reported comparisons: when adjusted for HIV-infected status, and when adjusted for current smoking, reduced FEV_1/FVC, or reduced D_{LCO} within HIV-infected subjects, saliva samples were less diverse and were enriched with three or four main bacterial genera. Although the authors adjusted for smoking in their multivariate analysis, the potential effect of active smoking cannot be fully discounted, given its direct impact on airway dysfunction and mucosal inflammation. Moreover, cigarette smoke can induce intestinal inflammation and has been associated with altered intestinal microbiota patterns (13–15) (somewhat surprisingly, the latter was not observed here, which may relate to insufficient statistical power). Nonetheless, returning to the oral cavity, it is important to consider the oral mucosa as an immunologically very active interface. Thus, dysbiotic oral microbiota signatures could exert significant distant effects, constituting a potential "oral–lung axis." Although more experimental work will be needed to discern these causal scenarios, the current investigation invites us to consider that when we look for pulmonary disease, we should think beyond a single site of microbial–host interaction. ■

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Against the Odds: Risk Stratification with Cardiac Magnetic Resonance Imaging in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a rare, heterogeneous disease characterized by a distinct microvascular remodeling with a concomitant increase of pulmonary arterial pressure and resistance (1). As a central pathophysiological element, the right ventricle eventually reacts to the increased load, leading from adaptation to maladaptation and beyond as eventually failure ensues (2). The state-of-the-art therapeutic strategy to address this pathophysiological progression is based on individual risk stratification (3). This risk assessment integrates pulmonary hemodynamics, symptoms, functional capacity, laboratory values, and echocardiographic parameters to classify the patient

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as low, intermediate, or high risk (3). Although the included variables, number of patients, geographical heterogeneity, and definition of the average low-risk score vary among studies, recent analyses of large PAH registries have proven the clinical and therapeutic relevance of this risk assessment (3).

Cardiac magnetic resonance imaging (CMRI) is currently considered the gold-standard technique to evaluate right ventricular (RV) volumes and function (4), and is recommended for the follow-up of patients with pulmonary hypertension (5), but it has not been integrated into risk stratification. One might argue that this is overdue, as CMRI-derived volumetric measures, including stroke volume (SV), RV end-diastolic volume, and RV end-systolic volume (ESV), mirror the RV adaptational process, have prognostic value, and are easy to assess. The RV ejection fraction (EF) and the SV/ESV ratio have also been shown to have prognostic value (6, 7), and a low SV index at baseline and a reduction in the SV index during treatment have both been associated with increased mortality (8). Assessment of RV mass is also of great importance; it provides a valuable prognostic parameter when combined with volume in a mass/volume ratio, as lower mass/volume ratios (signifying eccentric hypertrophy) are associated with more severe functional impairment (9) and independently predict clinical worsening. Furthermore, RV mass was recently shown to predict outcomes in PAH (10). Although longitudinal relaxation time mapping has the potential to be a marker of fibrosis (11) and could allow early detection of myocardial involvement in pulmonary hypertension, it was not found to be prognostic independently of RV size and function in patients with PAH.

The evaluation and validation of CMRI for risk stratification in PAH by Lewis and coworkers (pp. 458–468) in this issue of the *Journal* (12) might pave the way for CMRI to become part of risk assessment. Using a referral center registry, the authors carefully analyzed CMRI data in a large population of patients with PAH at baseline and, for a proportion of the patients, at the first follow-up. The majority of the included patients ultimately received PAH-specific combination therapy. Overall 1-year mortality was 8.7%, although the majority of patients entered the study in an advanced state of disease (72% of the patients were in functional class $\geq$III) and a substantial proportion were classed as high risk at baseline. This indicates the following: first, the call for early combination therapy has reached daily clinical practice; second, 1-year survival of this incurable disease has improved dramatically during the last decade; and third, the goal of earlier disease recognition and identification of patients at lower risk (13) has not yet been realized (although the results might be biased by the fact that the authors included a population of patients with incident and prevalent PAH).

The authors were able to identify patients at low, intermediate, and high risk of 1-year mortality based on the RV EF, whereas only patients at low and high risk were identified using the RV ESV index % predicted and left ventricular (LV) end-diastolic volume index. In addition, transition to or maintenance of a lower RV ESV or higher RV EF was associated with better survival at follow-up. Besides representing the gold standard for volume assessment, what might be the added value of CMRI in the assessment of patients with PAH?

