Dynamic cerebral autoregulation during cognitive task: Effect of hypoxia

Shigehiko Ogoh [1], Hiroki Nakata [2], Tadayoshi Miyamoto [3], Damian Miles Bailey [4] and Manabu Shibasaki [2]

[1]Department of Biomedical Engineering, Toyo University, Saitama, Japan

[2] Department of Health Sciences, Faculty of Human Life and Environment, Nara Women's University, Nara, Japan

[3] Morinomiya University of Medical Sciences, Osaka, Japan

[4] Neurovascular Research Laboratory, Faculty of Life Sciences and Education, University of South Wales, UK

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Corresponding author: Manabu Shibasaki

Department of Health Sciences, Faculty of Human Life and Environment, Nara Women's University

Kitauoya-Nishi Machi, Nara, 630-8506, Japan

Tel.: +81-742-20-3992

Fax: +81-742-20-3578

E-mail address: shiba@cc.nara-wu.ac.jp

ABSTRACT

Changes in cerebral blood flow (CBF) subsequent to alterations in the partial pressures of oxygen and carbon dioxide can modify dynamic cerebral autoregulation (CA). While cognitive activity increases CBF, to what extent it impacts CA remains to be established. In the present study we determined if dynamic CA would decrease during a cognitive task and whether hypoxia would further compound impairment. Fourteen young healthy subjects performed a simple Go/No-go task during normoxia and hypoxia (F_IO_2 =12%) and the corresponding relationship between mean arterial pressure (MAP) and mean middle cerebral artery blood velocity (MCA V_{mean}) was examined. Dynamic CA and steady-state changes in MCA V in relation to changes in arterial pressure were evaluated using transfer function analysis (TFA). While MCA V_{mean} increased during the cognitive activity (P<0.001), hypoxia did not cause any additional changes (P=0.804 vs. normoxia). Cognitive performance was also unaffected by hypoxia (Reaction time, P=0.712; Error, P=0.653). A decrease in the very low and low frequency Phase shift (VLF and LF; P=0.021 and P=0.01) and increase in LF gain were observed (P=0.037) during cognitive activity implying impaired dynamic CA. While hypoxia also increased VLF gain (P<0.001) it failed to cause any additional modifications in dynamic CA. Collectively, our findings suggest that dynamic CA is impaired during cognitive activity independent of altered systemic O_2 availability though we acknowledge the interpretive complications associated with additional competing, albeit undefined inputs that could potentially distort the MAP-MCA V_{mean} relationship.

Key words: cognitive function, cerebral blood flow regulation, transfer function analysis

New and Noteworthy

44 During normoxia, cognitive activity while increasing cerebral perfusion was shown to
45 attenuate dynamic CA yet failed to alter reaction time thereby questioning its
46 functional significance. No further changes were observed during hypoxia suggesting
47 that impaired dynamic CA occurs independently of altered systemic O_2 availability.
48 However, impaired dynamic CA may reflect a technical artefact given the confounding
49 influence of additional inputs that could potentially distort the MAP-MCA V_{mean}
50 relationship.
51
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INTRODUCTION

Adequate supply of oxygen and substrates to the human brain is essential for the maintenance of metabolism and function (7). It has been well established that dynamic cerebral autoregulation (CA) is an important cerebral blood flow (CBF) regulatory mechanism. CBF is regulated via dynamic CA over a wide range of cerebral perfusion pressures (25) and altered by various stressors. At rest, hypocapnia has been shown to enhance dynamic CA with constriction of cerebral vessels known to further extend the autoregulatory plateau by attenuating the rise in pressure (1). In contrast, hypercapnia-induced cerebral vasodilation attenuates dynamic CA (1). Interestingly, dynamic CA is impaired by exhaustive exercise (26), hypoxia (37) or moderate exercise during acute hypoxia (2, 3) despite the potentially neuroprotective benefits of hyperventilation-induced hypocapnia. In addition, neural or visual stimulation modified dynamic CA (12, 21, 31). These findings indicate that subtle alterations in CBF through environmental/physical stress can modify dynamic CA.

