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Right ventricular function across the spectrum of health and disease

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ABSTRACT

Knowledge of right ventricular (RV) structure and function has historically lagged behind that of the left ventricle (LV). However, advancements in invasive and non-invasive evaluations, combined with epidemiological analyses, have advanced the current understanding of RV (patho)physiology across the spectrum of health and disease, and reinforce the centrality of the RV in contributing to clinical outcomes. In the healthy heart, ventricular-arterial coupling is preserved during rest and in response to increased myocardial demand (eg, exercise) due to substantial RV contractile reserve. However, prolonged exposure to increased myocardial demand, such as endurance exercise, may precipitate RV dysfunction, suggesting that unlike the LV, the RV is unable to sustain high levels of contractility for extended periods of time. Emerging data increasingly indicate that both LV and RV function contribute to clinical heart failure. Reductions in quality-of-life, functional capacity and overall clinical outcomes are worsened among patients with heart failure when there is evidence of RV dysfunction. In addition, the RV is adversely impacted by pulmonary vascular disease, and among affected patients, overall RV function differs based on mechanisms of the underlying pulmonary hypertension, which may result from variations in sarcomere function within RV cardiomyocytes.

INTRODUCTION

Knowledge of right ventricular (RV) function in health and disease has historically lagged behind that of the left ventricle (LV).[1 2] Early on, it was concluded that a normally functioning RV 'is not necessary for the maintenance of a normal circulation'[3] and one whose function was limited to that of a conduit between the venous and pulmonary circuits.[4] However, the centrality of the RV to normal cardiovascular and pulmonary physiology, as well as symptom burden and overall outcomes in cardiovascular and pulmonary disease, is increasingly recognised.[5 6] Nevertheless, large gaps in knowledge persist regarding function of the RV in normal healthy individuals, as well as RV pathophysiology in cardiovascular and pulmonary disease, and finally, effective methods for managing RV dysfunction in these populations.[5 6] The *American Heart Association* recently emphasised that 'It is remarkable how misunderstood are some basic concepts of right sided heart dysfunction among practicing clinicians and the impact that such misunderstanding can have on appropriate patient management'.[5] Over the past several years, however, the RV has been increasingly scrutinised and new insights have been made, both by advanced imaging techniques and pressure-volume (PV) analysis, a gold standard method of characterising ventricular function.[2 7–11] The epidemiology of RV dysfunction in cardiovascular disease has been previously reviewed.[5] In this review, we provide a comprehensive yet concise review on advancements in understanding of RV physiology across the spectrum of health and disease, from elite athletes to normal healthy individuals, as well as RV function in heart failure with preserved ejection fraction (HFpEF), pulmonary vascular disease, heart failure with reduced ejection fraction (HFrEF) and HFrEF patients supported by mechanical circulatory support. Finally, we highlight the centrality of the RV as evidenced by its impact on clinical outcomes, and emphasise knowledge gaps that must be overcome to improve outcomes in this area.

THE NORMAL RIGHT VENTRICLE

The normal RV is thin-walled (~3–5 mm) and highly compliant when compared with its left-sided counterpart.[12] Under resting conditions, RV afterload (pulmonary arterial pressure) is low and deoxygenated blood is transited into the lungs at minimal cost to overall myocardial oxygen demand. For example, the resting RV extracts ~50% of oxygen (O_2) supplied by coronary blood flow, whereas the LV extracts ~75% under resting conditions.[12] In response to an increase in LV O_2 demand, coronary blood flow increases, whereas increases in RV O_2 demand are met either by an increase in coronary blood flow or O_2 extraction.[12] It was recently demonstrated that the RV has substantial stroke volume reserve and in the setting of increased O_2 demand, that is, exercise, RV cardiac output (Qc) and myocardial energetics increase by ~fourfold from rest to peak effort (figure 1A), with some metrics of RV systolic function approximating levels observed in the LV.[7]

