SCHOOL OF MEDICINE AND HEALTH SCIENCES
UNIVERSITY OF OTAGO, WELLINGTON

Ollie Ball

Assessment of Cerebrovascular Reactivity in Response to an Alpha1-Adrenergic Blocker

Supervised by: Dr Shieak Tzeng

Sponsor: The Surgical Research Trust

LAY REPORT

Blood vessels in the brain constrict and dilate under a number of circumstances in order to adequately regulate flow to the brain. Altered carbon dioxide (CO_2) in the blood is one such mechanism which alters brain blood flow. Increased CO_2 dilates blood vessels resulting in an increase in flow, and vice versa (termed CO_2 reactivity – defined as a change in flow per millimetre of mercury change in CO_2 levels). This change in blood flow can be measured in a blood vessel supplying the brain called the middle cerebral artery (MCA) using transcranial Doppler ultrasound.

It is not definitively known whether the sympathetic nervous system (SNS) has any role in CO_2 reactivity. However it has been shown that a reduced reactivity to CO_2 predicts poorer outcomes in stroke, sub-arachnoid haemorrhage and brain injury.

Ten young, healthy participants consented to breathing normal room air, followed by breathing a gas mixture of increased CO_2, oxygen and nitrogen balance for 90 seconds, followed by hyperventilation for 90 seconds. Participants were then given a drug (prazosin) which blocks the SNS's ability to constrict blood vessels and the protocol repeated. We measured the MCA flow velocity before and after prazosin, to give us pre and post prazosin CO_2 reactivities.

We found that after blocking the SNS with prazosin, there was a reduced reactivity to CO_2, specifically this was found when CO_2 in the blood is decreased. These results may have future implications for manage of stroke, sub-arachnoid haemorrhage and traumatic brain injury risk.

SCIENTIFIC REPORT

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SAPERE AUDE

Te Whare Wānanga o Otāgo

NEW ZEALAND

Assessment of Cerebrovascular Reactivity in Response to an Alpha$_1$-Adrenergic Blocker

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Abstract

Background and purpose – There is no clear consensus whether the sympathetic nervous system (SNS) has an effect on cerebrovascular CO_2 reactivity. This study was designed to investigate whether SNS suppression, using an alpha$_1$-adrenoreceptor antagonist (Prazosin) affected CO_2 reactivity in young, healthy humans.

Methods – CO_2 reactivity was assessed in 10 healthy participants (23 ± 2 years, 5 females) using a protocol involving 60 seconds baseline air breathing, followed by a graded hypercapnia, followed by a graded hypocapnia before and after an oral dose of 0.05 mg kg^{-1} prazosin. Cerebral blood flow velocity (MCAv), mean arterial blood pressure (MAP), heart rate (HR) and the partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) were recorded throughout testing.

Results – Prazosin had no effect on HR, $P_{ET}CO_2$, MAP or MCAv at baseline. However, prazosin reduced i) the absolute (2.40 ± 0.54 cm s^{-1} mmHg^{-1} *vs.* 2.13 ± 0.48 cm s^{-1} mmHg^{-1}; $p < 0.05$), and normalised (3.79 ± 0.75 % mmHg^{-1} *vs.* 3.40 ± 0.56 % mmHg^{-1}; $p < 0.05$) integrated CO_2 reactivity (reactivity for both hypercapnic and hypocapnic ranges); and ii) the absolute (2.00 ± 0.87 cm s^{-1} mmHg^{-1} *vs.* 1.32 ± 0.50 cm s^{-1} mmHg^{-1}; p value < 0.05), and normalised (3.36 ± 1.56 % mmHg^{-1} *vs.* 2.18 ± 0.78 % mmHg^{-1}; $p < 0.05$) hypocapnic CO_2 reactivites. Prazosin had no effect on CO_2 reactivity in the hypercapnic range.

Conclusions – These data show that SNS suppression with prazosin reduces cerebral CO_2 reactivity, specifically in the hypocapnic ranges.

