failure requiring hemofiltration in 2 patients. 4 patients developed marked hypoalbuminemia in the post-operative period.

In those that survived the initial operation median follow up was 26 months (8 – 42). Overall 12 (67%) patients experienced significant symptomatic improvement post-surgery (greater than 1 grade improvement in NHYA Class) (table

6.3). I and 2 year survival rates were 55.6% and 44.4% respectively. There was no significant difference in survival between those in NYHA Class I and II and those in NYHA classes III and IV (figure 6.1), p= 0.49. There was no significant difference in survival between those with a NT-proBNP greater than 1245pg/ml compared to those with a NT-proBNP below 1245 pg/ml (figure 6.2), p=0.43. No significant differences in survival was found between those with mild/moderate pre-operative right ventricular dilatation and those with severe dilatation (figure 6.3), p= 0.91.

Table 6.3 Functional New York Heart Association Class Pre and Post Cardiac Valve Surgery.

		Prior to surgery	3 months post surgery
New York Heart Association Class	I	1	11
	II	9	5
	III	7	2
	IV	1	0

Figure 6.1 Kaplan-Meier Survival Curves Stratified according to New York Heart Association Class

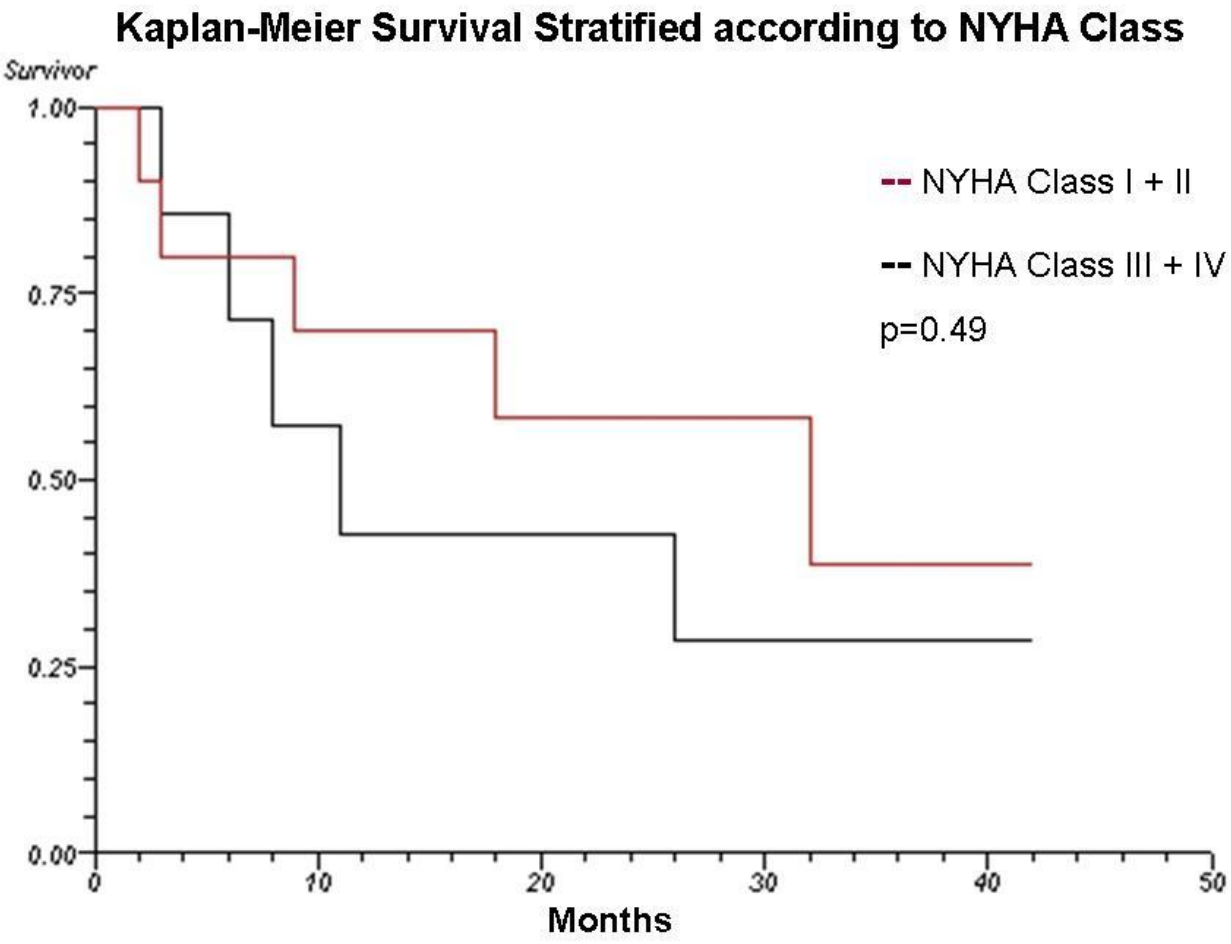


Figure 6.2 Kaplan-Meier Survival Curves Stratified according to N Terminal-pro Brain Natriuretic Peptide