The RV and pulmonary circulation are best viewed as a combined functioning unit.[13] Ventricular-arterial (VA) coupling describes the relationship between a ventricle and the circulation (pulmonary for the RV, systemic for the LV) it supplies and is quantified by the ratio of end-systolic elastance (E_{ES}, contractility) to effective arterial elastance (E_A, afterload).[7] The contractile reserve of the RV ensures that E_{ES} increases sufficiently in response to increases in afterload, ensuring that VA coupling is preserved when metabolic demand increases.[7] The RV also has substantial lusitropic reserve, meaning that during increased metabolic demand, it facilitates venous return in conjunction with the muscle pump and vasodilatory forces.[7 14] Thus, throughout

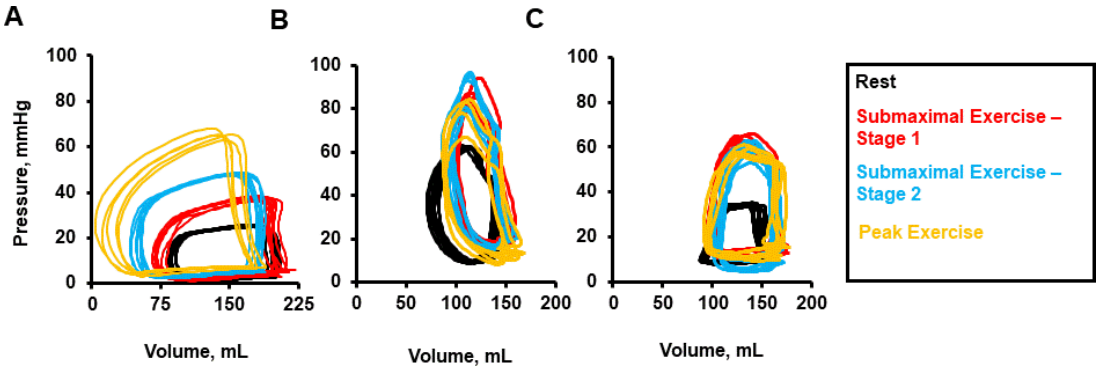

Figure 1 Example of right ventricular pressure-volume analysis derived from (A) a healthy control[7]; (B) a patient with heart failure with reduced ejection fraction (unpublished data from senior author's laboratory); and (C) a patient with heart failure with reduced ejection fraction supported by a continuous-flow left ventricular assist device.[8] All data obtained from senior author's laboratory.

all phases of the cardiac cycle, under resting conditions and in response to increased metabolic demand, the healthy RV precisely regulates forward flow of blood to the LV to support systemic perfusion.

RV FORM AND FUNCTION IN HIGHLY TRAINED ATHLETES

The heart of an endurance athlete exhibits enlargement of both the LV and the RV (figure 2), supporting the concept of what has been referred to as 'balanced dilatation'.[15 16] In a case-control analysis of elite endurance athletes (n=127) participating in orienteering, cross-country skiing or middle-distance running, athletes had enlarged RV chamber sizes compared with historical controls.[17] Specifically, RV mass (77±10 g vs 56±8 g) and RV end-diastolic volume (160±26 mL vs 128±10 mL) were significantly greater among athletes versus controls.[17] In contrast, static exercise (strength-training) does not significantly impact RV size. Among collegiate athletes participating in either endurance (rowing, n=40) or strength training (football, n=40), who were evaluated prior to and following 3 months of training, RV dilatation was observed among endurance-trained athletes (baseline vs follow-up RV end-diastolic area: 1460±220 mm/m^2 vs 1650±200 mm/m^2), along with enhancements in parameters of RV systolic and diastolic function.[18] However, no changes in RV size or function were observed among strength-trained athletes.[18]

Sustained increases in RV afterload, such as occurs during endurance athletics, may increase RV wall stress according to the *Law of Laplace*. In some cases, this increase in RV stress may precipitate RV dysfunction (RVD), the degree to which is in proportion to the duration of exercise.[19] In a series of highly performing endurance athletes, compared with pre-race baseline assessments, metrics of RV systolic function, including ejection fraction, tricuspid annular plane systolic excursion (TAPSE), and strain, declined and RV volumes increased when assessed following completion of the event.[19] Furthermore, athletes competing in longer races of ≥11 hours had greater decrements in RV systolic function than individuals completing races of 3–5.5 hours' duration.[19]

