ABSTRACT

Tricuspid regurgitation natural history and treatment remains poorly understood. Right ventricular function is a key factor in determining prognosis, timing for intervention and longer-term outcome. The right ventricle is a thin walled chamber with a predominance of longitudinal fibres and a shared ventricular septum. In health, the low-pressure pulmonary circulation results in a highly compliant RV well equipped to respond to changes in preload but sensitive to even small alterations in afterload. In the first of two articles discussion focuses on key principles of ventricular function assessment and the importance of right ventricular chamber size, volumes and ejection fraction, particularly in risk stratification in tricuspid regurgitation. The second article provides an understanding of the causes of tricuspid regurgitation in the contemporary era, with emphasis on key patient groups and their management.
INTRODUCTION

Tricuspid valve regurgitation (TR) presents challenges to modern day clinical practice. Its natural history is not well understood. Previously, uncertainty existed as to whether TR is an independent factor of outcome or rather a surrogate marker of right ventricular disease and other co-morbid conditions including pulmonary hypertension(1). However, more recently studies has shown increasing TR severity is associated with worse survival regardless of left ventricular (LV) function and pulmonary hypertension(2). Both late residual TR seen post mitral valve surgery(3) and isolated severe TR(4) have excess mortality and morbidity. Management guidelines remain ill-defined since prospective outcome data is limited(5). Further, surgical TV intervention studies have suggested variable outcomes and this conflicting data has led to confusion as to optimal management in this cohort. This heterogeneous patient group includes right ventricular (RV) dysfunction, pulmonary hypertension and multiple associated comorbid conditions. Recent publications have assisted in defining patient cohorts who may benefit from surgical intervention(6). In the first of two articles discussion focuses on key principles of ventricular function assessment and the importance of right ventricular chamber size, volumes and ejection fraction, particularly in risk stratification in tricuspid regurgitation. The second article provides an understanding of the causes of tricuspid regurgitation in the modern era, with emphasis on key patient groups and their management.

RIGHT VENTRICULAR PHYSIOLOGY WITH ALTERATIONS IN LOADING CONDITIONS

Anatomy and Basic Concepts

For a long time, right ventricular (RV) function was considered, based on its morphology (low myocardial mass, thin walls) as simply a transferring chamber; where the cardiac output would remain unaffected by its exclusion. In the last 30 years publications have highlighted RV dysfunction as an independent prognostic factor in left heart disease. Heart failure morbidity and mortality is worse in those with similar degrees of LV impairment but concomitant RV dysfunction (7)(8)(9)(10). Much of this understanding has evolved through advancements in cardiac imaging.

Fundamental anatomical differences between the right and left ventricles reflect their distinct embryological origin and haemodynamic physiology. The heart is derived from cardiac mesoderm that forms a cardiac crescent(11). Using murine models, this mesoderm has been shown to be partitioned into two cell populations, named the primary and secondary heart fields(12). These fields have distinct transcriptional identities. Although these fields merge to form a single heart
tube, which later loops and ultimately forms a 4 chambered structure, lineage tracing experiments reveal the primary heart field gives rise to the left and right atria and left ventricle whereas the secondary heart field gives rise to the right ventricle and outflow tract during development. Taken together with the fact that the right ventricle is exposed to a unique flow and pressure environment compared to the left ventricle as the heart continues to develop after birth, it is plausible that these differences could lead to distinct functionalizations and behaviours between the right and left ventricle that may contribute to differences in disease manifestation.

RV ejection performance and stroke volume are determined by several factors namely; preload, afterload, myocardial wall thickness and contractility as well as constraint from the intact pericardium. The RV mass is approximately one-sixth that of the LV, its wall thickness no more that 3-4mm. The RV is adapted to eject blood against a lower pulmonary vascular resistance. Low afterload results in reduced wall tension and characterises RV physiology as a low pressure highly compliant pumping chamber. An appreciation of myocardial fibre orientation (inner longitudinal fibres extend from base to apex; outer circumferential fibres run parallel to the tricuspid valve (TV) annular plane) and their continuity with the shared ventricular septum assists in our understanding of RV pump action and highlights two key characteristics. Firstly, that of ventricular interdependence determined by the higher LV pressures in normal circumstances; the ventricular septum moves towards the centre of the LV cavity during systole and outwards in diastole (circumferential fibre contraction). Hence, RV contraction has been compared to a bellows like action where the lateral free wall contracts against a relatively rigid ventricular septum. Secondly, the RV base contracts towards the apex, resulting in longitudinal RV shortening. Thus, cardiac imaging modalities utilise circumferential and longitudinal contraction when assessing RV function.

Right Ventricular Response in Disease States

RV response to disease can result from volume or pressure overload and myocardial disease. In reality a combination of these factors coexists, where understanding the primary aetiology leading to the observed findings is fundamental to risk stratification and further disease management.

The RV is able to accommodate changes in preload far better than afterload. Thus, where the principal lesion is volume overload (i.e. increase in preload) as in the case of primary tricuspid regurgitation or left-to-right shunting, the RV tolerates this high-volume state; remaining well adapted to maintain RV contractility and cardiac output for prolonged periods before progressive RV
dilatation, dysfunction and failure ensue. This may occur with or without the development of pulmonary vasculopathy (from chronic high flow). With chronic volume overload the crescent shaped RV becomes increasingly spherical and since pericardial capacity is limited ventricular interdependence shifts the ventricular septum leftward. LV filling is impaired further compounding a fall in cardiac output.

Pressure overload states typically describe increases in RV afterload from pulmonary arterial hypertension (PAH) since pulmonary stenosis is rare. Adaptive mechanisms designed to reduce RV wall stress and maintain normal cardiac output result in ventricular hypertrophy and dilatation. However progressive functional (secondary) tricuspid regurgitation (consequent to TV annular dilatation as the RV dilates) and paradoxical ventricular septal motion (through increasing RV filling pressure) increase load to the failing RV worsening cardiac output. As with volume overload ventricular interdependence impairs LV filling contributing to the further decline in cardiac output and hypotension.

