which pathways to prioritize in future studies. Given the great efforts it takes to generate such rich datasets and the importance of the information contained within them, I would implore the authors of both of these innovative and well performed studies to attempt to replicate each other's findings on the datasets they have, or, even better, come together to perform a meta-analysis.

Despite this weakness, which can easily be overcome through further collaboration and data sharing, these studies have revealed the importance of microbe–host interactions in the progression of IPF, and represent a significant step forward in defining the role of infection in the development of pulmonary fibrosis. Whether infection is an etiological factor for pulmonary fibrosis, and whether antimicrobial treatment can alter the course of progressive pulmonary fibrosis, are fundamental questions that still need to be definitively answered, but these studies raise the realistic prospect of replacing “IPF” in some with the diagnosis of this disease with a more meaningful label: infectious pulmonary fibrosis. ■

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Accelerometry: Improving Objective Assessments of Therapeutic Impact in Pediatric Pulmonary Arterial Hypertension

Although a variety of therapies are now available for the care of children and adults with pulmonary arterial hypertension (PAH), morbidity and mortality remain high, and no curative therapies exist (1, 2). Current medical approaches use drugs that target signaling

pathways relevant to pulmonary vasodilation but are unlikely to prevent or reverse the underlying causative factors of PAH (3). Although adult-focused studies have demonstrated the short- and intermediate-term benefits of such therapies, quality of life and long-term mortality remain poor, highlighting the importance of developing and testing novel therapeutic approaches as well as a need for meaningful clinical endpoints (recently reviewed by Bonnet and colleagues [4]).

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Unfortunately, there is a paucity of human data to support the use of any therapeutic approach to the care of children with PAH, and no therapeutic is approved by the U.S. Food and Drug Administration for chronic use. Although numerous reasons exist for the lack of pediatric clinical studies, one major cause is a lack of validated study endpoints applicable to a wide range of pediatric subjects (5). Without such endpoints, and robust clinical trials, pediatric care remains based largely on extrapolation of adult study data, provider experience, and guidelines lacking a complete evidence base (6, 7). In this issue of the *Journal*, Zijlstra and colleagues (pp. 220–227) test a novel metric to quantify activity in pediatric patients with PAH using accelerometry, while also providing some additional understanding of this population's exercise limitations (8). Because symptomatic improvement may serve as a surrogate for improved outcomes, reliable objective assessment of activity may ultimately provide a meaningful clinical endpoint for the conduct of studies, whether for pharmaceuticals, formal exercise training, psychosocial support, or other supportive care.

In clinical trials of PAH, as well as clinical care, the objective determination of a patient's functional capacity is highly valuable. The change in 6-minute-walk test (6MWT) distance has long been used as a short-term endpoint for clinical trials in adults; in addition, other components of the 6MWT (i.e., self-reported shortness of breath, change in heart rate, and change in pulse oximetry values) are valuable in the clinical care of many patients with PAH. Although pediatric providers do use the 6MWT routinely when able, age and developmental-related variations among children reduce its generalizability, especially in young children (9). Composite endpoints, incorporating multiple individual metrics (e.g., time to death or lung transplant, hospitalization, and subjective functional status) into a unified assessment, have recently been proposed as promising alternatives (10, 11). However, composite endpoints are only as good as their weakest individual component and may not directly solve the complex problem of determining functional change objectively over time (12).

The development of small portable electronic devices, such as the accelerometer, to continuously and accurately determine physical activity, may provide continual information about our patients' exercise capacity and activity far beyond a 6MWT performed intermittently in the clinic or a self-report of exercise capacity. Although several adult PAH studies recently demonstrated the utility of accelerometers to quantify patterns of physical activity during activity and at rest, the current study is the first to investigate children with PAH (13, 14). Of particular importance, Zijlstra and colleagues found that not only was reduced physical activity as determined by accelerometry a feature of pediatric patients with PAH but also accelerometry correlated well with 6MWT distance, World Health Organization functional class, and even time to a deleterious clinical event (8). Their findings suggest that either alone, or as part of a composite clinical endpoint, accelerometry may become a useful determinant of clinical condition for observational studies and clinical trials.

