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The Kety-Schmidt Technique for Quantitative Perfusion and Oxygen Metabolism Measurements in the MR Environment

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Abstract

The Kety-Schmidt technique provides quantitative measurement of whole brain cerebral blood flow (CBF). CBF is measured as the area between the arterial and venous washout curves of a diffusible tracer. Oxygen extraction and metabolism may be calculated from arterial and venous samples. In this report we present a method for performing these measurements in an MR environment. This technique could be useful for validation of MR methods of hemodynamic and metabolic measurements in humans.

Introduction

Accurate, quantitative and non-invasive measurements have great potential for advancing the studies of human cerebral hemodynamics in health and disease and clinical patient care. Magnetic Resonance (MR) methods for measuring cerebral blood flow (CBF) have yielded results in animals and human that are consistent with positron emission tomography (PET)[1,2]. However, direct quantitative validation of MR CBF measurements with the gold standard is yet lacking.

The seminal studies of CBF and oxygen metabolism performed by Seymour Kety and Carl Schmidt [3] and their tracer kinetic methods were the basis for validating PET measurements of CBF using O-15 labeled water. The method entails placement of jugular venous and arterial catheters. During either wash-in our washout from equilibrium of a freely-diffusible tracer (generally nitrous oxide), the arterial and venous content of tracer are plotted over time. The area between the arterial and venous curves provides the quantitative measurement of CBF. In addition, the arterial-venous difference in oxygen content may also be measured. This parameter can be used to calculate oxygen extraction fraction (OEF) and the metabolic rate for oxygen consumption ($CMRO_2$) .

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The purpose of this technical note is to describe a system for the quantitative Kety-Schmidt measurement of CBF in a high-field MR environment that could be applied to human or animal studies.

Technique

ANIMAL PREPARATION

This study used two male cynomolgus macaques, *Macaca fascicularis*, and one female baboon, *Papio anubis*. The baboon was ultimately preferred for its larger size which facilitated percutaneous placement of lines.

VASCULAR INTERVENTIONS

After fasting 12 hours, including 2 hours without water, and receiving atropine 50 μg/kg IM, the animal was brought to an interventional suite and given ketamine, 10 - 15 mg/kg IM. A soft-cuff endotracheal tube was placed and general anesthesia obtained with isoflurane vaporized into medical grade oxygen (Airgas Puritan Medical, St. Louis, MO) using an MR-compatible ventilator (Surgivet, Waukesha, WI). Anesthesia delivery, blood pressure, pCO_2, and oxygen saturation were monitored continuously (Surgivet). Following anesthesia induction, 22-gauge angio-catheters (Terumo Medical, Elkton, MD) were percutaneously placed in the femoral artery and contralateral femoral vein. Both angio-catheters were exchanged for 4-Fr catheters (Cook Medical, Bloomington, IN). The venous catheter typically required a J-wire to advance through the femoral sheath to the jugular bulb. Placement was verified under fluoroscopy (Optiray ioversol 68% , Mallinckrodt, St. Louis, MO). Unfractionated heparin was administered to 20-40 USP units/kg (Abbott Laboratories, Chicago, IL).

The animal was subsequently transported to the MR imaging suit. The animal rested quietly for a minimum of fifteen minutes to attain physiologically steady conditions. At least three hours separated ketamine administration from hemodynamic measurements to minimize drug effects on CBF. Line placement was confirmed with MP-RAGE or MRA. To initiate Kety-Schmidt measurements, the animal was ventilated with 25—45% N_2O, 21% O_2 and 1-2.5% isoflurane, balanced with room air. Sequential arterial and venous samples were collected in one-milliliter syringes (Becton Dickinson, Franklin Lakes, NJ) for a minimum of 20 minutes. Syringes were disconnected, held orifice-down, sealed with plastic Monoject tip caps (Tyco Healthcare Group, Manfield, MA) and placed on ice. Primary standard nitrous oxide tracer was delivered via MR-compatible cylinders (Airgas Puritan Medical). Syringes were attached to Luer-Lok valves (Medex, Monsay, NY) and approximately 0.5 mL of blood was extracted at 30, 60 or 120 second intervals. The time of extraction was annotated with MR-compatible microphones and digital audio capture (High Criteria, Richmond Hill, ON) to a laptop computer. The dead-space for the arterial catheter and valve was 0.2 mL; for the venous catheter: 1.0 mL; for blood-collection syringes: 0.03 mL.

At the conclusion of procedures, all catheters were removed and hemostasis obtained by vascular compression. The animal was allowed to recover from anesthesia while continuing monitoring. All animal procedures were reviewed by the institutional review board and animal studies committees of Washington University School of Medicine.