Primary myocardial disease such a RV infarction or primary cardiomyopathy (e.g. arrhythmogenic right ventricular dysplasia) results in RV contractile dysfunction. A fall in RV forward flow reduces LV preload with a reduction in systemic cardiac output. Ventricular interdependence and functional TR (through RV dilatation and wall motion abnormalities disrupting the TV subvalvular complex) with a superimposed volume overload state may further worsen RV dysfunction.

PARAMETERS FOR RIGHT VENTRICULAR FUNCTION ASSESSMENT

RV function assessment presents challenges to all two-dimensional imaging techniques. The RV lies anteriorly and wraps around the conical shaped LV. The RV consists of TV inflow, RV body and apex, and outflow (infundibulum). Since the RV outflow is orientated in a different plane, integration of multiple image views is necessary for comprehensive assessment. Currently, imaging techniques lack a precise tool to predict RV recovery following intervention. Therefore, the ability to accurately diagnose RV dysfunction remains vital. A checklist of key parameters is summarized in table 1.

Ventricular Interdependence

Ventricular interdependence plays an important role in RV dysfunction. RV-LV interaction can be assessed through paradoxical ventricular septum (VS) motion. Since VS configuration is determined by the pressure gradient between the LV and RV throughout the cardiac cycle, its behaviour lends insight into states due to pressure (systolic septum flattening) or volume (diastolic septum...
flattening) overload. This can be quantified by the eccentricity index (see figure 1). Indeed VS
contraction contributes to RV systolic function by as much as 24% in health to 35% in pathological
states, when there is RV free wall impairment, maintaining RV output(13). Conversely, this
mechanical interaction may be the cause of RV dysfunction in the setting of left sided heart disease,
being independent of RV afterload effects, and may predict postoperative RV dysfunction in severe
organic mitral regurgitation(14). Figure 1 illustrates the clinical utility of cardiac imaging in
differential diagnosis of RV volume and pressure overload states.

Quantitative assessment of RV function in severe Tricuspid Regurgitation

Right Ventricular Size

RV function is the major determinant for morbidity and mortality in many diseases including
pulmonary hypertension, left ventricular dysfunction and heart failure and heart valve disease. As
described above the RV is sensitive to changes in loading conditions. Typically, early signs in RV
disease are manifested through alteration in RV size. RV dilatation can be described by dimension,
area and volume measurements. International guidelines for echocardiographic assessment of the
right heart define a systematic approach to two-dimensional (2D) measurements taken from the RV
focused apical four chamber view and parasternal (PS) windows in end diastole(15), see table 1.
Similarly, RV area is assessed in the RV focused apical four chamber view. RV volumes can be
assessed with three-dimensional echo (3DE) and cardiac magnetic resonance imaging, further details
of which are described in the sections below.

RV Contractile Function

During RV contraction long axis shortening from base to apex together with lateral wall contraction
towards the ventricular septum form the basis for RV function assessment. The LV is conical shaped,
where geometric assumptions are more readily applied in volumes and ejection fraction
calculations. However, a similar approach to the right ventricle is not feasible given its shape and
inability to integrate all three regions within a single imaging plane. Thus, quantitative assessment of
RV function by 2D echo modalities relies on surrogate markers and includes long axis function (M-
mode and tissue Doppler imaging), fractional area change, RV index of myocardial performance, RV
global longitudinal strain and three-dimensional RV volumes and ejection fraction. No single
measurement has been validated in different conditions and hence a combined approach integrating
several measurements is advocated(15). A large number of potential measurements are described,
however for the purpose of this review key parameters needed in risk stratification, in routine clinical practice will be discussed, see figure 2 and table 1. For a comprehensive overview the reader is referred to international guidelines(15)(16).

**Long axis function**, peak systolic motion of the RV base towards the apex, represents longitudinal myocardial fibre shortening. This can be easily documented using M-mode (Tricuspid annular systolic plane excursion, TAPSE) and tissue Doppler imaging (TDI S wave) placed over the lateral wall at the TV annular plane. To avoid underestimation optimal alignment to the annular plane motion in the apical four-chamber view is recommended. Both methods correlate strongly with radionuclide angiography(17), biplane Simpson RV ejection fraction and RV fractional area change(18). It is the most utilised parameter in RV function assessment due to its ease of acquisition and reproducibility(19)(20). A TAPSE <17mm or TDI S wave <9.5cm/s are considered abnormal(15). An important limitation is the assumption that lateral wall motion (local basal function in the case of TDI) reflects global function. Therefore, assessment should be in the context of wall motion and integrated with all other RV function parameters. In severe TR with preserved systolic function TAPSE and TDI have supra-normal values (due to a hyperdynamic volume loaded RV); thus measurements falling into the normal range indicate RV dysfunction.

The percentage **RV fractional area change** (FAC), defined as end diastolic area – end systolic area/end diastolic area x100, is a measure of RV systolic function(21). FAC has been shown to be an independent prognostic predictor in a wide range of disease states including pulmonary embolism(22), pulmonary hypertension, myocardial infarction and heart failure(23); Importantly, RV FAC has demonstrated good correlation with RV ejection fraction (RVEF) by MRI(21)(24). Therefore, this surrogate marker has merit in serial monitoring of RV contractility in patients with severe TR particularly if asymptomatic and who may be considered for corrective surgery in the future. Normal values are ≥35%, and typically in severe TR with significant volume overload are often above 40% where RV function is preserved.

**RV index of myocardial performance** (MPI) is a global estimate of both systolic and diastolic ventricular function since it includes the isovolumic periods in its calculations. It describes the relationship between ejection and non-ejection work of the RV and has been shown to be a prognostic marker in pulmonary hypertension(25). In the normal RV isovolumic periods are near absent, however as RV ejection falls these intervals gradually extend. The MPI is particularly useful in serial measurements correlating well with clinical status(26), However there are important limitations to its routine clinical use including load dependency and inaccuracy with irregular heart rates(27). In the setting of severe TR, high right atrial pressures shorten isovolumic periods making
this measure unreliable.

