The optimal use of cardiac imaging in the quantification of carcinoid heart disease

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Abstract
Carcinoid heart disease is a rare cause of right-sided valvular dysfunction, primarily mediated by serotonin. It is an important complication in patients with carcinoid syndrome and occurs in 20–50% of such patients. Echocardiography is the main technique used for the assessment of carcinoid heart disease, but other imaging modalities are also important, particularly in the quantification of the severity of the disease. We sought to review the role of cardiac imaging in the assessment of carcinoid heart disease.

Key Words
- carcinoid heart disease
- imaging
- valvular disease

Introduction
Neuroendocrine tumours (NETs) are a varied group of tumours that arise from neuroendocrine precursor cells. They are rare occurring in 1.2–2.1/100 000 of the general population (Modlin & Sandor 1997). Carcinoid syndrome, which is often a sign of disseminated disease in patients with a primary tumour within the midgut or the bronchial system, comprises secretory diarrhoea, episode flushing and bronchospasm (Palinswamy et al. 2012).

Carcinoid heart disease, first described by Biorck et al. (1952), is a major cause of morbidity and mortality in patients with carcinoid syndrome, and in up to 20% of patients, it may be the presenting feature of the disease (Lundin et al. 1988). Cardiac involvement is thought to occur in 20–50% of patients with carcinoid syndrome (Connolly & Pellikka 2006) and is characterised by a fibrous reaction causing retraction and fixation of the right-sided valve leaflets, leading to a combination of regurgitation and stenosis, which ultimately can progress to right heart failure. A minority of patients develop left-sided lesions, believed to be mediated by patent foramen ovale or bronchial carcinoid tumours.

As stated previously, carcinoid heart disease affects the right side of the heart in the vast majority of patients. This creates a challenge when assessing the degree of cardiac involvement as it is notoriously difficult to image the right heart using echocardiography. These difficulties arise from the position of the right heart in the chest and its complex anatomy. The right ventricle lies beneath the sternum, is heavily trabeculated and has a triangular shape that wraps around the left ventricle (Buechel & Mertens 2012). Because of these factors, no single echocardiographic view will provide enough information to enable comprehensive assessment of right ventricular structure and function (Horton et al. 2009).

The cardiac manifestations of carcinoid disease are a consequence of the paraneoplastic effect of vasoactive substances secreted by the tumours, including 5-hydroxytryptamine (serotonin), prostaglandins, histamine and tachykinins. Hepatic metastases enable large quantities of such tumour products to reach the right heart without being inactivated. The evidence for serotonin being a key factor in the development of carcinoid...
heart disease is strong. First, serotonergic drugs used in the treatment of Parkinson’s disease, obesity and migraine are known to cause valvular fibrosis (Bhattacharyya et al. 2009). Secondly, in an animal study, valvular fibrosis was induced by long-term administration of serotonin to rats (Gustafson et al. 2005). Thirdly, a high circulating level of urinary 5-hydroxyindoleacetic acid (5-HIAA), a breakdown product of serotonin, is an independent predictor for the development and progression of carcinoid heart disease (Bhattacharyya et al. 2011). However, there are additional mechanisms thought to contribute to the pathophysiology of the disease, with both activin A (Bergestuen et al. 2010a) and connective tissue growth factor (Bergestuen et al. 2010b) associated with the development of carcinoid heart disease.

The diagnosis and quantitative assessment of the progression of carcinoid heart disease are essential parts of clinical care. Transthoracic echocardiography (TTE) is a well validated technique for the diagnosis and surveillance of carcinoid heart disease, and its use is guided by biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP; Ramage et al. 2012). Other biomarkers that have been used in the assessment of the disease include chromogranin A (Korse et al. 2009) and urinary 5-HIAA (Zuiterhorst et al. 2003). Monitoring of progression of cardiac involvement is important as carcinoid heart disease can affect drastically on long-term survival, and timely valve replacement is the only definitive treatment option (Moller et al. 2005). Although the principal echocardiographic features of carcinoid heart disease have been well characterised (Pellikka et al. 1993), there is no current consensus on how to most accurately define and quantify carcinoid heart disease. This has led to several different echocardiographic scoring systems being developed to describe the disease, which have been used with limited evaluation of validity and utility.