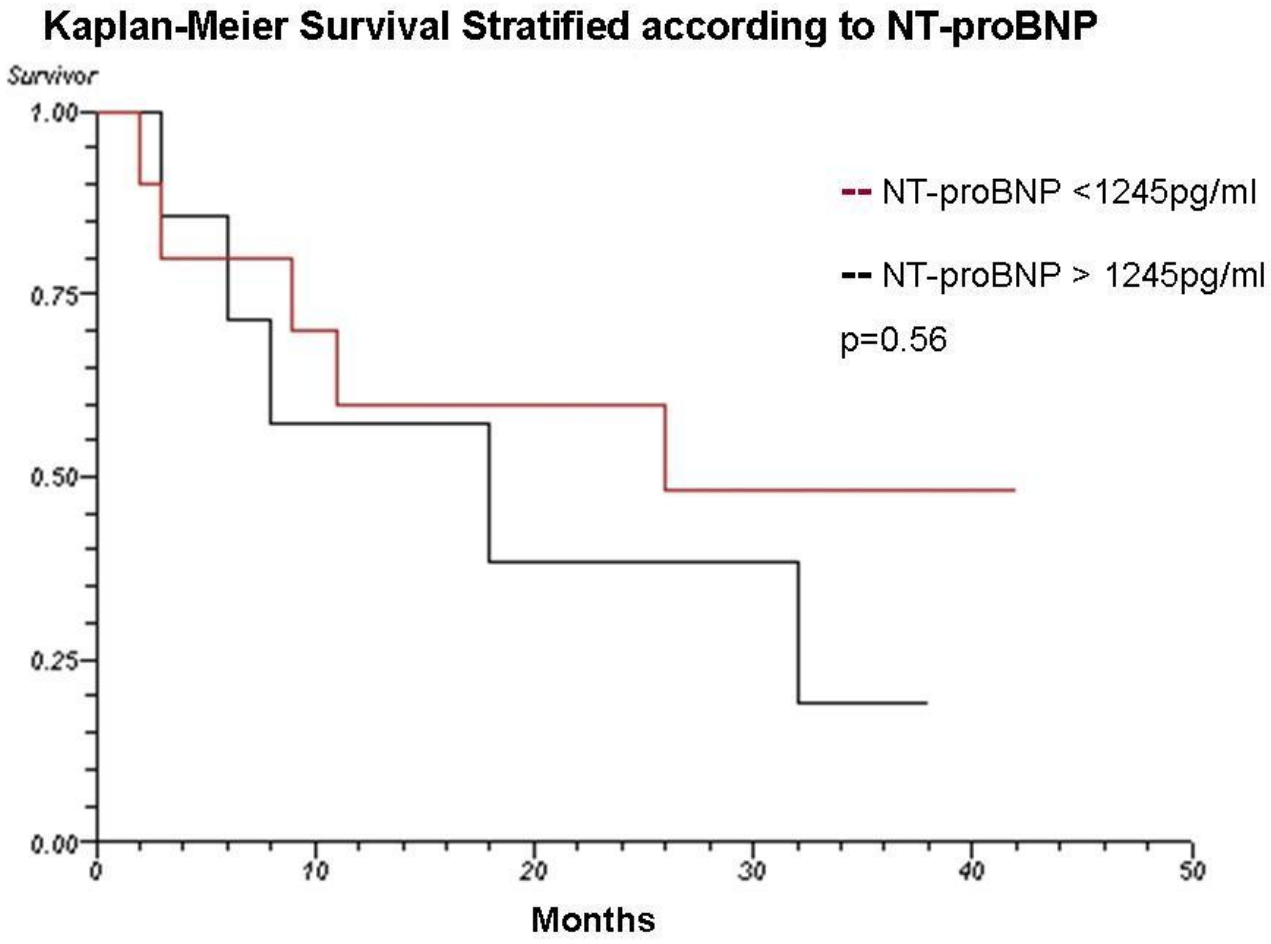
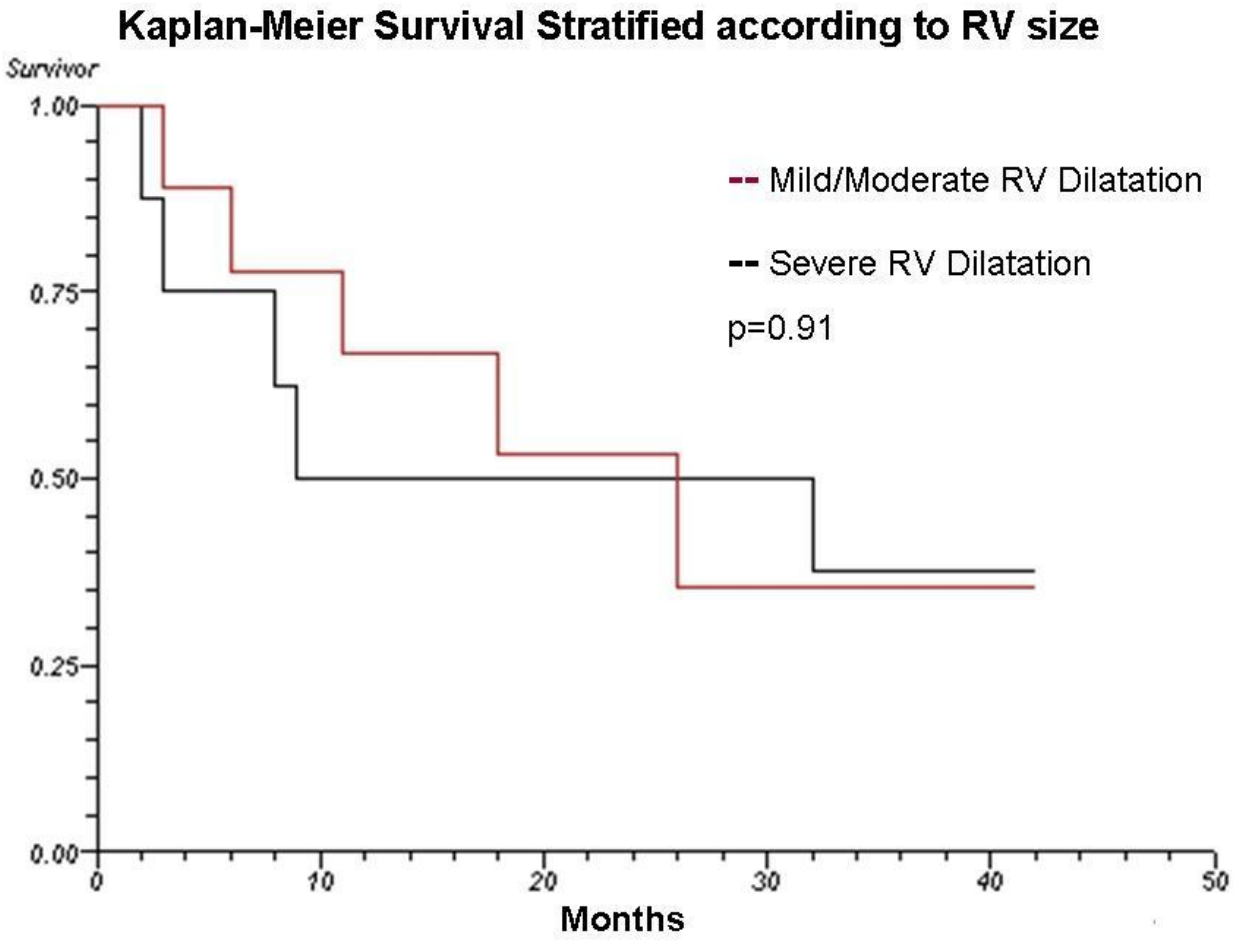


Figure 6.3 Kaplan-Meier Survival Curves Stratified according to Right Ventricular Size



