Mechanical Ventilator for Delivery of $^{17}O_2$ in Brief Pulses

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Abstract: The ^{17}O nucleus has been used recently by several groups for magnetic resonance (MR) imaging of cerebral metabolism. Inhalational delivery of $^{17}O_2$ in very brief pulses could, in theory, have significant advantages for determination of the cerebral metabolic rate for oxygen ($CMRO_2$) with MR imaging. Mechanical ventilators, however, are not typically capable of creating step changes in gas concentration at the airway. We designed a ventilator for large animal and human studies that provides mechanical ventilation to a subject inside an MR scanner through 25 feet of small-bore connecting tubing, and tested its capabilities using helium as a surrogate for $^{17}O_2$. After switching the source gas from oxygen to helium, the 0-90% response time for helium concentration changes at the airway was 2.4 seconds. The capability for creating rapid step changes in gas concentration at the airway in large animal and human studies should facilitate the experimental testing of the delivery $^{17}O_2$ in brief pulses, and its potential use in imaging $CMRO_2$.

INTRODUCTION

^{17}O is a stable isotope of oxygen that has been used in several recent studies for magnetic resonance imaging (MRI) of the cerebral metabolic rate of oxygen utilization ($CMRO_2$) [1-8]. Prior studies have delivered gaseous $^{17}O_2$ by inhalation for a period ranging from 2 minutes [9] to 40 minutes [5]. Delivery of $^{17}O_2$ in very brief (less than 2 minutes) pulses could, in theory, provide significant advantages for imaging of $CMRO_2$, but mechanical ventilators for large animals and humans are not typically designed to provide rapid step changes in gas concentration at the airway. Modern, servo-controlled, open-circuit ventilators that are commonly used in the intensive care unit can provide a change in inspired gas concentration with a time constant of a few seconds [10, 11]. The use of an open-circuit ventilator, however, would lead to tremendous waste of $^{17}O_2$ gas, currently priced at approximately $2000/liter for a 40% enrichment fraction. Closed-circuit and low flow, semi-closed systems for mechanical ventilation are designed to conserve administered gases such as inhaled anesthetics. These systems, however, have time constants for changes in gas concentrations at the airway that are on the order of a few minutes [12]. We designed and tested a mechanical ventilator specifically developed to produce rapid gas concentration changes at the airway through long runs of tubing between the ventilator mechanical parts outside an MRI scanner and a subject inside the scanner.

Rationale for Delivery of $^{17}O_2$ in Brief Pulses

^{17}O incorporated into water, $H_2{}^{17}O$, produces an MR signal, but gaseous $^{17}O_2$ does not [2]. MR imaging with ^{17}O therefore provides a way to image metabolically produced water, $H_2{}^{17}O$, without any need to account for concurrent changes in $^{17}O_2$. Ideally, $CMRO_2$ could be calculated from a local signal that is a simple function of the water produced locally in the mitochondria. Some of this metabolically produced $H_2{}^{17}O$, however, leaves the region of interest (ROI) by diffusing to the venous circulation. Additionally, water produced outside the ROI also diffuses to its venous circulation, and re-circulates into the ROI in the arterial blood. The changes in $H_2{}^{17}O$ in the ROI, therefore, are related not only to $CMRO_2$, but also to cerebral blood flow (CBF), and to the arterial input function for $H_2{}^{17}O$ [2]. Zhu *et al.* [2] have presented a comprehensive model of the relationship between local concentration of $H_2{}^{17}O$ and $CMRO_2$, based on the mass balance principles first developed by Key and Schmidt [13]:

$$\frac{dC_b(t)}{dt} = 2\alpha f_1 CMRO_2 + CBF f_2[C_a(t) - C_v(t)] \quad \ldots \quad (1)$$

where $C_b(t)$ is the local concentration of $H_2{}^{17}O$ in excess of natural abundance, α is the ^{17}O enrichment fraction of the inhaled $^{17}O_2$ gas (treated as a constant for long administration times), CBF is cerebral blood flow, $C_a(t)$ and $C_v(t)$ are the concentrations of $H_2{}^{17}O$ in excess of natural abundance for arterial and venous blood, and f_1 and f_2 are unit conversion factors.

