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Review

Vive la résistance! The role of inspiratory resistance breathing on cerebral blood flow

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ABSTRACT

Prolonging the therapeutic window for treatment is imperative for survival from a multitude of life-threatening events such as hemorrhage, cardiac arrest, and stroke. Inspiratory resistance breathing is a therapeutic approach that augments the reduction in intrathoracic and intracranial pressure during inspiration, facilitating improvements in vital organ perfusion under conditions of ischemia, such as blood loss and cardiac arrest. In this review a series of studies will be presented assessing the role of inspiratory resistance breathing on responses of cerebral blood flow and cerebral tissue oxygenation under conditions of cardiac arrest and blood loss in animal models, and simulated hemorrhage in humans. Knowledge gaps in this field of investigation will be presented, and future research directions will be discussed.

1. Introduction

Cerebral blood flow is controlled by numerous inter-related factors, including metabolic demand of the surrounding neural tissue, arterial blood gas concentrations, prevailing arterial pressure and cardiac output, intracranial pressure (ICP), and neural control [see reviews by Willie et al., (Willie et al., 2014) and Rickards (Rickards, 2015)]. When describing the role of breathing on cerebral blood flow, we commonly consider the effect of breathing on arterial blood gases, specifically the partial pressure of arterial carbon dioxide (P_aCO_2) and oxygen (P_aO_2), and their subsequent influence on cerebral vessel calibre and flow. The cerebral vasculature is exquisitely sensitive to changes in P_aCO_2; with an increase in P_aCO_2 (hypercapnia), the cerebral vessels dilate, inducing an increase in cerebral blood flow; with a decrease in P_aCO_2 (hypocapnia), the vasculature constricts and cerebral blood flow decreases (Kety and Schmidt, 1948; Kontos et al., 1977). Fluctuations in arterial PO_2 have less of an effect on cerebral blood flow until a critical threshold of ~60 mmHg, which induces a vasodilation and an increase in cerebral blood flow (Ainslie and Ogoh, 2010; Rowell, 1993). Factors including the local environment (e.g., elevation from sea level, room ventilation), alveolar gas exchange, and metabolic activity will drive changes in arterial blood gases, and subsequently, respiratory activity, which in turn will impact cerebral blood flow.

An equally important, but less commonly considered factor that also influences cerebral blood flow with breathing, is the change in ICP. During inhalation, intrathoracic, intracranial, and central venous/right atrial pressures decrease (Convertino et al., 2011; Moreno et al., 1967) (Fig. 1). The reduction in central venous pressure increases the pressure gradient (ΔP) between the peripheral circulation and the heart, eliciting an increase in blood flow from the venous circulation through the inferior vena cava and into the right heart (Brecher and Hubay, 1955; Hubay et al., 1954; Innes et al., 1993). Similarly, at the level of the brain, a decrease in ICP with inhalation elicits an increase in cerebral perfusion pressure (CPP), where CPP is equal to mean arterial pressure (MAP) minus ICP. This increase in CPP will subsequently increase cerebral blood flow which is equal to CPP divided by cerebrovascular resistance. This increased pressure gradient occurs with every inhalation, resulting in pulsatile flow into the vital organs with every spontaneous breath (Fig. 2A).

Indeed, the impact of inhibiting the reduction in ICP with spontaneous inspiration is highlighted in studies exploring the role of mechanical positive pressure ventilation on cerebral blood flow (indexed by flow through the internal carotid artery) (Skytioti et al., 2016) or cerebral perfusion pressure (Yannopoulos et al., 2005a). Positive pressure ventilation forces air into the lungs, opposing the reduction in intrathoracic pressure with inhalation. While this increases delivery of oxygenated air into the alveoli for gas exchange, the attenuated decrease in intrathoracic pressure can limit venous return, and result in impaired stroke volume and cardiac output, particularly under conditions of reduced central blood volume (e.g., with acute application of lower body negative pressure) (Cheifetz, 2014; Skytioti et al., 2018). Similarly, over-ventilation or incomplete chest wall recoil during cardiopulmonary resuscitation (CPR) can lead to excessive positive intrathoracic pressure resulting in reduced arterial pressure, cerebral

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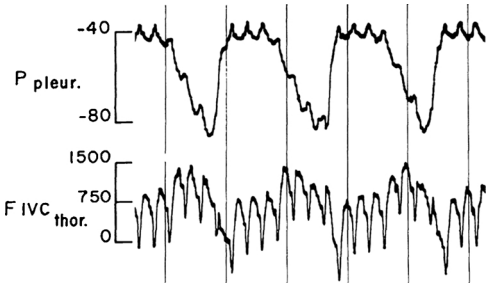

Fig. 1. Relationship between decreases in intrapleural pressure ($P_{pleur.}$) and increased flow to the right heart through the inferior vena cava (F IVC_{thor}) with each inspiration. Reprinted with permission (Moreno et al., 1967).

perfusion pressure, and coronary perfusion pressure (Aufderheide and Lurie, 2004; Yannopoulos et al., 2005a, 2004).

