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The cerebrovascular and executive function responses to increased inspiratory muscle work

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ABSTRACT

We investigated the cerebrovascular and executive function responses to increased inspiratory muscle work. Eight healthy men (33 ± 6 years) performed two separate 10 min bouts of inspiratory pressure threshold loading (ITL) targeting 70 % of maximal inspiratory mouth pressure (P_{Imax}) (ITL-Load) and two separate 10 min bouts of ITL targeting 2 % of P_{Imax} (ITL-Control). The order in which each participant undertook ITL-Load and ITL-Control conditions was randomized. Transcranial Doppler ultrasonography was used to measure middle cerebral artery blood velocity (MCA_V) and executive function was measured using the trail making task (TMT) Parts A and B during the 4–6th min of ITL-Load and ITL-Control. The cerebrovascular conductance index (CVCi) and cerebrovascular resistance index (CVRi) were calculated. There were time x condition interactions ($P < 0.01$) for MCA_V, CVCi and CVRi. This demonstrated during ITL-Load a small time-dependent increase ($P < 0.01$) in MCA_V and CVCi, and a small time-dependent decrease ($P < 0.01$) in CVRi. Part A ($P = 0.007$) and Part B ($P = 0.013$) times for the TMT were slower for ITL-Load compared to ITL-Control. There were significant correlations between the change in MCA_V from rest to the end of ITL and TMT times for Part A ($r = 0.81$, $P = 0.009$) and Part B ($r = 0.67$, $P = 0.048$). This is the first study to demonstrate that high-intensity ITL results in an increase in MCA_V, and a decreased executive function measured by the TMT, and these two measures were related in that the increase in MCA_V resulted in slower TMT times.

1. Introduction

Elevated inspiratory muscle work is encountered during stress, anxiety, whole-body exercise, and exacerbations of respiratory disease (Boulding et al., 2016; Paulus, 2013). Inspiratory muscle work can also be elevated in healthy humans whilst at rest using inspiratory pressure threshold loading (ITL). ITL requires participants to inspire through a device whilst at rest which increases the load of the inspiratory muscles (Nickerson and Keens, 1982). When ITL is performed at ~60 % of maximum inspiratory mouth pressure (P_{Imax}) until task failure it can lead to diaphragm fatigue (Laghi et al., 1995, 1998). ITL at a similar intensity also results in a time-dependent acute increase in heart rate (HR), mean arterial pressure (MAP) and a reflex reduction in resting leg blood flow (e.g., metaboreflex) (Sheel et al., 2001, 2002; St Croix et al., 2000; Witt et al., 2007). However, the effects of this high-intensity ITL on cerebral blood flow (CBF) are unknown.

Low-intensity ITL at inspiratory mouth pressures of ~7–10 cmH_2O undertaken in a supine position result in small (+5–10 %) increases in middle cerebral artery velocity (MCA_V) measured with transcranial Doppler ultrasound (TCD) (Cooke et al., 2006; Hayen et al., 2013). MCA_V is an indirect measure of CBF and is based on the assumption that the MCA has a constant diameter and changes in MCA_V directly link to changes in regional CBF associated with MCA blood supply (Serrador et al., 2000). CBF may be altered during ITL by systemic factors including systemic vascular resistance, arterial blood pressure, venous return and the partial pressure of arterial oxygen (P_aO_2) and carbon dioxide (P_aCO_2) and by local factors within the brain (e.g., autoregulation) (Claassen et al., 2021). The increased CBF during low-intensity ITL is possibly related to an increase in stroke volume and cardiac output (Convertino, 2019; Convertino et al., 2004). This

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increased cardiac output contributes to a higher MAP (i.e., perfusion pressure) and CBF during ITL in pigs and therefore could also occur in humans (Yannopoulos et al., 2005). In addition, there exists the possibility that low-intensity ITL reduces intracranial pressure which could also increase CBF (Kiehna et al., 2013). However, high-intensity ITL may cause competition for blood flow between the respiratory muscles (i.e., the diaphragm) and the peripheral vasculature (Sheel et al., 2001, 2002; St Croix et al., 2000; Witt et al., 2007). Further, high-intensity ITL may cause internal jugular vein collapse (Tsao et al., 2014), increases in intracranial pressure and subsequent reductions in cerebral perfusion pressure (Chen et al., 2018; Winklewski et al., 2019; Zunino et al., 2024). One or all of these mechanisms may potentially lead to a transient decrease in CBF.

There is evidence that impaired CBF, and its regulation, can cause cognitive dysfunction which is present in patients with respiratory disease (Bliss et al., 2021; Chen et al., 2024; Reis et al., 2013). In contrast, it has been proposed that an increase in CBF can improve cognitive function, and during whole-body exercise when CBF is elevated there is an in increase in cognitive performance (Brisswalter et al., 2002; McMorris et al., 2011). The Trail Making Test (TMT) is a widely used test of speed of cognitive processing and executive function (Sánchez-Cubillo et al., 2009). Recently, Taytard et al. (2022) reported that moderate-intensity ITL undertaken at 45 % of P_{Imax} for 10 mins in young and healthy adults decreased Part B of the TMT compared to unloaded (control) conditions. The mechanisms for this are not well understood but could be due to sensory-cognitive interferences that lead to cognitive impairment in response to ITL. It could be hypothesized that impaired cognitive function during ITL would be due to reduced CBF. However, both the cerebrovascular and executive function responses to increased inspiratory muscle work using ITL have not been measured. This is important as cerebrovascular and cognitive function are interrelated and contribute to overall brain health, and both should be measured together to determine how these combined parameters are influenced by elevated inspiratory muscle work (Bliss et al., 2021).

Accordingly, we investigated the cerebrovascular and executive function responses to increased inspiratory muscle work using high-intensity ITL in resting healthy men. We hypothesized that impaired executive function during ITL would be due to reduced CBF.

2. Methods

2.1. Participants

Eight apparently healthy men with respiratory function within normal limits participated in the study (Table 1). We elected to focus upon males for the present study due to the potential sex-based differences in respiratory (Dominelli and Molgat-Seon, 2022) and cerebrovascular (Robison et al., 2019) physiology. The exclusion criteria were current cigarette smokers; history or current symptoms of cardiopulmonary disease; contraindications to exercise testing; and a body mass index of < 18.5 or > 30 kg/m^2. A self-reporting medical history questionnaire confirmed that participants were free from illness and injury and not taking any medication and/or dietary supplements during the study. All participants provided written, informed consent. All study procedures were approved by the University of Southern Queensland Human Research Ethics Committee (H21REA244), which adheres to the Declaration of Helsinki. The study was also registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12621001767897).

Table 1
Participant anthropometrics and respiratory function. Values are mean ± SD.

Age (years)	33 ± 6
Height (cm)	176 ± 3
Body mass (kg)	90 ± 9
Body mass index (kg/m^2)	29 ± 2
FVC (L)	5.45 ± 0.58
FVC (% predicted)	104 ± 10
FEV_1 (L)	4.38 ± 0.43
FEV_1 (% predicted)	102 ± 8
FEV_1/FVC (%)	81 ± 3
FEV_1/FVC (% predicted)	99 ± 3
P_{Imax} (cmH_2O)	105 ± 9
P_{Imax} (% predicted)	97 ± 9

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; P_{Imax}, maximal inspiratory mouth pressure. Predicted values for pulmonary volumes and capacities are from Quanjer et al. (2012) and for P_{Imax} are from Wilson et al. (1984).