In the patients who died more than 30 days post surgery causes of death were: progression of carcinoid tumour in 4 patients (22%), right ventricular failure in 1 patient (5.5%), pneumonia in 2 patients (11%) and cause unknown in 1 patient (5.5%). During follow-up 2 patients developed degeneration of their bio-prosthetic valve. One patients developed moderate pulmonary stenosis of a pulmonary homograft and one developed moderate tricuspid regurgitation due to degeneration of a bio-prosthetic tricuspid valve. No patient required re-operation for bio-prosthetic degeneration

6.4 DISCUSSION

The development of carcinoid heart disease imparts reduced survival and significant morbidity (41). Symptoms of right heart failure can considerably impair quality of life. Data on outcomes and risk of cardiac surgery in these patients has been limited to case reports and small case series in US patients (38,39,40). There are no studies on European patients. Standard surgical risk assessment such as Euroscore or STS Scoring system are based on data for patients undergoing coronary artery bypass grafting and aortic and mitral valvular disease (88,89).

In this cohort, 55% of patients with severe valvular dysfunction were referred for cardiac valve replacement surgery. The large proportion of patients who were not suitable for valve surgery reflects the complex nature of these patients. Complication including bowel obstruction, mesenteric ischaemia, uncontrolled symptoms of carcinoid syndrome or progressive increase in size of tumour require resolution prior to considering cardiac valve replacement.

Our data confirm previous finding of a high peri-operative risk. In our series 30 day mortality was 18.2%. This is line with data from New York of 20% and the Mayo clinic of between 10 and 30% (38,39). Complications included right ventricular dysfunction, carcinoid crisis, renal failure and sepsis. A large proportion of patients required a pacemaker implantation for complete heart block. A larger proportion developed asymptomatic conduction disorders.

Our data showed the majority of patients who survived valve surgery showed symptomatic improvement. Increased NYHA class, elevated BNP level and severe RV dilatation impart an impaired prognosis in those patients with carcinoid heart disease treated medically (7,41). However in our cohort, in those that survived the initial operation, pre-operative NYHA class, NT-proBNP level or RV size did not predict long term post-operative survival. This may be explained by a large number of late deaths due to complications related to the metastatic carcinoid tumour occurring during the follow-up period. This is in keeping with previous data where NYHA class and right ventricular enlargement did not affect not long term survival after valve surgery for carcinoid heart disease (38).

The indication and optimal timing of valve replacement surgery in carcinoid heart disease is controversial. Our data suggest valve replacement is indicated in symptomatic patients. There is no data to support the use of valve replacement surgery in asymptomatic patients with or without dilatation of the right ventricle.

In our cohort, 4 patients noticed a marked reduction in serum albumin for several weeks post valve surgery which resulted in generalised oedema. This may well be due to physiological stress and associated inflammatory response evoked by surgery. However it poses particular problems for the patients with carcinoid tumour. Patients with carcinoid tumour may have underlying nutritional deficiencies. Patients

with advanced carcinoid may have mesenteric fibrosis with desmoplasia. This may cause partial compression of branches of the superior mesenteric artery and vein leading to subsequent development of mesenteric ischemia and post-prandial pain. This may manifest as weight loss, malnutrition and cachexia (90). Our patients found it difficult to increase their calorie intake and required intensive nutritional support in the post-operative period. As a result we now have a specialist dietician in neuroendocrine tumours to assess patients both pre and post-operative period.

The choice of valve replacement has been debated in the literature. There have been isolated reports of bio-prosthetic degeneration (43,44). In our series only two patients showed evidence of valve degeneration. Neither of these was severe enough to either cause symptoms or require further intervention. Mechanical replacement of the tricuspid valve is associated with a higher risk of thrombosis compared to bio-prosthetic valves (46,91). Compounding problems in patients with carcinoid tumours include the risk of haemorrhage in patients with liver metastases and management of perioperative anti-coagulation if patients need non-cardiac surgery such as resection of liver metastases.

CONCLUSION

Valve surgery for carcinoid heart disease is higher risk than most other forms of valvular surgery. However in those that survive the operation significant improvement in functional class occurs. Bio-prosthetic valve degeneration was not significant in our series. Most long term complications were related to the tumour itself rather than cardiac complications.