The five scoring systems published in the literature (Denney et al. 1998, Westberg et al. 2001, Moller et al. 2003, Bhattacharyya et al. 2008, Mansencal et al. 2010b) vary considerably in complexity. The simplest score is an eight-point assessment of the tricuspid valve (Westberg et al. 2001) while the most comprehensive evaluation is a 66-point assessment of all four valves and right ventricular size and function (Bhattacharyya et al. 2008). The scoring systems incorporate different echocardiographic modalities to a varying degree, with one utilising two-dimensional (2D) and colour flow imaging only and others also using Doppler assessment.

There is ambiguity in international consensus guidelines over which patients should be screened for carcinoid heart disease. Ramage et al. (2012), on behalf of ENETS (European Neuroendocrine Tumour Society), recommend that all patients with midgut NETs, with or without hepatic metastases, and all patients with carcinoid syndrome should be screened for cardiac involvement. However, Pape et al. (2012), also on behalf of ENETS, recommend screening only for patients with carcinoid syndrome or those with elevated levels of chromogranin A or 5-HIAA. Regular echocardiographic screening for patients with carcinoid heart disease, supplemented or guided by NT-proBNP measurement where appropriate, is recommended by NANETS (North America Neuroendocrine Tumour Society) and ENETS (Vinik et al. 2010, Ramage et al. 2012, Pape et al. 2012). However, there is a lack of clarity in the guidelines regarding the frequency of screening for patients with NETs. For patients with a diagnosis of carcinoid heart disease, surveillance echocardiography should be performed annually (Erikkson et al. 2008). In this article, we review the role of cardiac imaging in the diagnosis and surveillance of carcinoid heart disease.

Pathology of carcinoid heart disease

The tricuspid valve is affected most commonly in carcinoid heart disease, followed by, in decreasing order, pulmonary, mitral and aortic valve involvement. Plaque thickenings cause characteristic distortion of the affected leaflets and cusps, leading to an irregular, nodular appearance. Consequently, impaired leaflet retraction leads to a reduced valve area. The septal and anterior leaflets of the tricuspid valve are most frequently affected, whereas the posterior leaflet may remain relatively mobile (Bernheim et al. 2007). The natural history of carcinoid heart disease is progressive fibrosis of the valves, which ultimately become immobile, leading to a fixed valve orifice in a permanent semi-open position (Nalawadi et al. 2010). Valvular regurgitation and some degree of concomitant stenosis result from the retracted, immobile valve leaflets.

Macroscopic inspection of hearts affected by carcinoid disease reveals pathognomonic white plaque-like thickenings on the valve leaflets, cardiac chambers and occasionally the intima of the coronary veins and aorta. The sub-valvular apparatus can also be involved, producing an appearance similar to chronic rheumatic valve disease. The ventricular aspects of leaflets and the arterial aspects of cusps tend to be the first and most severely

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affected areas (Simula et al. 2002). Plaques adhere to the mural endocardium creating a substrate for valvular regurgitation (Bhattacharyya et al. 2007).

Microscopic evaluation of carcinoid plaques within the heart reveals their contents to contain myofibroblasts within an extracellular matrix that consists mainly of collagen and a myxoid matrix (Lundin et al. 1991). Chronic inflammatory cell infiltration within the plaque and neovascularisation along the base of the plaque have been reported (Macdonald & Robbins 1957, Ferrans & Roberts 1976). Interestingly, in a surgical pathology series of 139 excised valves from 75 patients, tricuspid valve thickening was mainly caused by collagen deposition, and pulmonary valve thickening was a result of myofibroblast proliferation and myxoid matrix (Simula et al. 2002).

**Imaging modalities for carcinoid heart disease**

**Echocardiography**

**Two-dimensional echocardiography** As carcinoid heart disease progresses, its consequences for valve morphology and function can be demonstrated relatively easily with 2D TTE with good appreciation of primary valvular and sub-valvular involvement. However, in the early stages of carcinoid heart disease, 2D echocardiography may have limited sensitivity due to lower spatial resolution than other cardiac imaging modalities (Gardner et al. 2009) and may miss single leaflet involvement or diffuse thickening of all valve leaflets without significant reduction in leaflet mobility or development of regurgitation.

Imaging from the trans-oesophageal window allows accurate measurement of the thickness of the atrio-ventricular valve leaflets and the superficial wall layers of both atria (Lundin et al. 1990). Trans-oesophageal imaging is recommended (Ramage et al. 2012) for patients in whom comprehensive evaluation of the right-sided heart valves is not possible via the transthoracic approach. Reproducible and accurate quantification of right heart volume and function is challenging with 2D TTE, yet this is an important part of carcinoid heart disease assessment (Sandmann et al. 2009).