Delivery of a very brief pulse of $^{17}O_2$ could potentially simplify the relationship between locally measured $H_2{}^{17}O$ and $CMRO_2$. Immediately after a breath of $^{17}O_2$, the water that is produced outside the ROI should be delayed in its entry into the ROI, as it must diffuse to the local venous circulation and transit through the heart and lungs before entering the arterial circulation. The venous-arterial convection delay for an adult human is typically on the order of 10-15 seconds [14]. For a brief period immediately after beginning inhalation of $^{17}O_2$, therefore, the arterial input

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function of $H_2{}^{17}O$ should be zero, which would eliminate the Ca(t) term in equation (1). In contrast, the local production of $H_2{}^{17}O$ should commence almost immediately, as the expected diffusion lag for $^{17}O_2$ can be estimated to be less than one second. This diffusion time lag is characterized by the time constant δ^2/D, the average diffusing distance squared divided by the diffusivity of oxygen in tissue [15]. For an average capillary spacing in brain of 50 microns [16], each capillary can be estimated to supply a cylinder of radius 25 microns. The spatially averaged diffusing distance, assuming uniform distribution of mitochondria around the capillary, is then estimated at 17 microns. For a simple one-dimensional diffusion model into a finite slab, solution to the transient diffusion equation [15] with an oxygen diffusivity in tissue of 2.4 x 10^{-5} cm^2/sec [17] estimates that the average 0-90% rise time in mitochondrial concentration after a step change in arterial concentration would be approximately 130 msec. This diffusion delay in mitochondrial $^{17}O_2$ utilization can therefore be neglected for all but the shortest arterial pulses.

Additionally, because water movement through lipid bilayers tends to be restricted [18], locally produced water may be delayed in its egress to the venous circulation as it passes through the mitochondrial, the plasma, and the capillary endothelial membranes [2]. A diffusional delay in non-cerebral tissues would further extend the period of a negligible arterial input function. Additionally, substantially restricted diffusion of water from mitochondria to the venous circulation within the ROI would minimize the $C_v(t)$ term in equation (1). For a brief period after initiating a pulse of $^{17}O_2$ delivery, then, the relationship between $H_2{}^{17}O$ concentration and $CMRO_2$ should approximately obey the simplified relationship:

$$CMRO_2 = \frac{k_1}{C_a{}^{17}O_2(t)} \frac{dC_b(t)}{dt} \quad \ldots \quad (2)$$

where k_1 is a conversion constant, and $C_a{}^{17}O_2(t)$ is the time-dependent arterial $^{17}O_2$ concentration. The constant α of equation (1) has been replaced in equation (2) by $C_a{}^{17}O_2(t)$ because the kinetics of alveolar gas dilution cannot be neglected for brief pulses of $^{17}O_2$ (appendix).

Prior studies in small animals have used a simplified equation, similar to equation (2) with no arterial input and no venous washout terms, to successfully estimate $CMRO_2$ after inhaling $^{17}O_2$ [8, 19-21]. For large animals and humans, however, the length of this brief period of negligible arterial $H_2{}^{17}O$ input function, the quantitative importance of restricted water diffusion, and the time window in which equation (2) represents a useful approximation, remain to be determined. Experimental testing of these theoretical advantages would be greatly facilitated by a ventilator capable of delivering sharp step changes in gas concentration at the airway.

Design Criteria for the New Mechanical Ventilator

The main design consideration for the ventilator was the goal to produce sharp step changes in gas concentration at the airway. This dictated avoidance of any sudden transitions in diameter of the gas flow pathway (such as conventional one-way valves), which could slur a sharp gas concentration front. This also dictated that the inspiratory limb tubing be of the smallest diameter feasible, reducing transit time from the gas source to the airway and minimizing diffusive mixing between sharp concentration boundaries.

Some design constraints were imposed by the goal ultimately to apply this ventilator to functional imaging studies, where it is desirable to avoid stimulatory cues. For this reason, use of gas switching valves near the subject in the scanner was restricted, which in turn means that the gas switching valves and all mechanical devices would ideally be outside of the scanner. This in turn required atypically long tubing runs, placing an even greater premium on narrow-bore tubing.

