$PaCO_2$ measurement in cerebral haemodynamics: face mask or nasal cannulae?

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Physiological Measurement – Note

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Abbreviations list

ARI	Autoregulation index
BP	Blood pressure
CA	Cerebral autoregulation
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CO2	Carbon dioxide
CrCP	Critical closing pressure
dCA	Dynamic cerebral autoregulation
ECG	Electrocardiogram
$EtCO_2$	End-tidal CO_2
FM	Face mask
HR	Heart rate
MABP	Mean arterial blood pressure
MCA	Middle cerebral artery
NC	Nasal cannulae
$PaCO_2$	Partial pressure carbon dioxide
RAP	Resistance-area product
SD	Standard deviation
TCD	Transcranial Doppler

Abstract

Objective

$PaCO_2$ affects cerebral blood flow (CBF) and its regulatory mechanisms, but the effects of CO_2 measurement technique on cerebrovascular parameters are unknown. In order to determine if the two most commonly used approaches, face mask (FM) or nasal cannulae (NC), are interchangeable or not, we tested the hypothesis that the use of FM versus NC does not lead to significant differences in CO_2-related systemic and cerebrovascular parameters.

Approach

Recordings of CBF velocity (CBFV), blood pressure (BP), heart rate, and end-tidal CO_2 ($EtCO_2$) were performed in 42 subjects during normocapnia (FM or NC) and 5% CO_2 inhalation (FM) or hyperventilation (NC). Dynamic cerebral autoregulation was assessed with the autoregulation index (ARI), derived by transfer function analysis from the CBFV response to a hypothetical step change in BP.

Main Results

Significant differences in physiological parameters were seen between FM and NC: $EtCO_2$ (37.40 vs. 35.26 mmHg, p=0.001) and heart rate (69.62 vs. 66.69 bpm, p=0.001) respectively. No differences were observed for mean BP, CBFV or the ARI index.

Significance

Use of FM or NC for measurement of $EtCO_2$ leads to physiological changes and differences in parameter values that need to be taken into consideration when interpreting and/or comparing results in studies of cerebral haemodynamics.

Introduction

Continuous recordings of end-tidal CO_2 ($EtCO_2$) are increasingly used in physiological and clinical studies as surrogate estimates of $PaCO_2$. Capnographic estimates of $PaCO_2$ have been shown to be useful for continuously monitoring the respiratory status of patients in intensive care settings (Lui *et al* 1992). In addition to applications in exercise physiology and respiratory diseases, studies of the cerebral circulation require assessment of $PaCO_2$ changes due to its potent effects on cerebral blood flow (CBF) (Battisti-Charbonney *et al* 2011). Although face masks (FM) are the preferred option to sample respiratory gases, they are often poorly tolerated by patients and can induce changes in breathing frequency due to anxiety and discomfort. As an alternative, nasal cannulae (NC) have been preferred in many settings, despite concerns about their ability to reflect true expired $EtCO_2$ if subjects occasionally breathe through the mouth (Fukuda *et al* 1997). Given the need to determine if these two approaches are interchangeable or not, we tested the hypothesis that the use of FM versus NC does not lead to significant differences in CO_2-related systemic and cerebrovascular parameters.

Methods

The study was conducted in accordance with the Declaration of Helsinki (2000). Ethical approval was obtained from the University of Leicester Ethics Committee (Reference: jm591-c033). Healthy volunteers were recruited from University departmental staff, students and their relatives. Participants aged above 18 years were included. Exclusion criteria included physical disease in the upper limb, poor insonation of both temporal bone windows and any significant history of cardiovascular, neurological or respiratory disease. Subjects with mild, controlled hypertension were accepted as representative of active and otherwise healthy older adults.

The research was undertaken in the University of Leicester's Cerebral Haemodynamics in Ageing and Stroke Medicine research laboratory, maintained at a constant ambient temperature of approximately 24°C and free of distraction. For the purposes of the study, participants were asked to refrain from caffeine, alcohol and nicotine in the 12-hour period prior to measurements being undertaken. Beat-to-beat blood pressure (BP) was recorded continuously using the Finometer® device (FMS, Finapres Measurement Systems, Arnhem, Netherlands), which was attached to the middle finger of the left hand. The servo-correcting mechanism of the Finometer® was switched on and then off prior to measurements. The hand bearing the finger cuff was at the level of the heart to negate any hydrostatic pressure artefact. Heart rate (HR) was recorded using a standard 3-lead electrocardiogram (ECG). $EtCO_2$ was measured

throughout the initial resting baseline and hypercapnic phase using the FM connected to a capnograph (Capnocheck Plus). During the second baseline and hypocapnic phase it was measured via NC (Salter Labs). Bilateral insonation of the middle cerebral arteries (MCAs) was performed using transcranial Doppler (TCD) ultrasound (Viasys Companion III; Viasys Healthcare) with a 2MHz probe. This probe was secured in place with a head-frame that was adjusted to ensure comfort at the outset. The MCAs were identified according to two main characteristics: signal depth and velocities.