2. Inspiratory resistance breathing

In the early 1990s, investigators from the University of Minnesota were motivated by the knowledge that reducing intrathoracic and intracranial pressures increased vital organ perfusion, and began to explore a therapeutic intervention that magnified this effect. In 1995, Lurie et al. reported that use of an "inspiratory impedance valve" (set at -40 cm·H_2O) during active compression-decompression CPR in a pig model of cardiac arrest, increased flow in the left and right ventricles, and in the brain (Lurie et al., 1995). In fact, cerebral blood flow (measured via the microsphere technique) increased by 127% and 111% compared with baseline following 2-min and 7-min of active compression-decompression CPR with the inspiratory impedance valve, compared with an 80% and 85% increase with active compression-decompression CPR alone (Fig. 3). In this experimental model, the pigs were intubated, and the inspiratory impedance valve was placed between the intubation tube and a manual ventilation bag. During the active decompression phase of CPR, intrathoracic pressure had to be below -40 cm·H_2O before the impedance valve would open to allow for movement of air into the lungs for gas exchange.

In early animal studies exploring optimal inspiratory resistance, Yannopoulos et al. (2006a) demonstrated that intrathoracic pressure fell in proportion to the threshold pressure of the valve; with valves set at -13.6 cm·H_2O (-10 mmHg) and -20.4 cm·H_2O (-15 mmHg), peak endotracheal pressures (ETP; as an index of intrathoracic pressure) decreased to -12.2 cm·H_2O (-9 mmHg) and -24.8 cm·H_2O (-18 mmHg) (Fig. 4). Similarly, when spontaneously breathing through an inspiratory resistance valve, intrathoracic pressure must fall below the "threshold" resistance of the valve before air can flow through the valve and into the lungs. For example, resistance valves set at -6 cm·H_2O and -12 cm·H_2O induced a decrease in peak mask pressure (a non-invasive index of intrathoracic pressure) to approximately -9 cm·H_2O and -14 cm·H_2O (Convertino et al., 2004a). The resultant cardiovascular effects of inspiratory resistance breathing are also in direct proportion to the resistance of the valve (Yannopoulos et al., 2006b), and will be described in more detail subsequently.

However, it is important to consider that high inspiratory loads can also increase afterload, which may diminish the cardiovascular benefit. Indeed, a number of studies have reported that stroke volume and ejection fraction decrease with inspiratory loading more than -20 cm·H_2O (Cheyne et al., 2018; Karam et al., 1984). While inspiratory resistance devices have been tested up to loads of -40 cm·H_2O (Lurie et al., 1995), hemodynamic benefit has been observed with loads as low as -6 to -7 cm·H_2O, which is the more common load used in more recent studies (see Inspiratory Resistance Breathing and Cerebral Blood Flow section for details of animal and human studies). Similarly, improvement in cardiovascular status must be balanced with the increased work of breathing for application of inspiratory resistance to the clinical setting. Idris et al. (2007) demonstrated that spontaneously breathing through an inspiratory resistance valve set at -7 cm·H_2O increased the work of breathing from ~1 J/min to ~8 J/min in healthy human subjects. However, the increased work of breathing was well-tolerated in this group of young healthy subjects (Idris et al., 2007), and has subsequently been reported to be tolerable in spontaneously breathing patients with hypovolemia-induced hypotension (Smith et al., 2011, orthostatic hypotension (Melby et al., 2007), postural tachycardia syndrome (Gamboa et al., 2015), and hypotension secondary to trauma (Wampler et al., 2014).

3. Inspiratory resistance breathing and cerebral blood flow

3.1. Animal studies

As previously stated, one of the first studies investigating the role of enhanced inspiratory resistance on cerebral blood flow was by Lurie et al., in a pig model of cardiac arrest (Lurie et al., 1995). Subsequently, a series of animal studies have been conducted assessing the role of inspiratory resistance breathing on intracranial pressure and cerebral perfusion pressure both at rest, and under the clinically relevant conditions of cardiac arrest, and hemorrhage (blood loss). Neurological outcomes have also been assessed to determine if the improvement in cerebral perfusion with inspiratory resistance breathing is related to improved cognitive function following these events.

