Measurement of Cerebrovascular Reactivity as Blood Oxygen Level-Dependent Magnetic Resonance Imaging Signal Response to a Hypercapnic Stimulus in Mechanically Ventilated Patients

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Background: Impaired cerebrovascular reactivity (CVR) is an important prognostic marker of stroke. Most measures of CVR lack (1) a reproducible vasoactive stimulus and (2) a high time and spatial resolution measure of cerebral blood flow (CBF), particularly for mechanically ventilated patients. The aim of our study was to investigate the feasibility of measuring CVR using sequential gas delivery circuit and gas blender for precise targeting of end-tidal PCO_2 ($P_{ET}CO_2$), and blood oxygen level-dependent magnetic resonance imaging (BOLD-MRI) signal as a surrogate of CBF, in mechanically ventilated patients. *Methods:* Four patients with known moyamoya disease requiring preoperative CVR measurements under general anesthesia were studied. All patients had standard anesthesia induction and maintenance with intravenous propofol and rocuronium. Patients were intubated and manually ventilated with a self-inflating bag connected to a sequential breathing circuit. A computer-controlled gas blender supplied the gas mixture in proportions to attain target $P_{ET}CO_2$. BOLD-MRI was performed at 3.0 Tesla magnet. Changes in signal per change in $P_{ET}CO_2$ were calculated, and their magnitude color-coded and mapped onto the anatomic scan to form CVR maps. *Results:* CVR studies were successfully performed on all patients, and the CVR values were lower in both gray and white matter bilaterally when compared with healthy volunteers. In addition, CVR maps in 3 patients showed intracerebral steal phenomenon in spite of having had cerebral revascularization procedures,

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Conflict of interest: RespirAct is currently a non-commercial research tool approved by Health Canada, assembled, and made available by Thornhill Research Inc. (TRI), a spin-off company from the University Health Network, to research institutions to enable CVR studies. J.A.F. is the Chief Scientist and J.D. is the Senior Scientist at (TRI), and J.P., O.S., J.S.H., K.S., and D.J.M. have contributed to the development of RespirAct and have received payments from, or shares in, TRI.

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indicating that they are still at risk of cerebral ischemia. *Conclusions:* BOLD-MRI CVR studies are feasible in mechanically ventilated patients anesthetized with propofol.
Key Words: Cerebrovascular reactivity—MRI—carbon dioxide—cerebral steal—anesthesia.

Introduction

Carbon dioxide (CO_2) is a potent cerebral vasodilator, and increases or decreases in arterial PCO_2 cause corresponding changes in CBF.[1] The change in CBF in response to a vasodilatory stimulus is called cerebrovascular reactivity (CVR). Hypercapnia-induced increase in CBF, although not uniform throughout the brain, nevertheless, follows a consistent pattern in healthy brains.[2,3] In patients with intracranial steno-occlusive disease, the poststenotic blood vessels often undergo compensatory vasodilation, encroaching on their vasodilatory reserve. Hence, global vasodilatory stimuli such as hypercapnia can lead to paradoxical decrease in CBF in these regions as the blood flow is redistributed from more affected to lesser affected vessels.[4] This phenomenon is known as "intracerebral steal," and is a strong marker of the risk of stroke and a useful parameter to follow in considerations of when to surgically revascularize symptomatic patients.[5,6] The reverse phenomenon where there is a paradoxical increase in CBF with hypocapnia is known as "inverse steal" or "Robin Hood phenomenon." This phenomenon has been known for decades, but so far it has not been possible to demonstrate it visually, mainly because of nonavailability of titratable vasodilatory stimuli and also the lack of noninvasive method to measure CBF. We and others have shown CVR measurement using blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI) and precise controlled changes in CO_2 with a help of a computer-controlled gas blender and a sequential gas delivery breathing circuit (RespirAct; Thornhill Research Inc., Toronto, Canada) to be practical, safe, and reproducible in awake subjects.[4,7-9]

However, CVR measurements may be indicated in some patients who cannot tolerate MRI and also in patients on mechanical ventilation in neurointensive care unit. Although it may seem easy to control PCO_2 in anesthetized and mechanically ventilated patients, the manipulation of the alveolar ventilation to control the PCO2 is often slow, non-titratable, and final levels are difficult to predict. This is unsuitable for CVR studies using MRI where there can be a signal drift and, hence, the changes need to occur over seconds. In addition, anesthetic agents also have an effect on the cerebral blood flow and vascular reactivity, and it is unknown to what extent, if any, they would attenuate or mask the "intracerebral steal."[10,11]

The aim of our study was to demonstrate the feasibility of quantitatively measuring the CVR and to generate CVR color maps in mechanically ventilated patients under propofol anesthesia using precise, controlled changes in PCO_2 as the vasoactive stimuli and regional BOLD-MRI signal changes as the surrogate for CBF. We hypothesize that under propofol anesthesia, intracerebral steal physiology can be seen in patients with intracranial steno-occlusive disease with the changes in $ETCO_2$.

Materials and Methods

The hospital Research Ethics Board approved the study (UHN-REB No.12-5360 A), and every subject or substitute decision maker provided written informed consent. We studied 4 adults (ages between 18 and 21 years) with an intracranial steno-occlusive disease who required CVR assessment for clinical purposes and needed general anesthesia for MRI. The reason for general anesthesia includes development delay (3) and claustrophobia (1).

Anesthesia Management

All patients needing general anesthesia (GA) were seen by an anesthesiologist before the procedure and they received routine preparation as per our institutional standard. After a standard induction (propofol 2.0-2.5 mg/kg, rocuronium .8-1.0 mg/kg) and intubation with appropriate-sized endotracheal tube, anesthesia was maintained with the infusion of propofol at a rate of 80-125 mcg/kg/min. All patients were monitored with ECG, noninvasive blood pressure, SaO_2, and end-tidal $P_{ET}O_2$ via MRI-compatible monitors. During the CVR measurement, patients were disconnected from the anesthesia ventilator and manually ventilated with a self-inflating bag modified to provide a fresh gas component from the RespirAct and the balance of minute ventilation from previously exhaled gas (Fig 1). After the study, anesthesia was terminated, and the patients were allowed to wake up and their tracheas were extubated. Once they were awake, they were transferred to the recovery room.

Ventilation Protocol

Each subject received a square wave and a ramp pattern of end-tidal PCO_2 manipulation. The square wave increase consisted of a baseline normocapnia for 90 seconds and hypercapnia (resting $P_{ET}CO_2$ + 10 mm Hg) for 120 seconds. The ramp increase examined the relationship between the $P_{ET}CO_2$ and the BOLD signal over a linear increase of $P_{ET}CO_2$ over 4 minutes from 5 mm Hg below baseline to baseline +10 mm Hg. This has been our standard stimuli for CVR maps in spontaneously breathing patients. The