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ORIGINAL ARTICLE

Middle cerebral artery blood flow velocity during a 4 km cycling time trial

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Abstract
Purpose This study sought to describe middle cerebral artery blood flow velocity (MCA_v) during a 4 km cycling time trial, and relate it to different pacing strategies adopted by participants.
Methods After familiarisation and a standardised exercise protocol, 15 male trained cyclists rode a 4 km time trial on a cycling ergometer. MCA_v was assessed via transcranial Doppler ultrasound in the right hemisphere at resting baseline, and throughout the time trial. Mean arterial pressure, end-tidal partial pressure of carbon dioxide ($P_{et}CO_2$) and heart rate were assessed alongside MCA_v. Plasma lactate was assessed post time trial. Data were compared depending upon whether participants completed the time trial with a positive (first half faster than the last) or negative pacing profile although there was no difference in the time to completion with either pacing strategy (positive 344 ± 23 s, negative 334 ± 14 s; $p = 0.394$).
Results Lower mean MCA_v (positive pacing −7.6 ± 14.2%, negative pacing +21.2 ± 15.0% compared to resting baseline measures; $p = 0.004$) and lower $P_{et}CO_2$ (significant interaction $p < 0.001$) towards the end of the time trial were observed with positive compared to negative pacing. Heart rate and lactate did not differ between pacing strategies.
Conclusions Changes in MCA_v appear to depend on the pacing strategy adopted, with a positive pacing strategy likely to contribute to a hyperventilatory drop in $P_{et}CO_2$ and subsequent reduction in MCA_v. Although lower cerebral blood flow cannot be directly linked to an inability to raise or maintain power output during the closing stages of the time trial, this potential contributor to fatigue is worth further investigation.

Keywords Performance · Brain · Exercise · Pacing

Abbreviations

ANOVA	Analysis of variance
CBF	Cerebral blood flow
CO_2	Carbon dioxide
HREC	Human Research Ethics Committee
MAP	Mean arterial pressure
MCA	Middle cerebral artery
MCA_v	Middle cerebral artery blood flow velocity
$P_{et}CO_2$	Partial pressure of end-tidal carbon dioxide
P_aCO_2	Partial pressure of arterial carbon dioxide
RCT	Randomised controlled trial
RPM	Revolutions per minute
SD	Standard deviation
TCD	Transcranial doppler ultrasound
TT	Time trial

Introduction

Pacing, the efficient regulation of effort during a self-paced time trial, is considered crucial for optimal performance in tasks lasting more than 3 min (Thompson 2014).

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Appropriate pacing is considered complex (Tucker and Noakes 2009) and relies upon regulation by both physiological and psychological mechanisms which is refined through prior experience. Although the regulation of pacing compensates for some homeostatic disturbances, it is known that changes in physiological states including energy substrate use (Rauch et al. 2005), oxygen availability (Peltonen et al. 1997) and core temperature increases (Tucker et al. 2004) influence both pacing and overall performance. These biomarkers are most commonly linked to peripheral fatigue, or afferent feedback, but physiological processes, which act more directly on the central nervous system, could also play a role.

Cerebral blood flow (CBF) ensures the brain receives adequate oxygen, fuel and removal of waste products for normal function. Reductions in CBF occur during exercise in the heat (Périard and Racinais 2015), and these reductions have been subsequently associated with fatigue (Nybo and Nielsen 2001). Similar reductions are postulated to occur in athletes during strenuous exercise through hyperventilation-induced decreases in CBF (Nybo and Rasmussen 2007). These reductions in CBF are likely to be important as they may compromise oxygen delivery to active brain areas, particularly those areas with increased neuronal demand (Nybo and Rasmussen 2007). Decreases in localised cerebral oxygenation have been observed at the point of fatigue during incremental protocols (Bhambhani et al. 2007; Seifert et al. 2009), which could impact neuronal activation and exercise capacity (Amann et al. 2006; Bhambhani et al. 2007). Perhaps the most compelling argument that CBF is related to exercise performance is the recent observation that reductions in CBF are associated with lower voluntary activation from the motor cortex (Hartley et al. 2016).