In these animal studies, different methods have been used to augment the reduction in intrathoracic pressure, including 1) inspiratory threshold valves placed in series between the intubation tube and ventilator bag (Lurie et al., 1995); this system facilitates an enhanced reduction in intrathoracic pressure during the decompression phase of CPR; and, 2) an intrathoracic pressure regulator (ITPR) which maintains a constant intrathoracic pressure between -5 and -10 mmHg, but also allows for intermittent positive pressure ventilation to facilitate pulmonary gas exchange (Yannopoulos et al., 2005b).

Yannopoulos et al. utilized an ITPR during CPR in intubated and anesthetized pigs following 6-min of untreated ventricular fibrillation (Yannopoulos et al., 2005b). The ITPR was set to -10 mmHg (approx. -14 cm·H_2O) which reduced endotracheal pressure to approximately -9 mmHg during CPR. Common carotid blood flow and cerebral perfusion pressure were elevated during CPR + ITPR therapy compared with CPR alone, and 1-hour survival post treatment was 100% vs. 10% (Yannopoulos et al., 2005b). While inspiratory resistance breathing was originally developed to enhance vital organ perfusion during CPR following cardiac arrest, it has also been explored as a therapy to treat hypoperfusion as a consequence of blood loss. Following blood loss protocols in pigs that reduced blood volume up to 50%, use of either an inspiratory threshold device (spontaneously breathing) or an ITPR (set at -10 to -15 mmHg), decreased ICP and subsequently increased CPP; mean arterial pressure also increased contributing to the elevation in CPP (Yannopoulos et al., 2006a, b) (Fig. 5). Interestingly, these positive effects on ICP, CPP, and MAP are even seen under normovolemic conditions, and were magnified with hypovolemia (Yannopoulos et al., 2006b) (Fig. 5). In a follow-up study, again in a pig model with 55% blood loss, use of ITPR therapy resulted in an improvement in 24 h survival from 11% (1/9 animals) to 100% (9/9 animals), and 8 of these 9 surviving animals had normal neurological function (Yannopoulos et al., 2007).

More recently, Metzger et al. assessed the role of ITPR therapy on ICP, MAP, CPP, and cerebral blood flow in a pig model of traumatic brain injury (Metzger et al., 2015). Following induction of the injury that increased ICP from ~12 to 14 mmHg to ~26 to 28 mmHg, ITPR therapy increased MAP and decreased ICP, resulting in an increase in CPP and cerebral blood flow (assessed via an intracranial flow probe) compared with the control group. Similar findings have been reported in human patients with elevated ICP due to intracranial hemorrhage, trauma, and hydrocephalus; use of ITPR therapy (-12 cm·H_2O) for

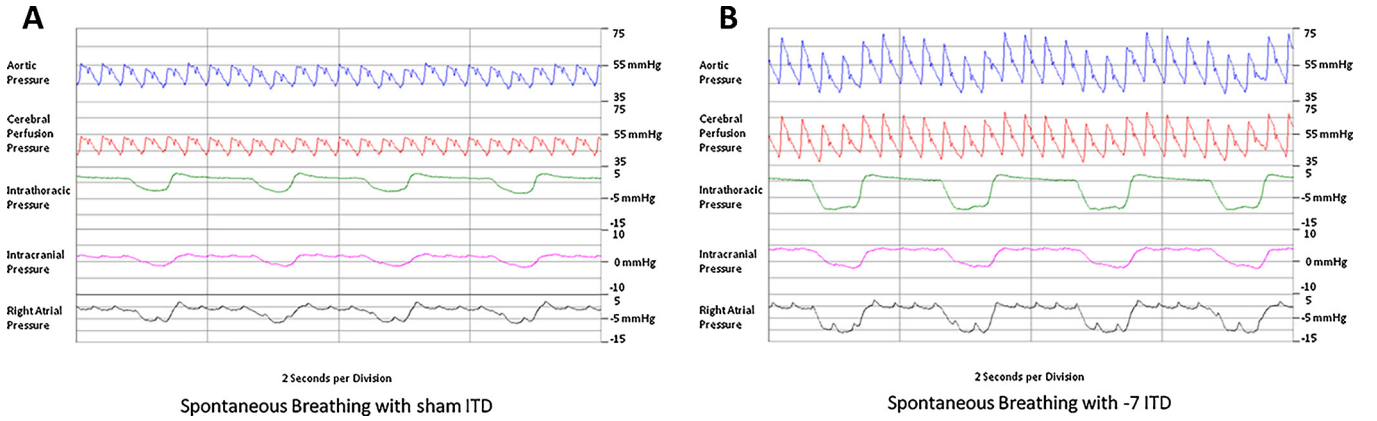

Fig. 2. Breath by breath changes in aortic pressure, cerebral perfusion pressure, intrathoracic pressure, intracranial pressure, and right atrial pressure during spontaneous breathing without (panel A), and with (panel B) an inspiratory threshold device (ITD) set at a resistance of −7 cm·H_2O in an anesthetized pig following 50% blood loss. Reprinted with permission (Convertino et al., 2011).

