Hearing the Right Heart’s *Sotto Voce*

**Running title:** Aneja *et al.*: Think right heart

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The left ventricle (LV) typically dominates the conversation around cardiovascular risk. This includes symptoms stemming from LV ischemia, signs of increased LV voltage by electrocardiography in hypertensive heart disease and, apparently, a focus on the LV to open an editorial devoted to the right ventricle (RV) in preclinical risk assessment.

That is not to say that the softer voice of the distressed right ventricle (RV) cannot be heard. While the RV generally labors in the shadow of the more massive LV, the astute clinician can ‘think right heart’ in the appropriate context of, for instance, a history of pulmonary or congenital heart disease. Furthermore, RV abnormalities can be recognized upon careful inspection of the electrocardiogram, albeit more easily appreciated in the absence of marked LV voltage increase.

But what attention does the RV require in the general populace at risk of but without apparent cardiovascular disease? In this issue of Circulation, Kawut and colleagues address this question in reporting their analysis of cardiac magnetic resonance (CMR) examinations and subsequent outcomes in over 4,000 participants in the Multi-Ethnic Study of Atherosclerosis (MESA). After adjusting for hypertension, tobacco use, C-reactive protein level, body mass index (BMI), demographic variables and LV mass, the presence of right ventricular hypertrophy (RVH) doubled risk of incident heart failure and cardiovascular death. This was observed in a cohort of mildly overweight adults in their early 60s who were, on average, normotensive at the time of baseline examination. In 65% of the study sample who had pulmonary function tested roughly 2 years after baseline assessment, the incremental predictive value of RVH for HF or death over the same covariates remained significant.

RVH may previously have been neglected in longitudinal, community-based studies due to lack of a technique for its reliable measurement. Electrocardiographic detection of ventricular...
hypertrophy (not surprisingly with more data accrued regarding LVH^3 vs. RVH^4) lacks sensitivity, and important feature for appropriate population-based screening. And even if ECG changes of RVH are appreciable over the din of left heart abnormalities, the reproducibility data presented in this work are consistent with prior studies establishing CMR as a reliable modality for RV quantification and affords efficient sample size requirements for clinical trials^5.

What we do not learn from this work is what incremental value RVH by CMR has over echocardiographic indices, especially estimation of pulmonary artery systolic pressure (PASP) using Doppler-based measurement of tricuspid regurgitation jet velocity. In 778 Caucasian individuals from Olmsted County, Minnesota without manifest cardiopulmonary disease at baseline evaluation, increased PASP conferred increased mortality in a stepwise fashion (age-adjusted hazard ratio of 2.74 per 10 mm Hg)^6. In this study, 69% of subjects had measurable tricuspid regurgitation (TR), considerably higher than a peak 26% prevalence (increasing with age and highest in octogenarian men) of mild or worse TR in the Framingham study^7. In contrast, 92% (4144/4484) of the present MESA cohort had interpretable RV CMR studies. While these data suggest that RV mass is a more reliable biomarker of right heart disease in community-based cohorts, some context of RVH by CMR amidst widely used echo-Doppler measurements would have been helpful.

Is the RV speaking to us directly through Kawut and colleagues’ parsimonious model, or is it simply a voice for so many unmeasured variables? While a subset had pulmonary function tests that would presumably capture latent obstructive or interstitial lung disease, we do not know to what extent sleep disordered breathing, occupational or travel exposures, silent chronic thromboembolism, undiagnosed left to right shunts and infections such as human immunodeficiency virus were responsible for right heart changes. Of these variables, sleep
disordered breathing may be the most significant due to marked increases in its recognized prevalence coupled with a propensity to cause subclinical RV enlargement and dysfunction\(^8\) that may reverse with treatment\(^9\). The inclusion of BMI in their model may have captured some instances of obstructive sleep apnea, but BMI alone is an inadequate surrogate for the varied forms of sleep disordered breathing.