Some design constraints were imposed by the expense of $^{17}O_2$ gas. Delivery of the gas in very brief pulses has a natural advantage of minimal gas use per $CMRO_2$ measurement. In addition, however, it is desirable to recover as much of the unused gas in the exhaled breaths as possible, making it advantageous to have a gas selection valve to direct the exhaled gas to recovery versus waste, with precisely controlled timing to select segments of exhaled gas with the highest $^{17}O_2$ concentrations. Maximal recovery of exhaled $^{17}O_2$ also dictates that the diameter of the exhalation tubing should be small, again to avoid diffusive slurring of concentration fronts. Additionally, from a financial perspective, it was considered desirable for the ventilator to be capable of pressurizing $^{17}O_2$ mixtures from un-pressurized sample bags rather than pressurized gas cylinders, thereby avoiding costly mistakes in gas handling that might occur in the early developmental stages.

Finally, in the interests of versatility, it was decided that the ventilator should be capable of either comfortable, supported spontaneous ventilation in awake subjects; or controlled mechanical ventilation in anesthetized subjects.

MATERIALS AND METHODS

The system for mechanical ventilation appears schematically in Fig. (**1**). Gases are pumped to and from the subject by two large peristaltic pumps (Cole-Parmer®, Chicago IL; Masterflex® I/P digital drive with dual standard pump heads and silicone I/P 73 tubing), one for assisting or controlling inhalation ("PPi" in Fig. **1**), and one for assisting or controlling exhalation ("PPe"). The pumps outside of the MRI scanner are connected to the subject inside the scanner by 25 feet of 0.25 inch ID Tygon® tubing (Cole-Parmer® L/S 17). At the maximum flow provided by the pumps of 16 L/min, the Reynolds number for pure oxygen is 3800, i.e. the flow is in the turbulent range at the maximal volumetric flow rate. At this maximal flow rate, the transit time for 25 feet of the 0.25 inch ID tubing is 0.90 seconds. The pressure drop across the transit tubing for maximal flow is 12 cm H_2O, which is over 100 fold less than the maximal operating range of the peristaltic pump. Pressure at the subject's airway ("Paw") is transmitted by 0.125 inch ID nylon tubing to a pressure transducer (Freescale Semiconductor, Chandler, AZ, MPX2010DP) with signal amplification by a custom op-amp circuit. Information on airway pressure is transmitted *via* a multifunction DAQ device (National Instruments™, Austin TX, USB-6008) to a computer that uses feedback control to adjust the pump speeds for both pumps during assisted spontaneous ventilation and for the exhalation pump during volume-controlled mechanical ventilation. Inhaled

gases can be chosen *via* a computer controlled stream select valve ("inh") (VICI® Valco Instruments, Houston, TX, Model C45) to select air, regular 100% O_2, oxygen with enriched $^{17}O_2$, or other test gases. The oxygen and test gases are sealed in Tedlar® gas sampling bags (Cole-Parmer®). Exhaled air can be directed, *via* a second stream select valve ("exh"), to either waste ("W"), or to recovery of the partially enriched $^{17}O_2$. All data acquisition and control software was written in Labview 7.1 (National Instruments™, Austin TX).

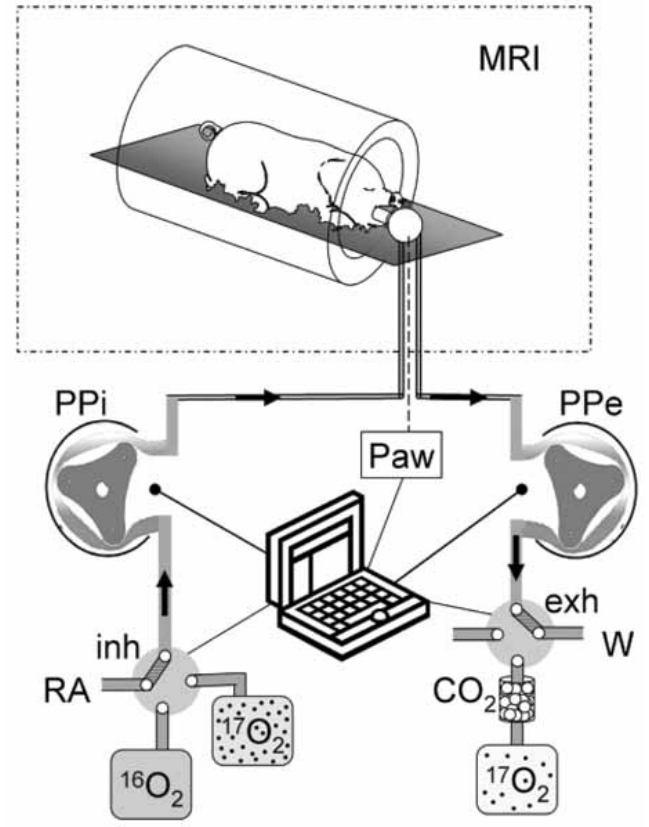

Fig. (1). Schematic diagram of the system for mechanical ventilation.