A previous study (36) demonstrated that cognitive activity increased anterior and posterior cerebral artery blood flow velocity (8) to satisfy neural/metabolic demand and neurovascular coupling (NVC) (5, 16). The superimposition of hypoxia and corresponding vasodilation and increase in cerebral perfusion could further compound the hyperemia. However, to what extent these individual and combined stressors impact dynamic CA has not previously been investigated. Likewise, acute exposure to inspiratory hypoxia increases cerebral perfusion.

In light of these findings, we designed a human study to explore this relationship. We hypothesized that a cognitive activity-induced increase in CBF would impair dynamic CA and this would be further compounded following the

77 superimposition of hypoxia given the additional hyperemia. We explored the
78 relationship between CBF and mean arterial pressure (MAP) to determine dynamic CA
79 before and after a cognitive task in both normoxia and hypoxia.
80
81 **METHODS**
82 Fourteen healthy young participants (9 females and 5 males, age 22 ± 1 years, stature
83 1.67 ± 0.06 m, body mass 62 ± 11 kg; mean ± SD) participated in the study. The
84 participants underwent a medical examination, including a detailed history and were
85 found without any cerebrovascular, cardiovascular, pulmonary, or kidney disease.
86 Participants were requested to abstain from caffeinated beverages for 12 h and from
87 strenuous physical activity and alcohol for at least 24 h before the day of the experiment.
88 The protocol was approved by the Ethical Committee for Human Research at Nara
89 Women's University and each subject provided written informed consent to participate
90 according to the principles of the Declaration of Helsinki.
91
92 *Experimental design*
93 All participants were familiarized with the equipment and procedures before any
94 experimental sessions. On the experimental day, participants arrived at the laboratory
95 at least 2 h after a light meal. They sat comfortably in a chair during the course of
96 instrumentation while breathing room air through a mouthpiece. After a 5 min baseline
97 measurement, each participant performed a simple cognitive task for 5 min and
98 followed by a 5 min recovery. Following this protocol, each participant started to breath
99 hypoxic gas (12%O_2 balanced with N_2, 0%CO_2) through a mouthpiece for 35 min to
100 achieve steady-state and the measurements subsequently repeated. Because of

prolonged hypoxic exposure, the sequence of protocol was fixed. In the pilot study, 5 subjects performed the cognitive task twice without hypoxic gas breathing, and we confirmed no influence of order.

Measurements

Cognitive task

We used the Go/No-go stimulus as a cognitive task in the present study. The Go/No task is a test originally developed to assess behavioral inhibition in animals (19) and subsequently in humans (10, 39) and is an important aspect of executive function. The Go/No-go task is a simple cognitive task; the Go stimulus was delivered to the second digit of the left hand, and the No-go stimulus to the fifth digit of the left hand. Subjects had to respond to the stimulus by pushing a button with their right thumb (contralateral to the stimulated side) as quickly as possible only after the presentation of the Go stimulus. Electrical stimuli were applied to the second or fifth digit of the left hand with ring electrodes. The electrical stimulus used was a current constant square-wave pulse 0.2 ms in duration, and the stimulus intensity was 2.0-fold the sensory threshold, which yielded no pain or unpleasant sensations. The probability of the stimulus for the second and fifth digit was even. Stimuli were presented in a random order, with the interval of presentation being fixed at 2 s. Reaction time was measured for the Go stimulus.

Cerebrovascular and cardiorespiratory measures

Heart rate (HR) was measured by a lead II electrocardiogram (Biomulti 1000, NEC, Tokyo, Japan). Beat-to-beat arterial blood pressure (ABP) was monitored continuously

with finger photoplethysmography (Finapres Medical Systems BV, Netherlands). Subjects pushed the response button with right thumb for the Go/No-go task, while the cuff of finger photoplethysmography was placed over right middle finger. They put their right hand on a cushion and required to keep stretching fingers except for thumb. Middle cerebral artery blood velocity (MCA *V*) was measured by transcranial Doppler ultrasonography (WAKI Atys Medical, St Genislaval, France). A 2 MHz Doppler probe was placed over the right temporal window and fixed with an adjustable headband. Minute ventilation (V_E), end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) and oxygen ($P_{ET}O_2$) were sampled from a leak-free mask and measured with a gas analyzer (ARCO2000-MET, Arcosystem, Chiba, Japan). Blood oxygen saturation (SpO_2) was monitored on the third digit of the right hand with finger pulse oximetry (Surface Monitor 9900MK; Kohken Medical, Tokyo, Japan).