RV volumes and RV Ejection Fraction: RV volume changes reflect the degree of volume overload and RV dysfunction. Therefore, quantifying RV volumes is important in diagnosis and risk stratification of patients with tricuspid regurgitation. As described above, both inflow and outflow lie in different planes to the body and apex of the RV. Hence geometric assumptions applied to the LV cannot be reliably used to calculate volumes using the standard 2D echocardiographic views. 3D techniques overcome such limitations. The current gold standard for calculating RV volumes and RV ejection fraction (RVEF) is cardiac magnetic resonance imaging (CMR). Recent pooled data(28) defined normal values for RV end systolic and diastolic volumes indexed to body surface area and RV ejection fraction, see table 1. However, CMR is relatively expensive and not widely available. 3DE techniques are improving and although not available in the majority of Echo Labs as yet show considerable promise. Current guidelines(15) cut-off values are given in table 1. Despite a systematic underestimation of volumes (although not ejection fraction) of approximately 20% by 3DE (likely reflecting limitations in endocardial border detection and incomplete capture of the entire RV within the 3DE window), studies comparing 3DE with CMR have shown good correlation(29) (30). The semi-automated border detection method is recommended(15). RV end diastolic volume index (RVEDVI) has been shown to be a predictor of post-surgery RV dysfunction in a number of patient groups in volume overload states. This includes, congenital heart disease patients undergoing pulmonary valve replacement in Tetralogy of Fallot’s for pulmonary regurgitation, where a RVEDVI > 150-170 mls/m² suggested reverse remodeling was unlikely to occur. Preoperative RVEDVI of 164 ml/m² effectively discriminated patients with normal from those with reduced RVEF post-surgery, with a sensitivity of 77% and a specificity of 72% (p=0.01)(31). Therefore, significant RV dilatation can be considered when indexed values reach 150ml/m² and beyond.

RV global longitudinal strain (GLS) is calculated as the percentage of systolic shortening of the RV, from base to apex. While this parameter is load dependant, it is less confounded by heart rates (as compared to strain rate). RV GLS provides important insights into RV performance, offering useful indicators of prognosis and functional capacity in a number of disease states(32)(33)(34). It has been shown to correlate with myocardial fibrosis, a marker of poor prognosis(35). Two methods for strain analysis exist and each has limitations in image acquisition. Speckle tracking echo relies on image quality, while colour tissue Doppler echo is angle dependant. The RV focused four-chamber view is acquired with care taken to ensure the endocardium and mid wall of all segments are optimised and seen throughout the cardiac cycle, with correct alignment in the case of TDI. Previously, differing cut-off values have been published using a variety of vendors, with a range of different image
acquisition and software analysis methodologies, making its clinical use challenging. Data can be
analysed from the lateral wall alone or in combination with the septal wall, 3 or 6 segment methods
respectively. The former method typically yields higher averaged values (absolute value, normal
>23%) than the latter (normal >20%)\(^\text{36}\). Current published data are limited and guideline
recommendations consider normal GLS of the RV lateral (free) wall to be \(<-20\%\) \((\text{absolute value of } >
20\%)\(^\text{15}\) although specific vendors may have a slightly higher absolute cut-off value (as in the case
of GE healthcare >23\%)\(^\text{36}\)). Recent taskforce recommendations have set out a standardised method
for data acquisition and analysis\(^\text{37}\) with the aim of improving agreement between vendors in the
future.

RV diastolic dysfunction, similar to the LV, can give important insights into early disease when
abnormalities in contractility, through other parameters, may not be evident. Increased wall
thickness in response to pressure overload is seen later in disease progression. In addition diastolic
dysfunction is a marker of poor prognosis in many RV pathologies and usefully reflecting response to
pharmacological interventions\(^\text{38}\)(\text{39}). Typically, a combination of trans-tricuspid inflow Doppler
pattern, TDI of the basal RV lateral wall and right atrial (RA) size help to describe the severity of
diastolic dysfunction. In severe TR, as in other conditions where RA pressure is raised, diastolic
function can be challenging and difficult to interpret, particularly in the presence of atrial fibrillation.

Right atrial dilatation is a marker of poor prognosis and is seen is RV systolic and diastolic
dysfunction, pulmonary hypertension with raised RV filling pressures and severe TR. Unlike LA
measurements performed using two orthogonal views, the RA size is assessed in the RV focused
four-chamber view. The frame where the RA appears largest (usually ventricular end systole) is
traced. From this single-plane view the RA volume is calculated using the area-length or summation
of discs method. Absolute RA values tend to be slightly larger in men \((25 \pm 7 \text{ mL/m}^2)\) than in women
\((21 \pm 6 \text{ mL/m}^2)\) and are given as indexed values for body surface area \((15)\). RA dilatation is a common
finding in chronic severe TR.

Assessment of RV function During Exercise: Contractile Reserve Concept

Dynamic evaluation of cardiac structure and function under physiological or pharmacological stress
can unmask underlying abnormalities including the development of symptoms, exercise limitation,
valve and ventricular dysfunction and pulmonary hypertension\(^\text{16}\). RV function at rest has been
shown to be a useful predictor of those with an abnormal cardiopulmonary exercise response in
heart failure, where a reduced exercise capacity is known to be a poor prognostic marker\(^\text{8}\).
However, additional information on RV function and its response to altered loading conditions during exercise has merit. RV contractile reserve has been assessed non-invasively by a number of markers including long axis parameters, FAC and global longitudinal strain\(^{(40)}\)(\(^{(41)}\)(\(^{(42)}\)). In a normal population TAPSE, TDI S wave, pulmonary artery systolic pressure (PASP) and TAPSE/PASP ratio were shown to correlate with maximal exercise capacity\(^{(43)}\). RV response during exercise appears to be a surrogate marker of ventricular-arterial coupling in chronic RV pressure overload states\(^{(44)}\) and may unmask underlying RV dysfunction in a number of conditions. Further, RV contractile reserve offers incremental prognostic value, in addition to LV contractile reserve, in dilated cardiomyopathy\(^{(41)}\).