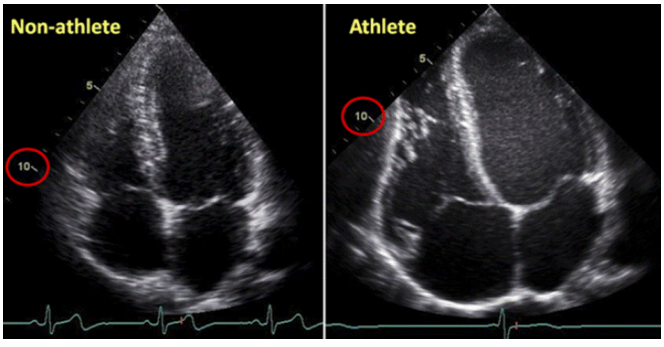

Figure 2 Apical four-chamber two-dimensional echocardiogram of the heart of a 23-year-old non-athlete (left) and a 23-year-old professional cyclist. The volume load of endurance athletics results in dilatation of all four cardiac chambers. The 10 cm echocardiographic field depth is marked in red to highlight the differences in cardiac size. Reproduced with permission.[16]

IMPACT OF PULMONARY VASCULAR DISEASE ON RV FUNCTION

Pulmonary arterial hypertension (PAH), previously defined as a mean pulmonary artery pressure greater than 25 mm Hg, has been recently redefined as a mean pulmonary artery pressure greater than 20 mm Hg along with a pulmonary vascular resistance (PVR) of ≥3 Woods.[20] The reason for this change stems from the somewhat arbitrary and historical assignment of 25 mm Hg as a cut-off value to define abnormal mean PAP.[20] Data from 1187 normal subjects demonstrated that a normal resting mean PAP is 14.0±3.3 mm Hg and 2 standard deviations above the upper level of normal, that is, a mean PAP>20 mm Hg, represents a more scientifically based cut-off value for identifying PAH.[20] In addition, exercise PAH (mean PAP>30 mm Hg during exercise) has been removed from the diagnostic criteria[20], since even normal individuals experience large increases in mean PAP during exercise by ~1 mm Hg for every 1 L/min increase in Qc[20] that are frequently well above 30 mm Hg (figure 3). In the healthy RV, VA coupling is maintained even in response to this acute (short-term) rise in afterload. Thus, an increase in mean PAP during exercise is not necessarily indicative of a pathological state, particularly if RV contractility is able to appropriately compensate in response to the increase in afterload and metabolic demand. However, in a study of 26 patients with PAH, RV-PA coupling predicted time to clinical worsening, even in patients with preserved RV systolic function.[21]

Elegant studies by Tedford *et al* demonstrated that resting and exertional RV performance are quite different from what has been observed in the healthy RV, and furthermore, RV performance varies according to the aetiology of PAH.[2 22] For example, for any given RV afterload, RV systolic function is worse among patients with PAH related to systemic sclerosis (SSc) than patients with idiopathic PAH.[2] Using RV PV

