PHIL project summary

This European project called PHIL (Polarized Helium for Imaging the Lungs) started in December 2000, just 4 years after the discovery that one can visualise the internal volume of the lungs by Magnetic Resonance Imaging (MRI) using inhaled polarised gas. It was quickly understood that the new method had unprecedented potential for morphological and functional analysis of the lung. It was decided to put forward a European consortium, linking the efforts of nine teams in six different countries, with the general objective of demonstrating the potential and the validity of this new non invasive, imaging MRI method using Hyper-Polarized Helium (HP-He MRI), applying it to a well chosen lung pathology. All Partners of the consortium were selected for their pre-existing know-how and complementary competences in atomic physics, MRI methodology and instrumentation, radiology and respiratory medicine.

The HP-He MRI method makes use of ^{3}He gas, which is chemically inert, non radioactive and harmless when introduced in the body. The helium atoms, which have a ½ nuclear spin, are spin polarized prior to inhalation, which means that a large non equilibrium magnetization is obtained by orientation of the magnetic moments of the gas nuclei. The polarization technique is the so-called “metastability exchange optical pumping method”, based on commercial lasers, producing large quantities of highly polarized gas but requesting compression. This gas is further inhaled in the lungs and imaged by MRI in conventional scanners, after modification of the electronics and software in order to shift the nuclear resonance frequency from proton to ^{3}He. This method allows visualising the intrapulmonary airspace filled with the gas, instead of the lung water content examined by conventional proton MRI. The large polarization of the gas (possibly ranging from 40 to 80%) compensates for the lower density of nuclear spins. Even if the imaging resolution is insufficient to delineate alveolar clusters directly, measurements of apparent diffusion coefficients (ADC) are sensitive to alveolar sizes and ADC imaging may reveal subtle changes in the microstructure of the airways.

The consortium chose emphysema and selected Chronical Obstructive Pulmonary Diseases (COPD) such as bronchitis and bronchiolitis to test and to study the possibilities of the new method. This choice was motivated by the frequent occurrence of these diseases and the very high cost of their treatment for society: 10% of the population and 25% of the smokers suffer from COPD, which is the fourth cause of mortality in Europe. It was thus decided to set a clinical trial applying the HP-He MRI method to a significant group of selected patients with a well defined standardized protocol, which could allow the comparison of the new method with conventional ones: lung function tests, High Resolution Computed Tomography (HRCT), Krypton scintigraphy. A clinical group was set, linking three teams (in Mainz, Sheffield and Copenhagen) having complementary expertise in radiology and respiratory medicine. Simultaneously, various methodological developments were requested, as the HP-He MRI method was just emerging at the start of the project. Two physics groups (in Paris and in Mainz) were responsible for the progress of polarised gas production and transportation. Two other groups (in Orsay and in Lyon) started studying how to adapt the MRI techniques to the fast lung ventilation studies with helium. Another group (in Krakow) was incorporated, with the goal of constructing a low cost low field scanner. Finally a team (in Madrid) with expertise with animal models was added to the consortium, in order to validate the HP-He MRI method on rats with induced emphysema.

The HP-He MRI measurements were performed with polarized gas delivered to the clinical sites by a centralised production unit in Mainz. This facility became fully operational during the project and delivered remarkably large flux (several 10 bar litres per day) of high grade polarizations: over 80% at the production unit, still reaching 60% after shipping by air to the clinics, sometimes at large distances (from Mainz to Copenhagen or to Sheffield). The transportation problems were solved by special containers preserving spin relaxation, as well as appropriate material for the storage cells containing the gas. In parallel, helium polarizers for on site production were developed in Paris, delivering smaller and slightly less polarized doses of HP helium (typical polarizations are of order 40%). Two different prototypes of such compact robust and reliable polarizers were built, and are ready for possible commercialisation. They have been duplicated among partners inside the consortium.

The groups working on MRI methodology obtained significant results, liable to further improve the clinical protocol. On one hand, studies in Lyon demonstrated the potential of new fast acquisition MRI sequences with the so-called SPIRO technique. They allow deriving quantitative and regional information of the gas dynamics in human lungs from a single helium inspiration of polarized gas. Such sequences have already been successfully tested at hospitals in Sheffield and Copenhagen. On the other hands the group in Orsay with help of those in Lyon and Paris explored the HP-He MRI technique for a better understanding of the image contrast mechanisms and to determine the best magnetic field strength to be used. Experiments were performed on whole-body MR systems at 0.003 T, 0.1 T and 1.5 T. Better accessible image quality was demonstrated at 0.1 T over the other field strengths, taking advantage of both optimal RF detection and MR signal-sampling bandwidth. A spin-echo approach was used to investigate ADC as well as transverse relaxation parameters. The transverse relaxation times were found to strongly depend on the field strength. Both multiple spin-echo ADC and transverse relaxation were shown to provide sensitive information about lung microstructure, of potential interest to further improve diagnosis of mild COPD and emphysema. Transverse relaxation could be further lengthened by the proper injection of a ferromagnetic contrast agent, modifying the susceptibility of the lung tissues right to matching that of air. New sequences, that simultaneously achieve a standard static ventilation image and a parametric image of one or other new parameters, have been successfully implemented and tested on healthy volunteers on a standard 1.5 T MR.

