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VIEWPOINT

Understanding right ventricular dyssynchrony: Its myriad determinants and clinical relevance

Alan G. Fraser[1,2,3] | Bart H. Bijnens[4,5] | Mark K. Friedberg[6]

[1] School of Medicine, Cardiff University, Cardiff, UK

[2] Department of Cardiology, University Hospital of Wales, Cardiff, UK

[3] Cardiovascular Imaging and Dynamics, Catholic University of Leuven, Leuven, Belgium

[4] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[5] Catalan Institute for Research and Advanced Studies (ICREA), Barcelona, Spain

[6] Labatt Family Heart Centre, Division of Cardiology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Correspondence
Alan G. Fraser, Department of Cardiology, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, UK.
Email: fraserag@cardiff.ac.uk

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It is a well-worn cliché that the right ventricle (RV) is forgotten or neglected, yet it is already the subject of a huge scientific literature. It is clear that pulmonary arterial (PA) pressure and RV function are major predictors of morbidity and mortality in many cardiovascular diseases, but improving RV function as a therapeutic target remains elusive. It is likely that changes in global and regional function are more often consequences of disease than primary causative factors; therefore, understanding their pathophysiological mechanisms is a prerequisite to using indicators of RV function as a guide to clinical decisions.

Myocardial segmental deformation as a function of time is related to the local balance of its contractile force and counteracting loading forces, consisting of cavity pressure (modulated by local shape), neighbouring force development (potentially with a different onset of activation) and tissue elasticity (Bijnens et al., 2007). This leads to a more-or-less straightforward interpretation in the normal left ventricle (LV) with its ellipsoid shape and more homogeneous conduction system, but in the RV interpretation remains challenging.

Firstly, the conduction system in the RV is not as homogeneously distributed over the endocardium as in the LV. The RV apex contains many more Purkinje fibres, especially within the moderator band

and on top of its trabeculations. Secondly, its shape is not ellipsoidal but more crescent shaped, with a much smaller and narrower cross-section at the apex compared with the base. Owing to the orientation of myocardial 'fibres', the RV contracts in health more like a pair of bellows, compared with the piston-like function of the LV, with the free wall deforming circumferentially towards the septum and longitudinally towards the apex. However, if the RV endocardium were to be activated instantaneously (like the LV), especially during exercise, there would be a risk that blood would be trapped in the apex, thus inducing an important intra-cavitary pressure gradient. That is avoided, and the bloodstream is guided efficiently from the RV inlet to its outlet, by the RV contracting in a peristaltic way, moving initially towards the inlet or base and activating the outlet last. This can be observed from myocardial deformation traces, where a small but noticeable delay is present between the onset of contraction of basal segments compared with the apex. In a healthy RV, there is little inhomogeneity of regional function (Hui et al., 2010), but in disease this becomes important. Delayed activation of the RV from right bundle branch block, such as commonly occurs after repair of tetralogy of Fallot and in some other congenital heart diseases, exaggerates this effect and results in

TABLE 1 Summary of the findings of Ewalts et al. (2021)

Conditions	RV 'preload' (measured end-diastolic area)	RV 'afterload' (estimated mean PA pressure)	RV dyssnchrony (SD-4)
Normoxia (control)	N	N	N
Acute hypoxia(F_{I,O_2} 12%)	N	↑↑	↑↑
Acute hypoxia and increased preload (LBPP 10 mmHg)	↑	↑↑	↑
Sea level (control)	N	N	N
Sustained hypoxia (altitude 3800 m)	↓	↑	↑↑
Sustained hypoxia and restored preload (saline infusion)	N	↑	↑

N means normal or baseline levels. The arrows indicate changes compared with normal values: either mildly or moderately increased, or reduced.
Abbreviations: F_{I,O_2}, fraction of inspired oxygen; LBPP, lower-body positive pressure; RV, right ventricular; SD-4, standard deviation of times to peak contraction in four RV segments.

electromechanical dyssynchrony between the early activated apex and the basal RV free wall, where there is early stretching followed by pronounced lengthening.