CBF is tightly regulated by various mechanisms, including neurovascular coupling, humoral factors, and cardiac output (Ogoh and Ainslie 2009). Arterial partial pressures of CO_2 (P_aCO_2) and mean arterial blood pressure (MAP) are central to this regulation. Middle cerebral artery blood flow velocity (MCA_v), indicative of CBF, is highly sensitive to changes in CO_2 pressures (Lucas et al. 2010; Willie et al. 2011) similar to those experienced during exercise. As such, an inverted-U relationship is observed during incremental exercise as MCA_v increases during submaximal exercise intensities (~60% maximal oxygen uptake) and declines at higher intensities (~ >80% maximal oxygen uptake) (Ogoh and Ainslie 2009; Ogoh et al. 2005) when hyperventilation induces a decrease in $PaCO_2$ (Bhambhani et al. 2007). During time trials, exercise intensities often exceed the ventilatory threshold potentially impacting CBF. Although better maintenance of cerebral oxygenation in elite Kenyan runners was used to partially explain their superior 5 km time trial performance over European counterparts (Santos-Concejero et al. 2015), to the best of our knowledge MCA_v has not been assessed during intense time trial performance (<30 min).

Central fatigue has previously been shown to contribute to 4 km cycling time trial performance (Thomas et al. 2015) and, due to the high intensity associated with efforts of this length, we sought to profile MCA_v throughout the performance. Associated with the expected hyperventilation at this level of intensity, we hypothesized that MCA_v would decrease through the time trial. We observed different pacing strategies between participants in the time trial, allowing us to determine if negative or positive splits (first half slower than the second half, or vice versa) were related to MCA_v and its peripheral regulatory measures.

Methods

Participants

Fifteen trained male cyclists, aged 18–40 years volunteered to participant in the study. Participants were non-smokers, had no pulmonary or cardiovascular disease or any musculoskeletal injuries and did not report taking any supplements (known to affect CBF; caffeine, nitrates) or prescription medication. This study complied with the Human Research Ethics Committee at the University of Canberra (HREC 15-46).

Design

This study describes the cross-sectional observations of a small portion of a larger randomised-controlled-cross-over trial (RCT). In the larger RCT, participants were required to undertake five sessions: a preliminary testing session to determine maximal aerobic power, a familiarisation session of the cycling protocol, and three intervention trials. During the control (no active intervention) trial participants wore loose fitting shorts. The three intervention trials consisted of an incremental cycling protocol, short rest, and then a 4 km time trial. In the current investigation, we report data from the time trial of the control condition only. As participants completed the trials in a randomised order, the control condition took place after at least one familiarisation trial, but possibly up to three trials before completion of the time trial in the larger RCT (there was no trial order effect; $p = 0.440$). Potential fatigue effects between trials were minimised by ensuring a minimum of 48 h between trials, and participants were asked to abstain from alcohol and vigorous exercise in the 24 h prior to their intervention trials and caffeine 12 h prior.

Procedures

Preliminary testing

Participants performed an incremental test to exhaustion on a Velotron ergometer (RacerMate, Seattle, USA) to determine maximal aerobic power. Individuals began cycling at 125 W and undertook 25 W increments every 3 min until exhaustion. Exhaustion was based on volitional fatigue, where the participant could not maintain a cadence above 60 RPM for at least 5 s despite verbal encouragement.

Familiarisation trial

Participants undertook a familiarisation session to become acquainted with the equipment and protocols, and to limit learning and training effects. As well as undertaking a submaximal incremental test (see below) participants completed the time trial which they were informed to complete as fast as possible.

Intervention trial

Upon presentation to the laboratory, participants were re-familiarised with all testing procedures. Baseline measures of haemodynamics (MCA_v, MAP, heart rate), respiratory gases ($P_{et}CO_2$) and blood plasma markers (lactate) were taken after participants were seated and rested on the cycle ergometer for at least 3 min. In the intervention trials, participants completed an incremental cycling protocol involving four 8 min increments of 30, 50, 70 and 85% maximal aerobic power at a self-selected and consistent cadence between 70 and 100 RPM. At the completion of the incremental test, a 5 min recovery period (30% maximal power cycling intensity) was employed prior to the 4 km time trial. The drag factor on the Velotron ergometer was set at 76% for the time trial as used previously (Ross et al. 2011). During the time trial participants and researchers were blinded to all performance data except distance and gearing. Verbal cues and encouragement were standardised and given at each kilometre, as well as with 500, 300, and 100 m remaining.