Data analysis

Dynamic CA was assessed using transfer function analysis during each steady-state condition. Briefly, mean ABP (MAP) and MCA *V* (MCA V_{mean}) were calculated across each cardiac cycle, linearly interpolated, and resampled at 2 Hz for transfer function analysis (42). Data analysis and interpretation were conducted according to established guidelines published by the International Cerebral Autoregulation Research Network (9) including the removal of negative values for phase indicative of "wrap-around" artifacts for frequencies < 0.1Hz. The transfer function gain, phase shift and coherence between fluctuations in MAP and MCA V_{mean} were calculated in the very low-frequency (VLF; 0.02–0.07 Hz), low-frequency (LF; 0.07–0.20 Hz) and high-frequency ranges (HF; 0.20–0.30 Hz) in accordance with our previous reports (26, 27). Transfer function

149 analysis in the low frequency range of 0.07–0.30 Hz can model short-term regulation of
150 CBF in response to changes in arterial pressure (42). The transfer function gain and
151 phase shift reflect the relative amplitude and time relationships, respectively, between
152 the changes in perfusion pressure and blood flow over a specific frequency range (26, 27).
153 Phase shift was considered the primary criterion for evaluating dynamic CA, where a
154 decrease in phase shift reflects a more pressure-passive relationship between MAP and
155 MCA V_{mean} associated with a reduction in dynamic CA. In contrast, an increase in gain
156 indicates a greater influence of MAP on CBF and thus reflects an impairment in
157 dynamic CA. The squared coherence function reflects the fraction of CBF power that
158 can be related linearly to the MAP power at each frequency. Similar to a correlation
159 coefficient, it varies between 0 and 1 and reflects the strength of linear relationship
160 between two values. All hemodynamic variables were averaged over the last minute of
161 each steady-state period for further analyses. As behavioral data, reaction time and
162 error rate in normoxia and hypoxia conditions were analyzed.
163
164 *Statistical analysis*
165 Analyses were conducted using SigmaStat (Jandel Scientific Software; SPSS Inc.,
166 Chicago, IL, USA). Hemodynamic and cerebral autoregulation data were analyzed
167 using a two-way repeated-measures ANOVA (condition: normoxia *vs.* hypoxia x task:
168 rest *vs.* Go/No-go *vs.* recovery) with Student–Newman–Keuls *post hoc* tests. In the
169 case if normality was failed, Krustal-Wallis Analysis of Variance of Ranks was
170 performed. Behavioral data were analyzed by Student's *t*-test. Significance was set at
171 $P < 0.05$. Data are expressed as means ± SD.
172
173

RESULTS

Cerebrovascular and cardiorespiratory data (Table 1)

As expected, $P_{ET}O_2$, SpO_2 and $P_{ET}CO_2$ decreased during hypoxia (P<0.001, P<0.001 and P=0.009) but were unchanged during the cognitive task (Table 1). MAP and V_E were unchanged by Go/No-go task and hypoxia condition (Table 1). MCA V_{mean} increased during the cognitive task under both conditions (P<0.001), but was not different during hypoxia (P=0.804) despite ventilation-induced hypocapnia (P=0.009).

Cognitive task

Behavioral data were no difference between normoxia and hypoxia (Reaction time: 292±74 vs 293±77 ms, P=0.712; Error rate: 1.26±1.35 vs 1.11±0.96 %, P=0.653).

Dynamic cerebral autoregulation

Both VLF and LF coherence ranges consistently exceeded 0.6 (Table 2).

The VLF and LF Phase shift decreased during the cognitive task (VLF and LF; P=0.021 and P=0.010). However, these were not further modified by hypoxia (P=0.602 and P=0.236). While the LF gain increased during the cognitive task (P=0.037) and VLF gain increased during hypoxia (P<0.001), no additional changes were observed during the combination of the two stimuli (i.e. no interaction effect).

