Realization of administration unit for $^3$He with gas recycling

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Abstract. Hyperpolarized (HP) noble gases ($^3$He, $^{129}$Xe) are used for MR-imaging of the lung. In the majority of case the HP gas is filled in Tedlarbags and directly inhaled by the patients. Starting from an earlier pilot device, an administration unit was built respectively to the Medical Devices Law to administer patients HP noble gas boli in defined quantities and at a predefined time during inspiration with high reproducibility and reliability without reducing MR-quality. The patient’s airflows are monitored and recorded. It is possible to use gas admixtures, measure the polarization on-line and collect the exhaled gas for later recycling. The first images with healthy volunteers were taken with this setup in a clinical study. Current results will be presented.

1. Introduction

Hyperpolarized (HP) noble gases are used for MR-imaging of the lung for many years[1]. In case of the rare isotope $^3$He this technique requires efficient polarization, storage, transport, gas administration and recovery of the gas [2, 3]. In recent development all steps of this cycle have been optimized. In the beginning the HP gas was filled in Tedlarbags and directly inhaled by the patients. However for follow-up studies a better reproducibility and monitoring is desirable. Starting from an earlier pilot instrument [5, 6] which has been used in the European PHIL-study [7], an advanced administration unit was built which will be presented in the following.

2. Requirements of the administration unit

Tedlarbags (Fig. 1) were used in $^3$He-MR-lung-Imaging for many years. Because of this experience several problems with the use of Tedlarbags are well known:

First, automatic filling is not available; so the reproducibility of the bolus volume strongly depends on the user. Spirometry is not included; therefore no information about the breathing parameters as the depth of the inhalation and the flow rate is available. This means the amount of gas remaining inside the Tedlarbag after inhalation is unknown, too. Further, Tedlarbags are only available with a very thin tube (inner diameter about 3 mm). So the patients have to inhale against an unphysiological high breathing resistance. This effect can be seen in the dynamic images which were taken in the clinical study presented below. Gas collecting for later recovery is difficult, as the gas is inhaled via the thin tube with the mouth, but for gas collecting a mask is needed. And without using a pump Tedlarbags can be filled only with one bar remaining in the gas cell.
So these problems form the requirements for the administration unit: First of all the filling should be automatic and controlled via laptop. There should be a high reproducibility of the preset bolus volume (accuracy: \( \Delta V / V < 3\% \)) and the time of administration (accuracy: \( \Delta t < 100 \text{ ms} \)); with the administration unit it is also possible to predefine the time during inhalation when the gas bolus should be administered, for example either at the beginning or 300 ms after the start of the inhalation. The presented administration unit can further be equipped with an on-line polarimeter to monitor the HP gas polarization with an accuracy of \( \Delta P / P < 7\% \). It is essential to conserve the polarization during the whole process (\( T_1 \) has to be as long as possible), which constricts in addition to the required biocompatibility, the choice of materials used for the construction of the administration unit. The control and monitoring should be as easy and comfortable as possible via laptop, especially the breathing curve should be visible all the time. The automatic filling should be user-friendly such, that one can save typical administration settings and the log-files should be stored automatically. Especially for structure analysis like measuring the apparent diffusion coefficient (the ADC), it is useful to have an option to administer gas admixtures, as different gases such as air, \( \text{N}_2 \), \( \text{SF}_6 \) or \( \text{Xe} \) have an influence on the apparent diffusion coefficient. As \( ^3\text{He} \) shortage is a serious problem efficient gas collecting for later recycling is included in the administration unit presented below.

One of the most important aspect for the construction of the presented administration unit concerns the obligations (safety and hygiene aspects) given by the Medical Devices Law.