Introduction

Normal brain function is critically dependent on the maintenance of adequate cerebral blood flow (CBF). The control of CBF is achieved through a variety of physiological mechanisms, allowing it to respond to alterations in the physical and chemical environment. Alterations in the partial pressure of arterial CO_2 ($PaCO_2$) has a profound effect on the cerebral vasculature in healthy adults, and is termed cerebrovascular CO_2 reactivity. An increase in $PaCO_2$ (hypercapnia) produces a reduction in the tone in cerebral resistance arteries/arterioles, resulting in vasodilatation. Conversely, a decrease in $PaCO_2$ produces a reciprocal response. Within the $PaCO_2$ range normally studied (~30-70 mmHg); the CBF- $PaCO_2$ relationship is essentially linear. Hence CO_2 reactivity can be quantified by measuring the slope of this line.

Mechanisms by which alterations in $PaCO_2$ evoke changes in the cerebral vascular tone have not yet been fully elucidated. Available evidence supports the current thinking that a change in $PaCO_2$ influences vascular tone through a complex interplay of ion channel activation and release of vasoactive factors (1–3). However, there is some evidence suggesting that the sympathetic nervous system (SNS) may contribute, at least in part, to $PaCO_2$ stimulated changes in cerebral vascular tone (4,5). In support of this suggestion is the evidence that the cerebral vessels are extensively innervated by noradrenaline-containing sympathetic fibres originating from the superior cervical ganglion (6–8). In human cerebral vessels, these fibres primarily act on alpha(α)$_1$-adrenoreceptors and have been shown to be blocked by a post-synaptic α_1-adrenergic antagonist (prazosin) (9,10). Despite this, there remains disagreement as to whether or not the SNS contributes to CO_2 reactivity (5,11–14). D'Alecy *et al.*, 1979 and Jordan *et al.*, 2000 found attenuating the SNS reduced CO_2 reactivity (4,5). However, a number of studies found that blocking the SNS had no effect on CO_2 reactivity (11–14). The methods used in these studies are indirect and it is difficult to ascertain whether their findings do actually represent the effect of an altered sympathetic activity on CO_2 reactivity.

The aim of this study was to directly assess the contribution of the sympathetic nervous system to CO_2 reactivity using α_1-adrenergic blockade (prazosin). Since sympathetic excitation evokes vasoconstriction in most vascular beds we hypothesized that α_1-adrenergic blockade would attenuate CO_2 reactivity. Impaired CO_2 reactivity has been found to be associated with an increased risk of stroke and subarachnoid haemorrhage (SAH), and predicts poorer prognosis in traumatic brain injury (TBI) (15–19). Therefore, results in support of this hypothesis may have clinical implications by identifying the mechanisms

underlying impaired CO_2 reactivities in these conditions, which may help identify potential targets for therapy to improve prognosis.

Methods

Participants

Ten healthy participants with a mean age of 23 years (range 21-26, 5 women), and a mean body mass index of 22.8 ± 1.7 kg m^{-2} participated in this study. All participants were screened for respiratory, cardiovascular and cerebrovascular disease, and gave informed written consent. Participants were non-smokers, and were not taking any respiratory or cardiovascular medications. Procedures were approved by the New Zealand Central Regional Ethics Committee and conformed to the standards set by the *Declaration of Helsinki*.

Measurements

Cerebral blood flow velocity was measured in the middle cerebral artery (MCA) using 2-MHz pulsed wave transcranial Doppler ultrasound (DWL Doppler, Sterling, VA, USA). The probes were positioned over the temporal window, and the M1 segments of the MCA were found using standard search techniques (20). Non-invasive beat-to-beat systolic (SBP) and diastolic blood pressures (DBP) were measured at heart height via finger photoelectric plethysmography (FinometerPRO®, Finapres Medical Systems, Amsterdam, The Netherlands). Mean arterial pressure (MAP) was calculated from SBP and DBP measurements. Manual blood pressure recordings were taking at regular intervals to verify these measurements. Heart rate (HR) was recorded from a three lead electrocardiogram (ECG) (ADIstruments, Colorado Springs, CO, USA). End-tidal O_2 ($P_{ET}O_2$) and CO_2 ($P_{ET}CO_2$) sampled from a nasal cannula were measured using a high speed gas analyser (gas analyser model ML206, ADInstruments, Colorado Springs, CO, USA). Data were attained continuously at 1 kHz per channel via an analog-to-digital converter (PowerLab/16SP ML795; ADInstruments, Colorado Springs, CO, USA), and stored for offline analysis.