Events such as heart failure (N=78, 2%) and cardiovascular death (N=34, 0.8%) were expectedly low. This number of events still allowed for subset analysis by pulmonary function measures, but the primary analysis did not include several key risk factors for heart failure that were addressed in an earlier publication in this journal reporting heart failure events in the MESA-RV cohort\(^10\). In that work, a high prevalence of baseline hypertension, obesity, COPD, smoking, LV hypertrophy and LV systolic dysfunction were rated as significant contributors to subsequent heart failure. Those results remind us of the difficulty in attributing events to RV hypertrophy beyond what could be predicted by classic left heart failure risk factors.

The finding of a higher event rate in subjects with RV hypertrophy in conjunction with a relatively low LV mass is interesting, and is perhaps accounted for by the LV’s propensity to overwhelm the RV’s independent contribution to symptoms in the vast majority of heart failure cases and cardiovascular deaths. This is evident in the moderating effect of LV indices on the clinical impact of the other RV measures that did not survive multivariable analysis, such as RV end-diastolic and end-systolic volumes. These data endorse an association between RV mass and events, but causation requires further investigation.

Even as CMR offers a gold standard to quantify RV size and systolic function, the assessment of RV mass can be time-consuming and prone to significant inter-observer variability without dedicated core laboratory facilities or clinical staff adept at RV endocardial and
epicardial contour delineation. However, this should not deter further investigation into the independent role of the RV in cardiovascular events and deaths to focus more attention on right heart-centric therapeutic approaches. Clinical data do suggest an independent role of RV function in prognosis\textsuperscript{11,12}, and preserved RV function in the setting of left heart failure predicts improved outcomes and functional capacity\textsuperscript{13}. Future investigations should seek to elucidate related versus distinct pathways of RV and LV dysfunction.

The right ventricle is susceptible to dysfunction concomitantly with the LV due to not only increases in afterload from pulmonary venous hypertension but also ventricular interdependence, shared cellular myopathic processes and ischemia. Evidence describing separate LV and RV embryogenesis, with recent discovery of a ‘second heart field’ from which the RV (but not the LV) develops\textsuperscript{14}, lends further credence to the existence of distinct LV and RV signaling mechanisms and processes that could serve as future diagnostic and therapeutic targets. Preclinical mechanistic studies challenge existing notions of RV failure associated with pulmonary hypertension and increased RV afterload. Bogaard and colleagues produced RV hypertrophy without failure via pulmonary artery banding in Sprague-Dawley rats, whereas RV failure ensued in an angioproliferative model of pulmonary hypertension\textsuperscript{15}. The latter was produced via administration of a vascular endothelial growth factor receptor blocker in the setting of hypoxia that, in turn, caused myocyte apoptosis, decreased RV capillary density, myocardial fibrosis and decreased vascular endothelial growth factor mRNA and protein expression. In the angioproliferative model, RV function could be preserved with a dietary supplement that induced myocardial nuclear factor E2-related factor 2 and heme-oxygenase 1, preventing myocardial fibrosis and capillary loss\textsuperscript{15}. Such RV-targeted interventions remain poorly queried in clinical trials, just as descriptions of distinct molecular and signaling
mechanisms to explain RV dysfunction in humans are gaining momentum but remain rudimentary compared to the LV\textsuperscript{16}. Recognizing these gaps, a working group of the National Heart, Lung and Blood Institute has delineated a roadmap to target translational research in these critical areas\textsuperscript{5}.

This work is a valuable and provocative addition to the literature that lends a stronger voice to the soft-spoken RV, which may be the ‘good listener’ among cardiac chambers – taking in the effects of a variety of other conditions and presenting it through structural changes to the attuned observer. This trial’s meticulous measurement of RV parameters coupled with long-term follow-up represents an important step forward in population-based research that should foster novel translational efforts. Ultimately, multifaceted, longitudinal outcomes studies that track the onset and progression of structural and functional changes should yield better identification of at-risk individuals who would benefit from population-based strategies to prevent adverse cardiovascular events.

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**References:**


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