3. Realization of the \( ^8\text{He} \) administration unit

In the picture of the setup Fig. 2 on the left compensation coils (blue) provide a homogenous field at the HP gas cell position in the stray field of the tomograph. The sketch of the setup (Fig. 3) point the magnetic field lines up. The piston pump which controls the administered HP gas bolus is placed below. Behind the patient’s head the administration box is positioned containing spirometers and valves (Fig. 2). The patient is wearing a breathing mask and is connected directly to the administration box. On the floor the bag collecting the exhaled air can be seen. Later on the exhaled air/\( ^3\text{He} \) mixture is compressed into a steel bottle and shipped to a central recycling station which recovers the \( ^8\text{He} \) with 95\% efficiency and ppm purity level \([3, 4]\). Around the patient’s thorax one recognizes the RF-coil to excite and receive the MR-signal. Outside the scanner room the control unit is placed. In the following all components will be described in detail.
4. Gas storage and filling unit
A pair of coils with a diameter of 0.7 m compensates the stray field of the scanner. The coils have 150 windings each; the distance between the two coils is 0.35 m. In contrast to the Helmholtz-configuration the current in each coil can be regulated separately. The height of the table can be changed, depending of the given height of the scanner. Thus, the administration unit can used at different scanners without changing the construction. For example at the distance of 3 m from the Magnetom Siemens Sonata scanner in the Universitätsmedizin Mainz, where the clinical study was accomplished, the height was 1.01 m, a current of + 0.5 A for the first coil and -0.5 A in the second one was calculated in a simulation and set at the power-supply-unit of the control-unit to compensate the field.
gradient \[8\]. (For this calculation the stray field of the scanner was measured once without compensation and different configurations were then simulated to achieve the best compensation. For each scanner this optimization has to be done separately, as the stray fields vary. In this case the strength of the stray field at the position of the storage cell varied from 3.5 to 4.8 \(10^{-4}\) T without compensation (Fig. 4). Using the compensation coils the field strength is about 3.8 \(10^{-4}\) T at the storage cell position and the field homogeneity over the cell volume is \(3 \cdot 10^{-6}\) T/cm. The spherical HP storage gas cell has a volume of about 1.14 l and is filled up to a pressure of 2.7 bar, (the upper limit is given by the IATA Dangerous Goods Regulations).

Figure 4. Magnetic field strength in the region of the storage cell volume without (left) and with (right) compensation coils.

Inside thus homogenized field the HP storage gas cell and the piston pump, which defines the amount of administered gas, are placed. Moreover, it allows using up the HP gases from the storage cells down to a residual pressure of about 200 mbar. The piston as well as the cylinder head, shown in Fig. 5, is manufactured of titanium to minimize the relaxation of the gas. A buffer volume behind the compression volume is added, which is flushed with N\(_2\) to avoid contact to the oxygen of ambient air. To regulate the pneumatically driven stroke of the piston and thus the amount of gas sucked into the compression volume and administered to the patient, a mechanical end stop is mounted at the piston pump. It is driven by a non-magnetic attraction by the scanner, pneumumatic engine (to avoid magnetic First the physician has to define a bolus volume. At the control unit typical settings can be stored in and loaded from setting files.

Figure 5. Sketch of the piston pump.
In the presented clinical study 0.2 standard litre (stdl) $^3$He were used and 0.3 stdl of $N_2$ were added, except for measurements of the partial oxygen pressure ($pO_2$) in the lung, where 0.2 stdl pure $^3$He were used. The used hp gas polarization for all volunteers was 60-65% (the MR-signal intensity is direct proportional to the hp gas polarization). The volume of administered hp gas was kept constant and independent of this small variation of polarization. Before administration the piston is moved into top position and the pressure in the gas cell is measured. Then the control unit calculates the required piston volume depending on the pressure in the gas cell. In the next step the mechanical end stop is driven into the calculated position. Finally the piston transports the gas to the administration box via a thin tube (to minimize the dead volume). As the gas transfer is quite fast (about 0.3 l/s) shielding is not required. The material of this tube, S-50-HL of the company liquidscan, is Tygon, the inner diameter is 2.4 mm with a length of 3 m.

5. Administration box

The administration box is positioned behind the patient’s head. Fig. 6 shows the sketch of the administration unit, containing spirometers and valves. The patient is wearing a breathing mask with a microbiological filter/HME. This minimizes the humidity and fulfills hygienic obligations. The patient valve is a membrane valve and it is added to strictly separate inhalation from exhalation via the pressure on the two membranes.

![Figure 6. Diagram of the administration box.](image)

The inhalation tract is directly connected to the outlet of the administration box. The patient must not be directly connected to the HP gas or gas admixture arriving from the piston pump on the left side (see Fig. 6). This would force a barotrauma to the patient’s lung because the pressure might considerably exceed the atmospheric pressure. Therefore safety provisions are added inside the administration box. To disconnect the patient from any excess pressure, the gas is filled into a storage volume (breathing bag), from where the patient can inhale the gas at atmospheric pressure. The relaxation times $T_1$ from many breathing bags were measured: Therefore different bags were filled with 0.5 l pure $^3$He each at atmospheric pressure and every minute a FID in a NMR-system of the institute of physics was started. The best results (with $T_1$ about 10 min in this setup) were achieved with the breathing bag of chloroprene manufactured by the company Draeger (http://www.draeger.com/media/10/01/80/10018034/accessories_catalog_compl_9066485_en.pdf).

The administration is controlled via a pneumatic valve which is positioned directly behind the breathing bag. This valve is permanently closed, in particular during filling of the breathing bag. It is only opened for administration of the HP gas. To ensure that there is no accidental high pressure towards the patient’s lung (in case of a failure of the administration...
valve) an additional safety high-pressure valve was added. It is a membrane valve, with the membrane being pressed by a non-magnetic spring. This security valve is positioned directly in front of the outlet of the administration box. It obviates pressures higher than 20 mbar above atmospheric pressure.