2.2. Experimental design

Participants attended the laboratory for two visits on separate days between 48 h and 1 week apart. During visit 1, height, body mass, pulmonary function and P_{Imax} were assessed according to published guidelines and statements (Graham et al., 2019; Laveneziana et al., 2019). Participants were also familiarized with all the study procedures. During the second visit, participants undertook 4 experimental conditions: 1) ITL targeting 70 % of P_{Imax}; 2) ITL targeting 70 % of P_{Imax} with cognitive testing; 3) ITL targeting 2 % of P_{Imax}; and 4) ITL targeting 2 % of P_{Imax} with cognitive testing. The order in which each participant undertook the conditions was randomized (i.e., they each commenced with a different condition). Each experimental condition lasted for 10 min with 3 min of rest and recovery before and after each condition. There was a 10 min washout period between conditions and the next condition was not commenced until HR, MAP and MCA_V had returned to resting values (Fig. 1). During conditions 2 and 4, participants used an iPad (6th generation, Apple Inc, Cupertino, CA, USA) and undertook the TMT parts A and B during the 4–6th min of ITL which was delivered using an application (https://apps.apple.com/us/app/trail-making-test/id6470496820). This cognitive test was chosen because it assesses central executive function and could be used during ITL and would be completed within approximately 2 min (Branch, 1944; Sánchez-Cubillo et al., 2009). The TMT Parts A and B were automatically randomized for each condition to reduce the chances of a learned effect taking place between measures. There were no significant differences in physiological variables between: 1) ITL targeting 70 % of P_{Imax}; and 2) ITL targeting 70 % of P_{Imax} with cognitive testing so the data were pooled together (ITL-Load). Similarly, there were no significant differences in physiological variables between: 3) ITL targeting 2 % of P_{Imax}; and 4) ITL targeting 2 % of P_{Imax} with cognitive testing so the data were pooled together (ITL-Control).

2.3. Anthropometrical measures and pulmonary function

Height and body mass were recorded using a wall mounted electronic stadiometer (Seca 213; Seca, Hamburg, Germany) and an electronic scale (Tanita BC-541; Tanita, Kewdale, Australia), respectively. Pulmonary function was assessed using a spirometer (Vmax® Encore PFT system; Vyaire Medical, Chicago, IL, USA) and measurements were expressed as absolute values and as percentages of predicted values (Quanjer et al., 2012).

2.4. Inspiratory pressure threshold loading

The ITL device has been described previously (Iqbal et al., 2023). Participants were seated with their feet and back supported and elbows resting on a table. The ITL device was placed on the table and its height adjusted so the participants could reach the mouthpiece with their head and neck in a neutral alignment. Participants wore a noseclip and breathed through a flanged mouthpiece. The ITL device was attached in series with a pneumotachograph (Model 3813; Hans Rudolph, Shawnee Mission, KS, USA) and the inspiratory port of a two-way non-rebreathing valve (Model 2730; Hans Rudolph, Shawnee Mission, KS, USA). Volume

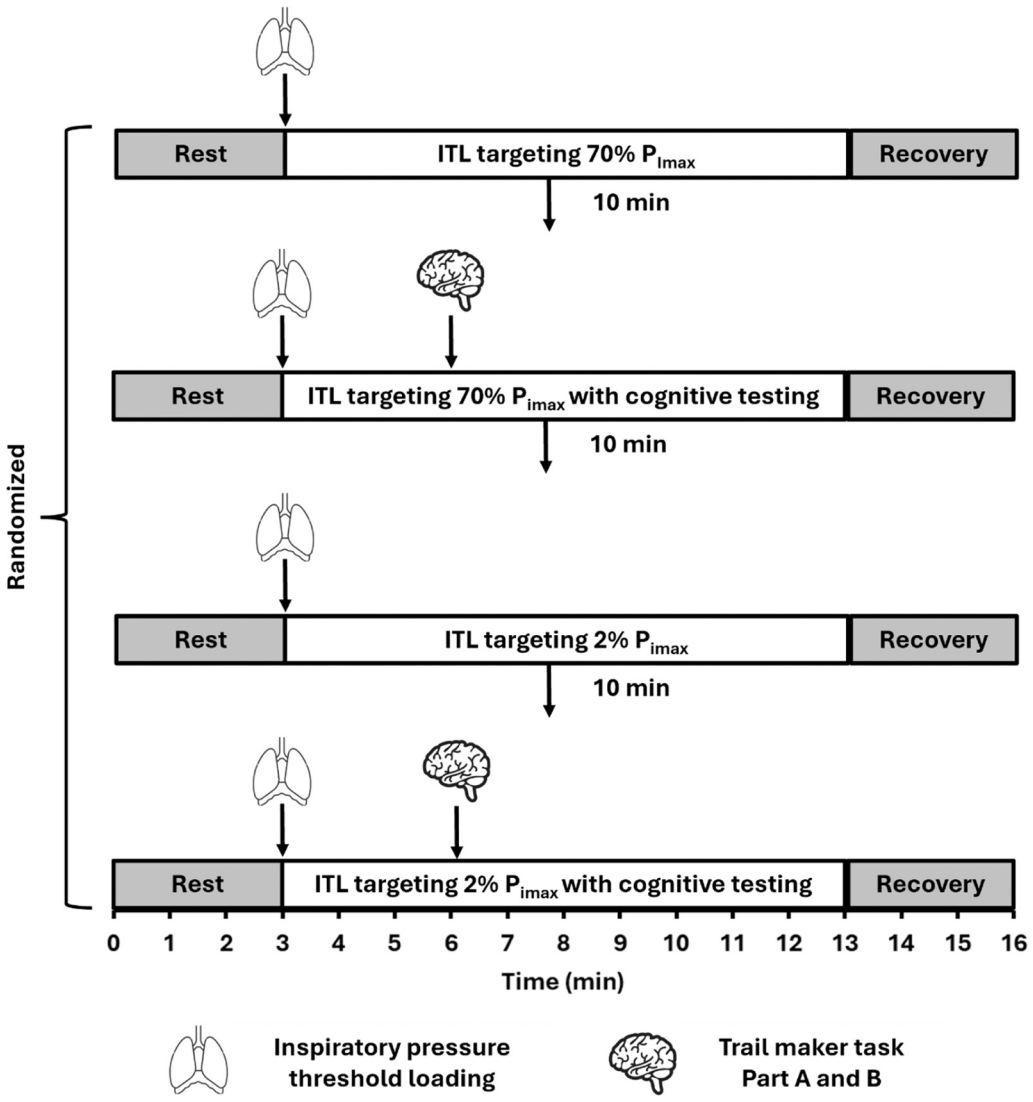

Fig. 1. Schematic of experimental design. Inspiratory pressure threshold loading (ITL) targeting either 70 % (ITL-Load) and or 2 % (lTL-Control) of maximal inspiratory mouth pressure (P_{Imax}).

was obtained by numerical integration of the flow signal. Adjustable weights were attached to a plunger with an inspiratory threshold load that had to be met for the participant to inspire. For ITL-Load, weights corresponding to a threshold pressure of 70 % of the participants P_{Imax} were attached to the ITL device. For ITL-Control, no weights were placed on the ITL device. In both ITL-Load and ITL-Control, participants maintained a breathing frequency of 15 breaths/min and a duty cycle (T_IT_{ToT}) of 0.5 by listening to a computer-generated audio signal with distinct inspiratory and expiratory tones. For ITL-Load, target inspiratory mouth pressure was displayed on a computer screen to provide continuous visual feedback. End-tidal partial pressure of CO_2 ($P_{ET}CO_2$) was measured via the expiratory port of the two-way non-rebreathing valve port, which was connected to a CO_2 gas analyzer (AD Instruments, Bella Vista, Australia).

