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Editorial

Cardiac magnetic resonance in pulmonary arterial hypertension: a step in the right direction

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This editorial refers to 'Prognostic value of right ventricular mass, volume and function in idiopathic pulmonary arterial hypertension'† by S.A. van Wolferen *et al.*, on page 1250

Pulmonary arterial hypertension as a clinical challenge

Pulmonary arterial hypertension (PAH) is clinically a highly malignant disease. Although pathological changes are limited to the vascular wall, uncontrolled proliferation is mostly directed towards vascular lumen. Pulmonary input impedance usually increases at a rate which cannot be effectively matched by the right ventricular (RV) adaptive mechanisms. A series of consequences including RV dilatation, functional tricuspid regurgitation, decreased pulmonary flow, compromised LV filling, and low systemic cardiac output contribute to a fatal vicious circle. The expected median survival of 2.8 years in conventionally treated idiopathic PAH is indeed similar to that of advanced lung or breast cancer.[1]

In the last decade, important progress has been made in the understanding of the physiopathology and therapy of this disease. Several drugs interfering with important physiopathological pathways of PAH progression were approved, based on the results of right heart catheterization (RCT).[2] None of those therapies permit a cure. Nevertheless, in many patients, it is now possible to slow, stop, and sometimes partly revert the otherwise progressive pulmonary vascular obliteration. This gives the RV chance to adapt to increased afterload. Sustained clinical improvement can sometimes be achieved already with a first-line oral drug. However, the individual long-term response to any form of medical therapy may vary and cannot be predicted. Monitoring of each patient, whether treated with oral calcium channel blockers (CCB), endothelin antagonists, PDE5i, or parenteral prostacycline analogues, is therefore very important. Wasting time for less effective therapy might result in irreversible progression of pulmonary vascular lesions with all clinical consequences.

Current therapeutic algorithm suggests haemodynamic test for pulmonary vasoreactivity and assessment of the WHO functional class (FC) as sufficient for selecting initial therapy. Decisions whether and when to change the oral drug, switch to combination and/or parenteral therapy, perform interventions such as atrial septostomy or list for lung transplantation require a more sensitive monitoring.

A number of non-invasive prognostic markers derived from exercise tests, echocardiography, and plasma biomarkers correlate with outcome in PAH, when assessed at baseline. Very few have been so far validated to have prognostic implications if used for follow-up assessment during treatment. On the basis of the current evidence, a patient who can be considered stabilized and therefore requires no escalation of current therapy should be in I or II FC, walk more than 380 m in 6 min, and have stable or decreasing brain natriuretic peptide (BNP) plasma levels.[2] Recently, a strategy utilizing a set of prognostic markers, including cardiopulmonary exercise test, has been suggested to assist stepwise therapeutic decisions.[3] Interestingly, none of those strategies included echocardiography, despite its common clinical use in patients with pulmonary hypertension. In fact, it remains unclear, which of a plethora of echocardiographic measurements are worth serial assessment, in view of their suboptimal reproducibility.

Cardiac magnetic resonance as a monitoring tool in pulmonary arterial hypertension

In their study,[4] Vonk-Noordegraaf and coworkers indeed left echocardiography aside. They leapt forward to cardiac magnetic resonance (CMR), an imaging method renown for its accuracy, lower operator dependency, and interstudy variability.[5] Although some experience with CMR in PAH has been already accumulated, this is the first report to identify variables useful for prognostic stratification. Assessed at baseline, RV stroke volume index >25 mL/m^2, RV end-diastolic volume <84 mL/m^2, and LV end-diastolic volume exceeding 40 mL/m^2, each indicated better chance of survival. In a multivariate analysis, only 6 minutes walk test (6MWT) added independent contribution to the prognostic message provided by those three CMR variables. Importantly, progressive dilatation of the RV, as well as decrease in the LV diastolic volume and a further decrease in the RV stroke volume at 1-year follow-up, was related to worse long-term

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outcome. In a multivariate analysis , only invasively assessed change in pulmonary vascular resistance (PVR) added independent prognostic information to that provided by the three CMR variables.

Although MRI has been generally contested as a monitoring tool because of complexity and cost, this may not necessarily hold true in PAH. The decision to continue or change the mode of treatment in a patient with PAH usually has long-term economic consequences, markedly exceeding the costs of a CMR examination. If limited to predefined, prognostically relevant variables, CMR should not last much longer than a complete state-of-the-art Doppler echocardiographic evaluation of a patient with pulmonary hypertension.

Effects of treatment as assessed with cardiac magnetic resonance

As CMR monitoring has just been validated, why not use it to assess the effects of modern pharmacotherapy applied to the study population. Patients with PAH who could be re-assessed at 1 year significantly improved as a group, in terms of morphology and function of the heart. This was evidenced by CMR-detected changes in RV and LV end-diastolic volume as well as in RV stroke volume.