The findings by Lewis and coworkers fit perfectly into the current pathophysiological concept of RV–arterial coupling in PAH. To remain "coupled" and maintain an end-systolic/arterial elastance (Ees/Ea) ratio of 0.8, the right ventricle reacts to chronic pressure overload with homeometric adaptation (increased contractility) and heterometric adaptation (increased dimensions) (14). However, evaluation of Ees/Ea based exclusively on CMRI RV volume measurements has been reported, with Ees/Ea simplified as SV/ESV (15). Alterations of SV/ESV are necessarily associated with an increase in RV volumes to maintain SV. Interestingly, the parameters proposed by the authors mirror an additional important fact: during RV maladaptation to chronic pressure overload, RV hypertrophy and dilation lead to septal bowing and compression of the left ventricle, resulting in impairment of LV filling (RV–LV interdependence). Reduced RV SV and progressive remodeling of the pulmonary vasculature may also impair LV filling. CMRI is probably the best possible way to determine RV adaptation and maladaptation in pulmonary hypertension because of its ability to provide a holistic assessment of RV and LV volumes and function.

The authors are to be commended for their work, which hopefully will introduce CMRI parameters into risk stratification in PAH. CMRI parameters such as SV/ESV, RV mass, measures of RV deformation such as feature-tracking strain, four-dimensional flow in the right ventricle including assessment of vorticity, late enhancement, and longitudinal relaxation time and transverse relaxation time mapping, in combination with right atrial phase assessment with strain imaging, are promising tools to be explored in the future in terms of prognosis and perhaps risk stratification. ■

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Modeling Treatment of Latent Tuberculosis: Shortening the Leap of Faith?

In the 64 years since preventive therapy for latent tuberculosis (TB) was first pioneered by Comstock and colleagues in Alaska, impressive treatment shortening has been achieved with two simple drug classes: isoniazid and rifamycins. In the last decade, the duration of therapy for latent TB infection (LTBI) has progressively decreased, going from 9 months to 3 to 4 months, and perhaps to 1 month. To guide these advances and design phase 3 prevention trials, investigators have designed and tested regimens of antimicrobial treatment in the chronic low-dose mouse model. Inconveniently, mice do not develop latent TB. Thus, to estimate drug/regimen efficacy, researchers have assessed rates of bacterial burden decline in mice as a surrogate for LTBI efficacy, coupled to a leap of faith.

In this issue of the *Journal*, Foreman and colleagues (pp. 469–477) now present a dramatic animal study suggesting that the novel 3-month 12-dose isoniazid–rifapentine (3HP) regimen for preventive treatment of LTBI has sterilizing capacity (1). For the TB world, these are impressive findings; validation of these findings in other, related settings would provide important support for the large-scale use of such interventions. Scale-up of this intervention is already underway in both low-burden (2) and high-burden/high-HIV settings (3), so the short-term validation may be soon achieved.

There are important strengths to the study, and there are important questions remaining. The study was performed in a well-documented nonhuman primate model (the rhesus macaque) in which the pathophysiology of tuberculosis appears to recapitulate the human analog well. In the particular model employed here, low-dose infection with *Mycobacterium tuberculosis* (MTB) leads to a state of chronic infection; in their study, rapid progression to active disease occurred in 2 of 16 animals, whereas the remaining 14 remained stable with minimal or no signs of active disease. In a classic approach, 3 months after infection, half the remaining infected animals were treated with the 3HP regimen administered in feed, and half received no treatment. At 7 months after infection, all animals received an infectious intravenous dose of simian immunodeficiency virus, leading to a well-recognized state of immune impairment in this host. High simian immunodeficiency virus viral loads were documented. After a 3-month period of observation, all surviving animals were killed, and multiple tissues (including lung, bronchial lymph nodes, liver, spleen, and kidney) from all 14 were cultured on solid media. Cultures were positive in all untreated animals, whereas only one culture from one of seven treated animals yielded a single colony on one plate. These results are indeed dramatic. On their surface, they may indicate that short-course rifamycin-based regimens for LTBI are highly sterilizing; in that case, the wide application of such regimens could presage a major step forward in TB prevention and control.

We have two sets of questions that help to place these results in perspective, and that temper these hopes with scientific caution. Our first questions concern the extent to which this model replicates the human response to MTB. The authors cataloged clinical parameters including tuberculin skin test conversion and chest X-ray scoring, as well as body weight and temperature, throughout the experiment. And as one would expect to see in humans, tuberculin skin test conversion occurred in the majority of animals by 30 days and in all of the animals by 70 days, and serial chest X-rays were essentially negative throughout until the reactivation phase. Importantly, the postmortem pathology observed in the nonhuman primates closely paralleled that of humans.

Our second set of (related) questions concerns exactly what biological state is being modeled. In recent years, there has been increasing evidence that TB infection exists in humans not as a

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