2.5. Maximal inspiratory mouth pressure

P_{Imax} was assessed using the same experimental equipment used for the ITL whilst participants were seated and wearing a nose clip. Participants breathed through a flanged mouthpiece attached to a manually operated occlusion valve. A minor leak was present to prevent glottic closure and recruitment of the orofacial musculature. After a small period of relaxed tidal breathing, the valve was closed at end expiration, and the participants were instructed to breathe to residual volume and then make a maximal inspiratory effort against the occlusion. Inspiratory mouth pressure (P_I) was measured using a calibrated transducer (MLT844; AD Instruments, Bella Vista, Australia) inserted into the side port of the flanged mouthpiece. Repeat efforts were separated by 30 s and were performed until three serial measures differed by no more than 10 % or 10 cmH_2O, whichever was smallest (Mills et al., 2013). The highest value recorded was used for subsequent analysis.

2.6. Cardiovascular hemodynamics and perceptual responses

HR and arterial blood pressure were measured on a continuous beat-to-beat basis using finger photoplethysmography (Human NIBP controller; AD Instruments, Bella Vista, NSW, Australia) placed on the middle finger of the non-dominant hand and supported on a front table positioned at the heart level. Stroke volume was derived from the blood pressure waveform using the Modelflow method (Kh, 1983). Cardiac output was calculated as the product of HR and stroke volume. Total peripheral resistance was calculated as MAP/cardiac output. Arterial oxygen saturation was estimated using infrared fingertip pulse oximetry (Model 8600; Nonin, Plymouth, MN, USA). The rating of perceived dyspnea [RPD; Borg modified CR10 scale (Borg, 1982)] was used as a measure of the effort required to overcome the pressure threshold load.

Participants were asked to rate their sensations of respiratory effort out of 10 at rest, every min during ITL, and in the first min of recovery.

2.7. Data capture and analyses

Flow, pressure, CO_2 and finger photoplethysmography data was continuously sampled at 1 kHz using a 16-channel analog-to-digital data acquisition system (PowerLab 16/35; AD Instruments, Bella Vista, Australia) and recorded using LabChart v8.1.2 software (ADInstruments, Bella Vista, Australia). Non-physiological data that resulted from swallowing, coughing, and breath holding was identified by visual inspection and removed.

2.8. Cerebral hemodynamics

TCD was used to measure cerebrovascular hemodynamics (DopplerBox X; Compumedics DWL, Singen, Germany). Participants were seated and fitted with a headpiece that houses two 2-MHz TCD ultrasound probes that will be fixed and aligned bilaterally to the left and right cranial temporal bone windows to insonate the middle cerebral artery at a depth of approximately 40–65 mm. Beat-to-beat measurements of MCA_V were recorded onto software (QL Reader; Compumedics DWL, Singen, Germany) sampling at 100 Hz and stored for subsequent offline analysis. If a bilateral signal was not obtained, then analysis took place with only the side that was able to be obtained. The cerebrovascular conductance index (CVCi) and cerebrovascular resistance index (CVRi) were calculated as MCA_V/MAP and MAP/MCA_V, respectively (Skow et al., 2022).

2.9. Statistical analyses

All physiological variables collected at rest and recovery and during ITL were averaged into 1 min epochs. Statistical analyses were performed using SPSS for Windows (IBM, Chicago, USA). A convenience sample size was used, as we did not have any published data to estimate the differences in MCA_V between the experimental conditions. Our between-day reliability in resting MCA_V assessed with a coefficient of variation from our previous studies is < 5 % and therefore we were confident in the ability of our study design to detect possible differences between our experimental conditions (Bliss et al., 2023, 2022; Downs et al., 2023). Normality was assessed using a Shapiro-Wilk test and the data was normally distributed. Comparisons between ITL-Load and ITL-Control for the TMT data were undertaken with paired t-tests. A two-way analysis of variance (ANOVA) was used to determine the effects of 'time' (rest, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 min and recovery) and 'experimental condition' (ITL-Load vs. ITL-Control). Significant interaction effects were followed by pairwise comparisons between experimental conditions using the Bonferroni method. A one-way ANOVA was also used to test the main effects of time for the cerebrovascular responses to ITL-Load and ITL-Control separately. Repeated measures correlations were used to determine the within-individual association for paired measures for multiple individuals (Bakdash and Marusich, 2017; Marusich and Bakdash, 2021). The repeated measures correlations coefficient (r_{rm}) is bounded by −1–1 and shows the strength of the linear association between two variables. We used this to determine the relationship between the absolute change in MCA_V from rest to the end of ITL: and 1) TMT times; and 2) TMT errors. Statistical significance was set at $P < 0.05$. Results are presented as means ± SD.

3. Results

3.1. Cardiorespiratory and perceptual responses to inspiratory pressure threshold loading

The cardiorespiratory and perceptual responses to ITL-Load and ITL-Control are shown in Fig. 2 and Table 2. There were time x condition interactions ($P < 0.05$) for MAP, HR and P_I (Fig. 2), and cardiac output, T_IT_{ToT} and RPD (Table 2). These responses were higher for ITL-Load compared to ITL-Control. There were main effects of time ($P < 0.05$) for stroke volume, estimated arterial oxygen saturation, $P_{ET}CO_2$ and minute ventilation, but no time x condition interaction effects (Table 2). The were no main or interaction effects for total peripheral resistance, tidal volume and breathing frequency.

