The Optimal Use of Cardiac Imaging in the Quantification of Carcinoid Heart Disease

Dobson, Rebecca\textsuperscript{1,2}, Cuthbertson, Daniel J\textsuperscript{2}, Burgess, Malcolm I\textsuperscript{1}

1\textsuperscript{1}Department of Cardiology, University Hospital Aintree, Lower Lane, Liverpool, L9 7AL
2\textsuperscript{2}Department of Obesity and Endocrinology, Institute of Aging and Chronic Disease, University of Liverpool, Liverpool.

Corresponding author and address for proofs and reprint requests:
Dr Rebecca Dobson
Clinical Sciences Centre
Aintree University Hospital
Lower Lane
Liverpool
L9 7AL
E-mail: rebecca.dobson@liverpool.ac.uk
Tel 0151 529 5917
Fax 0151 529 5888

Key words: Carcinoid heart disease; imaging; valvular disease
Short title: Imaging in carcinoid heart disease
Word count: 3322
Abstract

Carcinoid heart disease is a rare cause of right-sided valvular dysfunction, primarily mediated by serotonin. It is an important complication of patients with the carcinoid syndrome, and occurs in 20-50% of such patients. Echocardiography is the main tool used for the assessment of carcinoid heart disease but other imaging modalities are also important, particularly in the quantification of the severity of disease. We sought to review the role of cardiac imaging in the assessment of carcinoid heart disease.
Neuroendocrine tumours (NETs) are a varied group of tumours that arise from neuroendocrine precursor cells. They are rare, occurring in 1.2 – 2.1 per 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 Bjork et al. in 1952 is a major cause of morbidity and mortality in patients with carcinoid syndrome and in up to 20% of patients, 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 previously stated, 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 the right heart is notoriously difficult to image 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 which 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 para-neoplastic effect of vaso-active substances secreted by the tumours, including 5 hydroxytryptamine, (5-HT, 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. Firstly, 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 (Gustafsson 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 activin A (Bergestuen et al. 2010a) and connective tissue growth factor (Bergestuen et al. 2010b) both 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 is a well-validated tool for the diagnosis and surveillance of carcinoid heart disease, its use guided by biomarkers such as N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) (Ramage et al. 2012). Other biomarkers which have been used in the assessment of the disease include Chromogranin A (Korse et al. 2009) and urinary 5-HIAA (Zuetenhorst et al. 2003). Monitoring of progression
of cardiac involvement is important as carcinoid heart disease can impact 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 (Pelikka et al. 1993), there is no current consensus over 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 and Mansencal et al. 2010b) vary
considerably in complexity. The simplest score is an eight-point assessment of the tricuspid
valve (Westburg et al. 2001) whilst the most comprehensive evaluation is a sixty-six-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 2-dimensional 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. 2011, on behalf of ENETS (European
Neuroendocrine Tumour Society), recommends that all patients with midgut NETs, with or
without hepatic metastases, and all patients with the carcinoid syndrome should be screened
for cardiac involvement. However, Pape et al. 2012, also on behalf of ENETS, recommends
screening only for patients with the carcinoid syndrome, or those with elevated levels of
Chromogranin A or 5-HIAA. Regular echocardiographic screening for carcinoid heart
disease, supplemented or guided by NT-proBNP measurement where appropriate is recommended by NANETS (North America Neuroendocrine Tumor Society) and ENETS (Vinik et al. 2010, Ramage et al. 2011, 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 results 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 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 has been reported (Ferrans & Roberts 1976, Macdonald & Robbins 1957). 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**

*2-dimensional echocardiography*: As carcinoid heart disease progresses, its consequences for valve morphology and function can be demonstrated relatively easily with 2-dimensional (2D) transthoracic echocardiography 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. 2011) for patients in
whom comprehensive evaluation of the right-sided heart valves is not possible via the trans-
thoracic approach. Reproducible and accurate quantification of right heart volume and
function is challenging with 2D transthoracic echocardiography, 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 enables 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 less than 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).

3-dimensional echocardiography: 3-dimensional (3D) echocardiography, whilst 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 (Lang et al. 2012, Bhattacharyya et al. 2010). 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 to cardiac magnetic resonance imaging for the functional assessment of the right heart (Schattke 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 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:* Since the identification and timely treatment of carcinoid heart disease has significant prognostic implications (Moller et al. 2005), it is important to have a robust method of screening and following up patients. Transthoracic echocardiography 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 (Moller et al. 2005, Bhattacharyya et al. 2011, Mansencal et al. 2010b, Denney et al. 1998, Zuetenhorst et al. 2004). 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 than computed tomography and nuclear imaging, particularly for patients requiring serial studies. Echocardiography can be used in patients with pacemakers or other internal metalwork, in contrast to magnetic resonance imaging. Furthermore,
echocardiography offers both morphological and functional assessment, both of which are important in the assessment of carcinoid heart disease. Echocardiography is a relatively cheap investigation to perform, in comparison to cardiac computed tomography, magnetic resonance and nuclear imaging.

Other Imaging Modalities

Cardiac Computed Tomography: Imaging the heart using computed tomography (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 transthoracic echocardiography. However this modality is not superior to transthoracic echocardiography 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 Magnetic Resonance Imaging: Cardiac magnetic resonance imaging has an important role in the assessment of carcinoid heart disease, its main advantage being the reproducible and accurate assessment of the right heart which can be difficult using 2D transthoracic echocardiography 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 magnetic resonance imaging which 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 magnetic resonance imaging 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 magnetic resonance imaging 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. 2011).