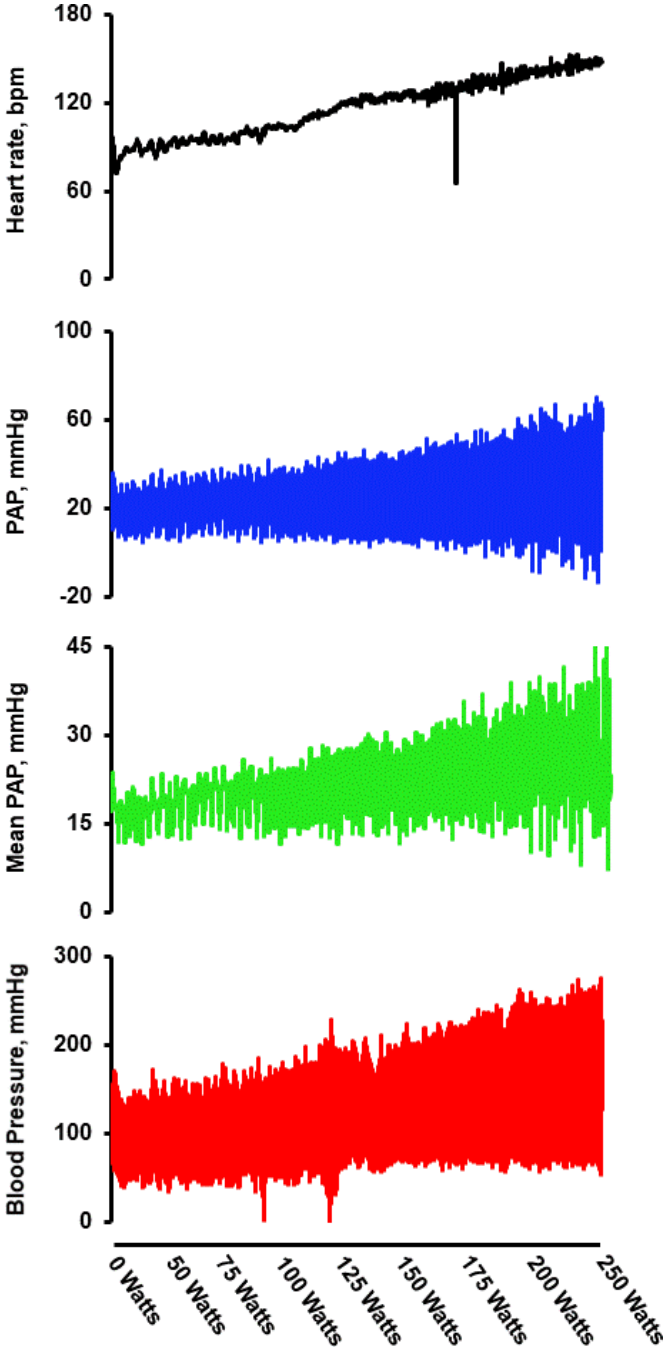

Figure 3 Example of tracings of haemodynamic response to exercise in a healthy 48-year-old man (185 cm, 92 kg) without any history of cardiovascular or pulmonary disease. Fick cardiac output and oxygen uptake (VO_2) values during exercise: Rest pre-exercise: 5.0 L/min, 3.8 mL/kg/min; 100 Watts: 10.2 L/min, 12.1 mL/kg/min;150 Watts: 14.6 L/min, 20.7 mL/kg/min; 250 Watts: 21.3 L/min, 31.1 mL/kg/min. Unpublished data from senior author's laboratory.

analysis during exercise, patients with SSc-PAH demonstrated an increase in RV end-systolic and end-diastolic volumes and there was a blunted increase in Qc, along with VA uncoupling. None of these abnormalities were observed among patients with IPAH (figure 4).[22] Interestingly, sarcomere function, isolated from cardiac myocytes, is depressed among patients with SSc-PAH but enhanced in IPAH, which may explain, at least in part, the difference in RV physiology in these patient populations.[9]