Experimental protocol

All experiments were conducted with participants lying supine in a temperature controlled laboratory (22-23°C). Studies took place in the morning, and participants had arrived at the laboratory having abstained from coffee and alcohol for at least 12 hours prior to starting the study. Once the participants acclimatised to the equipment and laboratory environment, 6 minutes of baseline resting data were recorded before commencing CO_2 reactivity testing. The cerebrovascular response to CO_2 was assessed by asking the patient to breathe normally (for at least 60 seconds) until $P_{ET}CO_2$ levels

reached a steady state. This was followed by 90 seconds of breathing a gas mixture of 5% CO_2 with 21% O_2 and balance nitrogen (timed to a rate of 8 breaths min^{-1} to a metronome), and then followed by 90 seconds of hyperventilation timed to a metronome to reach a $P_{ET}CO_2$ of between 25 – 30 mmHg. After control CO_2 reactivity testing was completed, all participants ingested 0.05 mg kg^{-1} of the competitive α_1-adrenergic blocker, prazosin. Participants then repeated the protocol 120 minutes post-ingestion to coincide with the peak plasma prazosin concentration (21).

Data Processing and analysis

Data were analysed using custom-written software in LabView 11 (National Instruments, Austin, TX, USA). The absolute CO_2 reactivity was measured by plotting a slope of the change in MCA flow velocity (in cm s^{-1}) per mmHg change in $P_{ET}CO_2$. Data were normalised to baseline blood pressure, with normalised CO_2 reactivity measured as percent change (compared to baseline flow) in mean blood flow velocity per millimetre of mercury $P_{ET}CO_2$. For a more complete evaluation of CO_2 reactivity we also analysed the hypercapnic and hypocapnic slopes independently. All slopes were presented as absolute and normalised values.

Statistical analysis

All data were analysed using the SPSS social statistics package (IBM SPSS statistics version 19, Surrey, UK). Multivariate linear regression analysis was performed to identify the presence of any confounding due to blood pressure changes during CO_2 reactivity testing. Comparisons of means were performed using paired t-tests having confirmed the presence of normality. Data are expressed as means ± standard deviation (SD). Significance was established with a p value < 0.05.

Results

Baseline parameters

Table 1 shows the supine baseline values for cardiovascular, cerebrovascular and respiratory variables before and after ingestion of 0.05 mg kg^{-1} prazosin. There was no change between pre and post prazosin baselines for mean arterial pressure (MAP), heart rate (HR), R-R interval, breathing rate, end-tidal CO_2 or $MCAv_{mean}$.

Table 1. Cardiovascular, respiratory and cerebrovascular baseline parameters before and after α-adrenergic blockade (with prazosin)

Variable	Control	Blockade	P value
Heart rate (beats min^{-1})	62 ± 6.2	62 ± 6.2	0.920
R-R interval (s)	0.98 ± 0.11	0.98 ± 0.09	0.904
$P_{ET}CO_2$ (mmHg)	37.4 ± 3.2	38.6 ± 3.4	0.309
SBP (mmHg)	109 ± 15	105 ± 11	0.379
DBP (mmHg)	57 ± 7	56 ± 7	0.517
MAP (mmHg)	72 ± 7	70 ± 7	0.271
MCA v_{mean} (cm s^{-1})	68 ± 9.5	63 ± 8.6	0.058

Values are means + SD. Data are for 10 participants. Abbreviations: $MCAv_{mean}$; mean middle cerebral artery flow velocity

CO_2 reactivity

There was no change in mean baseline $P_{ET}CO_2$ before and after α_1-blockade (37.4 ± 3.2 mm Hg [control] *vs.* 38.6 ± 3.4 mm Hg [blockade]; p = 0.309). Inhalation of 5% CO_2 produced similar increases in $P_{ET}CO_2$ before and after blockade (44.9 ± 2.8 mm Hg [control] *vs.* 45.4 ± 5.1 mm Hg [blockade]; p = 0.588). Likewise the reduction in $P_{ET}CO_2$ evoked by hyperventilation was unaffected by α_1-blockade (28.4 ± 2.9 mm Hg [control] *vs.* 28.6 ± 4.1 mm Hg [blockade]; p = 0.809).