Nuclear medical imaging: Positron emission tomography (PET) using a radionuclide tracer can be used to identify metastatic spread of carcinoid tumours, and has a role in the identification of cardiac metastases which occur in approximately 4% of patients with carcinoid syndrome (Bhattacharyya et al. 2010). A variety of tracers have been utilised including $^{18}$F-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 presented 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, transthoracic echocardiography 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 established disease.

The topic of serial studies for screening/disease surveillance requires much clarification with further work. Whilst less comprehensively validated, the role of other imaging, particularly cardiac magnetic resonance imaging, 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 magnetic resonance imaging for annual evaluation would be expensive (£527 per patient compared to £228 for transthoracic echocardiography (British Society of Cardiovascular Imaging, April 2013: http://www.bsci.org.uk/ct-cmr-tariffs & 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 computed tomography and magnetic resonance has increased markedly in the last five 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, transthoracic echocardiography 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 (figure 1).
Table and figures

Table 1 Comparison of imaging modalities for the assessment of carcinoid heart disease

Figure 1 2 dimensional transthoracic echocardiographic images (A-D)

Figure 2 Proposed algorithm for the investigation of carcinoid heart disease
Figure 1

A – Apical 4 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.

Figure 2

Proposed algorithm for the investigation of carcinoid heart disease
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.
References


Bhattacharyya S, Toumpanakis C, Caplin ME, Davar J 2008 Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease.
American Journal of Cardiology 102 (7) 938-42.


Bhattacharyya S, Toumpanakis C, Burke M, Taylor AM, Caplin ME, Davar J 2010 Features of carcinoid heart disease identified by 2-and 3-dimensional echocardiography and cardiac MRI. Circulation: Cardiovascular Imaging 3 (1) 103-11.


Differentiated Jejunal-Ileal Tumour/Carcinoma. *Neuroendocrinology* 87:8-19


Irwin RB, Luckie M, Khattar RS 2010 Tricuspid regurgitation: contemporary management of


Macdonald RA, Robbins S 1957 Pathology of the heart in the carcinoid syndrome. *A.M.A. Archives of Pathology* 63(2) 103-12.

Mahesh M, Cody D 2007 AAPM/RSNA Physics tutorial for residents: Physics of cardiac imaging with multiple-row detector CT. *Radiographics* 27 1495-1509


Mittal T. BSCI Cardiac CT Survey. Presented at The United Kingdom Radiological Congress. Manchester 2012.


quantitative volumetric analysis of the right ventricle. *JACC Cardiovascular Imaging* 3 10-18.


<table>
<thead>
<tr>
<th>Variable</th>
<th>2D TTE</th>
<th>3D TTE</th>
<th>TOE</th>
<th>Dual source</th>
<th>Cardiac MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spatial resolution</strong></td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Temporal resolution</strong></td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Approximate scan time (minutes)</strong></td>
<td>40–45</td>
<td>45–60; Full 2D exam +</td>
<td>45–60</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>12,000 scans per million population in 2006 (Boon 2006)</td>
<td>Now widely available</td>
<td>3500 scans per million population in 2006 (Boon 2006)</td>
<td>45 centres in the UK in 2011 (Mittal 2012)</td>
<td>60 centres in the UK in 2011 (Antony et al. 2011)</td>
</tr>
<tr>
<td>Radiation</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1.5 – 5 mSv (Leber 2010)</td>
<td>None</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>--------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Limitations</td>
<td>None known</td>
<td>Time required for reconstruction of images</td>
<td>Oro-pharyngeal injury, oesophageal laceration/perforation, gastric perforation, airway compromise</td>
<td>Anaphylactoid reaction, urticaria, contrast medium extravasation, contrast nephropathy, skin reaction</td>
<td>As for CT plus: Nephrogenic systemic fibrosis (April 2013: <a href="http://www.rcr.ac.uk/docs/radiology/pdf/BFCR(10)4_Stand_contrast.pdf">http://www.rcr.ac.uk/docs/radiology/pdf/BFCR(10)4_Stand_contrast.pdf</a>) Contraindicated in oesophageal pathology, recent GI bleed, severe cervical arthritis (Hilberath et al. 2010) Relatively contraindicated in patients with internal Contraindicated in CKD and pregnancy metal work</td>
</tr>
<tr>
<td>Evidence of correlation with other markers of carcinoid heart disease</td>
<td>BNP (Bhattacharyya et al. 2008)</td>
<td>Histopathological examination of excised valves (Nalawadi et al. 2010)</td>
<td>No data identified</td>
<td>No data identified</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Urinary 5HIAA (Denney et al. 1998)</td>
<td>examination of excised valves (Nalawadi et al. 2010)</td>
<td>2010, Bhattacharyya et al. 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromogranin A (Korse et al. 2009)</td>
<td>Histopathological examination of excised valves (Bhattacharyya et al. 2010)</td>
<td>2010</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2D – 2 Dimensional, TTE – Trans-thoracic echocardiography, 3D – 3 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, 5HIAA – 5 Hydroxyindoleacetic acid
Figure 1 - 2 dimensional transthoracic echocardiographic images (A-D)
254x190mm (300 x 300 DPI)
Fig 2 – Proposed algorithm for the investigation of carcinoid heart disease

Metastatic carcinoid tumour +/- carcinoid syndrome

- Clinical suspicion of extra-cardiac involvement
  
  - No
  
  - Yes
    
    Annual clinical assessment, 2D transthoracic echocardiography & measurement of NT-proBNP

- Cardiac MRI

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

  - No
    
    Perceived benefit from detecting early myocardial involvement

  - Yes
    
    Uncertain valve morphology

      - Uncertain right ventricular function

      - 2D +/- 3D TOE

      - 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

  - Any of:
    
    - Yes
      
      Refer to Cardiologist for clinical assessment and consideration of cardiac catheterisation.

    - No
      
      Repeat TTE in 6-12 months