CHAPTER 7: DISCUSSION

7.1 INTRODUCTION

7.1 CLINICAL FEATURES

7.2 THE VALUE OF CARDIAC BIOMARKERS IN CARCINOID HEART DISEASE

7.3 ROLE OF CARDIAC IMAGING IN CARCINOID HEART DISEASE

7.4. RISK FACTORS FOR THE DEVELOPMENT AND PROGRESSION OF CARCINOID HEART DISEASE

7.5 CLINICAL OUTCOMES AND COMPLICATIONS OF CARDIOVASCULAR SURGERY

7.6 CONCLUSION

7.1 INTRODUCTION

Carcinoid heart disease is a rare, but unique form of valvular heart disease occurring in patients with carcinoid syndrome. Although, not completely understood, the mechanism of development is thought to be linked to vasoactive substances, including serotonin, released by metastatic tumour cells in the liver which are able to reach the right side of the heart. Distinctive carcinoid plaques are found throughout the endocardium of the right heart. The functional consequence of which typically leads to tricuspid and pulmonary valvulopathy.

Much of our current understanding of carcinoid heart disease is based on retrospective studies conducted over 2 decades ago (5,6,19,20,24,25). There have been significant advances since this time. New therapeutic agents and anti-tumour treatment modalities including somatostatin analogues, interferon, targeted radionuclide therapy as well as small molecules have emerged. The ability of these agents to modulate production of tumour metabolites may alter the development of carcinoid heart disease. We undertook a large, prospective, observational cohort study to define the prevalence, clinical features, diagnostic biomarkers, echocardiographic details and risk factors for development of carcinoid heart disease as well as evaluate the outcomes of cardiac surgery for carcinoid heart disease.

7.1 CLINICAL FEATURES

The prevalence of carcinoid heart disease amongst patients with carcinoid syndrome has been reported to occur in up to 66% of cases (5,56). These studies have been based on retrospective reviews of patients referred for echocardiography.

Limitations of this type of study include selection bias as clinicians may only refer for echocardiography when clinical symptoms or physical examination suggests cardiac involvement. Therefore, we do not believe they represent the true prevalence of carcinoid heart disease as not all patients are screened.

Approximately 20% of patients present with carcinoid heart disease (74). Although symptomatic relief of severe valvular dysfunction is achieved by valve replacement surgery, right ventricular dysfunction does not improve post operatively and impaired right ventricular dysfunction is a predictor of poor prognosis (42). Therefore an early diagnosis of carcinoid heart disease prior to the onset of right ventricular dysfunction is desirable.

In our study (Chapter 2) we found 27% of patients with moderate or severe valvular dysfunction (tricuspid regurgitation) were initially in NYHA Class 1. Secondly, 37% of patients did not display clinical signs suggestive of cardiac disease. The study screened a cohort of patients of carcinoid syndrome irrespective of signs or symptoms of cardiac involvement. This suggests a significant proportion of patients may have sub-clinical valvular disease. This supports the need for screening patients with carcinoid syndrome for carcinoid heart disease in order to reach a timely diagnosis prior to onset of right ventricular dysfunction.

The prevalence of carcinoid heart disease in our cohort was only 20%. This is substantially lower than previously reported. The reason for the change is not fully clear. However it may related to the higher use of somatotatsin analogue in the current cohort of patients compared to previous studies conducted a decade occur where the use of somatostatin analogue was much less liberal.

7.2 THE ROLE OF CARDIAC BIOMARKERS (N-TERMINAL BRAIN NATRIURETIC PEPTIDES)

B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are neurohormones synthesized and secreted from ventricular myocardium (21). Median levels of NT-proBNP are higher in patients with carcinoid heart disease than those with only carcinoid syndrome (7). This may be explained by right ventricular dysfunction secondary to carcinoid valvular dysfunction. It is unclear whether NT-proBNP can be used as a biomarker of the onset of early carcinoid valvular dysfunction. In our study (Chapter 3) elevation of NT-proBNP above 260pg/ml had excellent sensitivity and specificity for the diagnosis of carcinoid heart disease. Furthermore the level of NT-proBNP correlated with severity of carcinoid heart disease and functional NHYA class. In Chapter 1, we proposed all patients with carcinoid syndrome be regularly screened for the development of carcinoid heart disease. We suggest a possible strategy would be screen patients who are completely asymptomatic be using NT-proBNP and only those with elevated levels undergo echocardiography.

7.3 THE ROLE OF CARDIAC IMAGING IN CARCINOID HEART DISEASE

Two dimensional echocardiographic features of carcinoid heart disease have been well described in several series (5,25,56). Typical features include thickened valve leaflets together with retraction, shortening and reduced excursion of valve leaflets. The limitation of all 2D cross sectional imaging is only partial visualisation of the tricuspid and pulmonary valve is achieved as only one or two leaflets can be

identified. Secondly, there is limited data on asymptomatic patients where the pattern of disease may be different.