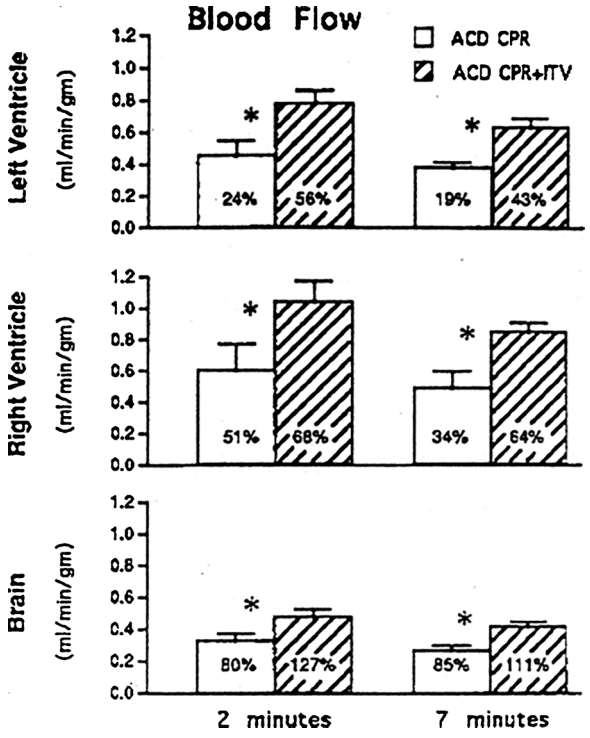

Fig. 3. Blood flow to the heart (right and left ventricles) and the brain in a porcine model of cardiac arrest following 2-min and 7-min of active compression-decompression cardiopulmonary resuscitation (ACD CPR) with (hatched bars) and without (white bars) an inspiratory threshold valve (ACD CPR + ITV). Percentage numbers represent comparison with baseline blood flow for each intervention. Asterisk (*) represents $P < 0.05$ between conditions. Reprinted with permission (Lurie et al., 1995).

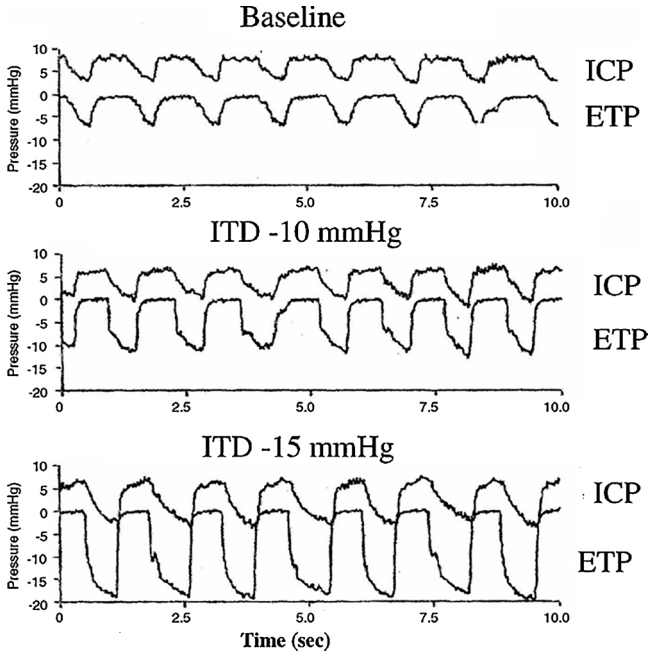

Fig. 4. Breath by breath relationship between endotracheal pressure (ETP; as an index of intrathoracic pressure) and intracranial pressure (ICP) at baseline, and with inspiratory threshold devices (ITD) set at −10 mmHg and −15 mmHg. The reductions in ETP and ICP are amplified with increasing inspiratory resistance. Reprinted with permission (Yannopoulos et al., 2006a).

10–30 min reduced ICP and increased CPP in these patients (Kiehna et al., 2013; Metzger et al., 2018).