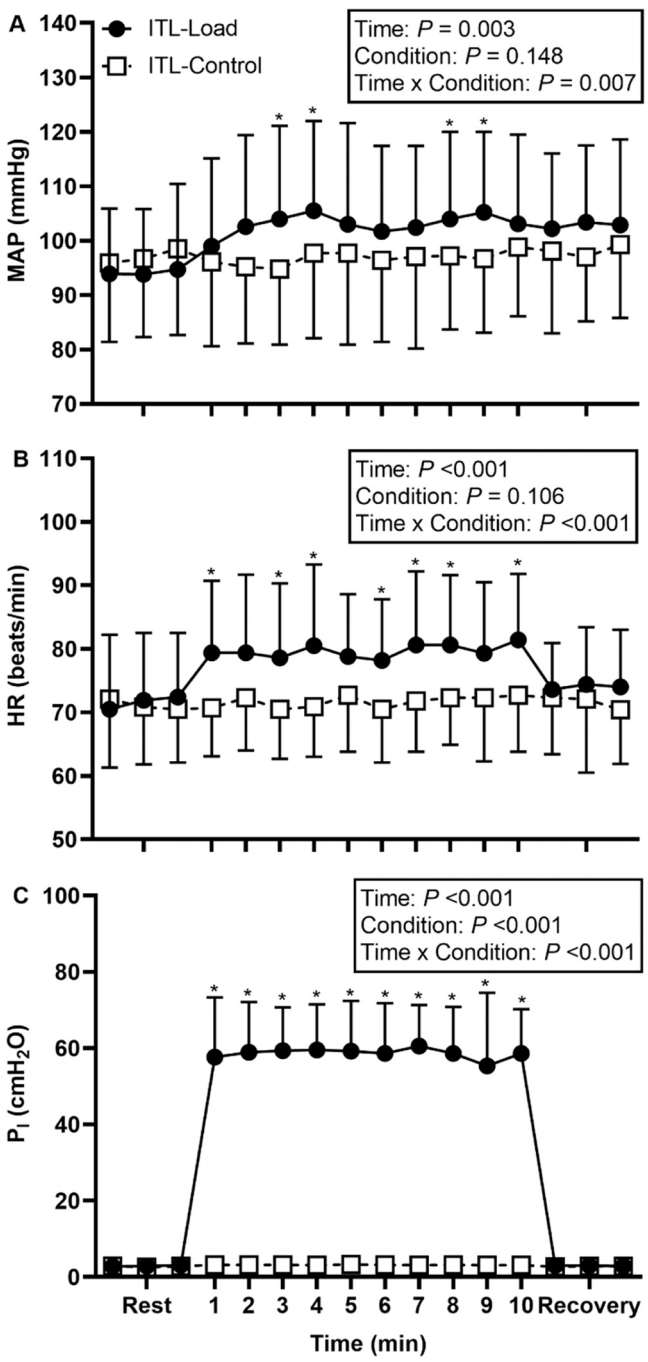

Fig. 2. Mean arterial pressure (MAP; A), heart rate (HR; B) and inspiratory mouth pressure (P_I; C) responses to inspiratory pressure threshold loading targeting 70 % (ITL-Load) and 2 % (ITL-Control) of maximum inspiratory mouth pressure. Main effects of time and condition and time x condition interaction effects are provided in each panel. *Significantly different between ITL-Load and ITL-Control ($P < 0.05$).

Table 2
Cardiorespiratory and perceptual responses to inspiratory pressure threshold loading (ITL) targeting 70 % (ITL-Load) and 2 % (ITL-Control) of maximum inspiratory mouth pressure. Values are mean ± SD. Bold values represent significant differences.

	Condition	Rest	1st Min	5th Min	10th Min	Recovery	Time	Condition	Time x Condition
$\dot{Q}$ (L/min)	ITL-Load	5.12 ± 1.41	5.91 ± 2.11*	6.02 ± 1.66*	6.50 ± 1.76*	5.45 ± 1.37	**0.007**	0.197	**0.005**
	ITL-Control	5.04 ± 1.09	5.04 ± 1.18	5.33 ± 1.43	5.57 ± 1.33	5.35 ± 1.33			
SV (mL)	ITL-Load	71.1 ± 14.0	74.0 ± 22.5	76.0 ± 16.6	80.1 ± 18.8	73.8 ± 16.6	**0.028**	0.469	0.163
	ITL-Control	71.1 ± 12.0	70.9 ± 12.5	73.4 ± 14.2	75.7 ± 15.0	74.5 ± 12.8			
TPR (mmHg/L/min)	ITL-Load	20.1 ± 6.4	19.2 ± 9.4	18.6 ± 7.8	16.8 ± 4.7	20.2 ± 6.4	0.204	0.751	0.451
	ITL-Control	20.2 ± 5.8	20.5 ± 7.7	19.2 ± 6.6	19.1 ± 5.8	19.5 ± 5.8			
SaO_2 (%)	ITL-Load	97 ± 3	97 ± 1	98 ± 1	98 ± 1	98 ± 2	**0.003**	0.758	0.412
	ITL-Control	97 ± 3	98 ± 1	98 ± 2	98 ± 1	98 ± 1			
$P_{ET}CO_2$ (mmHg)	ITL-Load	36.1 ± 3.9	36.5 ± 5.0	38.4 ± 3.4	39.1 ± 4.8	36.5 ± 3.4	**0.017**	0.237	0.455
	ITL-Control	36.2 ± 2.5	36.0 ± 3.3	36.7 ± 3.7	37.3 ± 3.9	36.0 ± 4.1			
f_B (breaths/min)	ITL-Load	15 ± 4	14 ± 2	14 ± 1	16 ± 3	17 ± 6	0.370	0.374	0.380
	ITL-Control	15 ± 4	15 ± 1	15 ± 1	15 ± 2	15 ± 5			
V_T (L)	ITL-Load	1.07 ± 0.58	1.17 ± 0.70	1.31 ± 0.56	1.28 ± 0.65	1.14 ± 0.65	0.212	0.709	0.512
	ITL-Control	1.22 ± 0.56	1.28 ± 0.39	1.23 ± 0.44	1.30 ± 0.41	1.23 ± 0.62			
$\dot{V}_E$ (L/min)	ITL-Load	14.5 ± 5.6	16.9 ± 10.2	18.9 ± 7.9	19.3 ± 9.2	17.9 ± 8.1	**0.005**	0.922	0.362
	ITL-Control	16.3 ± 4.6	19.3 ± 10.2	18.7 ± 6.1	19.5 ± 6.0	16.1 ± 5.6			
T_I/T_{ToT}	ITL-Load	0.48 ± 0.06	0.54 ± 0.09*	0.54 ± 0.07*	0.55 ± 0.08*	0.47 ± 0.06	**0.001**	**0.001**	**0.001**
	ITL-Control	0.47 ± 0.06	0.46 ± 0.05	0.47 ± 0.06	0.46 ± 0.06	0.46 ± 0.07			
RPD	ITL-Load	1.1 ± 1.3	5.0 ± 2.1*	5.0 ± 2.1*	7.0 ± 1.7*	2.7 ± 2.3	**< 0.001**	**< 0.001**	**< 0.001**
	ITL-Control	1.2 ± 1.3	1.6 ± 1.2	1.6 ± 1.2	1.5 ± 1.1	1.4 ± 1.0			

Abbreviations = $\dot{Q}$, cardiac output; SV, stroke volume; TPR, total peripheral resistance; SaO_2; estimated arterial oxygen saturation; $P_{ET}CO_2$, end tidal carbon dioxide pressure; f_B, breathing frequency; V_T, tidal volume; $\dot{V}_E$, minute ventilation; T_I/T_{ToT}, duty cycle; RPD, rating of perceived dyspnea. *Significantly different between ITL-Load and ITL-Control ($P < 0.05$).

3.2. Cerebrovascular responses to inspiratory pressure threshold loading

The cerebrovascular responses to ITL-Load and ITL-Control are shown in Fig. 3. There were time x condition interactions ($P < 0.01$) for MCA_V, CVCi and CVRi. Subsequent one-way ANOVAs revealed main effects of time ($P < 0.01$) for MCA_V, CVCi and CVRi during both ITL-Load and ITL-Control. This demonstrated that during ITL-Load there was a small time-dependent increase in MCA_V and CVCi and a small time-dependent decrease in CVRi. Conversely, this demonstrated that during ITL-Control there was a small time-dependent decrease in MCA_V and CVCi and a small time-dependent increase in CVRi.

