More on the right ventricle in pulmonary hypertension

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Decreased RVEF and PVR is associated with a decreased survival rate in PAH patients under targeted therapies http://ow.ly/EBK8U

In the present issue of the *European Respiratory Journal*, Courand *et al.* [1] report on the prognostic relevance of radionuclide angiography of the right ventricle (RV) in a cohort of 100 patients with idiopathic, heritable or drug-related pulmonary arterial hypertension (PAH). Patients with a baseline RV ejection fraction (RVEF) >25% had better survival than those with a RVEF <25%. Furthermore, patients with a stable or increased RVEF at 3–6 months had a trend to better overall survival and a significantly lower cardiovascular mortality. These results are in keeping with recently demonstrated prognostic relevance of baseline and follow-up RVEF, but measured by magnetic resonance imaging (MRI) in PAH patients [2]. A striking finding in both studies was the dissociation between RVEF and pulmonary vascular resistance (PVR). Thus, a decreased PVR under targeted therapies could be associated with either deterioration or improvement in RV function [1, 2]. The notion emerges that PAH is a disease of RV–arterial uncoupling rather than only of pathological pulmonary vascular remodelling [3].

Right ventricular failure in pulmonary hypertension is the obvious consequence of prolonged exposure to excessive afterloading [3]. So, how is it possible that patients with a treatment-induced decrease in PVR might present with a worsening of RV function? The first possible answer is that the RV follows its own course of adaptation or maladaptation in increased pulmonary artery pressure (PAP), with considerable individual variation as a persistent, possibly genetic, biological mystery [4]. A second possible answer is in the inevitable systemic effects of pulmonary vasodilators. This has already been discussed at a time when PAH patients were tentatively treated with calcium channel blockers, hydralazine or minoxidil. All these systemic vasodilators increased cardiac output with no significant change in pulmonary vascular pressures, thus, decreased PVR. But associated increased systemic venous return would increase RV end-diastolic volume (EDV), increase RV afterload because of an increased wall tension (estimated by EDV×PAP) and decrease RVEF. Sniderman and Fitchett [5] called this the paradox of therapeutic success and clinical failure. High normal cardiac output with unchanged PAP may also be observed with targeted therapies, which thus have the potential of the unwelcome combination of decreased PVR and RVEF. It is not known how often this happens and how clinically relevant this maybe. In any case, Courand *et al.* [1] clearly demonstrate that one cannot be satisfied with PVR alone as a therapeutic goal in PAH.

The study by Courand *et al.* [1] is reminiscent of the flurry of reports of radionuclide angiographic measurements of RVEF in patients with chronic obstructive pulmonary disease (COPD), which were published in the 1970s and 1980s [6–12]. About half of these patients had a RVEF <45–50%, which was taken as the upper limit of normal [6–8]; a less stringent value than 30% considered by Courand *et al.* [1]. One study reported failure of RVEF to rise during exercise, even in patients with a normal value at rest [9]. This was globally interpreted as "cor pulmonale" or RV failure on lung diseases and/or hypoxia. However, subsequent combined haemodynamic and radionuclide angiographic studies showed preserved

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systolic PAP to end-systolic volume (ESV) ratios [10], indicating preserved systolic function. RVEF was found to be more tightly correlated to fluid retention (on hypercapnia) rather to the severity of pulmonary hypertension [11]. RVEF predicted survival in COPD, but less significantly so than arterial blood gases or altered lung mechanics [12]. As correlations between RVEF and PAP or PVR were variable, sometimes tight [10] sometimes loose or even absent [6, 11], clinicians lost interest in radionuclide angiography of the RV for the diagnosis of cor pulmonale or detection of pulmonary hypertension.

Is there a brighter future for radionuclide RVEF in PAH? Probably not. COURAND *et al.* [1] argue that radionuclide angiography is affordable and widely available, and that radiation exposure is not a concern except for repetitions in the youngest patients. However the procedure requires appointments at specialised departments, with possible waiting lists, and age-independent unequivocal safety of repetitions of the assessment of RV function is exactly what the follow-up of PAH requires. Furthermore, radionuclide angiography is a planar measure of a three-dimensional (3D) change and suffers from somewhat arbitrary automated contour definition. This explains variable and occasionally very low RVEF reported in normal subjects.

COURAND *et al.* [1] selected a RVEF of 25% as critical for the separation between good and bad prognosis. But this was a median value rather than a more methodologically correct sum of the highest specificity and sensitivity derived from receiver-operating characteristic curves, which would probably have yielded an even lower number. When RVEF was measured with MRI in similar PAH patients, a rigorously defined cut-off of 35% was found [2].

So, what would currently be the best and most practical way to evaluate RV function in PAH? Right heart catheterisation can measure stroke volume (SV) and right atrial pressure, but cannot measure RV volumes, and is, therefore, an imperfect surrogate for gold standard RV function definition by pressure–volume relationships [3, 13]. COURAND *et al.* [1] express disappointment about echocardiographic measurements such as M-mode tricuspid annular plane systolic excursion or tissue Doppler imaging of the maximum velocity of tricuspid annulus isovolumic contraction, both previously shown to be independent predictors of outcome in severe PH [14, 15]. These turned out to be of little additional value to radionuclide RVEF [1]. However, modern echocardiography of the RV includes several further measurements of structure and function demonstrated to be of prognostic relevance [16] and nowadays preferably integrated in a multi-parametric evaluation [17, 18]. Furthermore, developments in 3D-echocardiography open the perspective of accurate RV volume measurements [19]. Thus, echocardiographic measurements of RVEF are now possible, and have already been reported to be of prognostic relevance [20]. It has recently been suggested that a SV/ESV rather than SV/EDV, *i.e.* ejection fraction, may be a less preload-dependent estimate of RV function, and superior for the prognostication of patients with pulmonary hypertension [21]. This requires confirmation and can be further explored by bedside 3D-echocardiography.

Further added value of both MRI and echocardiography is insight into regional function and dyssynchrony (or inter-regional changes in strain and velocity of contraction) and asynchrony (or delaying of RV systole into left ventricular diastole), also called "post-systolic shortening" [22–24]. Regional RV function is efficiently explored by speckle tracking echocardiography, which evolves from 2D [25] to improved 3D [20] assessments. Speckle tracking echocardiography still requires time-consuming off-line analyses, but opens a fascinating perspective for further noninvasive and flexible research on RV function integrated into the daily practice of echocardiography [26].

The understanding of RV function in severe pulmonary hypertension is making rapid progress. Radionuclide angiography has delivered, but is now being replaced by MRI and 3D-echocardiography. In this context, COURAND *et al.* [1] are to be commended for their enlightening contribution to the understanding of PAH as a RV failure syndrome.

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