However, a considerable early drop out of patients despite therapy should be noticed. Notably, 10 out of 64 patients died within this period. Those patients obviously failed to respond to the implemented therapy. This also points out a potential limitation of CMR as a monitoring tool in PAH: 1-year interval between the CMR examinations seems too long in this malignant disease. All efforts should be made to identify such patients earlier in order to try to maximize their treatment. Even if prognostically relevant changes could be detected by CMR performed at 3 or 6 months, increasing the frequency of CMR examinations for assessment of individual patients in clinical practice is probably not realistic. However, this might be different in the frame of clinical trials. Indeed, changes in serial CMR can from now on be considered as interesting endpoints, especially useful in smaller, proof-of-concept trials in PAH. Moreover, CMR was recently reported to be helpful in assessing different effects of specific treatments on adaptive RV hypertrophy, with yet unclear but potentially important clinical implications.[6]

'Absolute' prognostic markers in pulmonary arterial hypertension?

Concentrating on the potential clinical role of CMR in PAH, maybe we miss another message from Vonk-Noordegraaf and coworkers. Using MRI the 'definitive' imaging method, they seem to be indicating morphological and functional cardiovascular variables that are of absolute prognostic value, if measured accurately with whichever method.[7,8] The title of their paper avoids mentioning CMR. Can we extrapolate the reported results to MSCT, EBCT or—most of all—to echocardiography, saving time and concentrating predominantly on the few measurements suggested by CMR? Unfortunately, we will not learn it from this study. The authors missed the opportunity to directly compare prognostic value of CMR and echo in patients with PAH.

The key variables that emerge from the current CMR trial are diastolic volume indices of both RV and left ventricle (LV) (of note, manual rather than automated endocardial tracing is still preferred also for CMR volume calculations) and RV stroke volume measured in the main pulmonary artery.

Interestingly, surrogates of exactly the same variables, but measured with echocardiography, were previously reported to be most useful in following the changes induced by treatment of PAH with bosentan when compared with placebo.[9] At double-blinded, core laboratory planimetric assessment, RV end-diastolic area was smaller and LV end-diastolic area was larger at the end of the 4-month study period in the actively treated group. In addition, stroke volume calculated from the aortic flow velocity curve and outflow tract diameter became significantly higher in patients on active treatment when compared with those on placebo. The actively treated group showed a significant increase in 6MWT distance, indirectly suggesting improved prognosis.

A step forward in the understanding of pulmonary arterial hypertension

By conveying those similar messages, CMR and echocardiography help to better understand the critical consequences of PAH as well as key lines of potential support of the failing right heart. Among the triad of prognostic signs, the increasing RV end-diastolic volume appears as the most straightforward marker of progressive RV failure. It is a natural consequence of RV overload resulting in increased wall stress, which, in turn, is known to promote synthesis and release of BNP. This indirectly supports the significance of BNP changes in monitoring patients with PAH.

In contrast, the prognostic significance of LV 'shrinkage' suggests that interventions aimed at better LV filling, such as atrial septostomy, should not be neglected. Septostomy should be considered especially when modern pharmacological treatment fails to improve LV diastolic filling.

The CMR suggestion that the RV stroke volume changes may be more relevant than changes in cardiac index is quite interesting. In contrast to healthy subject, most patients with PAH fail to increase RV stroke volume during exercise.[10] With fixed, low stroke volume, the systemic pressure can be maintained only by over activation of sympathetic system and increased heart rate. Such sympathetic over activation, correlating with heart rate, was recently documented in PAH by direct sympathetic nerve recordings.[11] Control of sympathetic over activation is among the important therapeutic targets in chronic heart failure because of its detrimental effects on the LV. Unfortunately, the drugs that could blunt the potentially harmful excessive sympathetic stimulation of the failing RV are so far contraindicated in patients with PAH, because of risk of systemic hypotension.

Cardiac magnetic resonance in pulmonary arterial hypertension: future perspectives

The CMR-derived prognostic markers suggested by the current trial for clinical monitoring of PAH are very simple. Potentially, this powerful diagnostic tool offers much more possibilities for the assessment of RV function and its

coupling to pulmonary arterial system. Following reports on CMR phase-contrast flow quantification in the main pulmonary artery,[12] CMR-guided catheterization with simultaneous pressure-flow recordings,[13] exercise CMR examinations,[10] delayed contrast enhancement as a marker of RV ischaemia/fibrosis,[14] or myocardial 'tagging' for the assessment of RV dyssynchrony,[15] one has a *déjà vu* sensation. All this reminds of the steps echocardiography went through in the past. In fact, CMR is called by some a 'rich man's echo-machine'. It is clearly more 'three dimensional', precise, and reproducible. Let us hope that CMR will lead to similar progress in our understanding and managing PAH as that which we owe to echo, despite all its limitations. To move forward, we need validation of CMR in outcome trials. The study of Vonk-Noordgraaf and coworkers is a step in the right direction.

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