It is important to note that the hemodynamic and cerebrovascular effects of ITPR therapy and/or inspiratory resistance breathing only occur during the acute phase of the therapy; removal of resistance results in return of hemodynamic and cerebrovascular responses to baseline. This phenomenon is highlighted in the data presented in Fig. 5. While breathing with inspiratory resistance decreases intrathoracic, right atrial, and intracranial pressures and increases MAP, coronary perfusion pressure, and CPP, these effects are reversed when the resistance is removed. The advantage of this response is that the therapy can be easily removed if clinically indicated (e.g., if internal bleeding is detected). The disadvantage, however, is that the therapy needs to be continuous for the positive acute outcomes to be present; although increased survival and improved neurological function are important long-term outcomes that result from this acute intervention.

3.2. Human studies

3.2.1. Laboratory studies

In a series of experimental studies with human subjects, investigators have explored the role of inspiratory resistance breathing on cerebral blood flow at rest, and under conditions of reduced central blood volume, including a squat-to-stand test, and lower body negative pressure (LBNP). All of these studies used an inspiratory resistance valve set at −7 cm·H_2O. The rationale for use of this resistance load was based on initial studies in humans demonstrating similar hemodynamic benefit (heart rate and arterial pressure responses) between resistance valves set at either −6 cm·H_2O and −12 cm·H_2O (Convertino et al.,

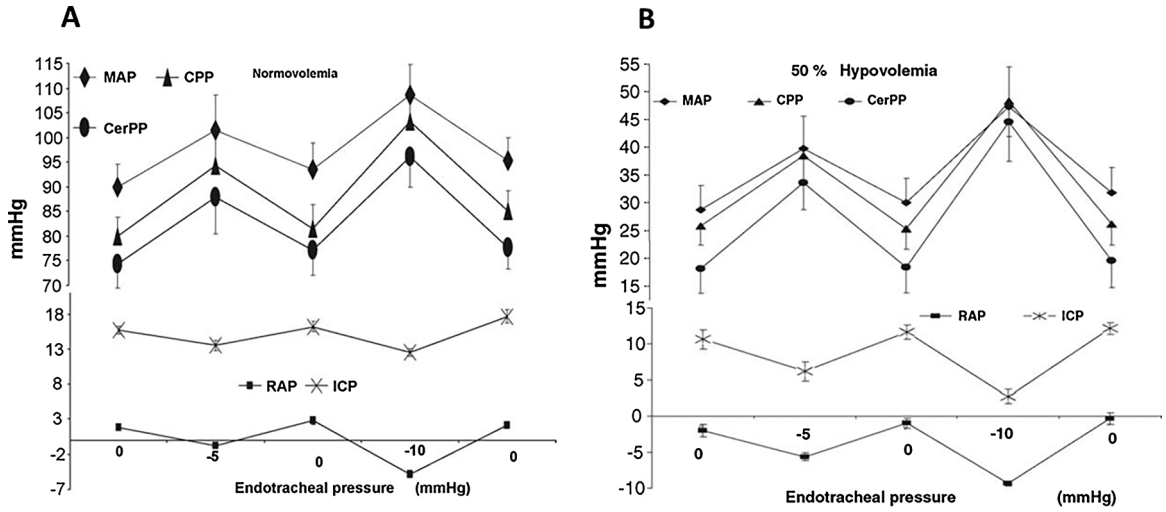

Fig. 5. Mean arterial pressure (MAP), coronary perfusion pressure (CPP), cerebral perfusion pressure (CerPP), right atrial pressure (RAP), and intracranial pressure (ICP) with inspiratory resistance-induced decreases in endotracheal pressure. The magnitude of responses increases when inspiratory resistance increases from −5 mmHg (~ −7 cm·H_2O) to −10 mmHg (~ −14 cm·H_2O) (x-axis). Panel A represents responses during normovolemia, and panel B represents responses following removal of 50% blood volume in a porcine model of hemorrhage. Reprinted with permission (Yannopoulos et al., 2006b).

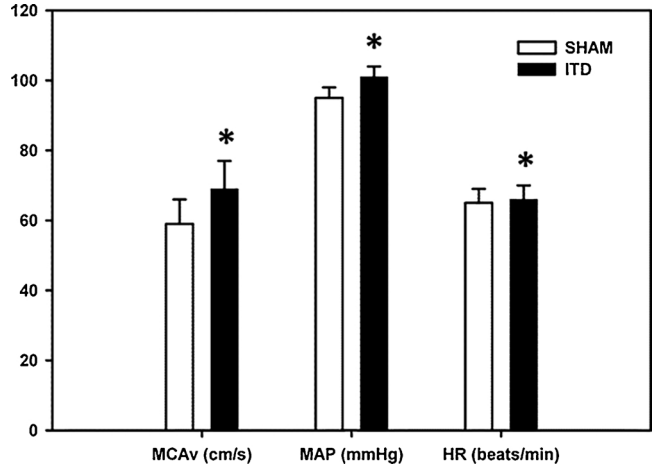

Fig. 6. Middle cerebral artery velocity (MCAv), mean arterial pressure (MAP), and heart rate (HR) in response to breathing through an active (black bars) or sham (white bars) inspiratory threshold device (ITD) in supine healthy human subjects. Asterisk (*) represents $P < 0.05$ between groups. Figure derived from tabulated data published in (Cooke et al., 2006).

