# Device to minimise cannula dead volume for the injection of hyperpolarised substrate

Steven Reynolds[1], Joanne Bluff[2], Samira Kazan[2], Michael Port[3], Emily Wholey[2], Gillian Tozer[2], and Martyn Paley[1]
[1]*Academic Unit of Radiology, University of Sheffield, Sheffield, South Yorkshire, United Kingdom,* [2]*Tumour microcirculation group, University of Sheffield, Sheffield, United Kingdom,* [3]*Department of Psychology, University of Sheffield, Sheffield, United Kingdom*

## Introduction

Recent use of hyperpolarised substrates has increased the accessibility of biological metabolic pathways to *in vivo* investigations, via MRS of nuclei other that protons . However, two issues arise for the injection of hyperpolarised substrate. Firstly, due to dose/volume limitations required for animal well-being, only restricted quantities of hyperpolarised substrate maybe injected. Secondly, physical constraints of placing an animal into an MRI scanner can require a long length of cannula for delivery of substrate into the animal, resulting in a significant dead volume. Typically, saline occupies the dead volume of the cannula, which does not contribute to the hyperpolarised signal but may contribute around 30% of the volume injected. To allow for a reduced effective dose due to the dead volume, the concentration of the substrate has to be increased. To reduce the issue of dead volume, we have developed an automated flow diverter, which permits the dead volume to be cleared to waste before the desired substrate is injected.

## Flow diverter system design

In order to create a flow diverter system, a cannula line must be able to split the liquid flow into two pathways. One pathway is for drug administration into the animal, whilst the other is used as a waste-stream for clearing the dead space volume. This was achieved, without introducing further dead volume, by gluing two cannula lines into a single Luer syringe hub, fed from a common source. One of the two cannula lines is inserted into the animal and the other is connected to a waste vessel. Both cannula lines were routed through separate pneumatic pinch valves, as shown in figure 1. Flow was then controlled by opening one of the pinch valves, whilst closing the other, using a custom made computer-controlled pneumatic system.

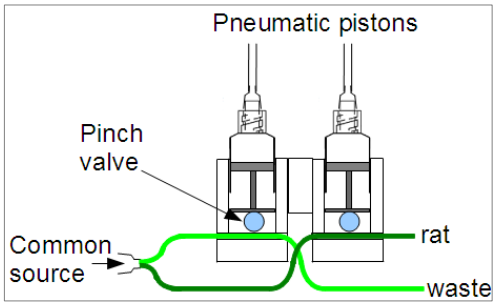


Figure 1: Schematic of double pinch valve to control fluid flow direction.

## Hyperpolarised Pyruvate experiment

A Hooded Lister rat (weight=280g) was anaesthetised using isofluorane and a femoral vein and tail vein cannulated. Isofluorane was withdrawn and general anaesthesia maintained by continuous infusion of propofol via the tail vein cannula. A dose of 1.40ml (~150mM) of hyperpolarised $^{13}$C-pyruvate (PA) (measured delivered volume, 1.36ml) was administered over 13s, via the cannulated femoral vein, using an automated injection system (2), which also controlled the diverter. The diverter was programmed to initially direct 0.6ml of fluid into a waste syringe and then direct 1.40ml into the animal. This resulted in ~0.1ml of PA being directed to waste, thus ensuring all of the saline had been displaced. Localisation was performed using a 20mm $^{13}$C/$^{1}$H surface coil positioned over the head, with 8mm slice selection in a coronal plane containing the brain. $^{13}$C spectroscopic data was acquired using a Gaussian pulse (20deg flip angle, TR=1s) in a Bruker 7T MRI system. Spectroscopic data containing the PA signal, and its metabolite lactate (LA), were processed in Matlab using customised software.

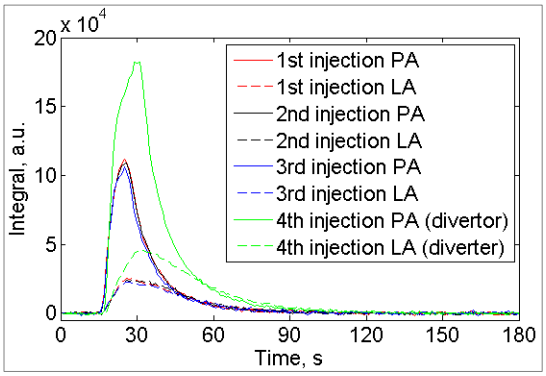


Figure 2: $^{13}$C spectroscopic data for 4 $^{13}$C-PA injections from the brain region. Fourth injections with diverter flow control.

## Results

Four automated injections were performed sequentially. The first three injections did not use the diverter and consequently ~0.5ml of the 1.36ml PA injected remained in the cannula. The PA that remained in the cannula was flushed with saline ~10 minutes post injection. On the fourth injection the diverter was used so that the saline present in the cannula was directed into waste prior to injection of PA into the rat. Figure 2 shows the time course $^{13}$C signal measured from the brain region for all four injections. It can be seen that on the fourth injection there was a large increase in observed signal as a consequence of using the diverter. Mean maximum PA signal (a.u.) for the first three injections was $1.1\times10^5$, which increased to $1.8\times10^5$ with the diverter. Using the diverter this represents a percentage increase in PA signal of 64%, which was close to the increase in injected volume of ~60%. For LA the mean maximum signal for the first three injections was $2.3\times10^4$, compared to $4.6\times10^4$ with the diverter, a 100% increase. Given that PA was administered over a longer time scale, this allowed the PA to LA conversion to develop over a longer time scale. The longer time scale allows the $^{13}$C lactate pool to build to a higher concentration, producing more signal before $T_1$ relaxation dominates. The diverter system provides a simple method for minimising the dead volume for administering substrate to animals whilst in a MR scanner.

## References

1. Golman K, in 't Zandt R, Thaning M. Proc Natl Acad Sci U S A 2006;103(30):11270-11275.
2. Reynolds S, Kazan S, Williams L, Kennerley, A, Berwick J, Tozer G, Paley M, Proc. ISMRM 2011, 3526