Contrast echocardiography should be performed in all patients with a diagnosis of carcinoid heart disease (Plockinger et al. 2009). This is the modality of choice to determine the presence of intra-cardiac shunts and the patency of foramen ovale. Simultaneous venous injection of an agitated mixture of saline, blood and air and ultrasound recording of 2D images enable identification of any communication between the right and left heart.

Doppler echocardiography is an accurate, non-invasive technique for detection of right-sided valvular regurgitation, with a higher sensitivity than cardiac catheterisation (Waggoner et al. 1981). Haemodynamic information, such as estimation of right ventricular systolic pressure, aids in the distinction between primary and secondary tricuspid regurgitation (significant regurgitation with a pressure of <40 mmHg often implies intrinsic valve disease; Irwin et al. 2010). This distinction is clinically important as it has fundamental implications for the patient’s treatment and prognosis. Furthermore, Doppler enables the study of pulmonary haemodynamics; where present, the peak velocity of the pulmonary regurgitant jet represents the diastolic pressure gradient between the pulmonary artery and the right ventricle (Abbas et al. 2003). Application of the modified Bernoulli equation to this value provides an estimate of mean pulmonary artery pressure (Masuyama et al. 1986). The end diastolic pulmonary regurgitant velocity enables calculation of the same gradient, but at end-diastole, and this added to right atrial pressure estimates diastolic pulmonary arterial pressure (Milan et al. 2010).

**Three-dimensional echocardiography** Three-dimensional (3D) echocardiography, while being more time-consuming, can offer supplementary information. It enables an in-depth characterisation of valve pathology with an en-face view of the tricuspid valve and has the ability to visualise all three leaflets simultaneously (Bhattacharyya et al. 2010, Lang et al. 2012). In this respect, it may more accurately delineate the precise extent of leaflet involvement. 3D echocardiographic imaging has recently demonstrated direct visualisation of echogenic areas consistent with carcinoid deposits, which has not previously been described (Dumaswala et al. 2012). 3D imaging enables a comprehensive assessment of right ventricular geometry, volumes and ejection fraction, which is not always possible with a 2D probe (Lang et al. 2012). Recent advances in transducers have enabled single beat 3D echocardiography, which is much quicker in terms of data acquisition time, and has a high correlation with cardiac magnetic resonance imaging (MRI) for the functional assessment of the right heart (Shattke et al. 2012).

**Tissue Doppler imaging** The more novel applications of tissue Doppler and strain rate imaging have been shown to have a higher sensitivity for the
Table 1  Comparison of imaging modalities for the assessment of carcinoid heart disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>2D TTE</th>
<th>3D TTE</th>
<th>TOE</th>
<th>Dual source multi-slice CT</th>
<th>Cardiac MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal resolution</td>
<td>+ + +</td>
<td>45–60; Full2D exam + focused 3D (Mor-Avi et al. 2009)</td>
<td>45–60 (BSE, April 2013: <a href="http://cdn1.cache.twofourdigital">http://cdn1.cache.twofourdigital</a>.</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Radiation</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Limitations</td>
<td>None known</td>
<td>Time required for reconstruction of images</td>
<td>Contraindicated in oesophageal pathology, recent GI bleed and severe</td>
<td>45 centres in the UK in 2011 (Mittal</td>
<td>60 centres in the UK in 2011 (Antony et</td>
</tr>
<tr>
<td>Evidence in serial studies</td>
<td>Well established (Denney et al. 1998, Zuetenhorst et al. 2004,</td>
<td>Not validated</td>
<td>Mainly validated for assessment of pulmonary hypertension (Ghaye</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>with other markers of carcinoid heart disease</td>
<td>Mansencal et al. 2010a, b, Bhattacharya et al. 2011)</td>
<td>Not validated</td>
<td>et al. 2006)</td>
<td>As for CT plus: nephrogenic systemic</td>
<td>As for CT plus: nephrogenic systemic</td>
</tr>
<tr>
<td>(Denney et al. 1998), chromogranin A (Korse et</td>
<td>2010)</td>
<td>Not validated</td>
<td>Gold standard, most accurate technique</td>
<td>rcr.ac.uk/docs/radiology/pdf/</td>
<td>rcr.ac.uk/docs/radiology/pdf/</td>
</tr>
<tr>
<td>Heart</td>
<td>2010)</td>
<td>Not validated</td>
<td>Gold standard, most accurate technique</td>
<td>BFCR(10)4_Stand_contrast.pdf)</td>
<td>BFCR(10)4_Stand_contrast.pdf)</td>
</tr>
<tr>
<td>Value in serial studies</td>
<td>Well established (Denney et al. 1998, Zuetenhorst et al. 2004,</td>
<td>Not validated</td>
<td>No data identified</td>
<td>As for CT plus: nephrogenic systemic</td>
<td>As for CT plus: nephrogenic systemic</td>
</tr>
<tr>
<td>Heart</td>
<td>2011)</td>
<td>Not validated</td>
<td>No data identified</td>
<td>rcr.ac.uk/docs/radiology/pdf/</td>
<td>rcr.ac.uk/docs/radiology/pdf/</td>
</tr>
<tr>
<td>Histopathological examination of excised valves</td>
<td>Bhattacharya et al. 2010, Nanawadi et al. 2010)</td>
<td>Not validated</td>
<td>No data identified</td>
<td>BFCR(10)4_Stand_contrast.pdf)</td>
<td>BFCR(10)4_Stand_contrast.pdf)</td>
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</tbody>
</table>