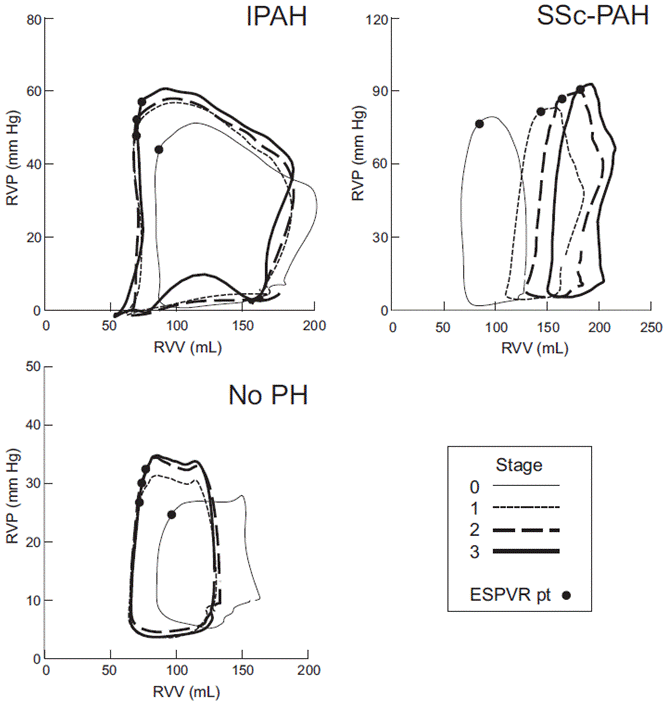

Figure 4 Example of right ventricular pressure-volume analysis during supine ergometry exercise from a patient with idiopathic pulmonary arterial hypertension (IPAH), systemic sclerosis-associated PAH (SSc-PAH) and a control patient with dyspnoea not related to pulmonary hypertension (PH). Data obtained at rest (stage 0), as well as progressive increases in exercise intensity (stages 1–3). Black point represents the point of end-systolic pressure volume relationship (ESPVR). Reproduced with permission.[22] RVP, right ventricular pressure; RVV, right ventricular volume.

CARDIOVASCULAR HAEMODYNAMICS AND RV FUNCTION IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION

HFpEF, accounting for ~50% of all cases of HF, is a complex multifactorial disease. While abnormalities in LV diastolic function play a prominent role in HFpEF, emerging data suggest that HFpEF is a biventricular phenomenon.[10] RV PV analysis performed during hand-grip exercise in patients with HFpEF versus controls revealed several abnormalities related to RV function among patients with HFpEF, including a marked upward increase in the RV end-diastolic pressure-volume relationship during exercise (figure 5), with an increase in β-stiffness constants, prolonged RV relaxation time, reduction in stroke volume and a blunted increase in Qc compared with controls.[10]

Among patients with HFpEF, abnormalities in RV function should be placed in the context of global abnormalities in cardiovascular and pulmonary disease, such as pre-capillary versus post-capillary pulmonary hypertension. Compared with controls, patients with HFpEF have a higher PAP and higher left-sided filling pressures,[23] as well as VA uncoupling during exercise.[24] In an analysis of resting haemodynamic parameters, patients with HFpEF had higher mean PAP (36±11 mm Hg vs 16±5 mm Hg) and lower PA compliance (3.0±1.4 mL/mm Hg vs 4.4±1.4 mL/mm Hg) than controls.[25] In an analysis of exercise haemodynamics, patients with HFpEF were limited by a blunted Qc relative to maximum oxygen uptake (VO_2max) and a steep PAP-Qc relationship compared with controls, indicative of RV-PA uncoupling.[24] In a subset of patients with HFpEF and severe obesity, mean body mass index (BMI) of 41 kg/m^2, endomyocardial

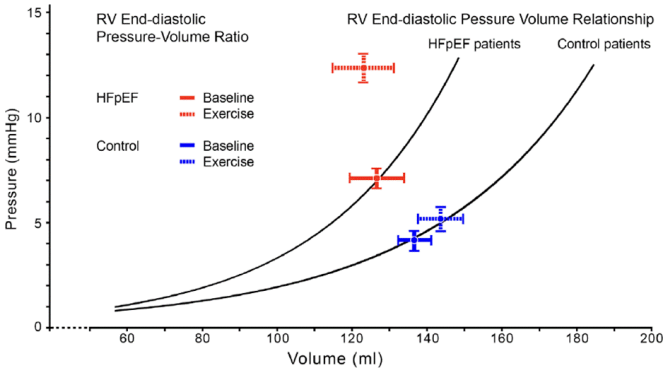

Figure 5 Right ventricular (RV) end-diastolic pressure-volume relations from patients with heart failure with preserved ejection fraction (HFpEF) and controls. Solid lines indicate resting condition and dashed lines indicate response to handgrip exercise. Black curves represent end-diastolic pressure volume curves determined vena caval occlusion. Note the upward shift in the end-diastolic pressure-volume relationship during exercise among patients with HFpEF compared with that of the control patients. Reproduced with permission.[10]

biopsy samples demonstrated substantially depressed RV systolic sarcomere function, but less passive myocyte stiffening when compared with samples from patients with a mean BMI of 30 kg/m^2,[26] reinforcing the notion that abnormalities in LV and RV function contribute to HFpEF.