2004a). The effect of inspiratory resistance breathing on improving central hemodynamics (including arterial pressure, stroke volume and cardiac output) both at rest and during central hypovolemia had been well established in prior studies (Convertino et al., 2004b, 2005, 2006). In the first study to explore the role of inspiratory resistance breathing on cerebral blood dynamics, Cooke et al. reported a small 10% increase in middle cerebral artery velocity (MCAv; assessed via transcranial Doppler ultrasound) in supine subjects, which was accompanied by increases in arterial pressure and heart rate (Cooke et al., 2006) (Fig. 6). Interestingly, Rickards et al., then reported that despite a reduction in subjective orthostatic symptoms, neither MCAv nor MAP were protected while breathing through a inspiratory resistance valve while standing following a 4-min squatting maneuver (Rickards et al., 2008). These divergent findings in resting supine subjects versus subjects under acute central hypovolemic stress led to the next series of studies exploring the role of inspiratory resistance breathing on cerebral blood flow responses to more prolonged and severe central hypovolemia reflecting blood loss (Kay et al., 2017; Rickards et al., 2007).

In these studies, LBNP was used as an experimental method to induce progressive reductions in central blood volume and cerebral blood flow. LBNP has recently been validated as an accurate method to simulate actual blood loss in healthy human subjects, with similar trajectories in the reduction of central venous pressure, stroke volume, arterial pressure, and MCAv (Johnson et al., 2014; Rickards et al., 2015). Stepwise LBNP was applied in healthy human subjects until the point of presyncope, indicated by a reduction in systolic arterial pressure to < 80 mmHg, and/or the reporting of presyncopal symtpoms (i.e., nausea, dizziness, vision disturbances, lightheaded). Approximately 5-min prior to the anticipated time of presyncope (ascertained from a prior maximal LBNP test) subjects breathed spontaneously through an inspiratory resistance valve and the time to presyncope was assessed. While tolerance time increased and MAP was protected with inspiratory resistance breathing compared with the control condition (Kay et al., 2017; Rickards et al., 2007), blood velocity through the MCA (Kay et al., 2017; Rickards et al., 2007) and the posterior cerebral artery (PCA), and cerebral oxygen saturation (derived from measurements of oxy- and deoxy-hemoglobin) of the frontal lobe (Kay et al., 2017) were not protected (Fig. 7). These findings were surprising as previous studies from this and other laboratories had demonstrated that subjects with higher tolerance to LBNP exhibited sustained protection of blood velocity or flow to the posterior cerebral circulation (Kay and Rickards, 2016; Ogoh et al., 2015), and reduced cerebral oxygen extraction (indexed by an attenuated reduction in oxy-hemoglobin and an attenuated increase in deoxy-hemoglobin in the frontal lobe) (Kay and Rickards, 2016).

These unexpected findings, in addition to the compelling results from animal studies demonstrating the protection of CPP and cerebral blood flow with use of inspiratory resistance, has led to a number of working hypotheses outlined in Fig. 8. It is important to note that all of these studies in human subjects have utilized transcranial Doppler ultrasound for non-invasive assessment of intracranial blood velocity within the major conduit arteries of the Circle of Willis. One important limitation of this technique is the assumption that the diameter of the measured vessel remains constant, so changes in velocity can be interpreted as changes in flow. This assumption, however, may not always be correct, particularly under conditions where ICP is changing with inspiratory resistance breathing. For example, in the studies of Rickards et al. (2007) and Kay and Rickards (2016), MAP was maintained with inspiratory resistance breathing, and presumably, ICP was reduced. If CPP is equal to MAP minus ICP, both the protection of MAP and reduction in ICP should have increased CPP, and subsequently,