Experimental measures

Performance measures

Time trial performance was recorded as the time in seconds to complete the 4 km time trial. Each 400 m increment was recorded to the nearest second.

Haemodynamics

MCA_v was measured continuously using 2 MHz transcranial Doppler ultrasonography (TCD) technology (DWL Doppler, Compumedics Ltd, Germany) by a single trained operator. The MCA was identified through the right temporal window using search techniques described previously (Willie et al. 2011) and secured with a manufacturer supplied headband to maintain optimal insonation of the target vessel. Raw analogue data were recorded in real time with PowerLab (Labchart 7, ADInstruments, Sydney, Australia). Baseline data were collected at rest, with the participant seated quietly on the cycle ergometer, positioned as though they were cycling.

A Finometer placed around the middle finger of the left hand for the entirety of the intervention trial was used to continually measure MAP by photoplethysmography at a 2 Hz frequency (Finapres Medical Systems BV, Amsterdam, The Netherlands) and real time data were captured with the PowerLab. Due to movement and exertion during the time trial, much of the blood pressure data could not be collected during this period. During the time trial, heart rate was calculated as the frequency of systolic velocity peaks from the raw MCA_v envelope, and was, therefore, collected as a continuous measure throughout the trial. During the preliminary testing, a heart rate monitor (Polar Electro, Kempele, Finland) was fitted to each participant and heart rate data has been expressed relative to the highest heart rate recorded for that individual. Heart rate measures were not collected during the time trial for one participant due to technical reasons. Each data point presented (haemodynamic and respiratory gases) represents the average of each 10% of the time trial distance covered.

Respiratory gases

$P_{et}CO_2$ was continuously recorded in the trials with a calibrated (3L syringe; 16% oxygen, 4% carbon dioxide, nitrogen balance) breath-by-breath $K4b^2$ COSMED system (COSMED, Rome, Italy). $P_{et}CO_2$ was utilised as an estimate of P_aCO_2, since one accurately reflects the other within a range of $P_{et}CO_2 \pm 25$ mmHg of baseline (Willie et al. 2012).

Blood markers

Capillary blood samples were collected using capillary tubes and analysed immediately to determine plasma lactate with an iStat Radiometer (CD4 + cartridge, Abbott Point of Care, Princeton, NJ, USA). Post-time trial lactates were taken ~1 min after the completion of the trial.

Statistical analysis

During the time trial it became apparent that participants adopted different pacing strategies. Two broad pacing strategies were used to analyse the data, either a negative or positive strategy based on whether the second half of the time trial was completed faster (negative, $n = 10$) or slower (positive, $n = 5$) than the first half. Data were thus analysed based on these two groupings. To ensure that the order of trials completed (i.e. whether the control was completed first, second or third) in the wider study did not contribute to the results, we investigated trial order effects using an independent samples Mann–Whitney *U* test. Normal distribution was confirmed by visual inspection of the data and overall time trial performance (time) and lactate levels were compared using a two-way heteroscedastic *t* test. The effects of pacing strategy on MCA_v, $P_{et}CO_2$ and heart rate were analysed using a 2-way ANOVA with repeated measures on the % distance covered. Mean cerebrovascular resistance (CVR), estimated by MAP divided by MCA_v, was also calculated where possible. Data are presented as mean ± standard deviation and statistical significance was defined at $p < 0.05$.