3.3. Within-breath middle cerebral artery velocity responses to inspiratory pressure threshold loading

Fig. 4 shows the raw MCA_V, arterial pressure, stroke volume and P_I responses during ITL-Load and ITL-Control in the same participant. During ITL-Load, the MCA_V, arterial pressure and stroke volume response varied cyclically in time with each respiratory phase of each breath and was reduced during inspiration and responded to increase again during expiration.

3.4. Executive function responses to inspiratory pressure threshold loading

The TMT test times and errors are shown in Fig. 5. Part A ($P = 0.007$) and Part B ($P = 0.013$) times for the TMT were slower for ITL-Load compared to ITL-Control. There were more errors for Part B ($P = 0.036$), but not Part A ($P = 0.356$) of the TMT for ITL-Load compared to ITL-Control. The time for Part B - Part A was longer (29.4 ± 12.7 s vs. 9.9 ± 10.1 s; $P = 0.049$) for ITL-Load compared to ITL-Control, respectively.

3.5. Relationships between changes in middle cerebral artery velocity and trail making task

The relationship between the absolute change in MCA_V from rest to the end of ITL and TMT times and errors is shown in Fig. 6. There were significant correlations between the absolute change in MCA_V from rest to the end of ITL and TMT times for Part A ($r_{rm}(7) = 0.81$, 95 % CI [0.307, 0.958], $P = 0.009$) and Part B ($r_{rm}(7) = 0.67$, 95 % CI [0.012, 0.924], $P = 0.048$). There were also significant correlations between the change in MCA_V from rest to the end of ITL and TMT errors for Part A ($r_{rm}(7) = 0.73$, 95 % CI [0.138, 0.94], $P = 0.024$), but not Part B ($r_{rm}(7) = 0.45$, 95 % CI [-0.309, 0.857], $P = 0.228$). These data indicate that the individual variability in MCA_V responses to ITL was associated with TMT times and Part A errors in that the increase in MCA_V resulted in slower TMT times and more errors for TMT Part A.

4. Discussion

4.1. Main findings

We investigated the cerebrovascular and executive function responses to increased inspiratory muscle work. Our main findings were that: 1) there was a time-dependent modest increase in MCA_V and CVCi with ITL-Load and a time-dependent modest decrease in CVRi with ITL-Load; 2) Part A and Part B times for the TMT were slower for ITL-Load compared to ITL-Control and there were more errors for Part B, but not Part A of the TMT for ITL-Load compared to ITL-Control; and 3) there were no significant correlations between the change in MCA_V from rest to the end of ITL and TMT times. This is the first study to demonstrate that ITL results in an increase in MCA_V, and a decreased executive function measured by the TMT, and based upon within-individual associations for paired measures, these two measures were related. Our findings contribute to the understanding of how cerebrovascular and cognitive function are interrelated and influenced by elevated inspiratory muscle work.

4.2. Cerebrovascular responses to inspiratory pressure threshold loading

To our knowledge this is the first study to demonstrate an increase in MCA_V in response during high-intensity ITL, although previous studies have investigated the effects of very low inspiratory mouth pressures of ~7–10 cmH_2O undertaken in a supine position (Cooke et al., 2006; Hayen et al., 2013). These studies also reported small (+5–10 %) increases in MCA_V. The change in MCA_V during ITL may be altered by systemic factors including systemic vascular resistance, arterial blood pressure, venous return, P_aO_2, P_aCO_2 and by local factors within the

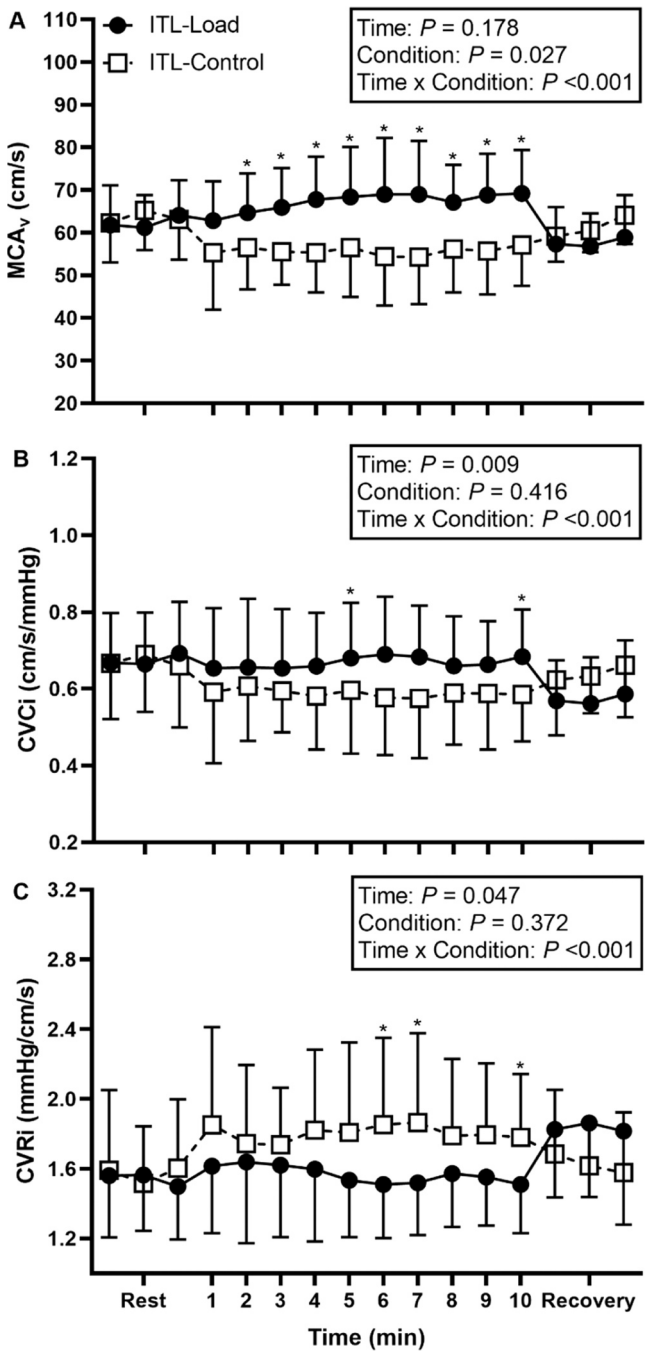

Fig. 3. Middle cerebral artery blood velocity (MCA_V; A), cerebrovascular conductance index (CVCi; B) and cerebrovascular resistance index (CVRi; C) responses to inspiratory pressure threshold loading targeting 70 % (ITL-Load) and 2 % (ITL-Control) of maximum inspiratory mouth pressure. Main effects of time and condition and time x condition interaction effects are provided in each panel. *Significantly different between ITL-Load and ITL-Control ($P < 0.05$).

brain (e.g., autoregulation) (Claassen et al., 2021).