RV FUNCTION IN HEART FAILURE WITH REDUCED EJECTION FRACTION

Up to 50% patients with HFrEF suffer from biventricular dysfunction,[27] and the prevalence and severity of RVD increase in proportion to the severity of LV dysfunction.[28] While RVD may be present in a large portion of patients with both HFpEF and HFrEF, the determinants of RV dysfunction, and characteristics of RV dysfunction, differ according to the type of HF. In an analysis of 1663 patients with HF, among those with HFrEF, a non-sinus rhythm, high heart rate, ischaemic aetiology and E-wave deceleration time <140 ms were associated with a reduced TAPSE, whereas among patients with HFpEF, pulmonary arterial systolic pressure (PASP) >40 mm Hg was associated with reduced TAPSE.[29] The pulmonary artery pulsatility index (PAPi, ratio of PA pulse pressure to right atrial pressure), is a powerful predictor of RV failure and adverse clinical events in patients with advanced HFrEF.[30] For any PAP, RVD is also more severe among patients with HFrEF than HFpEF.[31] Additionally, the PAPi is an excellent predictor of RV sarcomere contractile dysfunction in patients with HFrEF.[32] In a cross-sectional analysis of patients with HFpEF (n=219) and HFrEF (n=219), after controlling for PASP, the ratio of RV longitudinal strain to PASP was lower in HFrEF versus HFpEF (−0.53±0.36 vs −0.75±0.32).[31]

RVD among patients with HFrEF is also associated with reduced VO_2max.[33] In an analysis of patients with HFrEF (n=25), VO_2max was 13±4 mL/kg/min and correlated with RV ejection fraction.[33] In another study of 97 patients with HFrEF, individuals were grouped according to TAPSE of <16 or ≥16 mm.[13] Those with TAPSE <16 mm were subdivided by whether TAPSE at peak exercise was >15.5 mm. Despite similar baseline characteristics, those with a higher TAPSE at peak exercise had greater RV contractile reserve and VA coupling was preserved during exercise, compared with individuals with a persistently reduced TAPSE throughout exercise.[13] These observations indicate that the lack of RV stroke volume reserve (figure 1B) significantly impairs exercise capacity and contributes to reductions in VO_2max in these patients.

IMPACT OF MECHANICAL CIRCULATORY SUPPORT ON RV FUNCTION IN HFREF

Continuous-flow (CF) left ventricular assist devices (LVADs) improve survival for patients with advanced HFrEF.[34] However, up to 40% of patients develop RV dysfunction over time, and when present, significantly impairs quality-of-life and survival.[8] Patients with HFrEF supported by CF-LVADs have limited RV stroke volume reserve during exercise (figure 1C).[8] Specifically, among 13 patients with normal supine resting RV function, Qc increased minimally from 5.1±2.3 L/min to 8.0±3.4 L/min during submaximal exercise below ventilatory threshold, with very limited increase when transitioning from submaximal to peak effort (9.1±3.3 L/min). Notably, the increase in RV stroke volume from rest to peak exercise was minimal (only 14 mL/beat), indicating that the increase in Qc was primarily driven by heart rate.[8]

There is also great interest in determining how variations in level of support, achieved through modulations in CF-LVAD pump speed, influence RV function. In an analysis of patients with CF-LVAD (n=35), increases in pump speed optimised unloading of the LV, as evidenced by a reduction in PCWP, but there were minimal changes in right atrial pressure.[35] Similarly, RV PV analysis has also demonstrated that adjustments in LVAD pump speed have little impact on RV function, with minimal change in metrics of contractility, lusitropy or myocardial energetics across a range of CF-LVAD pump