DISCUSSION

The present study has revealed two important findings. First, the cognitive task while increasing cerebral perfusion was shown to attenuate dynamic CA that could not be attributed to hypocapnia yet this failed to translate into any alteration in reaction time

thus challenging its functional significance. Second, hypoxia also attenuated dynamic CA, yet contrary to our original hypothesis, failed to further compound the cognitive task-induced reduction in dynamic CA. The lack of any additional modification in the face of marked arterial hypoxemia suggests that this phenomenon is independent of systemic O_2 availability.

CBF regulation and cognition in hypoxia

The brain's energy reserve is small, thus a continuous supply of glucose and oxygen is required to support neuronal function (24). Cerebral synaptic activity causes a relative lack of oxygen and glucose, increases acutely the demand for energy and consequently increases regional CBF known as neurovascular coupling. Therefore, any potential reduction in cerebral perfusion and corresponding O_2 delivery could impact cognitive function. Thus, we originally anticipated that the cognitive task would be impaired in the face of hypocapneic hypoxemia during acute exposure to inspiratory hypoxia consistent with the published literature (38). However, this was not the case although we acknowledge that the Go/No-go task addresses a singular albeit important domain, notably executive function. Functional magnetic resonance imaging studies have shown that activation of the prefrontal cortex and anterior cingulate cortex are associated with response inhibition (22). Interestingly, native highlanders born and raised at high-altitude present with structural modifications to the inferior/middle frontal gyrus and anterior cingulate cortex (41).

Dynamic cerebral autoregulation during cognitive task and hypoxia

Previous studies reported that brain activation (neural or visual stimulation) modifies

dynamic CA (12, 21, 31). In the present study, dynamic CA was consistently attenuated during the cognitive activity under both normoxic and hypoxic conditions highlighting that acute changes in arterial pressure may translate into cerebral hyper/hypoperfusion during the cognitive activity. It is well established that dynamic CA is affected by cerebral vasomotion. Indeed, hypocapnia-induced cerebral vasoconstriction has been shown to enhance dynamic CA, whereas the converse is true during hypercapnia-induced cerebral vasodilation CA (1). On the other hand, Panerai et al. (31) demonstrated that words and puzzle tasks attenuated dynamic CA and increased CBF. Similarly, Nakagawa et al. (21) showed that visual stimulation increased CBF and attenuated dynamic CA. Thus, it is conceivable that the cognitive task-induced increase in CBF (vasodilation) may prove the primary mechanism responsible for the observed attenuation in dynamic CA though the confounding influence of additional competing, albeit undefined inputs, that could potentially distort the MAP-MCA V_{mean} relationship is duly acknowledged.

These findings suggest that brain activation attenuates dynamic CBF regulation, indicating an unbenefited mechanism for oxygen supply in the brain. While a similar response was observed during hypoxia, contrary to our original expectations, the attenuation in dynamic CA was not further compounded suggesting an apparent disassociation between dynamic CA and systemic oxygenation when the brain is challenged if not indeed primed by “cognitive stress”. Nevertheless, the physiological role of modified dynamic CA during cognitive task remains unknown. Using the multiple analyses demonstrated by some groups (17, 18, 20, 32, 33), we might identify the relationship between multi-input and output to make clear the effect of dynamic CA and neural activity. In the present study, unfortunately, we could not measure any index

of neural activity. Using this analysis, we need further investigations to resolve this important question.

It was interesting to note that we failed to observe any evidence for hypoxic vasodilation, the likely consequence of hyperventilation-induced hypocapnia via the respiratory chemoreflex (6, 23, 28-30) and attendant cerebral vasoconstriction that would have effectively countered any potential increase in cerebral perfusion. It would be of interest from a mechanistic perspective if future studies were to compare isocapneic against hypocapneic hypoxia and further include an exercise challenge as a means of manipulating CBF (high and low) to determine consequent changes in dynamic CA during cognitive stress.

