Safety concept, experimental design and quality assurance for parahydrogen in a clinical setting

Jan-Bernd Hövener[1], Robert Borowiak[1], Sebastien Bär[1], Jochen Leupold[1], Jürgen Hennig[1], and Dominik von Elverfeldt[1]
[1]*Medical Physics, Dep. of Radiology, Medical Center, University of Freiburg, Freiburg, BW, Germany*

Motivation

The hyperpolarization of nuclear spins like ^{13}C e.g. by parahydrogen, is a promising approach to access the hidden orders of magnitude of signal in MR imaging and spectroscopy, holding great potential to improve medical diagnostics. The methodology of pH_2 production is known for decades (flow through catalyst at 20 K (1-3)). Its implementation and operation in a clinical setting, though, has not been attempted yet (to our knowledge), but is key if pH_2 - hyperpolarization is to disseminate in biomedical research of life sciences. Here, we present the **safety concept, experimental setup and quality assurance** with the goal to safely supply pH_2 for subsequent experiment in a hospital, facilitating preclinical (*in vitro* and animal) hyperpolarization research.

Methods:

The safety concept addresses the hazards of handling pressurized explosive gases and guides the entire design process: minimal total H_2, no H_2 indoors, minimal working pressure, avoidance of explosive H_2-air mix, avoidance of spark sources. For the construction of **the conversion unit**, as many commercially components as available were used (e.g. Helium compressor, cold finger, radiation shield, vacuum shroud, temperature controller, vacuum pump). Other parts, e.g. the housing for the setup, were constructed by a machine shop. The **quality assurance protocol** shall address (a) safety and (b) pH_2 enrichment, while being suited for a clinical setting.

Results:

A detailed **risk assessment** was developed, including rules for the construction, maintenance and operation of the pH_2 unit (e.g. protection of unauthorized use, operation by instructed personnel only). To comply with the safety concept, the **conversion unit** was divided: all electronics were installed on the inside wall of a maintenance building on the roof of the institute, all pH_2 containing parts on the outside, separated by a wall of approx. 30 cm (Fig. 1). The required footprint is less than 3 m^2. To **quantify the pH_2 enrichment fraction**, MR was chosen as all clinical MR sites with spectroscopy option are suited. The signal intensity, however, is very low, because of (a) the low spin density of H_2 gas at 1 atm (1/22 mol/l, water 110 mol/l), (b) the resonance is ~10^4 times as broad as H_2O, (c) only residual ortho-H_2 gives rise to MR signal (i.e. only 1 vol. % at a realistic pH_2 enrichment level of 99 %). As a result, the oH_2 signal is well below the background signal, requiring its subtraction (Fig 2) before the signal can be quantified. The pH_2 enrichment fraction is determined with respect to a H_2 sample at room temperature (rT-H_2, a mix of 75 % ortho-H_2 and 25 % pH_2): $f_{pH2} = 1 - 0.75*S_{pH2} / S_{rTH2}$.

Conclusion: A pH_2 production unit is presented which, meeting safety regulations, is run safely in a hospital. pH_2 enrichment levels of > 98 % are achieved regularly at a rate of several litters per minute. Typically, a relatively small amount of pH_2 is produced, stored in aluminum cylinders in gas cabinets and applied in hyperpolarization experiments *on demand*. On the road to *in vivo* (and eventually human) application, this is but the first step. Similar concepts are required for the subsequent parts of the hyperpolarization experiment, polarizer and chemistry (e.g. removal of the catalyst).

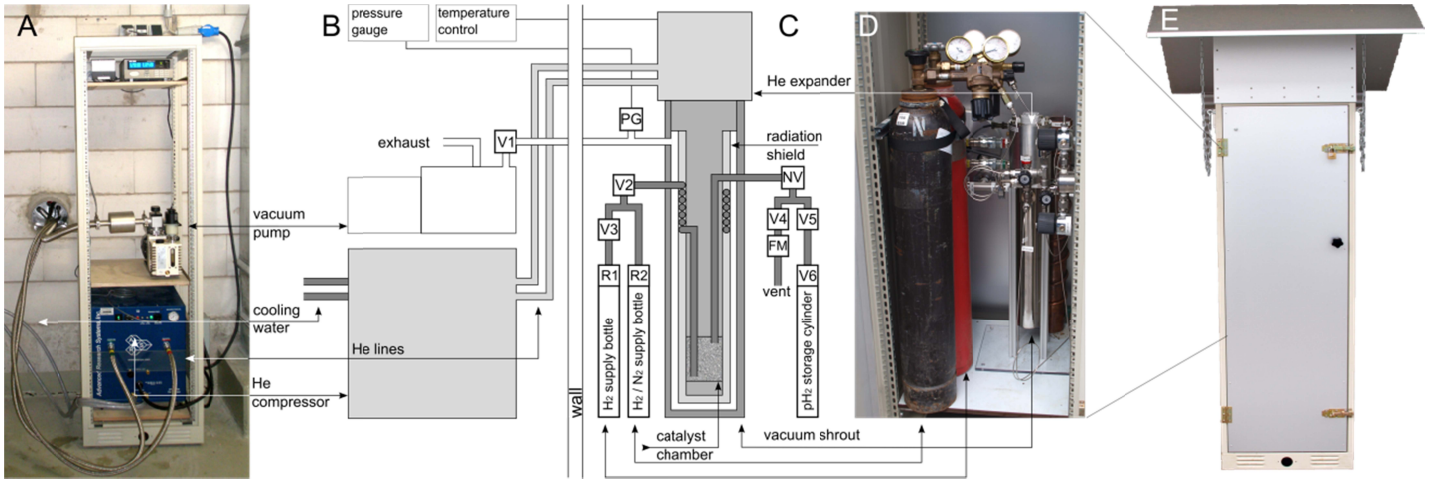

Figure 1: Pictures and schematic view of pH_2 production unit divided in electronics indoors (A, B) and H_2 - containing parts outdoors (C, D, E). Abbreviations: (N)V: (needle) valve, PG: pressure gauge, R: pressure regulator, FM: flow meter.

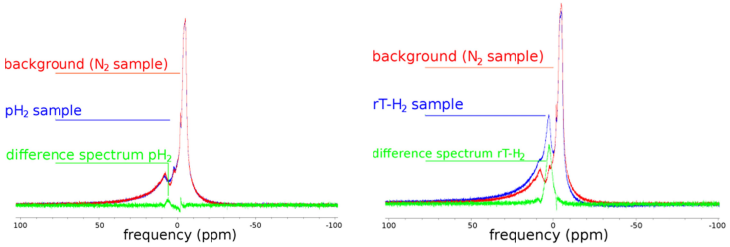

Figure 2: Quantification of pH_2 enrichment fraction: ^{1}H-MR spectra of glass-vials filled with air (red, background), pH_2 (blue, left) and room temperature H_2 (blue, right). By subtraction of the background (red), the signal of both samples is isolated (green, S_{pH2}, S_{rTH2}), allowing the quantification of the pH_2 enrichment: $f_{pH2} = 1 - 0.75*S_{pH2} / S_{rTH2} = 98$ % (pulse-acquire sequence, NA = 32, TR = 500 ms, B_0 = 7 T).

(1) S Tam, ME Fajardo. Review of Scientific Instruments 1999;70(4):1926-1932. (2) M Born, W Heisenberg. Annalen Der Physik 1924;74(9):1-31.
(3) KF Bonhoeffer, P Harteck. Naturwissenschaften 1929;17:182-182.