Therefore, RV contractile reserve evaluation during exercise may add valuable information. Physiological (treadmill or bike) and pharmacological (dobutamine) stress echo are described in the assessment of RV contractile reserve. Exercise bike stress echocardiography (our preferred method) allows evaluation of symptoms and acquisition of serial data. PASP is known to fall towards resting levels rapidly and peak stress data should be acquired within 1 minute of exercise cessation. The key RV parameters assessed should include TAPSE, TDI S wave, FAC, TR velocity, GLS. LV parameters are usually concomitantly assessed along with other valve lesions depending on the clinical scenario\(^{(16)}\).

Contractile reserve is considered present where RV cavity reduces in size with augmentation of all RV function parameters. Currently data is limited and standardised values are yet to be established. Studies demonstrate an increase in each value by at least a few points (typically TAPSE >3mm, TDI S > 2cm/s, FAC > 5% or GLS >2%) where RV contractile reserve is associated with improved prognosis\(^{(45)}\)(\(^{(46)}\)). When compared to baseline, no increase or reduction in values during exercise indicates absence of contractile reserve and underlying RV dysfunction; where early intervention may need to be considered.

SUMMARY

Tricuspid regurgitation natural history and treatment remains poorly understood. Right ventricular function is a key factor in determining prognosis, timing for intervention and longer-term outcome. Central to the assessment of TR is defining more precisely RV function. A practical and systematic approach should include RV dimensions, volumes and surrogate markers of contractility (RV long axis function, FAC) as well as RV EF (either 3DE or MRI). Where further clarification in terms of risk stratification may be required, GLS and functional testing with assessment of contractile reserve should be utilised. Part two of this article will provide an understanding of the causes of tricuspid regurgitation in the current era, with emphasis on key patient groups and their management.
TRICUSPID REGURGITATION AND THE RIGHT VENTRICLE IN RISK STRATIFICATION AND TIMING OF INTERVENTION: PART 2

INTRODUCTION

Tricuspid valve regurgitation (TR) presents challenges to modern day clinical practice. Its natural history is not well understood. Previously, uncertainty existed as to whether TR is an independent factor of outcome or rather a surrogate marker of right ventricular disease and other co-morbid conditions including pulmonary hypertension(1). However, more recently studies has shown increasing TR severity is associated with worse survival regardless of left ventricular (LV) function and pulmonary hypertension(2). Both late residual TR seen post mitral valve surgery(3) and isolated severe TR(4) have excess mortality and morbidity. Management guidelines remain ill-defined since prospective outcome data is limited(5). Further, surgical TV intervention studies have suggested variable outcomes and this conflicting data has led to confusion as to optimal management in this cohort. This heterogeneous patient group includes right ventricular (RV) dysfunction, pulmonary hypertension and multiple associated comorbid conditions. Recent publications have assisted in defining patient cohorts who may benefit from surgical intervention(6). In the first of two articles we discussed key principles of ventricular function assessment and the importance of right ventricular chamber size, volumes and ejection fraction and additional parameters in risk stratification of tricuspid regurgitation. The current article aims to provide an understanding of the causes of tricuspid regurgitation in the modern era, with emphasis on key patient groups and their management.

ASSESSMENT OF TRICUSPID REGURGITATION SEVERITY

Traditional severity grading has focused on colour Doppler regurgitant jet imaging and assessed from multiple echo windows. Reliance on jet size and expansion within the right atrium (RA) is limited by a number of technical and haemodynamic factors. Vena contracta width is the recommended parameter in TR severity grading, where ≥ 7mm is indicative of severe TR(47). Quantitative proximal isovelocity surface area (PISA) method (also known as flow convergence method) is possible, but less often used, where severe TR is defined as an effective regurgitant orifice (EROA) ≥ 40mm2 with a regurgitant volume ≥ 45mls(47). Available study data are less well defined than for mitral
regurgitation, and discrepancies in parameters may reflect the regurgitant orifice morphology, in
particular for functional TR, being more often elliptical rather than circular in shape. Newer
techniques such as vena contracta area(48) are likely to offer improved diagnostic accuracy. TR
defined by the EROA cut-off \( \geq 40\text{mm}^2 \) has been shown to be associated with excess mortality and
morbidity during 10 year follow up in a recent publication(49). Evaluation of TR severity requires a
holistic approach with supportive evidence for severe regurgitation, see figure 3. In the era of
transcatheter tricuspid valve therapies it has become clear that standard two dimensional (2D)
methods underestimate the true severity of TR. This is evident through three dimensional (3D)
assessment of the regurgitant orifice(50). A new grading system, utilising 3D vena contracta area as
an additional parameter, has been proposed with three grades within the ‘severe’ category (severe,
massive and torrential)(51)(52).

AETIOLOGY: MODERN DAY CAUSES OF TRICUSPID REGURGITATION AND CLINICAL GROUPS

PRESENTING WITH SEVERE TRICUSPID REGURGITATION

The relationship of the RV with TR is complex. Treatment options are governed by the underlying
aetiology (table 2) and hence an understanding the mechanisms for TR is essential(53), figure 4.
While mild tricuspid regurgitation is a common finding it is usually benign. However severe tricuspid
regurgitation is associated with poor outcomes(4). TR can occur as a result of primary valve disease
(20%) or more often, be secondary to annular dilatation usually from RV dilatation and dysfunction
(80%). However in the case of functional TR, an increasingly recognised cause is right atrial dilatation
in the setting of atrial fibrillation(53). Commonly encountered clinical groups who may be
consideration for intervention are discussed below.