The response of CBF to hypoxia is associated with ventilatory and cerebral vasculature acclimatization (4, 40). For example, acute hypoxia decreases or maintains CBF rather than increases by hyperventilation-induced hypocapnia via respiratory chemoreflex (6, 23, 28-30). More interestingly, preventing hyperventilation during hypoxia increases CBF (29, 30). Moreover, isocapnic hypoxia impairs dynamic CA, but hyperventilation-induced mild hypocapnia acts to improve dynamic CA during acute hypoxia (28). These findings suggest that hypoxia and its acclimation induced change in respiration affect cerebral vasculature and modify CBF and dynamic CA responses to hypoxia. However, in the present study, acute hypoxia did not change CBF. Thus, when the duration of exposure to hypoxia was longer, it is possible that CBF increases and this cerebral vasodilation may modify cognitive task-induced attenuated dynamic CA. However, effect of acclimation of CBF on dynamic CA is still unclear. In the present study, on the other hand, hypoxia did not cause further impairment in dynamic CA during cognitive task. This phenomenon may be supported by hypoxia-induced

hypocapnia that improves dynamic CA at rest. However, hypoxia without cognitive task also impaired dynamic CA despite a hypocapnia. Since the interaction effect in dynamic CA between O_2 and CO_2 blood concentration may be modified by cognitive task, we need further investigations to identify this interaction in dynamic CA.

Experimental limitations

It is important to consider the methodological limitations associated with this study. First, CBF was estimated by TCD determined-CBF velocity. Thus, this assumption is valid only when MCA diameter is constant. In humans, the MCA diameter has been shown to remain relatively constant under a variety of conditions (34, 35) and thus TCD is generally considered a useful surrogate measure of blood flow. In contrast, more recently, Coverdale et al. (11) identified that transcranial Doppler-determined cerebral blood velocity underestimates changes in CBF by 7-18% during modest hypercapnia and hypocapnia, though we only observed small(er) changes in $P_{ET}CO_2$ in our study. Second, the acclimation to hypoxia warrants consideration given its established heterogeneity. Third, the sample size of the present study may be considered small (n = 14) though sufficient given the observed (retrospective) power (>0.8 at $P < 0.05$) despite the variability of the TFA data. Fourth, we were not in a position to control/synchronize menstrual cycle phase in our female participants and although controversial (15) estrogen may have reduced the cerebral myogenic response (13, 14). A dedicated study focused on the effect of gender for CBF regulation in humans is warranted. Finally, we cannot exclude the possibility that our primary finding of impaired dynamic CA may simply prove a misinterpretation subsequent to a technical confound. During mental stimulation, it is known that MCA V_{mean} is not influenced solely by blood pressure, as

294 can be assumed at rest, but there are additional competing, albeit undefined (e.g.
295 metabolic) inputs that could potentially distort the ABP-MCA V_{mean} relationship.
296 Consistent with previous recommendations, (31), additional work is encouraged to
297 determine the suitability of transfer function analysis to provide authentic insight into
298 the extent to which pressure autoregulation is truly affected by cognitive stimulation.
299
300 *Conclusions*
301 In conclusion, our findings indicate that during normoxia, cognitive activity while
302 increasing cerebral perfusion was shown to attenuate dynamic CA yet failed to alter
303 reaction time thereby questioning its functional significance. No further changes were
304 observed during hypoxia suggesting that impaired dynamic CA occurs independently of
305 altered systemic O_2 availability. However, impaired dynamic CA may simply reflect a
306 technical artefact given the confounding influence of additional inputs that could
307 potentially distort the MAP-MCA V_{mean} relationship, highlighting the need for further
308 research.
309
310
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Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).

Author contributions

H.N., T.M., S.O., and M.S. conception and design of the research; H.N., and M.S. performed experiments; M.S. analyzed the data; S.O., H.N., T.M., S.O., D.M.B. and M.S. interpreted the results of the experiments; S.O. prepared figures; S.O., H.N., T.M., D.M.B. and M.S. drafted the manuscript and revisions thereof. All authors agreed to the final version submitted.

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449 **Figure Legend**

450 **Figure 1** Representative time series of middle cerebral mean blood velocity (MCA V_{mean}),
451 mean arterial pressure (MAP), and heart rate (HR) under normoxia (left) and hypoxia
452 (right) conditions.
453 Square blocks indicate while performing the Go/No-go tasks.
454

455 **Figure 2** Representative transfer function phase (left) and gain (right).
456 On the top panels, solid and gray lines represent at rest in normoxia and hypoxia,
457 respectively. On the middle (normoxia) and bottom (hypoxia) panels, solid and gray
458 lines represent at rest and during the Go/No-go task, respectively. Dashed lines indicate
459 the very low (VLF), low (LF), and high frequency ranges (HF).
460