An important consequence of the shape of the RV is that local curvature is very heterogeneous. This is important because local wall stress, which is the force that individual myocytes sense and need to overcome, will be higher where the wall is flatter. In the RV free wall, regional shape is balanced by regional thickness and by myocyte orientation, but as a consequence, differing segmental responses are observed during changes in afterload. For example, in patients with pulmonary hypertension there is prolonged contraction of the RV free wall (Dambrauskaite et al., 2007). Interaction attributable to pericardial constraint and the shared ventricular septum and myocardial tracts, means that RV function is also influenced by LV function, afterload and shape. The normal RV is balanced, synchronized and optimized, whereas all of the above determinants of magnitude and timing of regional deformation will change in disease and with altered loading.

In this issue of *Experimental Physiology*, Ewalts et al. (2021) report that the degree of RV intraventricular dyssynchrony is related to an interaction between RV preload (volume) and afterload (PA pressure). In their first experiment, PA pressure was increased acutely and modestly by normobaric hypoxic pulmonary vasoconstriction. Intraventricular systolic pressure increased, disproportionally increasing wall stress in the basal segments and resulting in some dyssynchrony because of prolongation of the time to peak contraction in the RV free wall (as explained by Palau-Caballero et al., 2017). When, in addition, preload was increased by exerting lower-body positive pressure, the time to peak contraction in the RV free wall did not change, but there was some increase in the time to peak contraction in the septum (presumably associated with a change in septal configuration and, perhaps, also LV loading, but that is not reported). Additionally, RV cavity size increased acutely, thus increasing basal wall stress but simultaneously invoking the Frank–Starling mechanism and increasing contractile force development. Thus, RV dyssynchrony was reduced (Table 1). In their second study, PA pressure was increased by sustained hypoxia at altitude. Compared with baseline measurements, RV dyssynchrony

was increased, but RV volumes were reduced. Reversal of the depletion of plasma volume by the rapid infusion of some saline restored RV volumes and reduced the degree of RV dyssynchrony.

These results should be interpreted with some caution. The subjects were all young and healthy volunteers, and induced changes in loading were too transient to produce chronic ventricular remodelling. The RV preload was estimated using the echocardiographic surrogate marker of end-diastolic area on an apical four-chamber image, meaning that changes in RV shape and global volumes and function were not explicitly measured. Afterload was estimated by the modified Bernoulli equation, using the tricuspid regurgitant velocity with the diameter of the inferior caval vein as an approximate guide for right atrial pressure. Timing of regional contraction was measured from strain curves obtained by speckle tracking, which has suboptimal temporal resolution compared with myocardial velocity imaging (Hui et al., 2010), and without discriminating between systolic and post-systolic shortening. Dyssynchrony was estimated as the standard deviation of times to peak shortening in only four segments (two mid and two basal) because of poor reproducibility in apical segments, although RV dyssynchrony is more accurately determined if apical segments are included (Murata et al., 2017).

Some methodological compromises were probably unavoidable, considering that studies were performed at altitude, but they mean that Ewalts et al. (2021) measured inhomogeneous motion of RV segments rather than electromechanical dyssynchrony *per se*. The illustrated strain curves lack detail. Nonetheless, their general conclusions appear valid and are useful; namely, that the timing of RV segmental function is influenced by an interaction of preload and afterload, making RV dyssynchrony both load and shape dependent. Presumably, the net effect of increasing dyssynchrony is reduced RV mechanical efficiency and reduced stroke volume. Their results also confirm that strain is a load-dependent index of myocardial function, whereas strain rate is much less sensitive to loading and should be measured instead if investigators want to estimate RV contractile function.