During ITL-Load, we observed increases in MAP and cardiac output, but the increase in cardiac output was due mainly to an increased HR, rather than stroke volume. Changes in blood pressure, cardiac output, and neural activity ensure sufficient blood flow for the peripheral and cerebral circulation (Claassen et al., 2021; Smith and Ainslie, 2017). This increased cardiac output contributes to a higher MAP (i.e., perfusion pressure) and CBF during ITL in pigs and therefore could also occur in humans (Yannopoulos et al., 2005). In addition, there exists the possibility that ITL reduces intracranial pressure which could also increase CBF (Kiehna et al., 2013). We also suggest that the increases we observed in MAP and HR would contribute to the increase in MCA_V and, therefore, the CVCi and CVRi responses to ITL to ensure cerebral partial pressure was maintained thus reflecting cerebral autoregulation integrity. The MAP and HR responses in our study are similar to those of others who have previously used ITL (Sheel et al., 2001, 2002; Witt et al., 2007). During ITL, it is postulated that there are both central and peripheral factors that increase MAP and HR above resting values. The increased inspiratory requirement to overcome the resistive load possibly resulted in vagal withdrawal (Hollander and Bouman, 1975) and the greater inspiratory contractile force probably increased the mechanical deformation of the diaphragm and the activity of the mechanically sensitive (type III) afferent fibers within the muscle (Dempsey et al., 2022). The changes to MAP and HR generated by mechanoreceptors appear earlier and are of a lesser magnitude than those of the more delayed-acting metaboreceptors. Therefore, it has been suggested that the MAP and HR increases observed in the early minutes of ITL to be mechanoreceptor and centrally mediated (Witt et al., 2007).

The primary factor involved in regulating CBF during whole-body exercise is P_aCO_2 (Smith and Ainslie, 2017). This concept is supported by the sensitivity of the cerebrovasculature to changes in P_aCO_2 at rest, but also that maximal incremental exercise first causes an increase in P_aCO_2, followed by a hyperventilation-induced decline in P_aCO_2 at near maximal intensity exercise. We did not measure P_aCO_2 directly, and instead used $P_{ET}CO_2$ as a noninvasive measurement of alveolar ventilation, and this is considered an adequate substitute for P_aCO_2 in healthy adults (Nassar and Schmidt, 2017). We did observe a small time-dependent increase in $P_{ET}CO_2$, but this was not different between ITL-Load and ITL-Control. Therefore, we suggest that P_aCO_2 either had little or no contribution to the increase in MCA_V during ITL.

Another factor for the regulation of CBF is cerebral metabolism. Although we did not measure cerebral metabolism, this may have contributed to the increase in MCA_V during ITL and this may be related to an increased cerebral uptake of O_2, glucose and/or lactate, as well as their metabolic by-products thus requiring increased CBF to ensure efficient removal via the venous circulation (Claassen et al., 2021). This may also increase due to the increased metabolic demands of the motor cortex during ITL, as the superior branches of the MCA supply blood to the primary motor cortex and this activity is increased during ITL (Gibo et al., 1981; Raux et al., 2007).

The final factor to explain the increase in MCA_V and, therefore, the CVCi and CVR responses to ITL is an increase in the activity of sympathetic nerves and brain activity. CBF may be controlled through either sympathetic or parasympathetic innervations (Brassard et al., 2017; Hamner and Tan, 2014). Although we did not measure neurogenic control, this may have contributed to the increase in MCA_V during ITL based on previous findings that have demonstrated that the cerebral cortex is involved in the compensation of sustained ITL (Raux et al., 2013; Taytard et al., 2022; Tremoureux et al., 2010).

4.3. *Mechanical effects of inspiratory pressure threshold loading*

We observed that the MCA_V response varied cyclically in time with each respiratory phase of each breath and was reduced during inspiration and responded to increase again during expiration. The same response was observed in arterial pressure and stroke volume. During inspiration at rest, the diaphragm descends, resulting in a lowering of intrathoracic pressure and the expansion of the lungs. This reduced intrathoracic pressure decreases right atrial pressure, increasing the gradient for venous return and ultimately increasing both right and left ventricular stroke volume (Guyton et al., 1957). Large increases in intrathoracic pressure also occur during ITL, which further reduces left ventricular stroke volume due to direct ventricular interaction and increased left ventricular afterload (Cheyne et al., 2018, 2016; Natori et al., 1979). We speculate that the high intrathoracic pressures during ITL-Load may have resulted in a mechanical cardio-pulmonary