Our study (chapter 4) describes the echocardiographic features utilising 2D and 3D TTE as well as, in selected patients, 3D TEE and CMR. Transoesphageal techniques resolved the problem of limited acoustic windows and poor visualisation of right sided heart valves encountered with transthoracic techniques. 3D techniques produced an en-face view of the all three valve leaflet/cusps simultaneously. This allowed more detailed morphological assessment of each individual leaflet/cusp as well as coaptation between leaflets. Involvement of sub-valvular apparatus was identified and better characterised. There was improved delineation of the spatial relationship between valve, sub-valvular apparatus and the endocardium of surrounding chambers. CMR allowed better characterisation of myocardial metastases allowing measurement and assessment of invasion into surrounding structures.

Further research is needed to assess the optimal echocardiographic marker of right ventricular dysfunction. Data have emerged in other conditions which suggest identified 3D TTE quantification of RV dysfunction has good correlation to the current gold standard (CMR) (92).

7.4 Risk Factors For the Development and Progression of Carcinoid Heart Disease

The pathogenesis of carcinoid heart disease is incompletely understood. Although serotonin is thought to be a key mediator a large proportion of patients with elevated levels of serotonin do not develop carcinoid heart disease. In Chapter 5, we identified a 5-HIAA > 300 μmols/24 hours and median daily flushing > 3 episodes

over 24 hours as being the greatest predictor of the development or progression of carcinoid heart disease. These two variables are potentially modifiable with anti-tumour therapies. Currently, there are no guidelines with suggested targets for 5-HIAA levels or symptom control. A trial would be needed to test the hypothesis that reduction to below these levels may reduce the risk of developing carcinoid heart disease.

A second observation from the study was the development of valvular dysfunction in carcinoid heart disease may be rapid. Patients could progress from trivial/mild to severe tricuspid regurgitation in less than 6 months. This highlights the need to close monitoring of patients with carcinoid syndrome for the development of cardiac disease.

7.5 Clinical outcomes and Complications of Cardiovascular Surgery

The outcomes of medical management of carcinoid heart disease are poor. The Mayo clinic experience suggested the median survival of a patient treated medically was just 1.6 years based on data from the 1980's (5). Valve replacement surgery has been shown to offer symptomatic relief (defined as improvement in NYHA class) (38). The Mayo Clinic data also suggest there may be a survival advantage (41). In Chapter 6, we demonstrated a large proportion of patients are not actually suitable for valve replacement surgery due to uncontrolled symptoms of carcinoid syndrome, progressive tumour growth or other co-morbidities. In those that did undergo surgery, there was an improvement in functional status post valve surgery. Peri-operative mortality was high (30 day mortality 18.2%). 2 year survival

was only 44.4%. The majority of deaths were due to tumour related complications. This suggests although valve replacement therapy is an option in select patients a better strategy may to try to identify targets to prevent development of cardiac disease in the first place. As identified in Chapter 5, control of tumour metabolites is the key to this strategy.

7.6 CONCLUSION

- The prevalence of carcinoid heart disease has decreased from over 60% in historical series to under 20%.
- Clinical correlates (functional NYHA class and clinical examination) are poor markers of early cardiac involvement in patients with carcinoid syndrome. Screening is required to identify patients with carcinoid heart disease.
- NT-proBNP correlates with both severity of carcinoid heart disease, and functional class. A high sensitivity and specificity may allow its use a screening marker to target the use of echocardiography.
- Characterisation of valvular involvement in patients with carcinoid syndrome is better defined with the use of three dimensional echocardiography than two dimensional techniques.
- The risk of developing carcinoid heart disease is greatest in patients with a 5-HIAA and greater than 3 flushing episodes per day. Further studies are desirable to assess whether modulation of these variables reduces the risk of developing carcinoid heart disease.
- Cardiac valve surgery in carcinoid heart disease is associated with high peri-operative risk although significant functional improvement occurs in those that

survive the surgery. Long term mortality is influenced more by tumour factors than traditional cardiac markers.