Primary Tricuspid Valve Regurgitation

Primary tricuspid valve leaflet disease can occur from a number of aetiologies (see table 2). RV size
and function along with right atrial size are usually initially preserved with an absence of pulmonary
hypertension (PH). RV volume overload causes progressive RA and RV dilatation and over time RV
dysfunction. Clues to the possible aetiology are often evident from the patient’s history (e.g.
previous blunt trauma to the chest or radiotherapy treatment) and clinical examination (e.g.
autoimmune disorders). A detailed assessment of the TV anatomy is essential and 3D echo imaging
plays a crucial role. Identification of abnormalities including leaflet prolapse with chordal rupture or
leaflet thickening with retraction and chordal shortening may support the diagnosis. Isolated TV
surgery is indicated in symptomatic severe primary TR (Class I) and should be considered in
asymptomatic or mildly symptomatic patients with RV enlargement or deteriorating RV function (Class IIa)(54)(55). In asymptomatic severe primary TR functional testing may be useful to unmask symptoms and assess for the abnormal RV contractile reserve (see previous article). If serial follow up demonstrates evidence of gradual RV dilatation and particularly if RV contractile reserve is abnormal or falling, despite remaining asymptomatic, then in our institution consideration is given to early surgery if TV repair is likely.

Left Heart Disease and Tricuspid Regurgitation

The presence of TR in patients undergoing left heart (LH) valve surgery requires careful assessment to decide whether concomitant TV repair is indicated. Severe TR, even if functional in origin, does not predictably improve following correction of the left heart valve lesion despite a fall in RV afterload. Surgical correction for severe TR at the time of LH valve disease is a Class I indication(54)(55)(56). Further, less than severe TR may progress over months to years to severe symptomatic TR following left heart valve surgery with an associated poor survival(3). Therefore, concomitant TV repair should be considered in those undergoing left heart valve surgery, where TR is mild or moderate and there is evidence of TV annular dilatation (> 40mm or 21mm/m² measured on echo RV focused four chamber view) Class IIa indication for surgery.

Left heart disease (LHD) with progressive TR, is associated with pulmonary hypertension (PH) resulting from an increase in pulmonary venous (post-capillary) pressure, through backward passive transmission of filling pressures and is termed passive or isolated post-capillary PH (IpcPH)(57). Pulmonary arterial pressure and hence pulmonary vascular resistance (PVR) are initially not raised. This is typically seen with mitral valve disease (although increasingly aortic stenosis) and LV dysfunction (both systolic and diastolic). Increasing RV afterload results in RV dilatation. Progressive RV contractile dysfunction and remodelling exacerbates functional tricuspid regurgitation through a combination of tricuspid annulus dilatation and papillary muscle displacement from RV remodelling. Hence a superimposed volume overload state further adds to RV dysfunction triggering a vicious cycle of RV dilatation and progressive functional TR. Prolonged chronic IpcPH, can result in a reactive pulmonary arterial vasoconstriction characterised by an increase in PVR with a raised transpulmonary gradient. The increased pulmonary artery vasomotor tone initially is reversible. In some cases progressive pathological changes with fixed and obstructive remodelling of the pulmonary arteries may also occur. This combined post- and pre-capillary PH (CpcPH) causes further increases in pulmonary arterial pressures and PVR, further increasing RV afterload. TR may further worsen as RV dilation and dysfunction progress. Differentiation between isolated and combined
pulmonary hypertension has important implications in risk stratification and treatment options. A useful additional parameter is diastolic pressure gradient (DPG) which is thought to be more reliable in differentiating a true vasculopathy. A DPG > 7mmHg in combination with a raised PVR >3 wood units suggests CpcPH(57)(58) This finding is associated with a worse pulmonary arterial compliance, RV ejection fraction, exercise tolerance and life expectancy as well as higher surgical risk. Hence careful assessment including right heart catheterisation and RV function assessment may be necessary when considering treatment options.

Residual Tricuspid Regurgitation post MV surgery

Significant TR late after LH valve surgery is found frequently ranging from 8% to as much as 49%(59)(60)(61). Studies highlighting the association of TR severity with heart failure, hospital admissions and death often failed to assess RV function(59)(60)(61)(62). Kammerlander et al demonstrated RV dysfunction rather than severe TR to be the best predictor of outcome during long term follow up in 539 patients after LH valve surgery(1). Following surgery, the TV annulus may continue to dilate despite the improvement and/or absence of pulmonary hypertension. The reasons for this are not fully understood however age, presence of AF and left atrial dilatation are predictors of significant late TR (59)(60)(61)(62). Treatment of this patient group is challenging.

Redo TV surgery carries high early mortality(63); Guenther et al demonstrated operative mortality of 19% at 30 days(64). Careful risk stratification before considering corrective TV surgery should include not only RV function status and pulmonary vascular haemodynamic assessment, but also the consequences of chronic systemic venous hypertension resulting in congestion and hypoperfusion. Perioperative mortality usually results from right heart failure and hepatorenal syndrome, progressing to multi-organ failure and death. Patients who demonstrate a raised bilirubin and creatinine with evidence of hypersplenisim where haemoglobin and platelet counts are reduced, despite optimisation of right heart failure, typically reflect end stage disease. Conventional surgical intervention carries high mortality and those who might survive often show little symptomatic improvement.

Pacemaker, Cardiac Resynchronisation or Cardioverter-Defibrillator Lead Associated Tricuspid Regurgitation

Two patient groups exist, those with bradyarrhythmia indicated pacemakers who usually have preserved LV and RV function and those with LV impairment qualifying for LV function optimisation and/or prevention of sudden death. The incidence of TR has been reported between 6-10%(2)(65)-(66). Common to both groups is lead placement across the TV into the RV and its
potential to interfere with valve function. Mechanical complications of lead insertion were noticed
during post-mortem studies(67)(68) and confirmed during surgical procedures to correct pacing lead
related severe TR(69); falling into three categories TV chordal apparatus entanglement, septal leaflet
impingement and leaflet perforation. A longer-term fibrous reaction has been documented at the
site of lead contact with endocardium resulting in lead encapsulation, ensheathment or entrapment
further compounding valve dysfunction through tethering the leaflets and subvalvular apparatus.
Detail imaging is essential and 3D echo and multiplane reconstruction formats are particularly useful
to ascertain the relationship of the RV lead with the TV leaflets and subvalve apparatus.