Results

Pacing profile

The mean power output profiles of participants during the 4 km time trial are presented in Fig. 1. The time trial was completed in a mean time of 337 ± 17 s; 5 of the 15 participants completed the time trial with a positive pacing strategy (i.e. the first half was completed faster than the second half of the time trial). This breakdown was used for the analysis of other parameters to distinguish if pacing strategy resulted in different physiological responses. There was no difference ($p = 0.394$) for overall performance when positive (344 ± 23 s) and negative (334 ± 14 s) pacing profiles were compared. Although not strictly representative of pacing, since pacing is represented by speed or velocity (Abbiss and Laursen 2008), power output provides a better representation of the physical requirements of the effort. The mean power output for the entire sample was 324 ± 41 W.

Haemodynamics

Baseline MCA_v was recorded for the entire sample (60.5 ± 9.6 cm s^{-1}) with no difference between those with a positive or negative pacing profile ($p = 0.651$). Overall, MCA_v appeared to follow an inverted-U relationship over the course of the time trial, although this was not

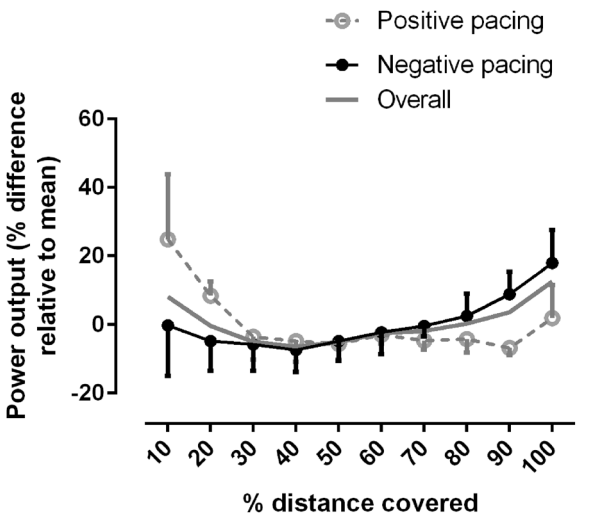

Fig. 1 Evolution of mean power output for the entire sample, and for both positive and negative pacing strategies. The power outputs are expressed relative to the mean power output of each participant. *Error bars* represent SDs

significant [$F(9117) = 1.90$; $p = 0.058$], with the highest MCA_v values typically recorded between the 400 and 1600 m distance markers (20–40% of total TT; Fig. 2a). When the sample was divided into participants with either positive or negative pacing profiles, participants in the positive pacing profile had lower mean MCA_v values overall relative to baseline than those with a negative pacing profile [−7.6 ± 14.2 vs +21.2 ± 15.0%, respectively; $F(1,13) = 12.7$, $p = 0.004$].

$P_{et}CO_2$

There was a significant interaction for $P_{et}CO_2$ [$F(10,130) = 3.46$, $p < 0.001$] between the pacing strategy and the relative distance covered in the time trial (Fig. 2c). Although it appears there were no differences at baseline, nor perhaps early in the time trial, quite large differences are evident towards the end of the time trial.

Mean arterial pressure

Continuous blood pressure assessment is problematic during high-intensity exercise. As a result, we provide a representative trace of blood pressure over the time trial effort from 2 participants. These participants represent the negative pacing profile only. Data from other trials were aberrant, perhaps due to relative occlusion in the finger tips during strong grip of the handlebars throughout the time trial, and were, therefore, not included. We have, however, presented this data when available given the role that MAP plays in the regulation of MCA_v. For these two participants,