The long tubing connections between the mechanical components and the subject required a significant departure from prior approaches to mechanical ventilation. Although a wide variety of ventilator modes are available from conventional ventilators, exhalation is almost universally passive, i.e. the exhalation pressure at the ventilator is set to a prescribed value and the lungs exhale passively against that exhalation pressure. Ventilator exhalation tubing is usually sized in a large enough diameter to make expiratory flow resistance negligible, thus keeping the pressure at the airway equivalent to the set exhalation pressure in the ventilator. For the system constructed here, large bore exhalation tubing would greatly increase the circuit priming volume, and would also tend to slur any sharp concentration fronts in the exhalation limb, making clean recovery of partially enriched $^{17}O_2$ more difficult. Passive exhalation, therefore, leads to design requirements for the exhalation tubing that are fundamentally at odds with the desire for efficient use and recovery of the expensive $^{17}O_2$ gas. The system depicted in Fig. (**1**) approaches these problems by actively assisting exhalation as well as inhalation. Pressure at the airway is monitored and fed back to the control system, which then adjusts the exhalation pump speed. The target exhalation pressure at the airway can then be specified at any given level, and for the subject it feels as though he or she is exhaling passively at that pressure, even though the pressure required at the end of the exhalation tubing varies markedly according to the expiratory flow rate.

At the inspiratory side, mechanical ventilators typically have either a gas bellows, or a piston and cylinder, both of which can slur rapid step changes in gas concentration [22], and both of which increase the circuit priming volume. We used an additional roller pump here which eliminates the reservoir volume and also avoids any large sudden changes in tubing diameter, helping to preserve step changes in gas concentration.

Control of the pumps was implemented with a sequential state machine, with a single inspiration state and a single expiration state for each breath. Within each state, the opposing pump was stopped and the appropriate pump for the state (for example the inhalation pump for the inspiration state) was controlled according to the airway pressure with simple proportional control. For transitioning between states, awake subjects were instructed to initiate inspiration by transiently (5 msec) reducing airway pressure below a critical value (-33 cm water) and then to inhale as normally as possible. Transition to the expiration state was signaled by a transient (5 msec) increase of airway pressure above a critical value (33 cm water). For safety, the awake subjects manually held a breathing mask to their faces for a tight seal and were instructed to remove the mask if breathing became uncomfortable.

For use in large anesthetized animals, we also implemented a much simpler algorithm for volume controlled ventilation. Transitions between the states were strictly determined by the inspiratory and expiratory times, as determined by the desired respiratory rate and inspiratory/expiratory ratio. For example, a respiratory rate of 10 breaths/min and an I:E ratio of 1:2 entered by the user would translate to an inspiratory time of 2 seconds and an expiratory time of 4 seconds. Inhalation pump speed was accelerated to a constant value, determined by the desired tidal volume, that was maintained throughout the inspiratory time. Exhalation pump speed during the expiratory state was again controlled according to airway pressure.

With Institutional Review Board approval, the system for mechanical ventilation was tested in a sitting human volunteer in spontaneous ventilation mode, with use of helium as a surrogate for $^{17}O_2$, and with monitoring of gas concentrations at the airway with a micropore membrane inlet respiratory mass spectrometer [23]. The time response of the mass spectrometer was determined by placing the sample port in a stream of flowing gas, directly downstream of a switching valve (Valco Instruments Model C45), and switching the gas source from 0% to 100% helium. The subject breathed through the circuit in assisted spontaneous ventilation mode, where both inspiratory and expiratory pump flows were controlled by the pressures generated at the airway by the subject. After switching to 100% O_2 and de-nitrogenation, the inhalation valve was switched to a source gas of 100% helium and the change in gas concentration at

the airway was recorded by the mass spectrometer. After two inhaled breaths of helium, the source valve was switched back to 100% oxygen. Exhaled gas was directed, by the exhalation valve, to the 'recovered $^{17}O_2$' gas sampling bag for these two breaths of helium and for the following breath. Helium concentration in the 'recovered $^{17}O_2$' bag was then measured with the respiratory mass spectrometer.