The aetiology of TR and its treatment should be placed in the context of baseline ventricular function
and the existence and severity of TR prior to RV lead implantation. Pre-existing functional TR as a
result of LH disease and pulmonary hypertension may worsen following pacing lead implantation,
where relatively small increases result in clinically significant TR. Accurate assessment of RV
function, pulmonary hypertension severity, LV dysfunction along with the consequences of venous
congestion is required to appropriately risk stratify and decide on the merits of treatment. CMR may
be contra-indicated in this patient group (although increasingly devices are becoming CMR
compatible). RV volumes and RVEF can be obtained using 3DE, but if not available, cardiac
computerised tomography may be a useful alternative. Treatment options may include minimising
pacing burden (in the case of brady-pacing where the native heart beat allows for a synchronised
ventricular contraction), lead repositioning with preferential His-bundle pacing to improve RV
dysfunction and subsequently TR severity, or surgical lead explanation and TV repair(70)(71). The
latter is usually reserved for those with previously preserved biventricular function where TR is a
consequence of RV lead interference. The RV is often dilated and function hyperdynamic from
volume overload. Patients typically present with progressive breathlessness sometime after
pacemaker implantation and if not recognised may progress to right heart failure. At this stage
careful assessment of RV function is needed to ensure a point where significant RV dysfunction has
not been reached, where surgically addressing the TR will not confer any benefit but instead present
significant perioperative risks. Lastly TR may also result from trauma during lead extraction or lead
related infection. Assessment of RV function should include RV contractile reserve, RV volumes and
RVEF. Pulmonary hypertension is not usually a feature in this patient group unless there is LH
disease.

AF associated Tricuspid Regurgitation
Recent studies have demonstrated isolated functional TR is associated with RA enlargement in the setting of chronic atrial fibrillation (72). RA remodelling has been shown to result in TV annular dilatation with a loss of annular leaflet coverage reserve without leaflet tethering (73). The TV annulus is more circular in shape, more dilated and planar when compared to functional TR due to LH disease in sinus rhythm. While TV annular area has been shown to be principally associated with RV volumes in LH associated TR, in the case of functional TR secondary to AF it strongly correlates with RA volumes. Typically, patients are more often older, female, hypertensive, have a greater degree of RA dilation compared to the left atrium and lower pulmonary artery pressures. However, in terms of treatment, surgical correction is considered only after heart rhythm and rate control, as well as ventricular function and heart failure, has been optimised. Once achieved waiting up to six months may be necessary to see the full effects of RA remodelling and TR improvements. If TR remains severe, then the standard work up focused on quantifying any RV dysfunction, pulmonary hypertension, associated co-morbidities and signs of end-organ damage will help determine the appropriateness for surgical intervention.

Tricuspid Regurgitation Secondary to Pulmonary Hypertension and RV Pressure Overload

Functional TR in the setting of progressive pulmonary arterial hypertension (PAH) reflects disease of the RV. RV dilatation and dysfunction is the precursor for secondary TR. Therefore, treatment is focused on diagnosing the cause of PAH and targeting appropriate therapy, which may include pulmonary vasodilators. Prognosis is associated with RV function and targeted therapy aims to reduce RV afterload with a concomitant improvement in RV function. Severity of TR often improves with RV reverse remodelling. Where severe TR persists, it usually reflects persistent RV dysfunction, where residual TR may paradoxically work to off-load the failing RV. Therefore, TV surgical intervention is rarely considered and reserved for carefully selected patients undergoing treatment. This includes pulmonary thromboendarterectomy, where the expected reduction in pulmonary hypertension and RV afterload will preserve RV function and support any concurrent TV intervention.

Lastly, for patients who are deemed high risk for surgery emerging transcatheter TV technologies may offer hope. These include leaflet repair e.g MitraClip (Abbott Vascular); annuloplasty repair e.g TriCinch (4TECH), Trialign (Mitraling), Cardioband (Edwards Lifescience); valve replacement e.g Caval valve replacement (CAVI) or a combination of these techniques (74). While feasibility has been established, this technology is at an early stage with patient selection and outcomes yet to be clearly defined.
SUMMARY (See table 3)

Tricuspid regurgitation natural history and treatment remains poorly understood. Right ventricular function is a key factor in determining prognosis, timing for intervention and longer-term outcome. The paucity of published data reflects some uncertainty in the management of tricuspid regurgitation. Historic data has suggested surgical treatment of tricuspid regurgitation carries high mortality. Central to the assessment of severe TR is a clear understanding of the underlying aetiology and defining more precisely RV dysfunction. RV function assessment is central to assessment in TR. Early surgery should be considered in primary severe tricuspid regurgitation with RV dilatation even prior to significant symptoms and underlines the importance of functional assessment and exercise contractile reserve. Functional severe TR represents a different cohort of patients who have pulmonary hypertension and/or primary RV dysfunction responsible for tricuspid annular dilatation and severe secondary TR. Those presenting with RV failure reflect a potentially high-risk group with often complex disease; involving RV dysfunction, pulmonary hypertension, hepatic and renal complications, with additional pulmonary and left heart disease, who may have undergone previous cardiac surgery. Optimising medical therapy is essential following which careful assessment and work up are needed to ensure intervention is performed in a timely and appropriate manner.

Declaration of interest

The authors declare there is no conflict of interest that could be perceived as prejudicing the impartiality of the content of the article. Petros Nihoyannopoulos is the co-editor-in-chief of Echo Research and Practice. He was not involved in the review or editorial process for this paper, on which he is listed as an author.

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triangular low velocity jet. In this setting, estimation of RV systolic pressures will be underestimated due to rapid pressure equalization between RA and RV. C, depicts systolic flow reversal, seen in severe tricuspid regurgitation, during hepatic vein flow interrogation. D, 3D echo format, X-plane, where orthogonal planes in 2D are imaged simultaneously. The vena contracta (red arrows) is longer in the left view and highlights an elliptical regurgitant orifice, confirming the findings in image A. E, shows multiplane reconstruction format of the 3D vena contracta and measurement of the vena contracta area and demonstrates massive TR VC area 95mm².