NITROUS OXIDE ANALYSIS

Sampling syringes were analyzed for nitrous oxide content. Each syringe was removed from ice, shaken to settle blood products, and the blood volume was measured to 0.01 mL accuracy. The syringe was held orifice-down, the tip cap was removed, an 18-gauge needle (Becton-Dickenson, Franklin Lakes, NJ) was attached and the needle was inserted into a 10

mL Vacutainer tube pre-filled with desiccated sodium heparin. The blood sample was injected; the syringe was rinsed with unfractionated heparin; the rinse was also injected into the Vacutainer. After mechanical mixing (VWR International, West Chester, PA), the Vacutainer was returned to ice.

The nitrous oxide analysis apparatus is sketched in Fig. 1. The circuit comprised Tygon tubing (Saint Gobain, Courbevoie, France), Luer-Lok valves and mechanical components as drawn in Fig. 1. The quantity of nitrous oxide gas present in each Vacutainer tube was measured with a non-dispersive infrared (NDIR) nitrous oxide analyzer (Liston Scientific and Teledyne Analytical Instruments, Irvine, CA). Our analyzer unit was equipped with: re-circulation pump, water adsorbing percolation filter, particulate filter, dual pressure regulators set to prevent exceeding the device tolerance of 206 mm Hg and emergency valve releases. Zero deflection of the NDIR unit was calibrated with ultra-high purity compressed nitrogen (Airgas Puritan Medical). A dual-stage fitting regulator was used to introduce the "zero gas" to the analysis circuit. Full deflection of the NDIR unit was calibrated with a primary standard mixture comprising 400 ppm (0.04 ± 0.0004%) nitrous oxide balanced with ultra-high purity nitrogen (Airgas Puritan Medical). A single-stage fitting regulator was used to connect the "span gas". The NDIR unit and the sampling circuit were calibrated with zero and span gases at regular intervals during processing to ensure acceptable instrument drift. Leakage and stability of the sampling circuit was also periodically tested with 400 ppm nitrous oxide in the presence of actively pumped recirculation.

KETY SCHMIDT CALCULATIONS

The presence of H_2O or CO_2 confounds measurements of N_2O in the gas analyzer; only H_2O was scrubbed. The analyzer's sample chamber was specified to hold 77 mL of sample gas. By dilution of a known volume of primary standard 400 ppm nitrous oxide, the total volume of the apparatus was determined to be 333 mL. The quantity of *in vivo* nitrous oxide was determined by back calculated serial dilutions and dead-space contributions. An example of measurement of nitrous oxide is shown in Fig. 2.

Dead-space was modeled using conservation of volumes and mass. The nitrous oxide concentration *in vivo*, c_m, for the mth sampling of volume Vm was expressed as:

$$\begin{aligned} c_1 &= N_{s,1} / \quad V_1 \\ c_m &= N_{s,m} + g_m \, g_{m-1} \, V_d \, c_{m-1} / \left(V_m + g_m \, V_d \right), m > 2 \\ g_m &= \mathrm{mod} \left(V_m, V_d \right) / V_d \end{aligned}$$

The measured quantity of nitrous oxide in the mth sample is N_m. The dead-space is V_d. The modulus is denoted by mod.

The cerebral up-take of N_2O at time t, $q(t)$, is proportional to both CBF and the gradient of N_2O concentrations between arteries, C_A, and veins, C_V: The change in time of the quantity of nitrous oxide in an organ, $q(t)$, is proportional to the arterial flow, F, the gradient of nitrous oxide concentrations between feeding arteries, $C_A(t)$, and draining veins, $C_V(t)$, as described by the Fick equation [4]. Integration over the experiment time yields the flow:

$$F = \frac{q\left(T\right)}{\int_0^T \left[C_A\left(t\right) - C_V\left(t\right) \right] dt}$$

The up-take of nitrous oxide, $q(T)$, is not directly measurable, but can be estimated from the steady-state nitrous oxide concentration in venous output weighted with a blood-brain

partition coefficient, empirically determined to be 1.0 in primates, and a blood-gas partition coefficient [5].

Discussion

There are several technical aspects of this technique related to arterial and venous sampling that may impact both the accuracy of the results and the success of the procedure. The tip of the venous catheter should be near the jugular foramen and not selectively into an external vein. If venous blood is contaminated from facial or other external veins, the measured nitrous content will not reflect the cerebral washout only. This effect is minimal, given the relatively small contribution of external venous drainage compared to the cerebral circulation. Samples can be also be confounded by significant dead-space effects. On the arterial side, repeated access to the common femoral artery in small animals may be challenging. Cut-down procedures can impede future vascular access.

While our study demonstrates feasibility of this technique in an MR environment, several limitations should be noted. First, the method only provides global, not regional data. In order to use this for validation purposes, it would be useful to make multiple measurements with different global CBF values. This could be accomplished by changing CBF through changes in pCO_2. These changes in CBF would lead to changes in OEF as well. Oxygen metabolism can be changed pharmacologically. Second, the technique requires 15 to 20 minutes per measurement, allowing for achieving steady state equilibrium of the tracer and subsequent wash out. For simultaneous measurements using Kety-Schmidt and MR acquisition, care would be required to maintain all the physiologic variables during the time of acquisition.