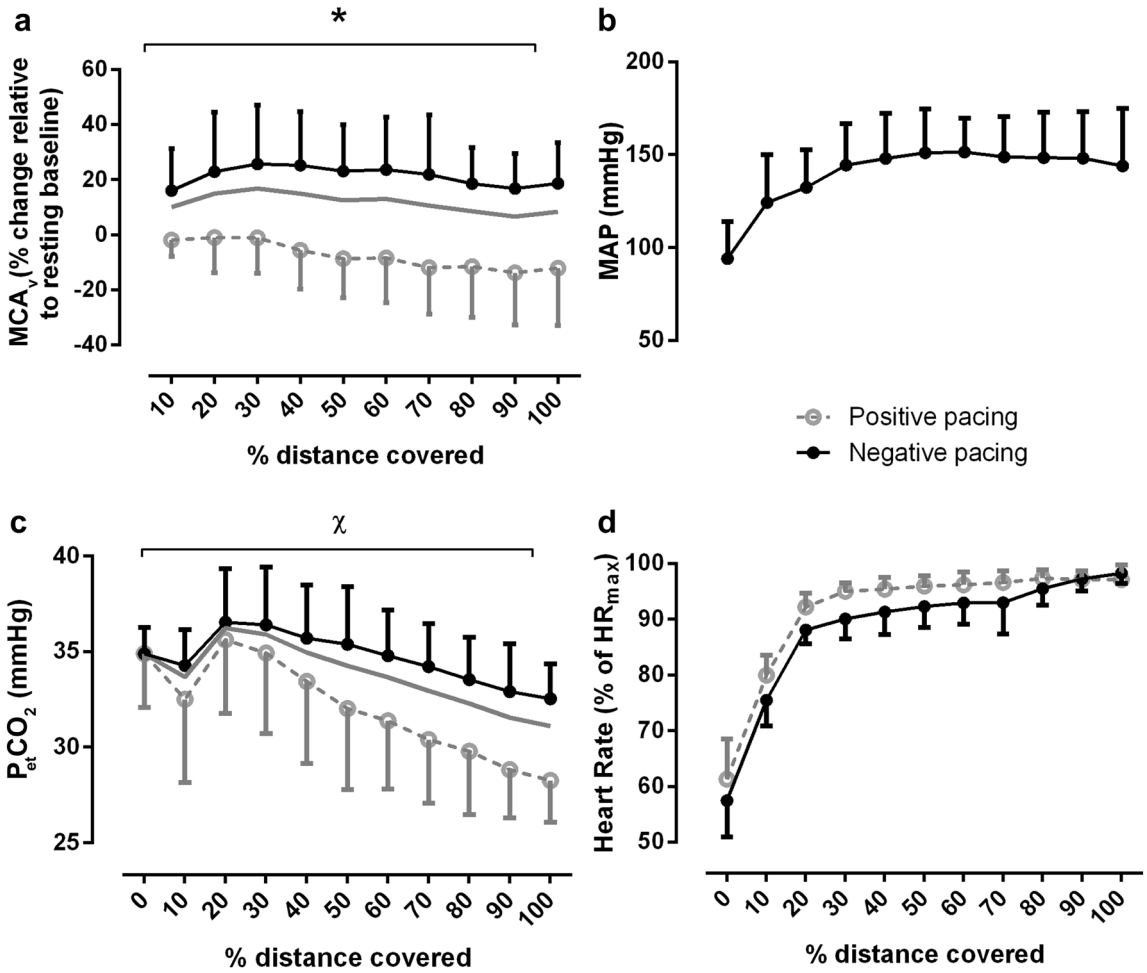

Fig. 2 **a** Displays relative MCA_v values throughout the 4 km time trial. Note there is no baseline in this measure as time points were made relative to the baseline. *Denotes significant difference between pacing strategies. **b** Displays representative ($n = 2$, from negative pacing group only) MAP measures across the time trial. **c** Shows the partial pressure of end-tidal CO_2, and **d** displays relative heart rate throughout the 4 km time trial and including baseline (0) for each of the pacing strategies observed. X denotes significant interaction. Group mean MCA_v and $P_{et}CO_2$ is represented as a single *grey line*

we additionally calculated cerebrovascular resistance, using MAP divided by MCA_v, and have presented this graphically over the course of the time trial (Fig. 3).

Heart rate

Participant heart rates during the time trial are represented in Fig. 2d. Relative heart rate increased over the time trial [$F(10,120) = 219$; $p < 0.001$] and there may have been a difference in heart rate between the positive and negative pacing profiles although this was only a trend [mean HR 94 ± 2 vs 91 ± 3% of HR_{max}; $F(1,12) = 4.20$, $p = 0.063$].