RESULTS

Acceleration to full speed from a full stop for the pumps of Fig. (**1**) was well described by a mono-exponential time constant of 0.88 sec. Similarly, deceleration was well described by mono-exponential decay with a time constant of 1.46 seconds. The inhalation and exhalation pump flow changes in response to changes in airway pressure were adequate to provide subjectively comfortable spontaneous breathing in the normal human subject.

The 0-90% response time of the respiratory mass spectrometer was 2.2 seconds (Fig. **2**). The step change in gas concentration at the airway provided by the ventilator circuit was fast enough to approach the temporal resolution of the mass spectrometer, with a measured 0-90% response time of 4.0 seconds (Fig. **2**). After correction for the mass spectrometer time response by de-convolution, the estimated 0-90% response time at the airway was 2.4 seconds.

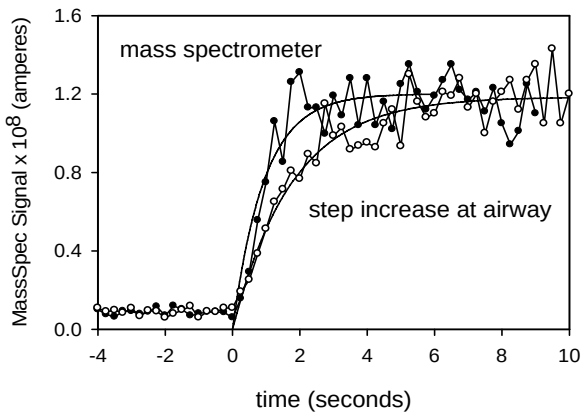

Fig. (2). Time responses after a step change in gas concentration for the mass spectrometer (solid circles); and the complete ventilator circuit (open circles).

The time course of helium concentration changes at the airway during two breaths of helium are shown in Fig. (**3**), with labeling of the phases of the respiratory cycle. The measured end-tidal helium concentration after a single deep breath was 41%.

After further practice by the subject breathing as deeply as possible with the ventilator system, the end-tidal helium after a single deep breath was 48%. For the idealized scenario of a perfect step change in gas concentration in a healthy individual breathing through an apparatus of negligible resistance, the maximum end tidal helium concentration predicted from standard pulmonary function testing (PFT) nomograms [24, 25] is 68%, with a conservative estimate (based on +/- one STDV for a coefficient of variation of 20%) of the range of normal values around this mean extending from 54% to 82%. Thus, achieving an end-tidal concentration of up to 48% in one individual after a single breath of helium indicates that the ventilator circuit is able to provide a change in gas concentration in the lung that is approaching the theoretical maximum, despite providing this breath of helium through 25 feet of narrow bore tubing. The measured concentration of helium in the 'recovered $^{17}O_2$' gas sampling bag was 47%, which compares favorably with the maximum possible recovered concentration of 49%.

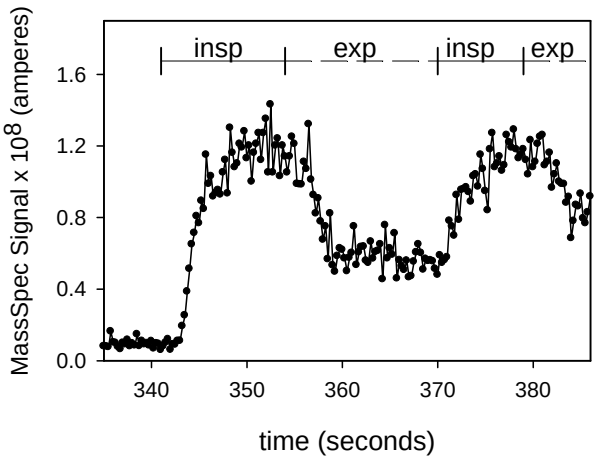

Fig. (3). Helium concentration at the airway for two breaths of 100% helium after equilibration with 100% oxygen.