Experimental protocol

All measurements were conducted at a single visit. An initial period of 15 minutes of stabilisation preceded a 5-minute baseline recording supine at rest using FM. This was followed by fixed inspiration for a minimum of 90 s (ideally 120 s) of 5% CO_2. After a further period of 5 min of stabilisation, participants performed a 5 min baseline recording using NC, which was followed by a set of hyperventilation measurements. Measurements were continuously recorded at a rate of 500 samples/s in the PHYSIDAS data acquisition system for subsequent off-line analysis. Systolic and diastolic brachial BP readings (OMRON Model 705IT) were performed at each stage of the protocol (hypercapnia and hypocapnia). These values were then used to calibrate the Finometer recordings.

Data Analysis

The data collected corresponded to six individual files for each participant: 2 at baseline, 2 hypercapnic and 2 hypocapnic. Data were initially inspected visually and calibrated to recorded systolic and diastolic OMRON BP. Narrow spikes (<100ms) were removed using linear interpolation and the CBFV recording was then passed through a median filter. All signals were low-pass filtered with a zero-phase Butterworth filter with cut-off frequency of 20Hz. The software was then used to ensure the R-R interval was marked correctly with the ECG trace. This allowed mean BP, HR, $EtCO_2$ and mean CBFV to be calculated for each cardiac cycle. The critical closing pressure (CrCP) and resistance-area product (RAP) were estimated using the first harmonic method (Panerai 2003). Dynamic cerebral autoregulation was assessed with the autoregulation index (ARI), derived by transfer function analysis from the CBFV response to a hypothetical step change in BP (Panerai 1998).

Statistical Analysis

Tests of normality were performed using the Kolmogorov-Smirnov test. The baseline measurements were assessed for differences between values derived for right and left hemispheres using a paired Student's t-test. These were averaged when no significant differences were found. Comparisons were made between FM and NC values using either the Student's t-test or Wilcoxon Signed Rank test as appropriate. Analysis of agreement was performed with Bland-Altman plots. Statistical significance was accepted at $p<0.05$.

Results

Forty-two subjects were recruited. Baseline systemic and cerebrovascular parameters for FM and NC are given in Table 1, showing highly significant differences for baseline $EtCO_2$ and HR (Fig. 1).. Noteworthy, ARI, CrCP, RAP and CBFV were not different. The differences between FM and NC for $EtCO_2$ can be better appreciated in the Bland-Altman plot (Fig. 2) indicating a significant positive bias due to higher values for FM compared to NC. The relatively large 95% limits of agreement should also be noted.

Discussion

Continuous recordings of $PaCO_2$ are essential for assessment of CBF regulatory mechanisms, such as dynamic cerebral autoregulation, CO_2 reactivity and neurovascular coupling. For this purpose, intravascular recordings are usually replaced by non-invasive measurements based on infra-red capnography which are safer, less costly and much better accepted by study participants. For a relatively large number of subjects, the higher values of $EtCO_2$ obtained for FM, compared to NC, were to be expected as NC does not provide perfect sampling of all expired CO_2, and mouth breathing can also contribute to missed sampling in some subjects. Despite this difference, it is reassuring that key parameters, such as the mean CBFV and ARI, were not influenced by the CO_2 sampling modality as it allows better comparability between studies. Accordingly, there is a potential opportunity to use both modalities interchangeably in complex multi-stage protocols where FM might not be a satisfactory option, for example in long duration baseline recordings.

Another important finding in our study was the elevated HR seen with FM, which is likely a sympathetic response to the discomfort or anxiety associated with using the mask. Sympathetic activation is also likely to have an effect on the autonomic nervous system regulation of CBF (Ainslie *et al* 2008). Although ARI was not different between FM and NC in the healthy population assessed in the present study, it is possible that particular patient sub-groups might be more susceptible to FM-induced sympathetic activation leading to alterations in cerebral autoregulation or neurovascular coupling (Maggio *et al* 2013).