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APPENDIX (I TO III)

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Appendix I: Consent Form

Royal Free Hampstead NHS
NHS Trust

Royal Free Hospital
Pond Street
London NW3 2QG

Tel: 020 7794 0500
Fax: 020 7830 2468
Department of Cardiology

CONSENT FORM (Confidential)

Title of project: **Carcinoid Heart Disease: Prevalence, progression and treatment.**

Name of Researchers: Dr J Davar, Dr S Bhattacharyya
Any questions to Dr. S. Bhattachayya, Department of Cardiology, Royal Free Hospital, Pond Street, London.NW3 2JN. Telephone 02077940500 extn 33573

Please initial box

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for Patient; 1 for Researcher; 1 to be kept with hospital notes

Appendix II: Patient Information Sheet

Royal Free Hampstead NHS
NHS Trust

Royal Free Hospital
Pond Street
London NW3 2QG

Tel: 020 7794 0500
Fax: 020 7830 2468

Department of Cardiology
Dr Joseph Davar

Patient information sheet

Study title : Carcinoid Heart Disease. Prevalence, progression and treatment.

How common is carcinoid heart disease in patients with carcinoid , what factors affect its progression and how can we better treat our patients.

Principal investigator:
Dr J Davar
Department of Cardiology, Royal Free Hospital, London, NW3 2QG
Tel: 020 7794 0500 extension 33573

We would like to invite you to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled "Medical Research and You". This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

Thank you for reading this.

What is the purpose of the study?

We are interested in the development of heart disease in patients with carcinoid disease. Some patients with carcinoid may develop a problem with the heart valves. In some patients, this may be serious leading to breathlessness although there may be several other, unrelated causes of these symptoms. The aim of the study, which will take place over two years, is to find out how common heart problems are in patients with carcinoid syndrome and if we can predict who will develop heart disease. We will see if the heart is involved by doing an ultrasound scan of the heart. This is called an echocardiogram and is similar to the type of scan that pregnant women have to see how their baby is growing. We will try to identify which patients may develop heart problems using simple blood and urine

tests. In certain patients who have involvement of the heart valves we routinely organise a special test called left and right heart catheterisation to measure the pressures of the right side of the heart and look for narrowing of the arteries that supply blood to the heart. We would want to take extra blood tests during this procedure to try to identify why the heart valves are affected. We would also organise a special ultrasound of the heart where you a given a medication to speed up your heart rate to assess how well your heart contracts and how good the blood supply to the heart is.

Why have I been chosen?

Because you have carcinoid disease we are interested to know whether your heart is affected and if so, to what degree.

Do I have to take part?

No, and if you do not want to join in the study, we will of course be pleased to look after you. Even if you do decide to take part, you can always leave the study at any time. Most of the tests are part of the usual care you would have.

What will happen to me if I take part?

You will be followed up and treated in the Neuroendocrine Tumour clinic by the neuroendocrine tumour unit team and by the cardiologists. We will take a history from you and examine you. You will have a detailed heart ultrasound scan which you may have already had in the past. This is a completely harmless test and quite interesting and you will be able to see the pumping action of your heart and hear blood flowing around your heart if you wish. The test takes around 30 minutes. You will also have some blood and urine tests which are part of the routine tests we do for patients with carcinoid disease. If you have carcinoid heart valve disease we will ask you undergo cardiac catheterisation of the right and left heart. This test measures pressures in the right side of the heart and looks for narrowing of the arteries of the heart. This is a routine test in people who have heart valve involvement with carcinoid as it helps decide how to manage each patient. You will also have a special ultrasound of the heart called a stress echo which helps us know how strong your heart muscle is and how good the blood supply to your heart muscle is.

What are the possible benefits of taking part?

The results of this study may help not only you but also other patients like you who have carcinoid disease.

What if something goes wrong?

The chances of something going wrong as a result of the study are no greater than if you were not taking part. If something did go wrong as a result of the study, there are no special compensation arrangements. If you are harmed due to someone's negligence then you have grounds for legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated, the normal NHS complaints mechanism is open to you.

If you decide to join in, then, if you agree, we will also write to you GP surgery to inform them that you are part of our study and that we have asked your permission and you have agreed to participate. We will also write to any other doctor who looks after you to inform them too if you agree.

Will my taking part in this study be kept confidential?

All information collected about you will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results will be analysed and may then be published in the medical literature. This may take some time (1-2 years) after the study is completed. You will not be identified in any report or publication.

Who has reviewed the study?

This study has been reviewed by the Royal Free Hospital NHS Local Research Ethics Committee.

Thank you for reading this information sheet.

We would like you to have two tests.