Absolute CO_2 reactivity

There was a significant decrease in reactivity to CO_2 post prazosin for the integrated CO_2 reactivity (reactivity to both hypercapnia and hypocapnia). The absolute CO_2 reactivity for the integrated slope was significantly decreased after blockade with prazosin (2.40 ± 0.54 cm s^{-1} $mmHg^{-1}$ *vs.* 2.13 ± 0.48 cm s^{-1} $mmHg^{-1}$; $p < 0.05$). Absolute CO_2 reactivity in the hypocapnic range resulted in a significant reduction in CO_2 reactivity from control conditions to after prazosin ingestion (2.00 ± 0.87 cm s^{-1} $mmHg^{-1}$ *vs.* 1.32 ± 0.50 cm s^{-1} $mmHg^{-1}$; p value < 0.05). Absolute CO_2 reactivity in the hypercapnic range showed no significance before and after prazosin (2.84 ± 0.88 cm s^{-1} $mmHg^{-1}$ *vs.* 2.66 ± 0.87 cm s^{-1} $mmHg^{-1}$ respectively; p value = 0.578).

Normalised CO2 reactivity

Normalised CO_2 reactivities showed a significant decrease after prazosin (3.79 ± 0.75 % $mmHg^{-1}$ *vs.* 3.40 ± 0.56 % $mmHg^{-1}$; $p < 0.05$) for the integrated hypocapnic and hypercapnic curve. Normalised CO_2 reactivity in the hypocapnic range also showed a significant reduction after prazosin ingestion (3.36 ± 1.56 % $mmHg^{-1}$ *vs.* 2.18 ± 0.78 % $mmHg^{-1}$; $p < 0.05$). Prazosin did not significantly alter normalised CO_2 reactivity in the hypercapnic range, with a

control reactivity of 4.53 ± 1.45 % $mmHg^{-1}$, and a post prazosin reactivity of 4.37 ± 1.12 % $mmHg^{-1}$; p = 0.735).

Table 2. CO_2 reactivity means for absolute and normalised values before and after prazosin

	Absolute			Normalised		
	Control	***Blockade***	***P value***	***Control***	***Blockade***	***P Value***
Integrated response	2.40 ± 0.54	2.13 ± 0.48*	P < 0.05	3.79 ± 0.75	3.40 ± 0.56*	P < 0.05
Hypocapnic response	2.00 ± 0.87	1.32 ± 0.50*	P < 0.05	3.36 ± 1.56	2.18 ± 0.78*	P < 0.05
Hypercapnic response	2.84 ± 0.88	2.66 ± 0.87	P = 0.578	4.53 ± 1.45	4.37 ± 1.12	P = 0.735

Values are means ± SD. Data are means from 10 participants.
Absolute units = cm s^{-1} $mmHg^{-1}$; Normalised units = % $mmHg^{-1}$
*indicates a significant difference in mean value after blockade with prazosin