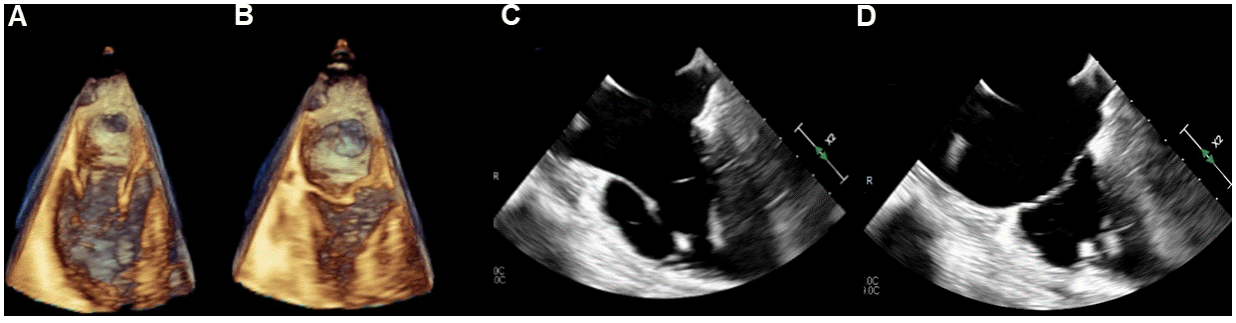

Figure 6 Echocardiographic assessment of an 83-yearl-old patient with a dilated right ventricle with systolic dysfunction. Three-dimensional echocardiography demonstrates the right ventricle during diastole (A) and systole (B). Transoesophageal echocardiography of the same patient demonstrates right ventricular structure during diastole (C) and systole (D).

Table 1 Non-invasive imaging assessment modalities of right ventricular structure and function

	Two-dimensional echocardiography (2DE)	Three-dimensional echocardiography (3DE)	Cardiac computed tomography (CCT)	Cardiac magnetic resonance (CMR)
Description	Conventional linear and area measures of ventricular size and function	Pyramidal data sets of right ventricular inflow, outflow and apex	Structural and functional assessment of RV with submillimeter special resolution	Multiparametric analysis allows for accurate assessment of volume/function, and identification of pathological processes
Advantages	► Portability ► Cost ► Automated functional imaging allows for global longitudinal RV strain assessment	► No geometric assumptions ► Volume-rendering and tomographic views ► Endocardial surface mapping	► No geometric assumptions ► Spatial resolution ► Advantageous for patients with CMR contraindications	► Reproducibility ► Spatial resolution ► RV size/function quantification ► Tissue properties (late gadolinium enhancement)
Disadvantages	► Difficulty visualising RV in its entirety ► Variability in measurements ► Assumptions about RV shape	► Dedicated software required ► Inability to visualise entire RV, particularly for cases of severe RV dilatation	► Dedicated software required ► Motion artefact from high heart rate ► Ionising radiation and contrast exposure	► Contraindications: claustrophobia, pacemaker/defibrillator ► Breath holds during acquisition ► Lack of availability
Notes	► Impossible to precisely quantify RV volume	► Volume measures comparable to CMR ► Recommended echocardiographic technique for assessment of RV size and function	► Requires dedicated study with right-sided contrast timing ► Reliably assesses volume/function compared with CMR	► Gold standard method of non-invasive assessment of RV volume and function

RV, right ventricular.

speeds.[8] These observations suggest that the aforementioned limitations in RV contractile reserve during exercise are, at least in part, related to underlying RV dysfunction resulting from HFrEF, as opposed to a direct effect of the pump on the RV.

There has been a recent movement towards implanting CF-LVADs by a lateral thoracotomy as opposed to median sternotomy.[36] Under normal conditions, the septum and its longitudinal shortening during systole account for the bulk (77%±14%) of overall contraction of the RV.[37] RV function is distorted—at least temporarily, following cardiac surgeries, particularly those that involve pericardiotomy,[38 39] due to a reduction in longitudinal shortening. Non-randomised studies suggest that thoracotomy may reduce the risk of postoperative complications including development of RVD and use of RV assist devices when compared with rates observed with sternotomy.[40]