DISCUSSION

The ventilator we designed and tested is capable of delivering step changes in gas concentration at the airway through long runs of narrow bore tubing between the mechanical pumps of the ventilator and a subject in the MR scanner. After this step change at the airway, the kinetics of $^{17}O_2$ uptake into arterial blood (the term $C_a{}^{17}O_2(t)$ in Equation (2)) should be easily predicted by mathematical models (appendix) [26]. A crucial remaining issue for the use of very brief pulses of $^{17}O_2$ for $CMRO_2$ measurement is the length of the time window for which equation (2) applies. The delay in the appearance of $H_2{}^{17}O$ owing to convection from the venous circulation to the arterial circulation is expected to be on the order of 10-15 seconds [14]. Diffusive delays from the mitochondria to the venules would add to this convective delay, but estimation of the diffusive delay from either theory or prior experimental data is difficult. Previous studies have almost universally assumed instantaneous equilibration between the tissue compartment and the vascular compartment, an assumption implicit in the use of Kety-Schmidt type well-mixed compartments. To our knowledge, however, there is currently no definitive experimental data to support the assumption of complete equilibration. From a theoretical perspective, it is known that water diffusion through lipid membranes is highly restricted in the absence of aquaporins [18]. It has also been recently reported that some tissues have abundant aquaporins to facilitate trans-membrane water transfer (for example, renal tissues [27]). In contrast, no

aquaporins have been found in other tissues, notably the majority of cerebral neurons [28]. The possibility that some tissues may in fact approximate the well-mixed model and have zero diffusional delay, whereas others may have substantial diffusional delay, suggests that the arterial input function might best be determined experimentally.

The limited experimental data that has been reported previously on this topic suggests that the arterial input function may be delayed beyond the expected convection delay. Zhu and coworkers, in a study presented in abstract form in 2002 and discussed in their 2005 review [2], showed in rats that cerebral washout of $H_2{}^{17}O$ after a bolus arterial injection was faster than washout after cessation of $^{17}O_2$ breathing, implying at least qualitatively that diffusion from the mitochondria to the venous circulation is restricted in the brain. Pekar and coworkers [3] measured the increase in arterial $H_2{}^{17}O$ every 30 seconds after the initiation of inhaled $^{17}O_2$, in cats, and estimated a delay in the increase in $H_2{}^{17}O$ on the order of 30-60 seconds, which exceeds the expected convective delay in these small animals. Mintun *et al.* measured the arterial input function of metabolically generated water in adult humans using PET techniques applied to ^{15}O isotopes [29]. They reported a peak in the arterial $H_2{}^{15}O$ that lagged the peak in $O^{15}O$ by approximately 70 seconds, which suggests that there are at least some tissues contributing to the $H_2{}^{15}0$ peak that had considerable diffusional delay. The availability of the new mechanical ventilator reported here should facilitate additional experimental studies on this issue using $^{17}O_2$ and either MR measurements of $H_2{}^{17}O$ in timed arterial blood samples, or in imaging of large arterial vascular structures in large animals or humans.

This new mechanical ventilator should also be useful in assessing the delay in cerebral venous washout of metabolically generated water due to restricted diffusion. In this situation also, predictions of the equilibrium between tissue and venous blood on theoretical grounds is difficult. It is certainly expected that water diffusion through the series of membranes from the mitochondria to the venous circulation (the mitochondrial inner and outer membranes, the plasma membrane, and the endothelial cell membranes) is diffusionally restricted [18], especially since the cerebral neurons appear to have limited aquaporins [28]. Predicting the quantitative importance of this restricted diffusion for a realistic three dimensional geometry, however, is challenging. The time window during which equation (2) applies might therefore best be determined experimentally. The ability to deliver $^{17}O_2$ in a brief pulse should facilitate this determination, either by timed cerebral venous blood sample collection and MR analysis of $H_2{}^{17}O$ concentrations, or by imaging of cerebral venous structures after delivery of a brief pulse by the ventilator.

After defining the time window for which equation (2) represents a reasonable approximation, the substantial remaining challenge in exploring the measurement of $CMRO_2$ using brief pulses of $^{17}O_2$ is the acquisition of images, within this narrow time window, with an adequate signal to noise ratio (SNR). This new ventilator has already proved useful in studies exploring new fast imaging techniques to improve SNR [30], and we anticipate that it will be advantageous in further studies in this area.