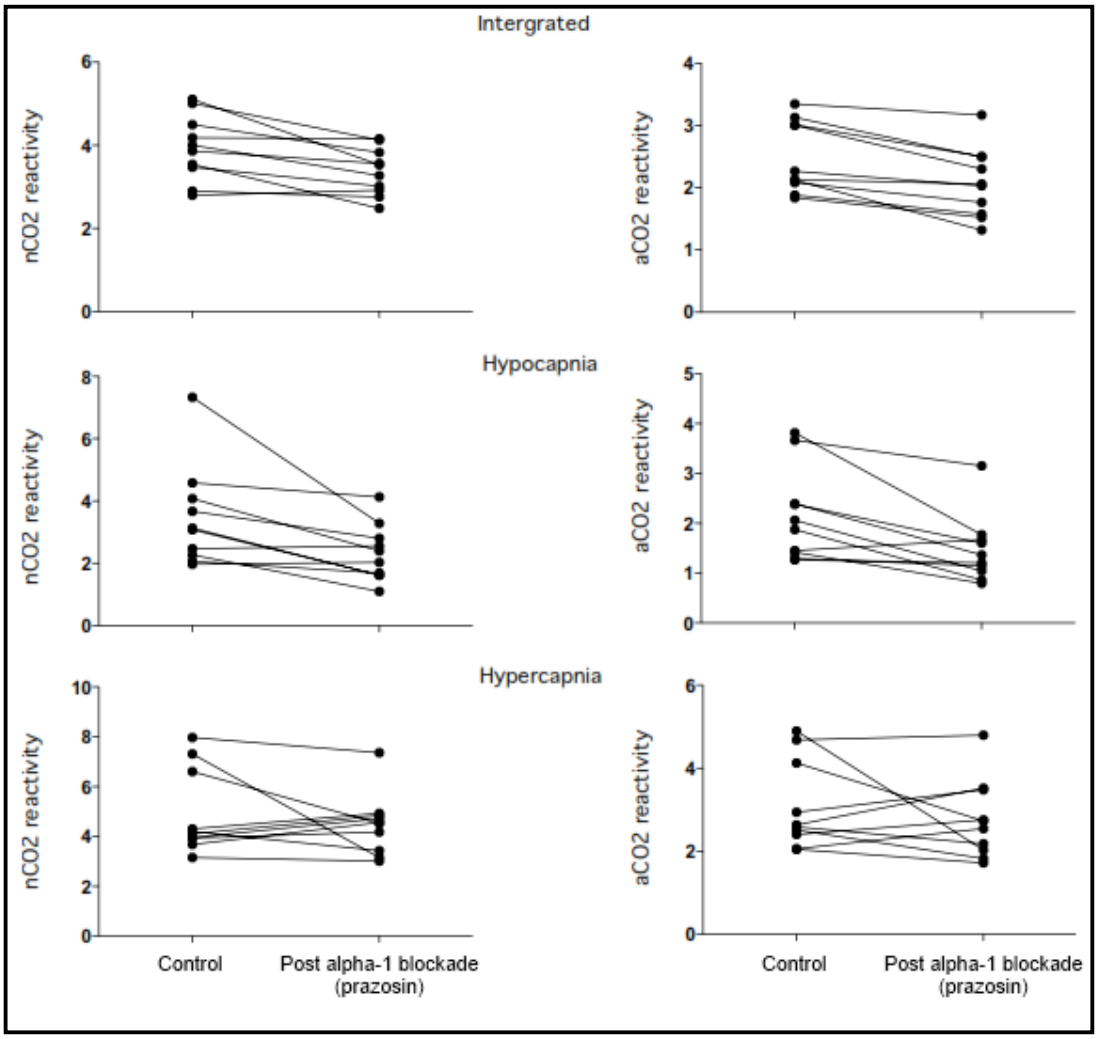

Figure 1: Individual normalised (nCO_2) and absolute (aCO_2) reactivities for each participant before and after prazosin.

Discussion

The main finding of this paper is that the sympathetic nervous system has a significant role in the cerebrovascular response to changes in CO_2 levels. We have been unique in differentiating CO_2 reactivity into separate hypocapnic and hypercapnic slopes, providing a clearer understanding of sympathetic tone relating to CO_2 reactivity. This allowed us to determine that this effect appears to be primarily in the hypocapnic ranges. This is of interest as it shows that sympathetic nerves produce their effect by stimulating vasoconstriction in response to a lower $P_{ET}CO_2$ (hypocapnia). Furthermore our results show that vasodilation in hypercapnia is unlikely to be caused by a reduction in sympathetic nerve activation on cerebral vessels, as sympathetic blockade with prazosin produced no significant difference in hypercapnic CO_2 compared to control.