VC, vena contracta

Figure 4 Examples of modern day aetiologies responsible for tricuspid regurgitation. Four chamber view showing RV pacing lead with echo bright regions (likely reflecting fibrosis) and tethering of the lead to the septal TV leaflet, which resulted in severe regurgitation. 3D imaging is an important adjunct in providing details of the underlying abnormalities and leaflet involvement; en face views from the RV surface and multiplane reconstruction formats are particularly useful in this regard. B TV posterior leaflet prolapse and flail segment resulting from a sheering injury with severe regurgitation. C, 3D zoom mode echo image of tricuspid valve viewed from the RV surface, demonstrating loss of coaptation in the central portion of the valve (*). This has resulted from TV annular dilatation as a consequence of RV dilatation in the setting of pulmonary hypertension. There is massive tricuspid regurgitation very, S septal, P posterior, A anterior leaflets. D, 3D zoom mode surgical view of the mitral valve depicting severe mitral stenosis (* denotes mitral valve orifice), a typical left heart valve lesion that may result in post capillary pulmonary hypertension and functional tricuspid regurgitation.

RV right ventricle, RA right atrium, LAA left atrial appendage, AV aortic valve
Ventricular interaction. Left panel depicts normal ventricular morphology in systole (S) and diastole (D), where LV pressures exceed RV pressures throughout the cardiac cycle and the ventricular septum (VS) assumes an outward curve towards the RV, such that the LV cavity is circular. Central panel shows RV pressure overload with significant VS flattening in systole. Right panel shows RV volume overload with significant VS flattening in diastole. Bottom panel shows how eccentricity index (EI) is measured, done in both systole and diastole and where EI >1.0 there is increasing volume (seen primarily in diastole) or pressure (seen primarily in systole) overload. Right example shows severe pressure overload with EI 2.4 in systole.
Figure 2
Right ventricular function parameters measured by echocardiography. A Tricuspid annular plane systolic excursion, TAPSE. B, tissue Doppler imaging at the RV base demonstrating regional longitudinal shortening, S wave. C 3D echo assessment of RV volumes and ejection fraction (RVEF). D Fractional area change calculation from the RV focused four chamber view. The endocardium is traced (beneath the trabeculations) in end-systole and end-diastole. E Lateral and septal wall strain(6 segment) imaging to calculate global longitudinal strain, GLS, of the RV. RV strain is reduced -10.1%.
Figure 3
Selection of tricuspid valve regurgitation parameters.
A, is a 3D colour flow full-volume acquisition of severe TR and demonstrates the flow convergence, vena contracta and jet expansion upwards into the RA (left image) and the en-face view of the flow convergence viewed from the RV aspect (right image). The regurgitant orifice is an irregular elliptical shape. B, Continuous wave Doppler profile of severe tricuspid regurgitation, demonstrating a triangular low velocity jet. In this setting, estimation of RV systolic pressures will be underestimated due to rapid pressure equalization between RA and RV. C, depicts systolic flow reversal, seen in severe tricuspid regurgitation, during hepatic vein flow interrogation. D, 3D echo format, X-plane, where orthogonal planes in 2D are imaged simultaneously. The vena contracta (red arrows) is longer in the left view and highlights an elliptical regurgitant orifice, confirming the findings in image A. E, shows multiplane reconstruction format of the 3D vena contracta and measurement of the vena contracta area and demonstrates massive TR VC area 95mm².

VC, vena contracta

254x156mm (150 x 150 DPI)
Figure 4 Examples of modern day aetiologies responsible for tricuspid regurgitation. Four chamber view showing RV pacing lead with echo bright regions (likely reflecting fibrosis) and tethering of the lead to the septal TV leaflet, which resulted in severe regurgitation. 3D imaging is an important adjunct in providing details of the underlying abnormalities and leaflet involvement; en face views from the RV surface and multiplane reconstruction formats are particularly useful in this regard. B TV posterior leaflet prolapse and flail segment resulting from a sheering injury with severe regurgitation. C, 3D zoom mode echo image of tricuspid valve viewed from the RV surface, demonstrating loss of coaptation in the central portion of the valve (*). This has resulted from TV annular dilatation as a consequence of RV dilatation in the setting of pulmonary hypertension. There is massive tricuspid regurgitation very, S septal, P posterior, A anterior leaflets. D, 3D zoom mode surgical view of the mitral valve depicting severe mitral stenosis (* denotes mitral valve orifice), a typical left heart valve lesion that may result in post capillary pulmonary hypertension and functional tricuspid regurgitation.

RV right ventricle, RA right atrium, LAA left atrial appendage, AV aortic valve

199x189mm (150 x 108 DPI)
Table 1 Checklist for right heart chamber assessment in tricuspid regurgitation