A recent expert consensus concluded that 'further insight into the functional significance and clinical relevance of [RV] dyssynchrony

TABLE 2 Some factors influencing right ventricular dyssynchrony

Right ventricular loading and haemodynamic status	Right ventricular structure and function	Left ventricular structure and function
Venous return	Local radius of curvature	LV shape (diastolic eccentricity index)
RV end-diastolic volume/RV end-diastolic area	Local wall thickness	Septal curvature
Heart rate	RV mass-to-volume ratio	Left bundle branch block
Pulmonary arterial pressure/compliance/ pulmonary vascular resistance	Change in RV shape during cardiac cycle	Systemic hypertension
Exercise	Local wall stress	
	Right bundle branch block	
	Ischaemia	
	Cardiomyopathy (e.g., arrhythmogenic RV cardiomyopathy)	
	Pericardial constraint and ventricular interaction	

Abbreviations: LV, left ventricular; RV, right ventricular.

is needed' (Lahm et al., 2018). What general conclusions can we draw? Dyssnchrony is a complex phenomenon that results from many interacting factors (listed in Table 2). Right ventricular diastolic loading influences regional myocardial stretch inhomogeneously because wall thickness and stiffness vary at different sites. Pulmonary arterial pressure and elastance vary during systole and are influenced by cardiac output. Conduction sequences and delays, in addition to regional variations in shape, are important modulators.

A unifying hypothesis is that 'preload' or end-diastolic sarcomeric length is the consequence of local end-diastolic wall stress and myocardial compliance, determined by wall thickness, local radius of curvature, and RV end-diastolic pressure and volume. Preload and heterogeneous activation influence the duration of the RV isovolumic contraction period (which is normally short) and prolong segmental contraction (which is exaggerated by increased 'afterload' that is determined by mid- and late systolic pressure in relationship to local shape) (Alkon et al., 2010). To understand RV dyssynchrony fully, all these factors would need to be documented and studied. Three-dimensional imaging (by echocardiography or magnetic resonance imaging) and invasive haemodynamic monitoring would provide more accurate and reliable information, when feasible. Although their aetiology is different, both RV electromechanical dyssynchrony and RV mechanical dispersion from increased afterload and/or altered pre-load cause different patterns of contraction and myocardial work in the septum and RV free wall. That reduces RV mechanical efficiency and leads to fibrosis and dysfunction (Ebata et al., 2020). The temporal dispersion of maximal segmental strains predicts the risk of arrhythmias.

A specific clinical consequence of the study by Ewalts et al. (2021) is that it supports advice to increase fluid intake to avoid dehydration while acclimatizing to altitude. Confirmation of the same possible explanation comes from other investigators who found similar effects of altitude on RV dyssynchrony and showed that it was correlated with arterial oxygen saturation and PA pressure (Yang et al., 2020). A partial clinical parallel might occur in conditions such as repaired tetralogy of Fallot, where the interaction between RV volume loading from chronic pulmonary regurgitation and RV electromechanical dyssynchrony is still unclear (Lumens et al., 2019); both are thought to contribute to

adverse RV function and clinical outcomes, rather than volume loading 'correcting' the dyssynchrony.

More generally, these reflections might help us to understand why, on the basis of epidemiological evidence, the recommended definition of PA hypertension has been revised to a mean pressure of only ≥20 mmHg, together with a pulmonary vascular resistance of ≥3 Wood units (Simonneau et al., 2019). Modest increases in PA pressure of the same order as that observed by Ewalts et al. (2021) are associated with RV dyssynchrony, which predicts exercise capacity measured as peak oxygen consumption (Badagliacca et al., 2017). Right ventricular dyssynchrony also predicts clinical deterioration (Murata et al., 2017) and survival (Cheng et al., 2019; Murata et al., 2017) in patients with pulmonary hypertension. Thus, the challenge now for clinical research is to investigate whether we can use reliable estimates of RV dyssynchrony to identify and guide effective therapeutic interventions.

COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

ORCID

Alan G. Fraser https://orcid.org/0000-0001-7083-6995

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