The animal models studies provided very complementary results. Different models of lung diseases were induced in rats, treated with chemicals such as elastase or cadmium chloride. To some extent these model mimic human emphysema. The animals were prepared in Madrid and studied in Lyon with the HP-He MRI method. The rat groups treated with cadmium showed clear ventilation defects, corresponding to non-ventilated areas of the partially collapsed lung. ADC and post-mortem morphometric measurements were compared. The most significant finding of this work is the excellent correlation between the ADC data and the morphometric ones, which allow direct quantification of alveolar size). Complementary to experiments in clinical trials, in which available population generally have or suffer chronic diseases, emphysema in animals was mildly developed to evaluate the technique for early diagnosis.

In that perspective, the low field home made scanner successfully built in Krakow could be highly valuable. It represents a low cost scanner adapted to imaging small animal lungs. It is based on a permanent magnetic material of new generation. The magnet is designed to have an open geometry for the imaged object, the field is 0.08T. Imaging gradients and radio frequency coils were also constructed and the NMR console adapted to experiments either on proton or helium frequency. The performances of this home built MRI scanner were evaluated on proton images. Finally in-vivo helium MRI images of rat lungs were obtained. This success opens up the possibility of a spread of the HP-He method, in particular for animal studies. It could also be scaled up for whole body scanners.

The multicentre clinical trial first had to upgrade the MR system hardware and software in all three centres, according to the HP-He MRI standards. Pre-existing sequences used in Mainz were adapted and optimized at the different sites and, for the trial, standard sequences were used throughout the study. The sequences employed are: ventilation distribution (breath-hold), apparent diffusion coefficient (breath hold) and dynamic ventilation (single respiratory cycle). The protocol also includes pulmonary function tests to assess severity scores. The trial successfully enrolled a total of 116 subjects (62 COPD, 17 alpha-1-antitrypsin deficiency (ATD) and 37 healthy volunteers). Data are recorded in a data base and finally submitted to a statistical analysis.

The clinical trial work proved that the method could be successfully implemented in two new sites (Sheffield and Copenhagen). Furthermore, the analysis of the data bank provided very rich information. The subjects were divided in three groups: those with COPD, those with alpha-1-ATD and healthy volunteers. A score number referring to the degree of abnormality was attributed to each subject. Comparison between HRTC, MRI findings and abnormality scores showed that MRI correlates better with lung function tests than HRCT, even if morphological information is superior to MRI. The vast majority of MRI findings consisted of wedged shaped defects, even subjects with normal HRCT showed ventilation defects. The comparison of diffusion measurements (MRI) with emphysema index and mean lung density (HRCT) was also exploited. ADC measurements clearly separated the healthy subjects from those with emphysema of any type. HP-He MRI proved also to be able to distinguish between different diseases by using a combination of ventilation distribution and ADC mapping. After assessing all the results, one general finding is that HRCT is more sensitive but MRI more specific. Comparison of MRI with scintigraphy showed that equivalent information on ventilation can be derived from both methods provided the best scintigraphy parameters are used. A positive feature of the HP-He MRI method is that even a single patient exam provides unique complementary information at the same time (morphology, ventilation defects, average of air spaces, even in vivo oxygen measurements that can be derived from the local relaxation times).

In conclusion, the PHIL project has demonstrated that European collaboration successfully put the groups at the forefront of developments of novel and challenging technology. Not only has gas production been optimised to unprecedented levels, but a central production facility was put in place and a multinational trial performed.

Hyperpolarized ^{3}He MRI was both feasible and showed interesting new insights into a common lung disease, emphysema. It proved superior in attaining 3D lung function in the lungs, and was more closely correlated with routine lung function tests than HRCT.

The method has already been tested in other lung diseases, and more studies are planned or have started. These include lung transplant assessment, cystic fibrosis (the most common genetic lung disease), asthma and lung cancer. The technology has proved of huge potential interest in these areas, because it is non-invasive and does not require ionising radiation (both extremely important, especially in longitudinal follow-up of children). However, more research will need to be performed before it can be entered into clinical routine. Finally, the technique seems capable of reproducible morphological and dynamic assessment, which could prove extremely beneficial for the development of novel therapies. Thus, by using this technology the size of trials may be reduced, the need for animal tests could become something of the past and the time from concept to market could be shortened.

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