2D, two-dimensional; TTE, transthoracic echocardiography; 3D, three-dimensional; BSE, British Society of Echocardiography; TOE, trans-oesophageal echocardiography; CT, computed tomography; MRI, magnetic resonance imaging; GI, gastrointestinal; CKD, chronic kidney disease; BNP, brain natriuretic peptide; S-HAA, S-hydroxyindoleacetic acid.
identification of the early stages of carcinoid heart disease. There is evidence that patients with carcinoid disease but without overt cardiac involvement, have sub-clinical right ventricular dysfunction, with decreased right ventricular strain and tricuspid annular plane systolic excursion (TAPSE; Haugaa et al. 2011). Strain is a measure of tissue deformation and can be measured using a variety of echocardiographic techniques (tissue Doppler and speckle tracking). TAPSE is a simple measure of right ventricular function and is measured using m-mode echocardiography. Tissue Doppler imaging is recognised in international guidelines as likely to play a larger role in the assessment of carcinoid heart disease in the future (Pape et al. 2012).

Value of echocardiography in serial studies As the identification and timely treatment of carcinoid heart disease have significant prognostic implications (Moller et al. 2005), it is important to have a robust method of screening and following up patients. TTE is an ideal imaging modality to do this, with the ability to detect cardiac involvement before the patient develops symptoms, and with high sensitivity and specificity for the disease. It has been used in several studies of progression of carcinoid heart disease (Denney et al. 1998, Zuetenhorst et al. 2004, Moller et al. 2005, Mansencal et al. 2010b, Bhattacharyya et al. 2011). We were unable to identify any comparative studies of serial scanning with other imaging modalities.

Advantages of echocardiography over other imaging modalities Echocardiography has a number of advantages over other imaging modalities. The lack of radiation exposure makes it safer for patients when compared with computed tomography (CT) and nuclear imaging, particularly for patients requiring serial studies. Echocardiography can be used in patients with pacemakers or other internal metalwork, in contrast to MRI. Furthermore, echocardiography offers both morphological and functional assessment, both of which are

Figure 1
(A, B, C and D) Two-dimensional transthoracic echocardiographic images. (A) Apical four-chamber view demonstrating severely thickened, retracted tricuspid valve with severely dilated right atrium. (B) Colour flow across tricuspid valve illustrating severe tricuspid regurgitation with broad vena contracta. (C) Parasternal long axis view of thickened tricuspid valve. (D) Continuous wave Doppler across tricuspid valve; dense signal demonstrating severe tricuspid regurgitation.
important in the assessment of carcinoid heart disease. Echocardiography is a relatively cheap investigation to perform, in comparison to cardiac CT, magnetic resonance and nuclear imaging.

Other imaging modalities

**Cardiac CT** Imaging the heart using CT has been anticipated for many years but has been limited by the poor spatial and temporal resolution of previous generations of CT scanners (Mahesh & Cody 2007). However, the introduction of multi-row detector CT has dramatically improved spatial resolution, enabling an in-depth assessment of the right heart chambers and valves, which are often difficult to assess using TTE. However, this modality is not superior to TTE with regard to quantification of haemodynamics (valvular regurgitation or pulmonary artery pressure; Manghat et al. 2008), and the limited temporal resolution of cardiac CT can limit appreciation of valve motion.