This preparation will also provide measurements of global oxygen extraction and oxygen consumption. This requires measurement of arterial (CaO_2) and venous oxygen content (CvO_2). Once these values are known, the arterial-venous difference for oxygen content ($AVDO_2$) is calculated by subtraction (CaO_2 - CvO_2). OEF is equal to the $AVDO_2$ divided by the CaO_2. $CMRO_2$, the metabolic rate of oxygen consumption, is equal to CBF (the delivery of oxygen) times the OEF (the fraction of oxygen removed) times CaO_2 (the amount of oxygen in the arterial blood).

In summary, we present a simple method for adapting the Kety-Schmidt technique for quantitative CBF measurement in an MR environment. This system may also be used for the measurement of arterial-venous oxygen difference, which in turn may be used to calculate whole-brain oxygen extraction and metabolic rate of oxygen consumption. This technique may have value in validation of MR methods of measurement of CBF, oxygen extraction, and the metabolic rate of oxygen consumption in humans or other animals.

Abbreviations Key

CBF	cerebral blood flow
MR	magnetic resonance
DSC	dynamic susceptibility contrast
ASL	arterial spin labeling
PET	positron emission tomography
IM	intramuscular

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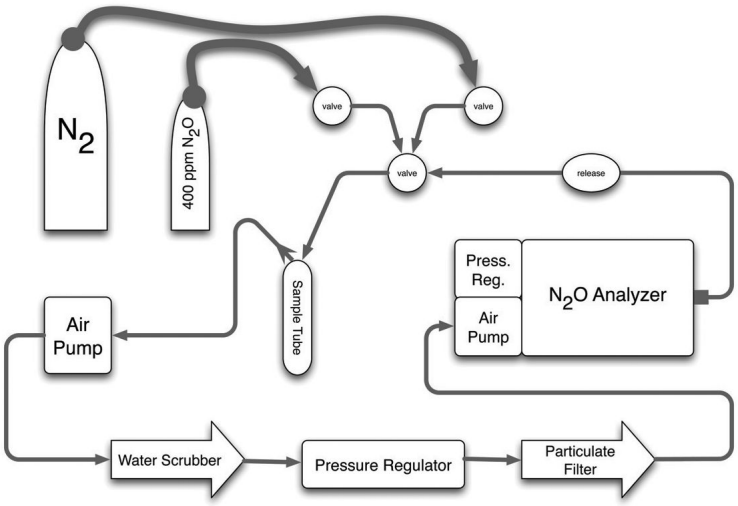

Figure 1.

Nitrous oxide concentration for each timed blood sample is measured with an IR gas-analyzer and sampling apparatus. Arrowheads indicate flow of gases. Valves introduce zero (N_2) and span (N_2O) gases.

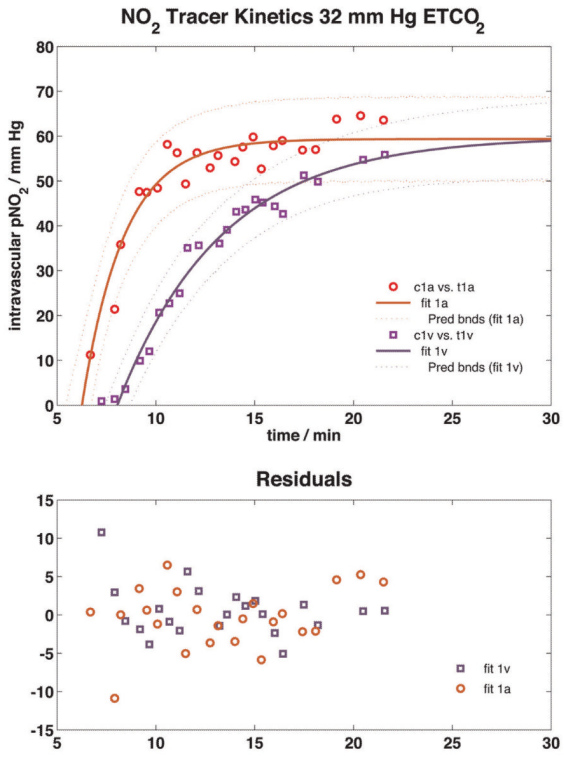

Figure 2.

Nitrous oxide wash-in with arterial and venous catheters, respectively. Dead-space corrections apply. Fitting of the Kety-Schmidt model, $p_aN_2O = 13.5 + 46\ (1 - \exp(-0.47\ (t - 6.81))$ and $p_vN_2O = 7.55 + 52\ (1 - \exp(-0.19(t - 8.76))$, is shown with 95% confidence intervals and residuals. The calculated global CBF is 52.5 mL/min/100 g.