Table 1 Hemodynamic and cardiorespiratory data

		Normoxia			Hypoxia			*P-values*		
		Rest	Go/No-go	recovery	Rest	Go/No-go	recovery	*task*	*cond.*	*inter.*
HR	(bpm)	71 ± 12	72 ± 13	73 ± 12	81 ± 13	78 ± 11*	76 ± 10*	0.534	0.024	0.022
MAP	(mmHg)	80 ± 6	83 ± 6	80 ± 7	82 ± 10	83 ± 11	82 ± 10	0.051	0.608	0.404
MCA V_{mean}	(cm/s)	70 ± 20	75 ± 22	67 ± 18	73 ± 25	74 ± 25	68 ± 25	<0.001	0.804	0.201
SpO_2	(%)	97 ± 1	96 ± 1	96 ± 1	80 ± 10$	80 ± 10$	85 ± 8*#$	0.012	<0.001	0.020
V_E	(L/min)	8.2 ± 2.0	8.3 ± 2.1	8.4 ± 1.9	9.0 ± 2.8	8.7 ± 2.5	8.5 ± 2.8	0.861	0.336	0.285
$P_{ET}O_2$	(mmHg)	105 ± 5	104 ± 3	106 ± 4	50 ± 9	50 ± 9	52 ± 10	0.214	<0.001	0.641
$P_{ET}CO_2$	(mmHg)	39 ± 2	39 ± 2	38 ± 2	35 ± 7	35 ± 5	35 ± 6	0.354	0.009	0.755

Values are mean ± SD (n = 14). HR; Heart rate, MAP; mean arterial pressure, MCA V_{mean}; middle cerebral mean blood velocity, V_E; minutes ventilation, $P_{ET}O_2$; end-tidal partial pressure of oxygen tension, $P_{ET}CO_2$; end-tidal partial pressure of carbon dioxide tension. *Different from Rest ($P < 0.05$), #Different from Go/No-go task ($P < 0.05$), $Different from Normoxia condition.

470 **Table 2** Dynamic cerebral autoregulation

			Normoxia			Hypoxia			*P-values*		
			Rest	Go/No-go	recovery	Rest	Go/No-go	recovery	*task*	*cond.*	*inter.*
Phase	(radian)	VLF	0.913 ± 0.251	0.588 ± 0.579	1.011 ± 0.520	0.597 ± 0.279	0.439 ± 0.344	0.673 ± 0.423	0.021	0.026	0.602
		LF	0.636 ± 0.260	0.506 ± 0.151	0.592 ± 0.164	0.488 ± 0.313	0.428 ± 0.239	0.545 ± 0.317	0.010	0.139	0.236
		HF	0.153 ± 0.277	0.111 ± 0.226	0.099 ± 0.215	0.051 ± 0.195	0.098 ± 0.220	0.078 ± 0.125	0.898	0.357	0.286
Gain	(cm/s/mmHg)	VLF	0.633 ± 0.222	0.573 ± 0.205	0.621 ± 0.246	0.914 ± 0.407	0.908 ± 0.467	0.789 ± 0.361	0.312	<0.001	0.301
		LF	1.019 ± 0.338	1.072 ± 0.369	0.973 ± 0.303	0.996 ± 0.356	1.021 ± 0.386	0.914 ± 0.234	0.037	0.361	0.846
		HF	1.156 ± 0.436	1.086 ± 0.354	1.133 ± 0.395	1.204 ± 0.376	1.110 ± 0.353	1.263 ± 0.621	0.383	0.351	0.831
Coherence	(U)	VLF	0.675 ± 0.100	0.535 ± 0.074	0.565 ± 0.145	0.691 ± 0.182	0.733 ± 0.128*	0.659 ± 0.148*	0.056	0.014	0.026
		LF	0.825 ± 0.084	0.842 ± 0.081	0.788 ± 0.096	0.831 ± 0.098	0.832 ± 0.091	0.767 ± 0.146	0.021	0.767	0.699
		HF	0.774 ± 0.117	0.710 ± 0.140	0.791 ± 0.126	0.805 ± 0.112	0.760 ± 0.133	0.806 ± 0.093	0.042	0.179	0.719