**Cardiac MRI** Cardiac MRI has an important role in the assessment of carcinoid heart disease, its main advantage being the reproducible and accurate assessment of the metastatic carcinoid tumour ± carcinoid syndrome

Clinical suspicion of extra-cardiac involvement

Annual clinical assessment, 2D transthoracic echocardiography and measurement of NT-proBNP

Presence of characteristic thickening, reduced excursion/retraction of right-sided valve leaflet with associated regurgitation or stenosis

Perceived benefit from detecting early myocardial involvement

No

Normal

Yes

TDI

Any of:
- Moderate–severe tricuspid/pulmonary regurgitation or stenosis
- Right heart dilatation (based on American Society)
  Echocardiography chamber dimensions
- Right ventricular functional impairment
- Extra-cardiac involvement
- Abnormal TDI with significantly raised NT-proBNP

Refer to cardiologist for clinical assessment and consideration of cardiac catheterisation

Repeat TTE in 6–12 months

Figure 2
Proposed algorithm for the screening and investigation of carcinoid heart disease.
right heart, which can be difficult using 2D TTE alone (Sandmann et al. 2009). The problem of sub-optimal visualisation of the right-sided heart valves, particularly the pulmonary valve, can be overcome with MRI that provides precise functional and anatomical information, allowing accurate quantification of regurgitant volumes (Franzen et al. 2009). In addition, this modality also allows identification of extension into extra-cardiac structures, an aspect less well appreciated by echocardiography (Bhattacharyya et al. 2010). Cardiac MRI offers the potential of more accurate quantification of right ventricular ejection fraction and one group has suggested that this modality should be the reference standard for patients with known carcinoid heart disease (Klobucic et al. 2012). Cardiac MRI is recommended in ENETS guidelines for evaluating the pulmonary valve, for identification of cardiac metastases and for assessment of right ventricular function (Ramage et al. 2012).

**Nuclear medical imaging** Positron emission tomography using a radionuclide tracer can be used to identify metastatic spread of carcinoid tumours and has a role in the identification of cardiac metastases that occur in ~4% of patients with carcinoid syndrome (Bhattacharyya et al. 2010). A variety of tracers have been utilised including ¹⁸F-dihydroxy-phenyl-alanine (Fiebrich et al. 2008) and octreotide labelled with Gallium 68 (Bhattacharyya et al. 2010). The advantages and disadvantages of the different imaging modalities are summarised in Table 1.

**Discussion**

Cardiac imaging is the cornerstone of diagnosis in patients with carcinoid heart disease. With its widespread availability, portability and low cost, echocardiography is well suited to screening for carcinoid heart disease in a population and is the initial modality of choice for diagnosis. In our centre, TTE is available in the neuroendocrine clinic, with instant results available to staff and patients alike. Also, because echocardiography can accurately depict involvement across a wide spectrum of pathology, it is well suited to evaluation of progression in an established disease.

The topic of serial studies for screening/disease surveillance requires much clarification with further work. While less comprehensively validated, the role of other imaging, particularly cardiac MRI, is being increasingly appreciated especially with reference to extra-cardiac extension in addition to accurate and reproducible assessment of the right ventricle – features more relevant to later stage disease. Using MRI for annual evaluation would be expensive (£527/patient compared with £228 for TTE (British Society of Cardiovascular Imaging (April 2013: http://www.bsci.org.uk/ct-cmr-tariffs) and Department of Health (April 2013, https://www.gov.uk/government/publications/payment-by-results-2013-14-road-test-package)) based on a median survival of 4.5 years).

A number of further developments in cardiac imaging are likely to improve our evaluation of carcinoid heart disease. Endomyocardial involvement has been documented and detection of this potentially early manifestation of the condition may be best facilitated by tissue Doppler echocardiography and strain rate imaging. These techniques suffer from signal-noise problems but are currently being refined with the development of automated methods. More validation work is likely to emerge in the near future. The availability of cardiac CT and magnetic resonance has increased markedly in the last 5 years with improving image quality and an increasing abundance of published studies.

The imaging techniques available have different strengths in specific clinical circumstances and are probably best regarded as complementary to each other. Despite the increasing availability of more sophisticated cardiac imaging modalities, TTE is well validated, widely available and very safe, making it the preferred primary investigation in the diagnosis and surveillance of carcinoid heart disease. The optimal approach is likely to involve the application of more than one modality depending on the stage of disease, functional state of the patient and likelihood of surgical intervention. We propose an algorithm for the investigation of carcinoid heart disease (Figs 1 and 2).

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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