The significance of these findings is that they provide insight to the mechanism by which the cerebral vessels react to CO_2 levels. The role that the sympathetic nervous system plays in the cerebral vessels reactivity to CO_2 has been controversial. For example previous studies have used ganglionic blockade to address whether sympathetic nerves have a function in CO_2 reactivity (5,11). However, due to its effects on both sympathetic and parasympathetic postganglionic receptors, plus effects on histamine receptors (22), caution should be used when interpreting the results to be solely due to its sympathetic effects. Other studies have used lower body negative pressure producing a pooling of venous blood in the lower limbs, a flow on reduction in venous return, and thus decreasing MAP as a driver of the baroreceptor reflex to stimulate sympathetic output (12) . This study assumes that the sympathetic outflow from the baroreceptor reflex affects cerebral vessels in the same was as that of the peripheral vessels (23–25). A potential problem with this technique is there is an overlying assumption that the effects in the cerebral vessels mimic those of the peripheral vessels. One study found that alpha-adrenergic blockade (phenoxybenzamine) had no effect on CO_2 reactivity, however participants in this study had suffered cerebral ischemia or infarction, and thus we cannot reliably assume their ability to react to CO_2 is fully intact (13). We feel we can credibly argue that the sympathetic nervous system provides a significant role in cerebrovascular reactivity. In support of our findings of an attenuation of CO_2 reactivity after sympathetic blockade was Jordan *et al*., 2000 (5). Several authors are in disagreement with our findings (11–14) we feel that their methods were not directly addressing the question of the effect of the sympathetic nervous system on CO_2 reactivity, and.

Methodological considerations

An important methodological consideration is that when using TCD probes, the diameter of the insonated blood vessel is unknown, and we can therefore only measure the velocity of blood flow through cerebral vessels, not absolute volumetric flow. The velocity of blood through cerebral vessels is inversely proportional to the fourth power of the radius of the vessel, and assumes that the diameter of the vessel does not change. The constancy of the middle cerebral artery to maintain its diameter has been shown by a number of studies. However, it is still thought that the cerebral vessels may change to small degrees, and under special circumstances (26,27). We aimed to mitigate any confounding by normalising data, which should compensate for any changes in MCA diameter. We found no difference between absolute and normalised CO_2 reactivity results suggesting that a change of diameter of the MCA was not of significance in our results.

Participants in this experiment were their own controls, with CO_2 reactivity measured before prazosin (control) and after prazosin. We cannot conclusively discount time as a factor for a reduced CO_2 reactivity after ingesting prazosin, as there was a period of 2 hours while we waited for prazosin to reach peak plasma concentration. A study by Ameriso *et al*., 1994 found that early afternoon (1-3 pm) CO_2 reactivity was significantly greater than early morning (6-8 am) CO_2 reactivity (28). These times do not quite correlate with our timing of CO_2 reactivity pre (≈ 10 am) and post (≈ 12 pm) prazosin. However, if we assume a relatively constant increase between these times, a decrease in CO_2 reactivity after prazosin (as we have found) would if anything be an underestimate of prazosin's effect of CO_2 reactivity.

Clinical implications

With the effect prazosin has to reduce cerebrovascular reactivity, it can be discerned from this that an attenuated CO_2 reactivity post TBI, stroke and SAH may be due to (at least in part) to a dysfunction in the sympathetic nervous systems innervation of cerebral vessels. Identifying the mechanism underlying this dysautonomia may be crucial in identifying potential targets for treatment to improve prognosis in these patients. Furthermore, we suggest that future clinical and experimental testing of CO_2 reactivity should analyse hypocapnia and hypercapnia separately, especially where autonomic dysregulation might occur. A significant attenuation of CO_2 reactivity in the hypocapnic range may be masked by any effect (or lack thereof) in the hypercapnic range.

Areas for further research

This study was performed in young, healthy participants and is likely to depict optimal cerebrovascular reactivity in response to changes in $P_{ET}CO_2$. Further research should be performed looking at elderly, and in participants with a variety of respiratory, cardiovascular and cerebrovascular conditions to determine its applicability in these populations.

SCIENTIFIC REPORT

▪Student:

Name: Ollie Ball
Email: balol129@student.otago.ac.nz

▪Supervisor:

Supervisor: Shieak Tzeng
Host Department: Department of Surgery and Anaesthesia
Institution: Wellington Medical School, University of Otago
Address: 21 Mein Street, Newton, Wellington

▪Acknowledgments

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