Enthusiasm for this study is enhanced by the critical need in pediatric PAH for objective measures to determine severity at diagnosis and disease progression over time. However, several potential limitations exist. First, although generally superior to self-reported physical activity, research-level accelerometers may insufficiently or inaccurately measure steps taken at slow walking speeds, due either to a lack of calibration to detect unstructured

activities or insufficient analytic algorithms to analyze low-movement activities (15). Second, this concern is amplified when considering the incorporation of retail-level accelerometer-based technology to clinical care due to the variability in quality and goals of the devices as well as their proprietary algorithms used for analysis (16). Third, although Zijlstra and colleagues studied a reasonably large sample of patients with PAH, replication in a larger and more diverse cohort, and longitudinally, will be necessary (8). Fourth, a validated instrument to assess pediatric quality of life was not concurrently administered and would be a valuable addition to future studies. Finally, as the authors point out, determination of the accelerometer's utility and practicality for younger children with PAH must be studied—particularly those children who are preambulatory or inconsistently ambulatory.

Despite tremendous pharmaceutical advances, the formation of multispecialty teams focused on pulmonary vascular disease, and broad supportive care approaches, we still lack the capacity to carefully determine the key features unique to the clinical course and response to care of each pediatric patient with PAH. Ideally, prospective observational research cohorts incorporating both research and retail accelerometers will study the relevance of this metric as an objective assessment of physical activity and capacity as well as its relationship to short- and long-term outcomes. If validated, given the ease of its use and low expense, accelerometry may one day become a reliable endpoint. This study by Zijlstra and colleagues will, we hope, launch a revolution in objective assessments for pediatric PAH that can be used in clinical trials and in clinical care (8). If the development of standard tools to comprehensively assess patients of all ages and backgrounds is ultimately successful, we will better tailor care to the unique needs of each pediatric patient. ■

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Magnetic Resonance Imaging in Pulmonary Arterial Hypertension Panacea or Pixelation?

We often plough so much energy into the big picture, we forget the pixels.

—Silvia Cartwright

Noninvasive assessment of the heart has evolved significantly during the last 50 years. The advent of magnetic resonance imaging, and its application to cardiovascular disease, has revolutionized our ability to identify the structural and hemodynamic perturbations that occur in a wide range of diseases. Cardiac magnetic resonance imaging (CMR) couples high-resolution imaging of right ventricular (RV) structure with precise measurement of function. Combined with recent population-based studies that have established normal values for a number of commonly assessed RV parameters across sex and ethnicity, CMR offers a powerful tool to detect and characterize the RV response to heart and lung diseases (1–3).

RV function remains the best determinant of outcomes in pulmonary arterial hypertension (PAH). CMR has been frequently employed in the evaluation of patients with pulmonary hypertension (PH) and, in particular, PAH. The modality allows for accurate and detailed assessment of RV chamber volume, muscle mass, and flow, which is particularly relevant considering the difficulties with measuring these parameters using two-dimensional echocardiography. CMR is the standard reference to evaluate RV structure and function in PH. RV ejection fraction was a strong predictor of mortality in a pooled analysis, whereas other measures of ventricular volume (RV end-systolic, RV end-diastolic,

and LV end-diastolic volumes) were also associated with survival, but to a lesser degree (4).

Although the focus of CMR studies has largely been on various aspects of RV structure and function, more recent studies have expanded the area of interest to include various assessments of blood flow within the heart and pulmonary vasculature, atrial and ventricular strain, and estimates of RV contractility (5) (Figure 1). Although these novel measures are not yet fully validated, they demonstrate the vast potential of CMR as a tool to further explore the relationship between structure and function in the heart and pulmonary vasculature. Importantly, neither these novel nor more established CMR parameters have been rigorously examined as potential biomarkers of survival in PAH.

In this issue of the *Journal*, Swift and colleagues (pp. 228–239) take an important step in the study of CMR and the cardiopulmonary interaction in patients with PAH (6). Using a cohort of nearly 600 patients with PAH who underwent CMR, the authors demonstrated the predictive value of indexed RV ejection fraction, RV end systolic volume, RV end diastolic volume, and LV end diastolic volume in univariable analyses. They also identify two additional predictors: CMR-derived estimation of RV coupling (the relationship between contractility and afterload in the RV) and the relative area change in pulmonary artery (PA relative area change), which have been shown to have prognostic value in smaller single center studies (7, 8). Importantly, only PA relative area change (along with indexed RV end systolic volume) persisted as a significant CMR-derived predictor of survival