Hello from the other side: Molecular imaging of the right ventricle

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For decades, the right heart was to some extent regarded merely as an extension of the venous system. This view was potentially introduced when the invention of the Fontan procedure showed that the right ventricle (RV) could be bypassed and children with univentricular circulation could live relatively normal lives for many years.[1] Over the last decade, right heart function is increasingly recognized as a key aspect of prognosis in many cardiac disease states emanating from the left side of the heart.[2] In hindsight, this is not surprising because any condition that increases pulmonary pressures will eventually require the right ventricle to work harder.[3] A recent realization is that LV pathophysiology does not necessarily translate directly to the RV, and further research is needed.[4]

Radionuclide-based studies focusing on the RV are scarce, but the message from studies in pulmonary hypertension with the most commonly used radiopharmaceuticals is clear: the ratio of RV/LV uptake is associated with RV pressures, RV hypertrophy, and prognosis using standard perfusion tracers,[5] as well as for FDG-PET.[6–8] However, the RV is less relevant in subjects with suspected CAD and no history or signs of heart failure, accounting for the vast majority of patients encountered by nuclear cardiologists. In addition, RV uptake and RV/LV-ratios are affected by scanner resolution and image reconstruction, the impact of which has not been well studied. As a consequence, most commercial software packages do not calculate RV or RV/LV uptake data. Recent guidelines on cardiac radionuclide imaging acknowledge the existence of the right ventricle,[9,10] and most practitioners are aware of the science, but left with qualitative assessments based on visual inspection it is not easy to integrate RV pathology into the report.

There are a range of opportunities for current nuclear cardiology technologies to contribute in the evaluation of RV function in heart failure.[11] However, the real promise of using radionuclide imaging in future studies of the failing RV is probably achieved by combining targeted molecular imaging with rigorous quantification, preferably in a setting using multimodality imaging approaches. So far, this is relatively uncharted territory. There are some indications that aerobic glycolysis is an early phenomenon linked to RV functional deterioration,[12] for which FDG-PET is the obvious tool for further research. ^{11}C-acetate is the tracer of choice to study the impact of novel heart failure therapies on the link between RV work and oxidative metabolic activity.[13–15]

Additionally, non-invasive characterization of RV neuronal function holds promise for further understanding of what is needed to reverse RV failure. Here, there are currently two relevant tracers: ^{123}I-metaidobenzylguanidine (MIBG) used with SPECT, and ^{11}C-meta-hydroxyephedrine (HED). Both are validated analogs of norepinephrine and have been used extensively in LV failure research, but RV-related data are only just emerging.[16]

In this issue, Ahmadi *et al*. present findings from a study using dynamic ^{11}C-acetate and ^{11}C-HED PET combined with echocardiographic assessments in the right ventricle. The data were obtained from a previously published study in a cohort of patients (n = 33) with reduced LVEF in the context of sleep apnea.[17] PET data were analyzed with the software FlowQuant,

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refined over many years in the same institution. In addition to the standard LV polar maps, the software also maps the RV.

Ten subjects were diagnosed with RV dysfunction. Although the sample was relatively small, there were significant associations of RV-MVO_2, derived from ^{11}C-acetate data, and echocardiographic function, and increased RV-MVO_2 predicted adverse events. ^{11}C-HED uptake (measured both as SUV, normalized to body weight, and as a retention index, normalized to the arterial input function integral) was significantly lowered in RV dysfunction.

RV-MVO_2 was calculated by measuring kmono, the monoexponential washout rate of ^{11}C-acetate metabolites from the wall. Washout rates are relatively insensitive to partial volume effects, which is why kmono values tend to be similar regardless of scanner resolution and can be used even in the thin RV wall.

On the other hand, HED SUV and retention index are uptake values that were basically measured from a static image obtained 30-40 minutes after injection. Uptake values are highly affected by partial volume effects, resulting in falsely low signal in thin walls and with a further reduction of signal proportional to the amplitude of motion. With this confounder in mind, the association of low HED uptake with RV failure found by Ahmadi *et al*. might actually be even more pronounced than what their numbers state. The initial consequence of pressure overload is development of hypertrophy, which reduces partial volume effect and increases signal recovery.

To compensate for variable wall thickness, the authors applied a correction for incomplete wall signal recovery using a fractional blood volume estimated from the ^{11}C-acetate scans (corrected uptake = uptake/(1 − blood volume fraction). However, this maneuver leaves the uptake value uncorrected for the partial volume effect induced by overlapping lung tissue.

Scanner resolution and reconstruction algorithms improve continuously with both SPECT and PET, which will lead to increasingly exquisite depictions of biology even in the right ventricular wall. Simultaneously, there is an ever-growing amount of tracers that might be relevant for research into heart failure. Combining these factors, it is a low-risk bet to assume that nuclear cardiology will continue to provide further insights into RV function and targeted restorative therapies in the years to come.

Disclosure

Jens Sörensen has no conflicts of interest to declare.

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