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Crossing the Chasm(s): Demonstrating the Clinical Value of Hyperpolarized Gas MRI

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The community of scientists and clinicians working to advance hyperpolarized (HP) gas magnetic resonance imaging (MRI) has long believed that its ability to image pulmonary function three-dimensionally, non-invasively, and in a single breath has enormous potential to advance pulmonary medicine. After all, the workhorse of this field is the pulmonary function test invented in 1846, which remains the oldest clinical diagnostic test still in use today (1). Yet, more than two decades after the first demonstration of HP gas MR images in humans (2,3), we are not exactly overrun by its widespread adoption. Of course, the technology has endured barriers associated with intellectual property rights and absence of regulatory approval, but these issues have now been addressed (4) and phase III trials are expected to start in 2017. However, even if approval from the Food and Drug Administration were in hand today, barriers to dissemination remain to be conquered.

In this regard, we can learn much from the seminal hightech marketing book by Geoffrey Moore, titled “Crossing the Chasm: Marketing and Selling Technology Products to Mainstream Customers” (5). Its thesis is that many novel technologies are quickly embraced by a few “early adopters,” but face a major gap in reaching a broader community of users. In the case of HP gas MRI, it must actually cross *two* chasms. The first is the technical one we have been crossing for years. HP gas imaging requires MRI to be conducted in ways not normally done—rapid scans of nuclei other than water, with signal transiently enhanced by ~100,000, but eager to return to thermal equilibrium. Thus, HP imaging does not even come naturally to experts in “normal” MRI. Fortunately, tremendous advancements have been made on this front by numerous centers around the world, leading MRI vendors to become increasingly supportive. Thus, making HP gas MRI routine and robust now appears within reach. But perhaps the larger chasm to cross is the one that leads to its embrace by pulmonary clinicians. Today, pulmonologists can go their entire careers without ever ordering an MRI scan.

Adding to the challenge is that all of this chasm-crossing must also be navigated in a setting of highly constrained healthcare spending. Whereas the introduction of MRI itself came in an era of relative enthusiasm for new technology in healthcare, the focus in today’s environment seems to be heavily weighted toward how we can reduce the use of advanced imaging (6).

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So what are the HP gas aficionados to do to advance this promising technology, when the barriers to adoption appear so formidable? The answer to this question is guided by the work of Sarah Svenningsen and coworkers in this issue, who show us the types of study designs needed to move this field from its strong technical foundation to establishing its clinical roots.

Today, many of us working in hyperpolarization are technology enthusiasts. We pursue it because it is novel, elegant, and non-invasive, and provides an endless series of intriguing technical puzzles to solve. To this end, our literature is filled with novel trajectories through k-space, reconstruction algorithms, new spectroscopic signatures, and a variety of correlation, and Bland-Altman plots. Although the technical work in hyperpolarization continues to lay important foundations, it does little to convince physicians to order an HP gas MRI for their patients. To make that happen, we must “sell the benefits, not the features,” as marketers would tell us. Simply put, we must *demonstrate* how HP gas MRI provides clinical value.

The clinical utility of a test can be defined in many ways and measured in a myriad more, but must start with the rec- ognition diagnostic testing itselfcannot generate health benefits for patients (7). This can only happen if test results are used to improve patient care. Tests must therefore help drive decisions to initiate, modify, stop, or withhold treatment. Although our community has done much to reveal the extraordinary promise of HP gas MRI, it has only begun to scratch the surface when it comes to demonstrating its clinical value.