The authors acknowledge two potential study limitations. First, an inability to randomise the order of the experiment, which was largely attributable to concerns that prior hypocapnia (as opposed to hypercapnia) may cause persistent cerebral vasoconstriction, thus affecting MCAv-CO2 response to hypercapnia. Secondly, possible physiological alterations associated with each CO2 sampling modality. In particular the heightened anxiety, cognitive stimulation and physical involvement required to maintain adequate respiration with the face mask as compared to the nasal cannulae.

Previous experimental work has determined that biological factors, such as tidal volume and respiratory rate, can impact on sampling accuracy via NC; a "clinically acceptable" upper limit for accuracy being 20 breaths/min (Fukuda *et al* 1997). Despite being at rest and with no participants likely to have achieved respiratory rates at this level, we demonstrated less effective delivery and measurement compared to the FM.

Lastly, previous work has shown that TCD-estimated CBFV and ARI (using TFA) during inhalation of O_2 and CO_2 have acceptable levels of reproducibility (Minhas *et al* 2016). However, further assessments of these parameters are warranted in diseased states using the most effective means of delivering and measuring $EtCO_2$ to ensure accuracy of baseline recordings.

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Figure legends

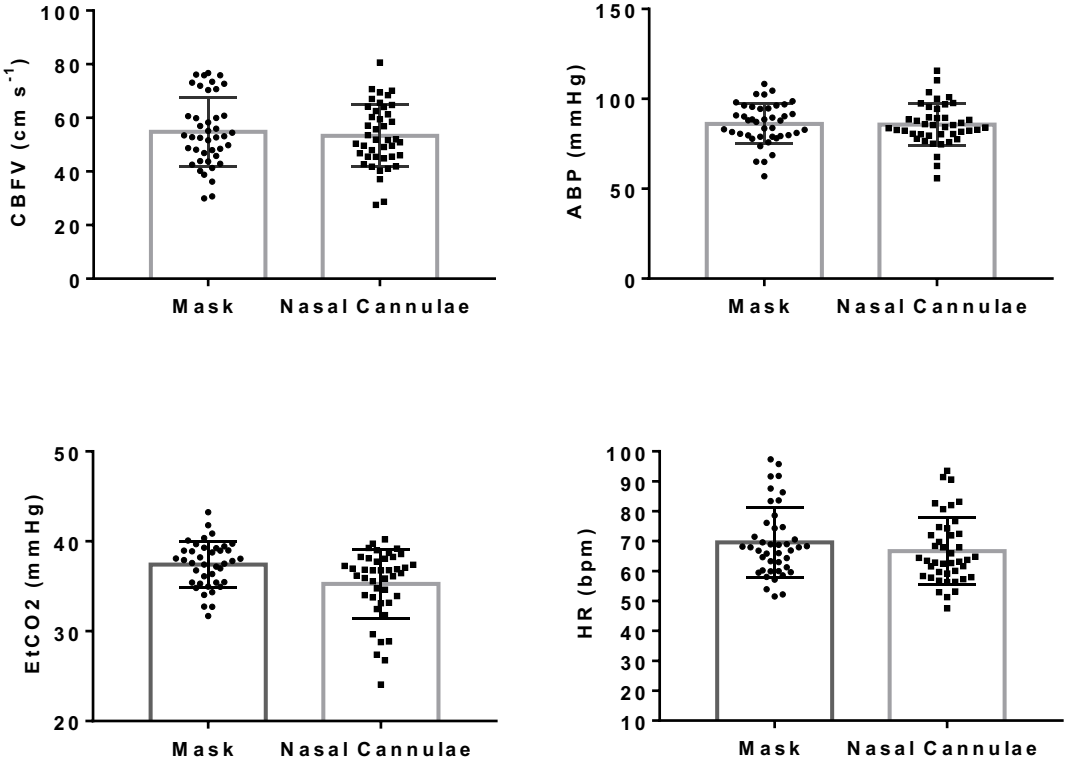
Figure 1. Distribution of CBFV (cerebral blood flow velocity), ABP (arterial blood pressure), $EtCO_2$ (end-tidal carbon dioxide) and HR (heart rate) for FM (face mask) and NC (nasal cannulae). Bar graphs represent mean ± SD.