IMPACT OF RVD ON CLINICAL OUTCOMES

Among the general population of patients who are referred for echocardiography studies, RV ejection fraction is a powerful and independent predictor of clinical outcomes,[41] and RV dysfunction is a more powerful predictor of outcomes compared with LV dysfunction.[42] Among elite athletes, studies evaluating RVD during long duration exercise have been limited to assessments of function prior to,and following the event. It is unclear how exercise tolerance changes as RVD develops. Available data suggest that RVD is temporary, with normalisation of function within 1 week of follow-up.[19] Some athletes may develop myocardial fibrosis, particularly in the interventricular septum. Generally, fibrosis seems to occur among athletes who have been competing in endurance sports for longer periods of time,[19] suggesting that cumulative bouts of long duration exercise may promote arrhythmias in these patients, particularly as scarring/fibrosis develops.[19 43]

Across the spectrum of cardiovascular and pulmonary disease, RV dysfunction, when present, adversely effects quality-of-life, functional capacity and overall outcomes. In a large community study of patients with HFpEF from Olmstead County, Minnesota, USA (n=562), the presence of RVD was associated with higher all-cause mortality (hazard ratio (HR) 1.35, 95% confidence intervals (CIs) 1.0 to 1.77), cardiovascular mortality (HR 1.85, 95% CI 1.20 to 2.80) and rate of multiple HF-related hospitalisations (HR 1.81, 95% CI 1.18 to 2.78).[44] In a group of 46 patients with HFpEF who underwent right heart catheterisation, the 2-year survival was 56% in those with RVD, compared with 93% in patients without RVD and on multivariable analysis, RVD was the strongest predictor of death.[25] Finally, RVD is associated with greater comorbidities, including atrial fibrillation and coronary artery disease, than HFpEF patients without RVD.[25 45]

RV dysfunction is the leading cause of death among patients with PAH[46] and VA uncoupling, when present, predicts time to clinical worsening.[45] In a haemodynamic study of patients with severe PAH (n=38) with mean PAP 47±15 mm Hg and pulmonary vascular resistance of 7 (interquartile range 5–11) Woods units, VA uncoupling (defined as an E_{ES}/E_A cut-off of 0.7 or below) was associated with a reduction in exercise capacity (−15% reduction on 6-minute walk test), worsening of World Health Organization functional classification, and clinical deterioration requiring hospitalisation.[45]

Among patients with HFrEF, the presence of RVD significantly increases risk of mortality.[47] Among patients hospitalised with decompensated HFrEF, RVD more than doubles the 90-day risk of mortality, cardiac transplantation and CF-LVAD implantation.[48] In both HFpEF and HFrEF, abnormalities in RV longitudinal strain increase risk of all-cause death and HF hospitalisation by more than threefold.[31] Among patients with HFrEF supported by CF-LVAD, survival is significantly worse among individuals with RVD than those without.[49] In an analysis of patients with CF-LVAD, 2-year survival was 60% among patients with RVD (defined as RVD requiring rehospitalisation or medical/surgical treatment after the index hospital discharge), but 85% among individuals without RVD.[49]

NON-INVASIVE ASSESSMENT OF RV STRUCTURE AND FUNCTION

Conventional two-dimensional echocardiography is insufficient for comprehensive assessment of the RV due to the unique geometry of the RV (triangular shape in the coronal plane and crescent shape in the transverse plane) as well as its superficial location (immediately posterior to the sternum), making it essentially impossible to view the RV in its entirety. However, more comprehensive and reliable assessments of the RV can be achieved with modalities such as three-dimensional echocardiography (figure 6), cardiac magnetic resonance imaging (MRI) which is considered the gold standard,[50] as well as cardiac computed tomography (table 1).

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Despite recent advancements in understanding of RV pathophysiology in different disease states, several areas of uncertainty persist. These knowledge gaps impair patient management and may adversely impact clinician decision-making and overall clinical outcomes. It remains to be determined how factors such as demographics, comorbidities and modifiable risk factors influence RV function across the lifespan.[5 6] Also unclear is how variations in genomic, proteomic and metabolomic profiles influence RV physiology in normal and diseased states, which may guide identification of novel therapeutic targets.[6] Finally, it is unclear whether improvements in RV contractility, lusitropy and VA coupling translate into enhancements in clinical outcomes.

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