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). Early on, it was concluded that a normally functioning RV ‘is not necessary for the maintenance of a normal circulation’ and one whose function was limited to the conduit between the venous and pulmonary circuits. 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. 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.

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’. 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. The epidemiology of RV dysfunction in cardiovascular disease has been previously reviewed. 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 (HFrEF), 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. 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 (O₂) supplied by coronary blood flow, whereas the LV extracts ~75% under resting conditions. In response to an increase in LV O₂ demand, coronary blood flow increases, whereas increases in RV O₂ demand are met either by an increase in coronary blood flow or O₂ extraction. It was recently demonstrated that the RV has substantial stroke volume reserve and in the setting of increased O₂ 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.

The RV and pulmonary circulation are best viewed as a combined functioning unit. 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 (Eₜₐ₅, contractility) to effective arterial elastance (Eₐ, afterload). The contractile reserve of the RV ensures that Eₜₐ₅ increases sufficiently in response to increases in afterload, ensuring that VA coupling is preserved when metabolic demand increases. 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. Thus, throughout
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 mm² vs 1650±200 mm²), 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

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 Qc20 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

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**Figure 1** Example of right ventricular pressure-volume analysis derived from (A) a healthy control; (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. All data obtained from senior author’s laboratory.

**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.

Review

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. 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.

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, as well as VA uncoupling during exercise. 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.

In an analysis of exercise haemodynamics, patients with HFpEF were limited by a blunted Qc relative to maximum oxygen uptake (VO₂ max) and a steep PAP-Qc relationship compared with controls, indicative of RV-PA uncoupling. In a subset of patients with HFpEF and severe obesity, mean body mass index (BMI) of 41 kg/m², endomyocardial

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). 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.

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 (VO₂) 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.

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. RVP, right ventricular pressure; RVV, right ventricular volume.
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/m², reinforcing the notion that abnormalities in LV and RV function contribute to HFrEF.

**RV FUNCTION IN HEART FAILURE WITH REDUCED EJECTION FRACTION**

Up to 50% patients with HFrEF suffer from biventricular dysfunction, and the prevalence and severity of RVD increase in proportion to the severity of LV dysfunction. While RVD may be present in a large portion of patients with both HFrEF 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 HFrEF, pulmonary arterial systolic pressure (PASP) >40 mm Hg was associated with reduced TAPSE. 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. For any PAP, RVD is also more severe among patients with HFrEF than HFrEF. Additionally, the PAPI is an excellent predictor of RV sarcomere contractile dysfunction in patients with HFrEF. In a cross-sectional analysis of patients with HFrEF (n=219) and HFrEF (n=219), after controlling for PASP, the ratio of RV longitudinal strain to PASP was lower in HFrEF versus HFrEF (−0.53±0.36 vs −0.75±0.32).

RVD among patients with HFrEF is also associated with reduced VO₂max. In an analysis of patients with HFrEF (n=25), VO₂max was 13±4 mL/kg/min and correlated with RV ejection fraction. In another study of 97 patients with HFrEF, individuals were grouped according to TAPSE of <16 or ≥16 mm. Those with TAPSE <16 mm were subdivided by whether TAPSE at peak exercise was >15.3 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. These observations indicate that the lack of RV stroke reserve (figure 1B) significantly impairs exercise capacity and contributes to reductions in VO₂max in these patients.

**IMPACT OF MECHANICAL CIRCULATORY SUPPORT ON RV FUNCTION IN HFRF**

Continuous-flow (CF) left ventricular assist devices (LVADs) improve survival for patients with advanced HFrEF. However, up to 40% of patients develop RV dysfunction over time, and when present, significantly impairs quality-of-life and survival. Patients with HFrEF supported by CF-LVADs have limited RV stroke volume reserve during exercise (figure 1C). 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.

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. 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 speeds.
develops. Available data suggest that RVD is temporary, with
been limited to assessments of function prior to, and following
studies evaluating RVD during long duration exercise have
for longer periods of time, suggesting that cumulative bouts
among athletes who have been competing in endurance sports
of long duration exercise may promote arrhythmias in these
athletes may develop myocardial fibrosis, particularly in the
interventricular septum. Generally, fibrosis seems to occur
RV dysfunction, when present, adversely effects quality-
speeds. 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. Under normal conditions, the septum and its
longitudinal shortening during systole account for the bulk
of right ventricular size and function. Non-invasive imaging assessment modalities of right ventricular structure and function

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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, and RV dysfunction is a more powerful predictor of outcomes compared with LV dysfunction. 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. 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, suggesting that cumulative bouts of long duration exercise may promote arrhythmias in these patients, particularly as scarring/fibrosis develops. Across the spectrum of cardiovascular and pulmonary disease, RV dysfunction, when present, adversely affects 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). In a group of 46 patients with HFpEF who underwent right heart catheterisation, the 2-year survival was 56% in those with RVD, with 93% in patients without RVD and on multivariable analysis, RVD was the strongest predictor of death. Finally, RVD is associated with greater comorbidities, including atrial fibrillation and coronary artery disease, than HFpEF patients without RVD. 

RV dysfunction is the leading cause of death among patients with PAH, and VA uncoupling, when present, predicts time to clinical worsening. In a haemodynamic study of patients with severe PAH (n=38) with mean PAP 47±15 mmHg and pulmonary vascular resistance of 7 (interquartile range 5–11) Woods units, VA uncoupling (defined as an Ees/Ea 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. Among patients with HFrEF, the presence of RVD significantly increases risk of mortality. Among patients hospitalised with decompensated HFrEF, RVD more than doubles the 90-day risk of mortality, cardiac transplantation and CF-LVAD implantation. In both HFpEF and HFrEF, abnormalities in RV longitudinal strain increase risk of all-cause death and HF hospitalisation by more than threefold. Among patients with HFrEF supported by CF-LVAD, survival is significantly worse among individuals with RVD than those without. 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. 42
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, 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. Also unclear is how variations in genomic, proteomic and metabolic profiles influence RV physiology in normal and diseased states, which may guide identification of novel therapeutic targets. Finally, it is unclear whether improvements in RV contractility, lusitropy and VA coupling translate into enhancements in clinical outcomes.

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