Figure 2. Agreement between $EtCO_2$ (end-tidal carbon dioxide) for measurements performed with either FM (face mask) or NC (nasal cannulae), expressed by a Bland Altman plot, representing the bias (dotted line) and 95% limits of agreement (bias ± 1.96SD, dashed line).

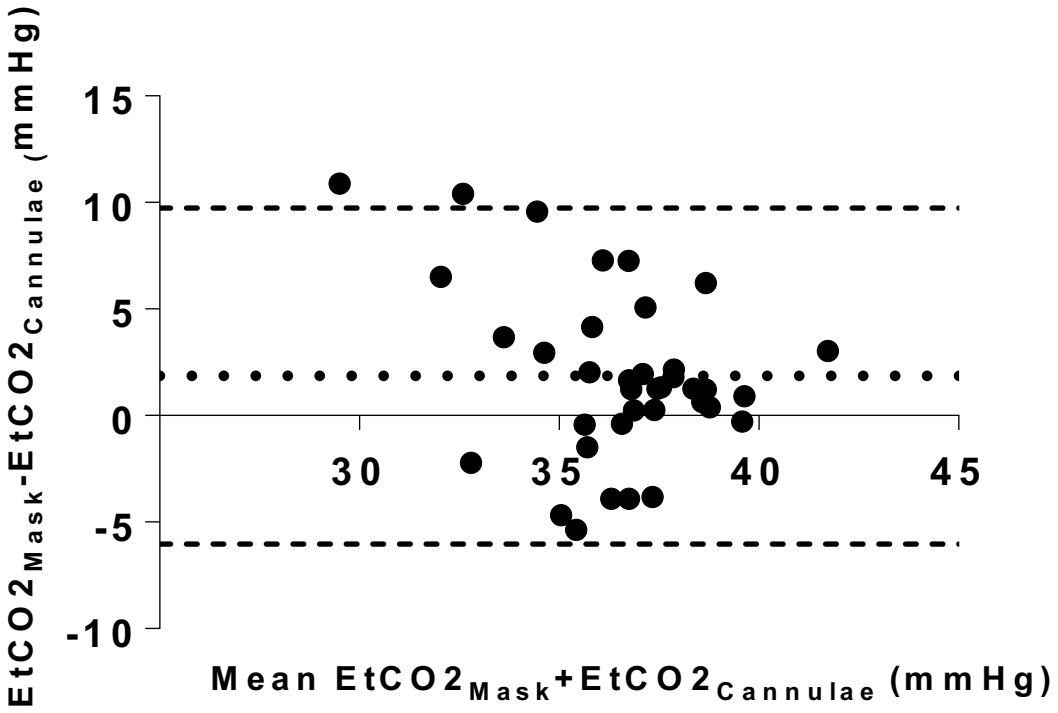
Table 1. Peripheral and cerebral haemodynamic parameters recorded with the face mask and nasal cannulae for continuous measurements of end-tidal CO_2 (n=42).

Parameters	Face mask	Nasal cannulae	p-value
CBFV (cm s^{-1})	54.8±12.9	53.3±11.6	0.094
Mean arterial BP (mmHg)	86.1±11.2	85.7±11.5	0.793
End-tidal CO2 (%)	37.4±2.5	35.3±3.8	**0.001**
Heart rate (beats.min^{-1})	69.6±11.2	66.7±11.1	**0.001**
CrCP (mmHg)	34.8±13.0	35.8±14.7	0.693
RAP (mmHg.cm s^{-1})	1.04±0.35	1.01±0.37	0.856
ARI	5.6±1.6	5.9±2.1	0.593

CBFV (Cerebral blood flow velocity), BP (Blood pressure), CrCP (Critical closing pressure), RAP Resistance area product) and ARI (Autoregulation Index). Values are mean ± SD.


CBFV (cm s-1)
100
80
60
40
20
0
Mask
Nasal Cannulae
ABP (mmHg)
150
100
50
0
Mask
Nasal Cannulae
EtCO2 (mmHg)
50
40
30
20
Mask
Nasal Cannulae
HR (bpm)
100
90
80
70
60
50
40
30
20
10
Mask
Nasal Cannulae

250


15
10
5
0
-5
-10
30
35
40
45
EtCO2Mask-EtCO2Cannulae (mmHg)
Mean EtCO2Mask+EtCO2Cannulae (mmHg)

251
252