Lactate

At the end of the time trial, blood plasma lactate was 13.8 ± 2.7 mM ($n = 12$). There was no difference

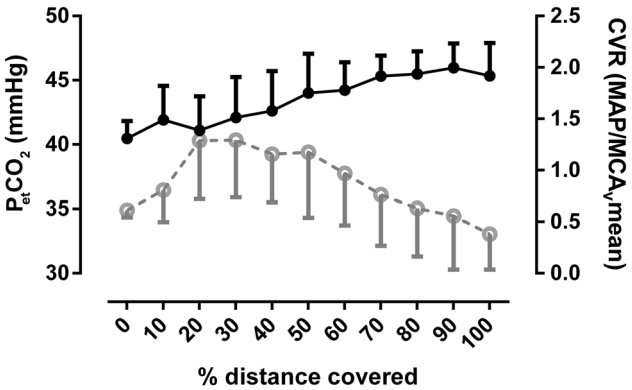

Fig. 3 CVR, calculated from MAP divided by MCA_v, is presented over the course of the time trial for the two participants in which MAP data exists. $P_{et}CO_2$ is also presented for these two participants for comparison

($p = 0.158$) in the post blood plasma lactate levels between the positive (15.0 ± 1.4 mM; $n = 5$) and negative (13.0 ± 3.1 mM; $n = 7$) pacing profiles. Three participants in the negative pacing profile did not have a blood plasma lactate sample recorded due to technical reasons.

Discussion

This study highlights the changes to MCA_v throughout a short (4 km), intense cycling time trial. Overall, mean MCA_v during the time trial is elevated above resting baseline, although changes in MCA_v appear to depend on the pacing strategy adopted. When participants start with high power outputs at a level that cannot be maintained in the second half of the effort, MCA_v is lower. This is most likely due to the reductions in $P_{et}CO_2$ associated with hyperventilation at suprathreshold loads. Although we cannot directly link lower cerebral blood flow with the inability to raise or maintain power output as high during the closing stages of the time trial, this potential link may be worth pursuing in the future as a contributor to fatigue. It is especially true given that peripheral indices commonly associated with fatigue, heart rate and blood lactate, did not appear to account for the different pacing strategies.

The 4 km time trial was completed at a very high intensity; ~94% of maximal heart rate, and a mean power output of 324 W. MCA_v was ~11.6% above resting baseline values for the entire group over the time trial (Fig. 2a). Comparable intensities (96% of VO_2max; 340 W) have been observed previously (Thomas et al. 2015). As with the similar absolute and relative intensities, the overall pacing strategies appear visually similar, representing a U-, J- or reverse J-shape as is commonly reported for efforts of this length (Abbiss and Laursen 2008). The visual representation in the work of Thomas et al. (2015) appears to show a reverse J-shape, akin to the positive pacing strategy group in this study. The work intensities observed in these efforts represent an intensity above ventilatory threshold, and, therefore, it is of no surprise that a hyperventilatory drop in $P_{et}CO_2$ results at the end of the time trial for the entire sample. The limited data we present in Fig. 3, suggests that hyperventilation may be driving the increase in CVR, at least for the two participants for whom we have the data. Perhaps what is surprising is that $P_{et}CO_2$ appears to drop at a much earlier time point in the time trial in the positive pacing group, a phenomenon that is not apparent in differences of heart rate throughout the time trial, nor blood lactate levels assessed immediately post time trial. The lower $P_{et}CO_2$ associated with the positive pacing likely explains the lower MCA_v observed in this group. We cannot exclude the possibility that MAP may have also been lower, decreasing MCA_v in the positive pacing profile, as we were not able to obtain reliable data. During the time trial, finger photoplethysmography is problematic due to the high intensity and strong grip that participant's exert on the handlebars of the bike to provide their best effort. At rest, cerebral autoregulation is thought to be maintained between MAP values of 60 and 150 mmHg (Lassen 1959), although the preservation of this relationship during exercise is unclear (Ogoh and Ainslie 2009). The MAP values observed in the present study, in at least two participants, are within the range expected to maintain static cerebral autoregulation. As such, we do not expect changes in mean arterial pressure to have contributed to the differences in MCA_v during the different pacing strategies especially since, if anything, the higher mean arterial pressures may have increased, not decreased CBF.