When the storage breathing bag is filled and the administration valve is open the patient first inhales the amount of gas stored inside the breathing bag. When the content of the breathing bag is completely inhaled, an additional opening is needed which allows the patient to continue breathing. This is achieved with a membrane valve, too. If the bag is empty the resistance on the patient’s side of the membrane valve is increasing and the patient is then inhaling ambient air through the membrane then. To monitor the amount of inhaled ambient air (flow rate), a spirometer was added. As the air has to flow into the box an opening in the box is needed. A ventilator can be connected there as an option or the ambient air just flows into the box. To measure the total volume of inhalation another spirometer is mounted in this place as well. From the difference between both flow signals the control unit calculates the HP gas-flow rate and thus the administered volume as integral of the flow of HP gas.

For monitoring the expiration air flow a third spirometer is added. To collect the gas for later recovery a collecting bag is used in which the patient exhales. Details about the used collecting bag are given below. In the presented clinical study 25 breathing cycles after administration have been collected. For a complete washout of $^3$He from the lung 20-25 consecutive breathing cycles should be collected. Hence this bag should be rather big (100-200 litres); it also has to be reasonably $^3$He tight. To minimize the volume of the collected gas one can add a three-way-valve in front of the collecting bag and switch it towards ambient air during $^3$He-free phases (as it was realized in the presented study). As the three-way-valve is not essential, it is not included in Fig. 6, to gain a better overview.

![Figure 7. Monitored signals of the spirometers.](image)

### 6. Monitoring and control unit

The control unit itself is placed outside of the scanner room and it is operated via a laptop computer. The currents of the two compensating coils can regulated there (via the two integrated power-supply-units) according to the calculated value (see Sec. 4), as well as the
control of the piston pump and the pneumatic administration valve of the administration unit. The signals of the spirometers are converted and monitored. Fig. 7 shows an example of the monitored signals. The upper curve (white) is showing the complete inspiration, while the lowest curve (green) the expiration. The red line is showing the signal of the flow of ambient air. When the HP gas bolus is administered a delayed increase is observed. This delay is due to the fact that the patient is inhaling the HP gas admixture first until the bag is empty. After that he starts to inhale ambient air, which causes the increase of this flow rate. If one does not want to administer the HP gas admixture at the beginning of the inhalation this shape is shifted to the right. From the difference of both signals, which is shown in yellow, the control unit calculates the flow of the HP gas admixture. In the beginning of the construction the cables of the spirometers have generated MR-noise. After accurate cable screening the whole administration unit does not increase the noise level and thus does not reduce the MR-quality as proved by Fig. 8.

![Figure 8. Noise level.](image)

7. Clinical study
First images of human lungs (healthy volunteers) were taken with this setup in a clinical study. These study was performed in the Department of Radiology at the Johannes-Gutenberg University Mainz using the Scanner "Sonata" Magnetom (Siemens Medical Solution, Erlangen) providing a magnetic field of 1.5 T. As RF-coils a double-tuned elliptical \(^3\)He-\(^{19}\)F TX/RX birdcage resonator (Rapid Biomedical) and a Spoiled Gradient Echo (SGRE) pulse sequence was used.

\(^3\)He-lung-MRI features four typical methods [1, 6, 7, 9-15]: a) morphological imaging at apnoea, which gives the spin density, b) measurement of the partial oxygen pressure (pO2), which makes use of the T1-relaxation of HP \(^3\)He by the paramagnetic oxygen, c) measurement of the apparent diffusion coefficient (ADC), which depicts the fine structure of the lung as this structure restricts diffusion and d) "dynamic ventilation" imaging, which visualize the process of \(^3\)He distribution in lung during in- and exhalation with high temporal resolution (10 fps). From these methods the following parameters are available: from morphological images the ventilation of the lung and the signal-to-noise-ratio (SNR), from b) and c) the parameters pO2 and ADC, from dynamic imaging the parameter "rise-time", which characterize the rate and amount of \(^3\)He delivery in different lung regions (influenced by the inflow of HP gas as well as by its relaxation in the lungs).

The clinical study compares the reproducibility of these MR-parameters of images taken by the administration unit with those taken by a Tedlarbag. To test the reproducibility, images were taken using each method twice, with Tedlarbag and as well as with the
administration unit. This means 16 measurements on each of the 10 healthy male volunteers which were all non-smokers. These data will be analyzed once for each volunteer separately to check the intra-individual reproducibility and once for the whole group of volunteers checking the inter-individual reproducibility. The analysis of this data is in progress.