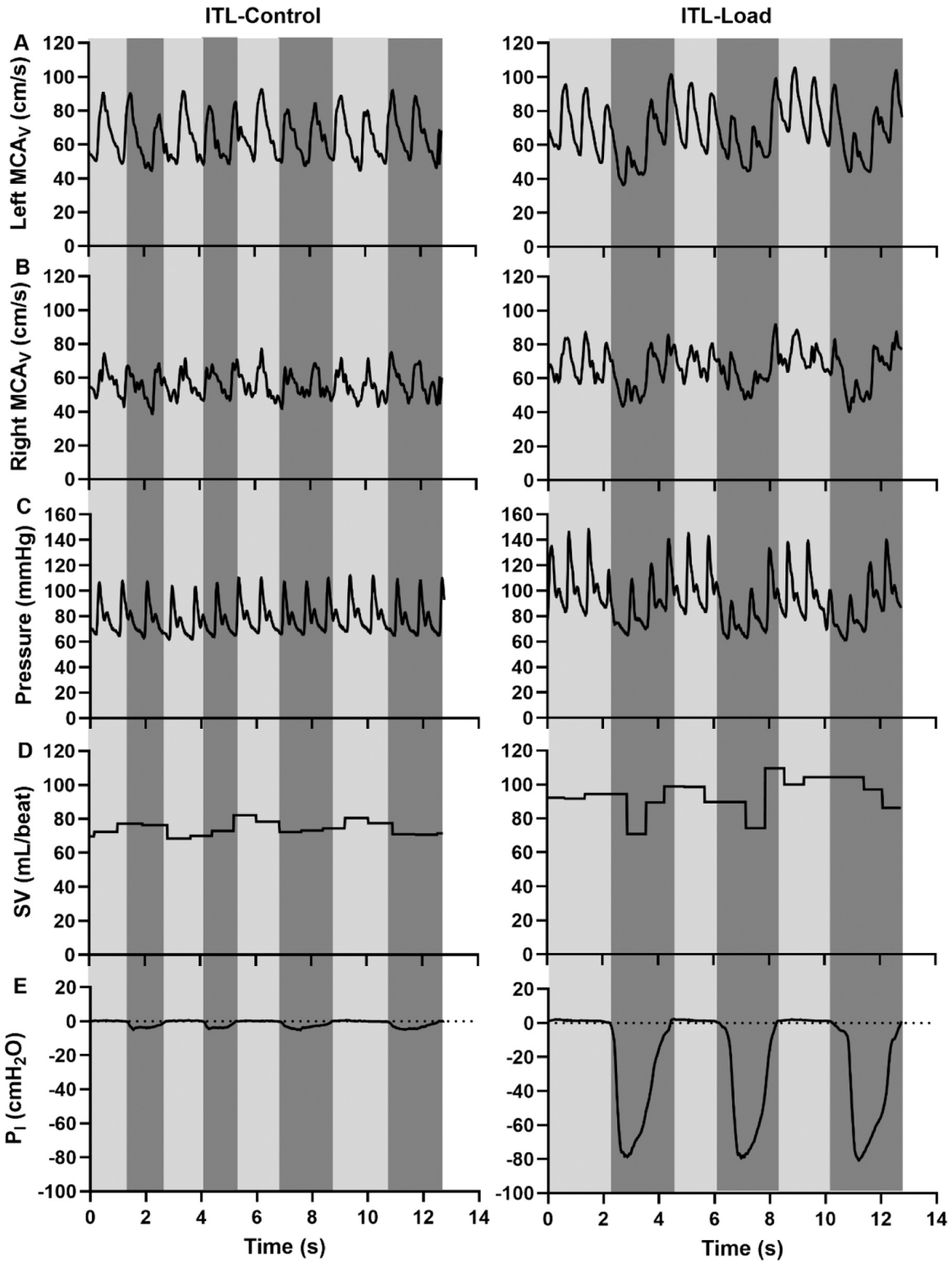

Fig. 4. Raw left (A) and right (B) middle cerebral artery blood velocity (MCA_V), arterial pressure (C), stroke volume (SV; D) and inspiratory mouth pressure (P_I; E) responses from a single participant to inspiratory pressure threshold loading targeting 2 % (lTL-Control; Left panel) and 70 % (ITL-Load; Right panel) of maximum inspiratory mouth pressure. Light and dark shaded areas denote expiration and inspiration, respectively.

interaction that transiently reduced MCA_V during inspiration. ITL-Load may have also caused internal jugular vein collapse (Tsao et al., 2014), increases in intracranial pressure and subsequent reductions in cerebral perfusion pressure (Chen et al., 2018; Winklewski et al., 2019; Zunino et al., 2024). One or all of these mechanisms may potentially lead to a transient decrease in CBF during inspiration.

4.4. Executive function responses to inspiratory pressure threshold loading

We observed that Part A and Part B times for the TMT were slower for ITL-Load compared to ITL-Control and there were more errors for Part B, but not Part A of the TMT for ITL-Load compared to ITL-Control. The time for Part B - Part A was also longer for ITL-Load compared to ITL-

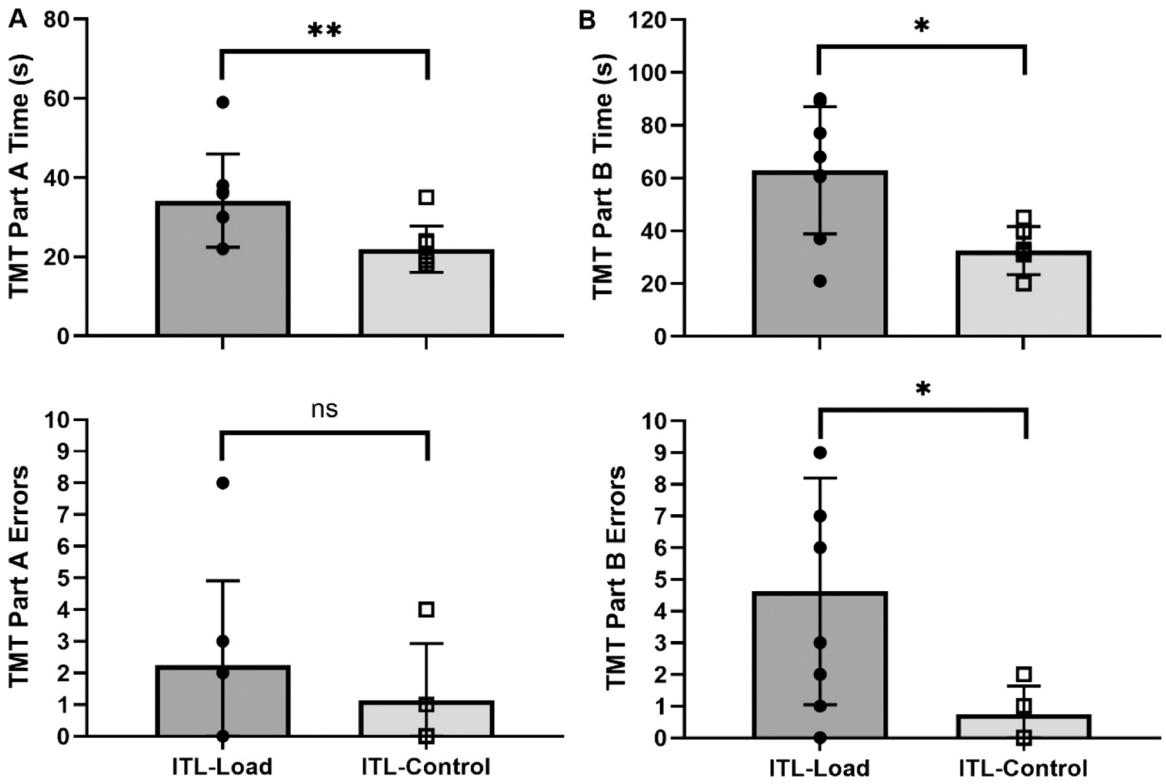

Fig. 5. Trail making task (TMT) times (Top panel) and errors (Bottom panel) for Part A (A; Left panels) and Part B (B; Right panels) during inspiratory pressure threshold loading targeting 70 % (ITL-Load; circles) and 2 % (lTL-Control; squares) of maximum inspiratory mouth pressure. Significantly different between ITL-Load and ITL-Control (*$P < 0.05$; **$P < 0.01$). ns = not significant.

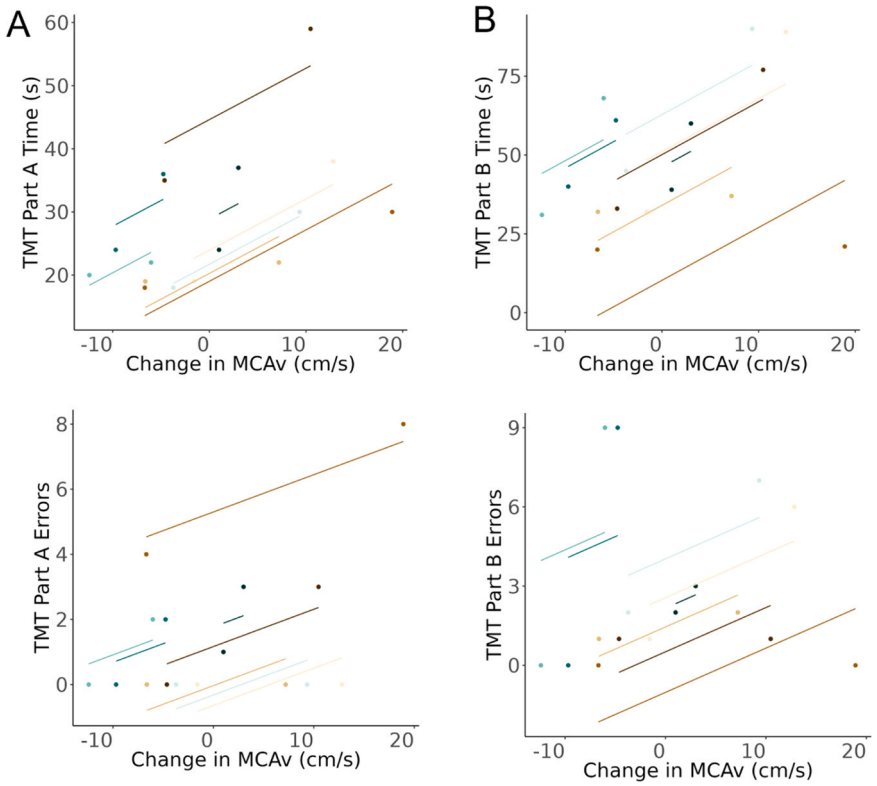

Fig. 6. Relationship between changes in middle cerebral artery velocity (MCA_V) and trail making task (TMT) times (Top panel) and errors (Bottom panel) for Part A (A; Left panels) and Part B (B; Right panels) during inspiratory pressure threshold loading targeting of maximum inspiratory mouth pressure. Circles represent individual participant data points and parallel lines are fit to the data from each participant.