We did not directly investigate whether changes in MCA_v during the time trial contributed to fatigue, but it is intriguing that considerably lower mean MCA_v were observed in the positive pacing strategy. With positive pacing, participants began at a higher intensity than they could maintain, and, therefore, the characteristic "sprint" often observed at the end of a known distance effort was not present. Whether the lower MCA_v contributed to the inability to complete this end-spurt is likely to be debated until clearer evidence can be observed. The rationale is, however, consistent with theories of fatigue in which reductions in CBF may compromise local cerebral oxygenation to active areas (Nybo and Rasmussen 2007) and, in turn, impact neuronal activity and exercise capacity (Amann et al. 2006; Bhambhani et al. 2007). Reductions in CBF may act as a modulator of voluntary motor drive as has been observed at rest (Ross et al. 2012; Hartley et al. 2016) although its effect through local tissue oxygenation cannot be excluded. $P_{et}CO_2$ may also play a role, although a recent study suggests that low $P_{et}CO_2$ increases corticospinal excitability (Hartley et al. 2016), which does not appear to reflect voluntary activation involving pathways prior to the motor cortex.

A number of limitations should be addressed in relation to this paper. First, we could only assess one major cerebral blood vessel during the time trial. The right MCA was chosen as it is the most likely candidate to relate to performance due to its role in blood supply to the primary and association motor cortices as well as a large portion of the prefrontal cortex (Afifi and Bergman 1998). Other major, and minor, vessels as well as hemispherical differences are likely to be of interest, but become increasingly problematic to assess particularly during efforts of such short and high intensity. Our interpretation of changes in the MCA is also subject to a number of assumptions. The MCA contributes the blood supply to the motor cortex, and the observation of reduced blood flow to the area could reflect decreased neuronal demand/activation in the area. That

is, fatigue contributing to a reduction in neuronal activity, by whatever means, could reduce MCA_v rather than the reduction in MCA_v causing the fatigue. As we did not assess neuronal activity, we cannot determine whether one has caused the other in this study. Future research may seek to address the assessment of CBF and neuronal activation simultaneously. Finally, TCD assessment and interpretation of CBF is based on an assumption that vessel size is unaltered, which we did not assess, but observations suggest that the MCA constricts with reductions in P_aCO_2 (Coverdale et al. 2014; Verbree et al. 2014), a phenomenon which, if anything, would suggest our observations underestimate the decrease in CBF (Ainslie and Hoiland 2014) towards the end of the time trial. Estimations of CVR, or cerebrovascular conductance, provide an indication of possible changes in cerebral artery diameter, and tighter monitoring of this index may be an avenue to help address this limitation.

This study would benefit from being repeated with a larger sample size but we believe the current data offers valuable insight into relationships between pacing and CBF. Other interventions are clearly needed to better control for pacing strategy, but this may be problematic in CBF investigations since the conscious awareness of pacing may also influence performance as well as regional activity and consequential blood flow in the brain. Innovative strategies to investigate the relationship between CBF and the free regulation of time trial performance are needed.

Recently, it was shown that the voluntary control of breathing, to suppress hyperthermia-induced hyperventilation during cycling in the heat, better conserved CBF over time, compared to uncontrolled ventilation (Tsuji et al. 2015). It may be that similar interventions enable the preservation of CBF and performance during high intensity time trial performance. Similarly, as sporting performance is often undertaken as a match race rather than a time trial, the end-sprint can be very important, and thus strategies ensuring the maintenance of this capacity, perhaps including sufficient CBF may be worth exploring. Further research is required to investigate this phenomenon.

Conclusions

This study is the first to report the response of MCA_v during a cycling time trial. MCA_v appears to change when differing pacing strategies are adopted during a 4 km cycling time trial. It is likely that high relative power outputs during the initial stages of an effort lead to hyperventilatory reductions in $P_{et}CO_2$, contributing to lower MCA_v. Although we cannot relate this reduction in MCA_v directly to fatigue, it is intriguing that when this occurred participants were also unable to increase, or maintain, power output during the second half of the time trial. This relationship is worth exploring but innovative strategies will be required to investigate CBF and the free regulation of time-trial performance.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflict of interest.

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