![Morphologic Images](image.png)

**Figure 9.** Morphologic Images taken by administration unit (left) and Tedlarbag (right).

Fig. 9 shows a morphological image taken by the administration unit in comparison to an image taken by Tedlarbag. The image quality is in a comparable range except that the right image is a bit brighter. The used matrix size was 128x128, the field of View (FOV) 320 mm x 320 mm, the slice thickness 10 mm, the flip angle 18°, the repetition time (TR) 11 ms and the echo time (TE) 4 ms. The SNR was analyzed according to the method described in [16]. The SNR was calculated using the software ImageJ (version 1.43u; National Institutes of Health, Bethesda, MD, USA). The mean signal intensity (SI) was measured in six circular (diameter = 27.5 mm) homogeneous regions of interest (ROIs) within the lung on each MR image (SI\_uncorr). In analogy the noise signal intensity (SI\_noise) was measured in six circular (diameter = 27.5 mm) homogeneous regions of interest (ROIs), too. These ROIs were placed at the corresponding height in the morphological image but outside of the lung. Noise correction was performed using the approach described by Gudbjartsson and Patz [17].

While the highest values of SNR of images taken by Tedlarbag are bigger than those images taken by the administration unit, the SNR-values of the administration unit scatter less, see Fig. 10. The reproducibility still has to be calculated. In all images the signal of ROIs in the right lung of this particular volunteer are higher than of those in the left lung. This effect can be seen in Fig. 9, too, where the signal of the patient’s right lung (left on image) is enhanced. It is a hardware effect caused by the proximity of the coil and the gradient system (which was established by several tests).
Figure 10. SNR of morphologic images taken by administration unit below and Tedlar bag above.

For dynamic imaging the administration unit clearly shows an advantage: The administration unit provides a very homogeneous intake of the gas. It is not yet clear if it is homogeneous in time or homogeneous in space. Looking at a movie taken by the Tedlar bag, on the other hand, one clearly observes the perturbation of signal-time curve during the time when the volunteer finishes with inhaling the $^3$He from Tedlar bag and after short breath hold changes to breathing in of the ambient air. In the movie it seems like a small exhalation. There is some sort of stock in the flow, the signal decreases a little and increases again. This effect can also be recognized in the graph of the MR-signal (Fig. 11). In the images taken by the administration unit one observes a steady rise of the signal during inhalation of HP gas followed by a steady decrease caused by the combined effects of exhalation and relaxation of the HP-gas. The detailed analysis of all MR-parameters and physiologic interpretation is still in progress.

Figure 11. Dynamic Imaging: Intensity of MR-signals in images taken with Administration unit (left) and Tedlar bag (right).
8. Collecting and recovery [3, 4]
In the presented study 25 exhalations after HP gas administration have been collected in a \(^3\text{He}\)-tight bag “Tecobag” manufactured by the company Tesseraux. The maximum capacity is 150 litres. The inner slice is made of Polyethylene, the middle slice is Aluminium, covered with Polyethylene terephthalate. A three-way-valve was used to switch between collecting exhaled air in the Tecobag and exhalation into the ambient air. When the collecting bag is full, its content is compressed into a steel bottle. The respective compressor, MCH6/EM manufactured by the company Aerotecnia Coltri, shown in Fig. 12, was designed for filling diving bottles. The collecting efficiency achieved in this clinical study was 80-83%.

![Gas collecting in the scanner room (left), compressing collected gas into steel bottle (right) (Fig. 12).](image)

After collecting and compressing the exhaled gas, it was transferred into a recovery unit at the institute of physics of the university Mainz. The percentage of He inside the mixture is usually quite low (around 1%), but the removal of all contaminant gases by LN\(_2\) cooled zeolith traps, followed by a cryopump working at 10 K is working very efficiently. Thus the recovery efficiency of this unit is 95% and the gas purity is in the region of ppm [3, 4]. The excellent gas purity has been confirmed by repolarizing it in our polarizer (Fig. 13). The graphic shows almost no difference between polarization curves obtained with fresh gas from the gas supplier and the recovered one. The whole recycling process is included now in our Manufacturing Authorization and allows re-using the recovered gas for clinical studies on humans.

![Recovery unit (left), polarization curve (right). (Fig. 13).](image)
The total efficiency at the presented study was 76-79% as a result of the multiplication of the collecting and the recovery efficiency. The very limited stock and production rate of $^3$He on one side and the growing demand on the other have led to a dramatic shortage and price explosion in recent years making gas recovery mandatory. In this study a total of 32 stdl HP $^3$He have been administered of which about 78 % have been recovered resulting in a loss < 10 stdl. Already modest increase in the total efficiency would cause a big reduction in loss of usable $^3$He. The aim is to increase the efficiency to 85% by optimizing the collection efficiency of the exhaled gas.

9. Summary
The presented administration unit allows fully automated administration of HP gases with high accuracy in volume and time. It shows great advantages for dynamic imaging and allows use of gas admixtures. Further it fulfills the obligations given by the Medical Devices Law and enables efficient and easy gas collecting for later recycling. The administration will now be tested on patients and further research is planned to increase the efficiency of gas collecting.

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