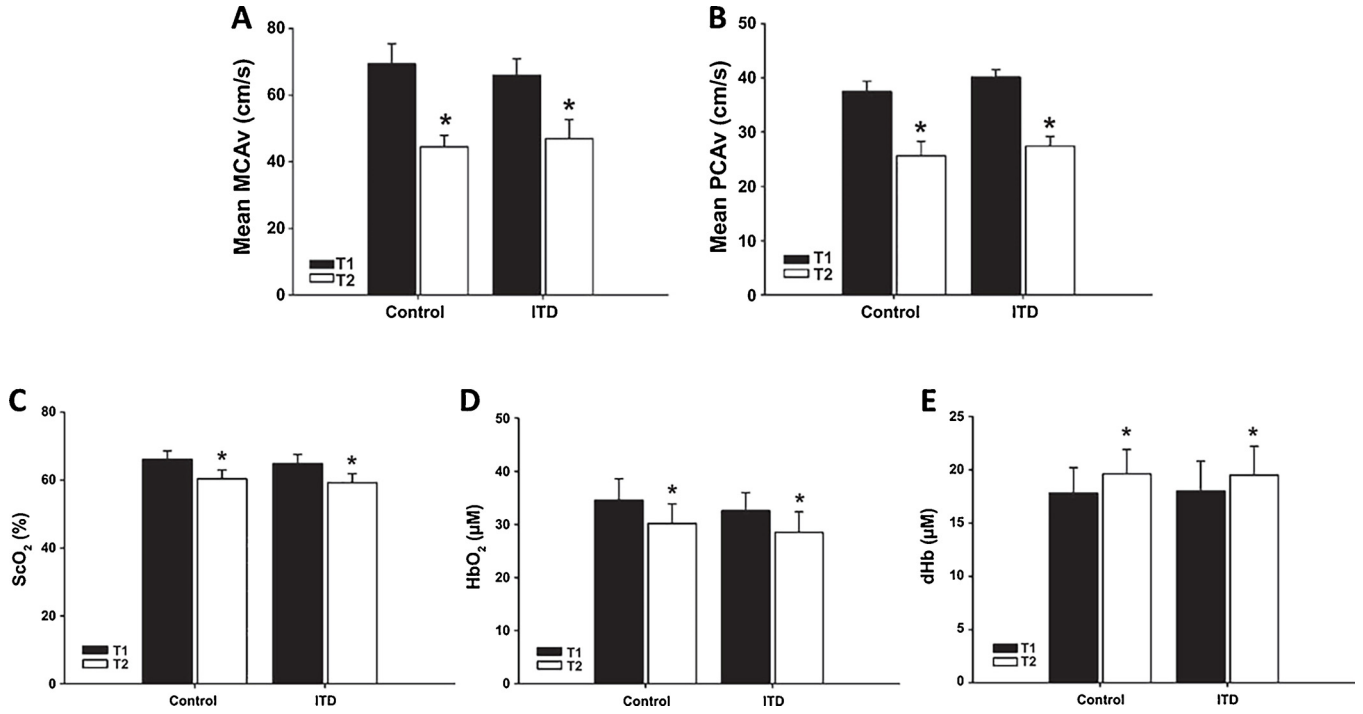

Fig. 7. Cerebral blood velocity and oxygenation responses to breathing with (ITD) and without (Control) inspiratory resistance during central hypovolemia induced by lower body negative pressure in healthy human subjects. Middle cerebral artery velocity (MCAv; Panel A), posterior cerebral artery velocity (PCAv; Panel B), cerebral oxygen saturation (ScO_2; Panel C), oxygenated haemoglobin (HbO_2; Panel D) and deoxygenated haemoglobin (dHb; Panel E) at baseline (black bars, T1) and at the time of presyncope in the control condition (white bar, T2). Asterisk (*) represents $P \leq 0.001$ compared with baseline within condition. Reprinted with permission (Kay et al., 2017).

increased cerebral blood flow. The measurement of blood velocity, however, may have masked this increase in cerebral blood flow. Similarly, it is possible that the oscillatory nature of cerebral blood flow with resistance breathing (Rickards et al., 2011, 2007) may induce a shear-stress mediated vasodilation, further facilitating an increase in cerebral blood flow. Further investigations exploring the effect of inspiratory resistance breathing on actual cerebral blood flow are necessary to address this methodological limitation. For example, extracranial inflow to the major intracranial vessels could be assessed via the internal carotid and vertebral arteries, or advanced imaging techniques could be used for assessment of global cerebral blood flow and metabolism (e.g., magnetic resonance imaging).