To this end, several aspects of Svenningsen et al.’s study provide important guideposts for the future development of our field. The study objective was to test, in patients with non-cystic fibrosis bronchiectasis, whether HP ^{3}He ventilation MRI could detect regional ventilation impairment and response to airway clearance therapy. Patients with this chronic disease have irreversibly dilated airways, leading to pooling and poor clearance of mucus in affected regions (8). Although no treatments are currently approved to treat this condition, numerous antibiotics, mucoactive therapies, antiinflammatory agents, and chest physiotherapy are being investigated. However, these trials struggle to measure treatment efficacy (9). This is clearly an example of a condition that urgently requires new, objective, and robust measures of functional disease burden. It is also clearly a disease where functional impairment is inherently regional, and therefore provides an ideal proving ground to demonstrate the potential value of spatially resolved markers. In fact, high-resolution computed tomography (CT) is routinely used to diagnose the disease, but it is not always clear how anatomic abnormalities relate to downstream function. By including both highresolution CT and HP ^{3}He MRI in their study, the investigators provide important context in which to interpret pulmonary functional MRI. In fact, the study was further enhanced by including an exceedingly complete battery ofadditional metrics that are being explored to evaluate bronchiectasis. These metrics included physiological testing with spirometry, plethysmography, 6-minute walk test, and validated questionnaires to assess health status, including the St. George’s Respiratory Questionnaire and Patient Evaluation Questionnaire. Importantly, the team designed its study around a therapeutic intervention—evaluating airway clearance therapy using oscillatory positive expiratory pressure (oPEP).

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This design provided a compelling test for all metrics (except for CT, which was not repeated) in terms of their ability to measure changes resulting from 3 weeks of daily oPEP.

The study reported some unsurprising findings, such as that bronchiectasis patients exhibited higher ventilation defect percentages (VDP) than healthy controls. Moreover, in lobes with CT evidence of bronchiectasis, VDP was significantly higher than in lobes where CT did not show bronchiectasis. But more intriguing was the finding that many of the lobes appearing normal on CT nonetheless exhibited ventilation defects. This could suggest that inflammation or mucus plugging was present in airways smaller than could be resolved by CT. This important result suggests that HP gas MRI may be more sensitive in detecting milder pathologies, including early airway wall changes and mucus plugging, which may precede advanced structural damage in the larger airways.

Perhaps a mild disappointment of the study is that although oPEP significantly improved patient-reported ease of bringing up sputum and global assessment, the mean VDP did not change significantly. Of course, non-cystic fibrosis bronchiectasis is a heterogenous disease with areas of normal and diseased lung interspersed with one another, and therefore more comprehensive quantification of the regional ventilation distribution may be needed to quantify subtle changes (10). Of course, we cannot know definitively whether oPEP was truly effective in each individual. Of interest, however, is that more than half of patients did exhibit an improvement in VDP that was greater than the smallest detectable difference in VDP of 2.3%. Here, the authors illustrate yet another important consideration, which is to introduce the concept of minimally important clinical differences in follow-up measurements (11). Although establishing minimally important clinical differences is beyond the scope of one study, the team instead used previously analyzed results of inter-visit variance to establish a smallest detectable difference (12). This value is remarkably small considering the comparable variability of PFT metrics such as FEV_1 is around 6% (13). The importance of such low variability cannot be underestimated, as required sample sizes will scale roughly as its square. Thus, markers such as VDP, even if more expensive to collect than FEVi, could result in far greater savings, if fewer patients are required to demonstrate a clinical benefit.

Of course, despite the strong study design, some limitations were evident. If a larger sample size had been used, a positive effect on VDP might have been demonstrated. It would ultimately be very powerful to be able to demonstrate that the patients who did exhibit reduced VDP after oPEP had better clinical outcomes. Perhaps the most significant limitation is that the study used ^{3}He gas, which while having pioneered the field of pulmonary functional MRI is not sustainable owing to its high cost and limited supply (14). As the authors point out, the future of this technology lies with ^{129}Xe gas, which is derived naturally from air separation, and in recent years has taken over from ^{3}He. In fact, the unique properties of ^{129}Xe actually permit a far richer set of information to be gathered. Recent work has demonstrated images of ventilation, and gas transfer to interstitial barrier and red blood cell components can now be acquired in a single breath (15,16). One can only imagine that if studies were designed with Svenningsen et al.’s level of clinical rigor and combined with ^{129}Xe gas exchange MRI techniques, it is likely that HP gas MRI would

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soon find itself on the other side of the chasm, serving as a workhorse of pulmonary medicine.

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