1. Heart ultrasound scan

We are interested in performing an ultrasound scan of your heart to examine whether your heart may be affected. This takes around 45 minutes and involves putting some harmless gel on the skin of your chest and then placing a probe on the skin to produce an image of your heart on a TV screen. We also measure pressures in your heart and you may hear a whooshing noise as the probe detects the flow of blood in your heart. We will place a small , sterile plastic tube into a vein your hand. This feels no different to the sharp pin prick you feel when you have blood taken. A special sterile solution is passed into this tube over a few seconds and travels to the heart. This allows us to look at the heart wall between two chambers of the heart better than we can with the ultrasound alone.

2. Blood tests and urine tests

Finally, we would like to take some blood samples and this is no different or extra from the samples we would usually take in patients with carcinoid disease.

Patients who are found to have carcinoid involvement of the heart valves will be asked to undergo two further tests in order to decide how best to manage them

3. Cardiac Catheterisation.

In patients who have heart valve involvement by carcinoid we routinely measure the pressures of the right side of the heart and take pictures of the arteries that supply blood to the heart. This involves coming to hospital for half a day. The procedure lasts about half an hour and is carried out under local anaesthetic. A small tube in placed into a vein and artery at the top of your right leg. You should not feel anything as local anaesthetic is put in the area first. Then a tiny tube is passed into the right side of the heart to measure the pressures in the right side of the heart. Some blood samples will be taken to help us find out why carcinoid affects the heart. A tiny tube is passed to the left side of the heart. Then a special dye (contrast) is used to take pictures of the arteries that supply blood to the heart. This procedure uses a special scanner which uses special radiation beams to take pictures. The amount of radiation you receive is equivalent to three plain x-rays of the bottom of your spine. Even if you decided not to take part in this research, if you had heart involvement by carcinoid, you would still undergo this test. Therefore there is no extra risk by taking part in the research.

4. Stress Echocardiogram and Tissue Doppler Echocardiogram

In patients who have heart valve involvement by carcinoid we routinely see how strong your heart muscle is and how good the blood supply to the heart muscle is. This involves putting a small plastic tube into a vein in your arm. A special mediation that speeds up your heart goes through the plastic tube into you. An ultrasound picture of your heart is taken. This involves putting some harmless gel on the skin of your chest and then placing a probe on the skin to produce an image of your heart. This allows us to measure how strong your heart is when your heart is beating faster than normal.

We will be keeping a close eye on you in clinic and will be available to answer any questions you have. We will also be pleased to inform you of the results of the tests and keep you informed of the results of our investigations.

Contact for further information:

To get answers to questions about the research and your rights as a patient in the study please contact the persons.

Dr Sanjeev Bhattacharyya, Cardiology Research Fellow, Telephone 020 7794 0500, ask to bleep 1048

Dr Joseph Davar, Consultant Cardiologist, Royal Free Hospital. Telephone: 020 7794 0500 extension 33573.

Dr Martyn Caplin, Lead Clinician Neuroendocrine Tumour Unit, Royal Free Hospital.
Telephone: 0207 830 2867

Appendix III: Letter to General Practitioner

Royal Free Hampstead NHS
NHS Trust

Royal Free Hospital
Pond Street
London NW3 2QG

Cardiology
Dr Joseph Davar MD PhD
Consultant Cardiologist
Tel: 020 7794 0500 Extension: 33573

Date:

General Practitioner's letter regarding
Carcinoid Heart Disease: Prevalence, progression and treatment.

Dear Dr ----------

We are interested in investigating the prevalence , natural progression, markers of progression and markers of improved outcome post cardiac valve surgery in patient with carcinoid disease who develop carcinoid heart disease. Your patient, Mr/Mrs ---------- of ---------- has consented us to write to you to inform you that she has agreed to be part of this long term study. The tests performed are all part of the routine clinical care of patients with carcinoid disease and suspected cardiac involvement.

It is not a drug trial. All patients will be seen and examined by both an gastroenterologist and cardiologist. They will have an echocardiogram to investigate whether they have carcinoid heart disease at set intervals as well as blood tests and urinary tests. Patient who need cardiac valve surgery will undergo right heart and left heart catheterisation and a stress echocardiogram. A special blood test to measure serotonin levels and NT-proBNP levels in the blood will be taken during cardiac catheterisation.

We will keep you posted, as usual about their clinical condition and their medication. Please contact us if you have any questions.

Yours sincerely,

Dr Joseph Davar MD, PhD
Consultant Cardiologist
Lead Investigator