Lucas et al. have demonstrated that simply reducing respiration rate to 6 breaths/min increases tolerance to the central hypovolemic challenge of combined head-up tilt plus −40 mmHg LBNP (Lucas et al., 2013). This improvement in tolerance is presumably due to an increase in tidal volume with a decrease in respiration rate, and the subsequent augmented reduction in central venous pressure and intrathoracic pressure. Similarly, spontaneous breathing through an inspiratory resistance valve often results in a reduction in respiratory frequency

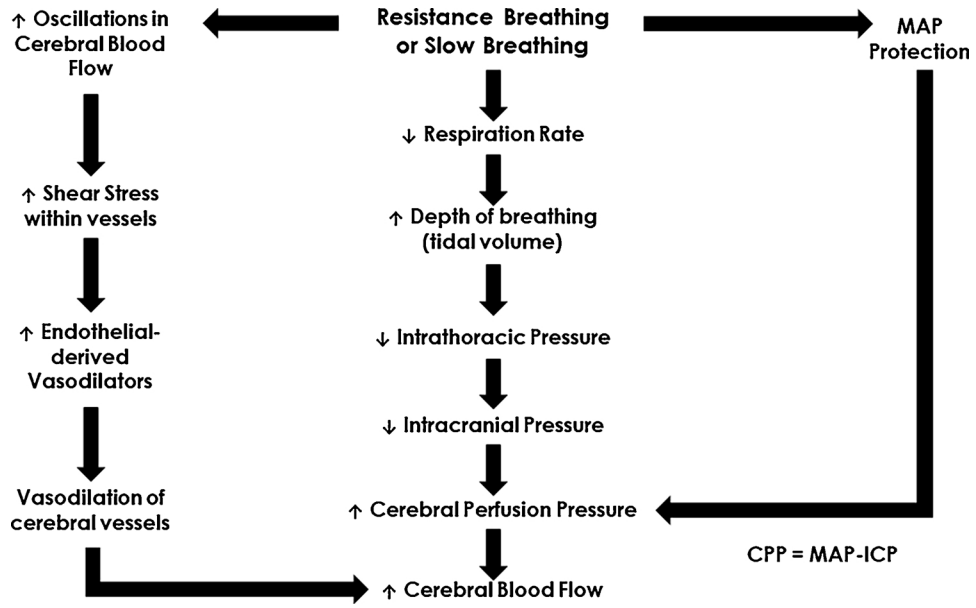

Fig. 8. Proposed mechanisms of cerebral blood flow protection with resistance breathing and/or slow breathing.

(Convertino et al., 2004b; Kay et al., 2017; Rickards et al., 2008, 2007) and an increase in tidal volume (Convertino et al., 2004b). As such, inspiratory resistance breathing likely increases venous return and cerebral perfusion simply by stimulating a simultaneous reduction in respiratory rate and increase in tidal volume which decreases central venous pressure and ICP.

3.2.2. Clinical studies

In addition to the previously described studies in patients with elevated ICP (Kiehna et al., 2013; Metzger et al., 2018), inspiratory resistance therapy has been applied to other clinical scenarios, including patients with hypotension in the prehospital and emergency department settings (Convertino et al., 2012; Smith et al., 2011; Wampler et al., 2014). While spontaneously breathing with inspiratory resistance increased arterial pressure in these patients, measures of cerebral perfusion were not obtained. Similarly, inspiratory resistance has been used extensively during CPR in patients following cardiac arrest (Adabag et al., 2017; Aufderheide et al., 2011; Plaisance et al., 2000; Sugiyama et al., 2016). While direct measures of cerebral perfusion and/or flow have not been evaluated in these patients, neurological performance scores (such as the modified Rankin scale) and long-term survival following hospital discharge have indicated cerebrovascular benefits with inspiratory resistance therapy (Aufderheide et al., 2011; Sugiyama et al., 2016).

4. Summary

Extensive evidence from animal studies have demonstrated that use of inspiratory resistance will decrease right atrial pressure, intrathoracic pressure, and intracranial pressure with each inspiration, resulting in increases in perfusion to the heart and the brain. These effects appear to be magnified under conditions of physiological stress, including cardiac arrest and hemorrhage. In human studies of experimentally-induced central hypovolemia, inspiratory resistance breathing maintains arterial pressure and prolongs tolerance to this stress, but the effect on cerebral perfusion pressure and cerebral blood flow is limited by current methodological approaches. While data from patients in the clinical setting is currently limited in regards to the effect of inspiratory resistance breathing on cerebral perfusion pressure and cerebral blood flow, improvements in arterial pressure, neurological function, and survival following hospital discharge, provides evidence of cerebrovascular benefits from inspiratory resistance breathing. Further investigations should be conducted to gain insight into the role of resistance breathing on cerebral perfusion and oxygenation in both healthy human subjects and patients in the clinical setting.

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