Control. Our findings are supported by Taytard et al. (2022) who reported that moderate ITL undertaken at 45 % of P_{Imax} for 10 mins in young and healthy adults decreased Part B of the TMT compared to unloaded conditions. Our results would support the hypothesis of a sensory-cognitive interference which caused the cognitive impairment in response to ITL. A connected activation of cortical networks and a decline in cognitive function during ITL would indicate motor-cognitive interference, particularly in case of a predominant alteration of executive cognitive performances (Taytard et al., 2022). This may occur through a possible "resource allocation" or "bottleneck effect" (Leone et al., 2017). This possibility may be more likely as the TMT test involves activation of frontal brain areas, including the supplementary motor area (Stuss et al., 2001), and the TMT Part B strongly activates the supplementary motor area and premotor cortex (Karimpoor et al., 2017), all structures that are involved in the brain response to ITL (Raux et al., 2013). We observed that the individual variability in MCA_V responses to ITL were associated with TMT times and Part A errors. The TMT assesses inhibitory control reflected by either a difference in the times between the components of the TMT (i.e. TMT B – TMT A) or by dividing the results of the components TMT (i.e. TMT B / TMT A) to obtain an inhibitory control index (Strauss et al., 2006). This is important as inhibitory control is a task involving the dorsolateral prefrontal cortex which is perfused by the MCA (Gibo et al., 1981; Oldrati et al., 2016). The dorsolateral prefrontal cortex during TMT testing would have increased metabolism resulting in increased MCA_V (McLaughlin and Malloy, 2017). Finally, the rating of perceived dyspnea was increased during ITL and adding the TMT during ITL increased perceived stress. The increased perceived stress during ITL may have increased amygdala cerebral metabolism. Any increases in blood flow to the amygdala resulting from this was not able to be measured in this experimental setup, as the amygdala is predominantly perfused by the anterior choroidal artery and segments of the posterior cerebral artery (Nikolenko et al., 2020). Hence, the cerebrovasculature may have regulated the needs for increased blood flow to the amygdala by redistributing blood flow to the amygdala during ITL.

4.5. Methodological limitations and future directions

The first limitation of the present study was that only men were included, which limits the generalizability of our findings. However, the purpose of this study was to elucidate the cerebrovascular and executive function responses to increased inspiratory muscle work, rather than to address potential sex-based differences. Future studies could investigate the differences in the CBF response to ITL in women and then between women and men.

The second limitation is that we evaluated changes in CBF indirectly by non-invasively measuring MCA_V using TCD. The rationale for the use of TCD to measure CBF is based on the assumption that the MCA has a constant diameter and changes in MCA_V directly link to changes in regional CBF associated with MCA blood supply (Serrador et al., 2000). However, there is evidence using magnetic resonance imaging that there is small (2 %) decrease in MCA cross-sectional area during rhythmic handgrip exercise in healthy participants (Verbree et al., 2017). Thus, we cannot assume that the MCA diameter did not also change during ITL. Indeed, a recent study that used incremental ITL with inspiratory mouth pressures of 46 cmH_2O found no change in internal carotid artery blood flow immediately after the resistive loading (Sato et al., 2025). The authors also reported that systolic blood pressure tended to be higher following ITL. Thus, in contexts where sympathetic nerve activity increases blood pressure, blood velocity may rise, yet CBF may not as there is no change in vessel diameter. Future research using ultrasound imaging to measure both velocity and diameter to determine blood flow is required to fully evaluate the effects of high-intensity ITL on CBF.

Finally, we used a T_IT_{ToT} of 0.5 and breathing frequency of 15 breaths/min which may limit comparisons against other studies that have reported a reflex reduction in resting leg blood flow using a T_IT_{ToT} of 0.7 (Sheel et al., 2001; Witt et al., 2007). We elected to do this because we wanted to replicate a natural breathing pattern with a high inspiratory resistance and during our pilot work participants found it challenging to complete the TMT and maintain and constant head position whilst breathing at a T_IT_{ToT} of 0.7.

The effects of respiratory muscle work on blood flow distribution to the respiratory and limb muscles have been studied previously by artificially manipulating the work of breathing (Sheel et al., 2018). When the work of breathing is elevated using ITL at rest or flow resistive loading during exercise, there is a decline in limb blood flow which may be directed towards the respiratory muscles (Dominelli et al., 2017; Harms et al., 1997; Sheel et al., 2001, 2002). Alternatively, when respiratory muscle work is unloaded using proportional assist ventilation and/or heliox, limb blood flow is preserved or increased (Dominelli et al., 2017; Harms et al., 1997). Recent research has also reported that internal carotid artery conductance was reduced during exercise with isocapnic hyperpnea following ITL (Sato et al., 2025). This may suggest that during whole-body exercise with a competition for blood flow, there may be a reflex reduction in CBF (i.e, metaboreflex). However, how manipulating the work of breathing during whole-body exercise impacts upon cerebrovascular and cognitive responses is unknown and is a future research direction. This may assist with our clinical understanding of cerebrovascular and cognitive function in patients who experience high levels of respiratory muscle work including those with chronic obstructive pulmonary disease or heart failure.

5. Conclusion

We investigated the cerebrovascular and executive function responses to increased inspiratory muscle work. We observed for the first time that there was a time-dependent small increase in MCA_V and CVCi with ITL-Load and a time-dependent small decrease in CVRi; 2) Part A and Part B times for the TMT were slower for ITL-Load compared to ITL-Control and there were more errors for Part B, but not Part A of the TMT for ITL-Load compared to ITL-Control; and 3) there were significant correlations between the change in MCA_V from rest to the end of ITL and TMT times. This is the first study to demonstrate that ITL results in an increase in MCA_V and a decreased executive function measured by the TMT, and these two measures were related. Our findings contribute to the understanding of how cerebrovascular and cognitive function are interrelated and influenced by elevated inspiratory muscle work. Future research may investigate how manipulating the work of breathing during whole-body exercise impacts upon cerebrovascular and cognitive responses.

Authors' contributions

EB and DM designed the project and aided in interpreting the results; EB and DM directed the project, developed the theoretical framework, and drafted the manuscript; DM performed the analysis, designed the figures and interpreted the results; EB and DM wrote the and edited the manuscript. EB and DM read and approved the final manuscript.

CRediT authorship contribution statement

Edward Bliss: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mills Dean Elliot:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of their data.

Ethical approval

All study procedures were approved by the University of Southern Queensland Human Research Ethics Committee (H21REA244), which adheres to the Declaration of Helsinki. The study was also registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12621001767897).

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Declaration of Competing Interest

The authors declare that they have no conflict of interests.

Data availability

Data will be made available on request.

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