<table>
<thead>
<tr>
<th>CHECKLIST of KEY RIGHT HEART PARAMETERS</th>
<th>Normal values (cut-off)</th>
</tr>
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<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
</tr>
<tr>
<td>RV dimensions</td>
<td></td>
</tr>
<tr>
<td>Proximal RVOT (AV PSAX view)</td>
<td>≤ 30mm</td>
</tr>
<tr>
<td>PLAX view</td>
<td>≤ 35mm</td>
</tr>
<tr>
<td>AV PSAX view</td>
<td></td>
</tr>
<tr>
<td>Distal RVOT (AV PSAX view)</td>
<td>≤ 27mm</td>
</tr>
<tr>
<td>RV dimensions (RV focused A4C view)</td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>≤ 41mm</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>≤ 83mm</td>
</tr>
<tr>
<td>Mid cavity</td>
<td>≤ 35mm</td>
</tr>
<tr>
<td>RA dimensions</td>
<td></td>
</tr>
<tr>
<td>RA area or indexed volume (RV focused A4C view)</td>
<td>&lt; 25 ± 7ml/m²</td>
</tr>
<tr>
<td></td>
<td>&lt; 21 ± 6ml/m²</td>
</tr>
<tr>
<td>RV function</td>
<td></td>
</tr>
<tr>
<td>TAPSE (focused A4C view)</td>
<td>&gt; 17mm</td>
</tr>
<tr>
<td>Lateral wall ‘S’ TDI (focused A4C view)</td>
<td>≥ 9.5 cm/s</td>
</tr>
<tr>
<td>Fractional area change (focused A4C view)</td>
<td>&gt; 35%</td>
</tr>
<tr>
<td>3D Echo</td>
<td></td>
</tr>
<tr>
<td>Indexed systolic/diastolic volumes *</td>
<td>27 ± 8.5ml/m² / 61 ± 13ml/m²</td>
</tr>
<tr>
<td></td>
<td>22 ± 7ml/m² / 53 ± 10.5ml/m²</td>
</tr>
<tr>
<td>RVEF</td>
<td>58% ± 6.6, where abnormal &lt;45%</td>
</tr>
<tr>
<td>Septal and lateral wall global longitudinal strain</td>
<td>&gt;20-23% (absolute values)</td>
</tr>
<tr>
<td>Additional parameters</td>
<td></td>
</tr>
<tr>
<td>Eccentricity index</td>
<td>&gt;1.2</td>
</tr>
<tr>
<td>Myocardial performance index</td>
<td>Limited use in severe TR</td>
</tr>
<tr>
<td>Diastolic function parameters</td>
<td>Limited use in severe TR</td>
</tr>
<tr>
<td>(TV inflow E and A velocities, E/A ratio, Lateral wall E’ TDI)</td>
<td></td>
</tr>
<tr>
<td><strong>Magnetic Resonance Imaging</strong></td>
<td></td>
</tr>
<tr>
<td>RV dimensions</td>
<td></td>
</tr>
<tr>
<td>RV systolic/diastolic indexed volumes * ml/m²</td>
<td>39 (±10 NR 19-59) / &lt;91 (±15 NR 61-121)</td>
</tr>
<tr>
<td></td>
<td>32 (±10 NR 12-52) / &lt;80 (±18 NR 19-59)</td>
</tr>
<tr>
<td>RV function</td>
<td></td>
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<tr>
<td>RVEF</td>
<td>62% (±5 NR 52-72)</td>
</tr>
<tr>
<td></td>
<td>61% (±6 NR 51-71)</td>
</tr>
</tbody>
</table>

*where RV volumes and RVEF cannot be calculated with echo or MRI techniques, alternative imaging modalities include CT or radionuclide ventriculography.

RV right ventricle, RVOT right ventricular outflow tract, PLAX parasternal long axis, AV PSAX parasternal short axis view at the aortic valve level, A4C apical four chamber, RA right atrium, TDI tissue Doppler imaging, 3D three-dimensional, RVEF right ventricular ejection fraction, TV tricuspid valve, TAPSE tricuspid annular peak systolic excursion, TDI tissue Doppler imaging, ♂males, ♀females.
Table 2

<table>
<thead>
<tr>
<th>Causes of Tricuspid Regurgitation</th>
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<tbody>
<tr>
<td><strong>Primary valve disease</strong></td>
</tr>
<tr>
<td>Congenital (e.g. Ebstein’s anomaly, Atrioventricular septal defect)</td>
</tr>
<tr>
<td>Leaflet prolapse</td>
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<tr>
<td>Rheumatic heart disease</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Carcinoid</td>
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<td>Radiation</td>
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<tr>
<td>Blunt trauma</td>
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<tr>
<td>Iatrogenic</td>
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<tr>
<td>Pacing or defibrillator lead implantation</td>
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<tr>
<td>Endomyocardial fibrosis</td>
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<tr>
<td>Rare causes</td>
</tr>
<tr>
<td>Drugs (e.g. methysergide, pergolide)</td>
</tr>
<tr>
<td>Autoimmune disorders (e.g. SLE)</td>
</tr>
<tr>
<td>Cardiac tumours</td>
</tr>
<tr>
<td>Endomyocardial fibrosis</td>
</tr>
<tr>
<td><strong>Secondary associated with right ventricular or atrial dilatation</strong></td>
</tr>
<tr>
<td><strong>Pressure overload states</strong></td>
</tr>
<tr>
<td>Secondary to raised pulmonary vascular resistance</td>
</tr>
<tr>
<td>Pre-capillary pulmonary (arterial) hypertension</td>
</tr>
<tr>
<td>Post-capillary pulmonary (venous) hypertension</td>
</tr>
<tr>
<td><strong>Volume overload</strong></td>
</tr>
<tr>
<td>Shunts e.g. atrial septal defects</td>
</tr>
<tr>
<td>Pulmonary regurgitation</td>
</tr>
<tr>
<td><strong>Intrinsic myocardial disease</strong></td>
</tr>
<tr>
<td>RV ischaemia</td>
</tr>
<tr>
<td>RV cardiomyopathy (e.g arrhythmogenic RV cardiomyopathy)</td>
</tr>
</tbody>
</table>
Table 3. RV function in risk stratification for surgical intervention in TR

<table>
<thead>
<tr>
<th>Summary of Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Where TR is the consequence of a failing RV surgical correction is unlikely to be beneficial. Evidence of significant right heart failure with chronic venous systemic hypertension typically reflects end stage disease. Conventional surgical intervention carries high mortality and those who might survive often show little symptomatic improvement.</td>
</tr>
<tr>
<td>2 Where TR is a primary event and RV dilatation is not excessive and RV function remains preserved then lead repositioning/extraction or surgical correction is likely to be beneficial.</td>
</tr>
<tr>
<td>3 Where TR is the result of primary RA dilatation or RV pacing lead interference and where RV dilatation is not excessive and RV function remains preserved, then surgical correction is likely to be beneficial.</td>
</tr>
<tr>
<td>4 Where TR is the result of residual regurgitation due to a combined aetiology of progressive TV annular dilatation and pulmonary hypertension, then in the absence of significant pulmonary vasculopathy and excessive RV dilatation and where RV function remains relatively preserved, surgical correction may be beneficial.</td>
</tr>
<tr>
<td>5 In patients considered unsuitable for conventional TV surgery, emerging technologies such as transcatheter approaches may have a role.</td>
</tr>
</tbody>
</table>