APPENDIX

After a step change in gas concentration at the airway, the dominant factor in the time course of alveolar and arterial $^{17}O_2$ uptake is the kinetics of gas dilution in the alveoli, as the tidal ventilation mixes with residual gas in the lung. The time course of arterial $^{17}O_2$ concentration ($C_a{}^{17}O_2(t)$ in equation 2) can be estimated from a mathematical model based on established principles of alveolar gas mixing [26]. In the general case, the estimation can be obtained easily with the evaluation of 2 integrals. In the particular case of volume controlled ventilation in a large anesthetized animal, with fixed inspiratory concentration and constant inspiratory flow, the integrals reduce to a simple algebraic equation for alveolar $^{17}O_2$ concentration that can be applied recursively to estimate the arterial $^{17}O_2$ input function over several breaths.

At end-exhalation, the lung is filled with a residual alveolar volume as well as deadspace volume in the airways. During the first part of inspiration, the deadspace gas re-enters the alveolus with no change in alveolar gas concentration. It is assumed as an approximation that the inspired gas/deadspace gas interface is transmitted to the alveolus as a sharp step change in concentration. At the moment this concentration front is entering the alveolus, the alveolar gas volume is the end-exhalation volume plus deadspace volume, at the end-exhalation gas concentration. From this point forward, the total amount of $^{17}O_2$ in the alveolar space, Y(t), at time t is given by:

$$Y(t) = \int_0^t (\frac{dV}{d\tau}) P_i(\tau)\, d\tau + (V_d + V_{ee}) P_{ET} \tag{A1}$$

where P_{ET} is the end-tidal $^{17}O_2$ partial pressure at the last exhalation, V_{ee} is the end-expiratory volume, V_d is the deadspace volume, dV/dt is the flow rate as a function of time, and $P_i(t)$ is the inspired $^{17}O_2$ partial pressure as a function of time. The total alveolar gas volume, X(t), as a function of time is given by:

$$X(t) = \int_0^t (\frac{dV}{d\tau})\, d\tau + (V_d + V_{ee}) \tag{A2}$$

The alveolar gas partial pressure versus time during inhalation is then simply Y(t)/X(t). For the large tidal volumes typically used experimentally, the delivery of $^{17}O_2$ in each breath far exceeds the gas volume taken up by blood, and to a first order blood uptake can be neglected.

The ventilator system presents a fixed $^{17}O_2$ partial pressure $P_i(t)$ throughout inspiration. The deadspace volume V_d and the residual volume at end expiration V_{ee} can be estimated from standard nomograms [24, 25]. Flow rate as a function of time (dV/dt) is known from the relationship between inspiratory pump speed (recorded by the data acquisition computer) and volumetric flow rate. In the general case, for example in spontaneous respiration, the two integrals A1 and A2 can be evaluated for each inspiration. To first order, it is assumed that the alveolar concentration does not change during exhalation, so that the end-inspiratory $P_i(t)$ becomes the end tidal P_{ET} for the next breath. The kinetics of gas dilution in the alveolus are therefore represented during the pulse of $^{17}O_2$ as a series of steps, one step for each breath, with the time course during inspiration represented by equations (A1) and (A2) (applied

recursively) and plateaus during exhalation. After the pulse of $^{17}O_2$, the kinetics of alveolar washout are described by a similar series of decreasing steps. Finally, for the healthy lung it is commonly assumed that the arterial concentration is equal to the alveolar concentration at all times [26].

For controlled ventilation in an anesthetized experimental subject, the target inspiratory flow is set to a constant value throughout inhalation, with the constant inspiratory flow determined by the software to achieve a specified tidal volume. The peristaltic pump, however, takes about 1 second to accelerate from a speed of zero to the target speed. For typical large animal subjects, therefore, the ventilator delivers the deadspace volume during the acceleration period, and at all times after that the inspiratory flow rate is constant at W ml/sec. The alveolar gas concentration changes in inspiration are therefore given simply by:

$$P_{alv}(t) = \frac{(P_I Wt) + (V_d + V_{ee})P_{ET}}{Wt + V_d + V_{ee}} \quad \text{(A3)}$$

where P_I is the constant inspired partial pressure in the current inspiration and P_{ET} is the end-tidal partial pressure in the last exhalation. This simplified equation is again applied recursively to describe the kinetics of gas dilution in the alveolus as a series of steps.

CONFLICT OF INTEREST

Oscillogy LLC has no financial interest in the subject of this study. All authors have been listed as inventors on a preliminary patent application concerning the subject of this study. No patent has currently issued, and the University of Pennsylvania has not entered any license agreements concerning intellectual property arising from this study.

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