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472 Values are mean ± SD (n = 14). VLF; very low frequency range (0.02-0.07 Hz), LF; low

473 frequency range (0.07-0.2 Hz), HF; high frequency range (0.2-0.3 Hz). *Different from

474 Rest ($P < 0.05$).

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Figure 1

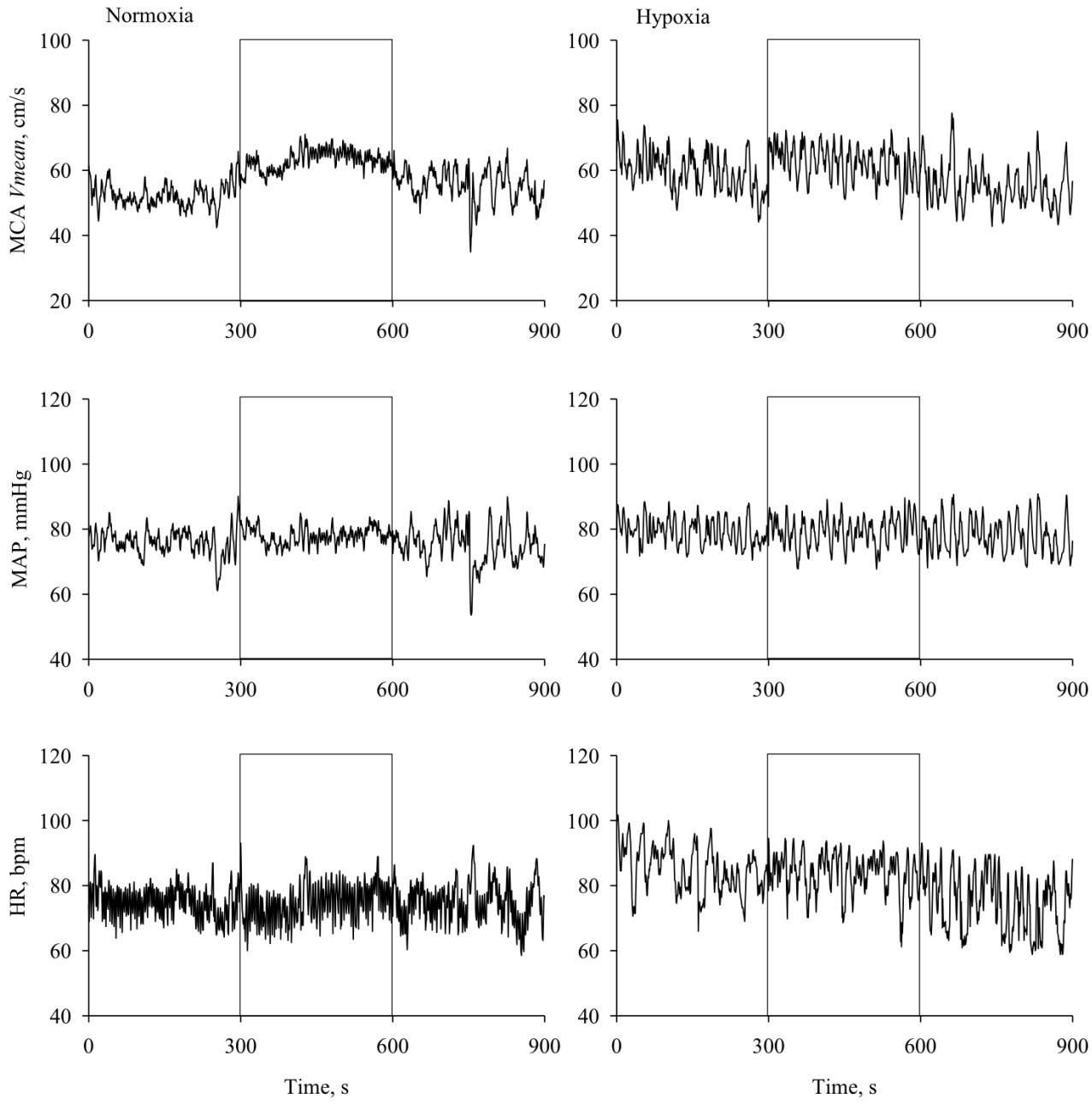
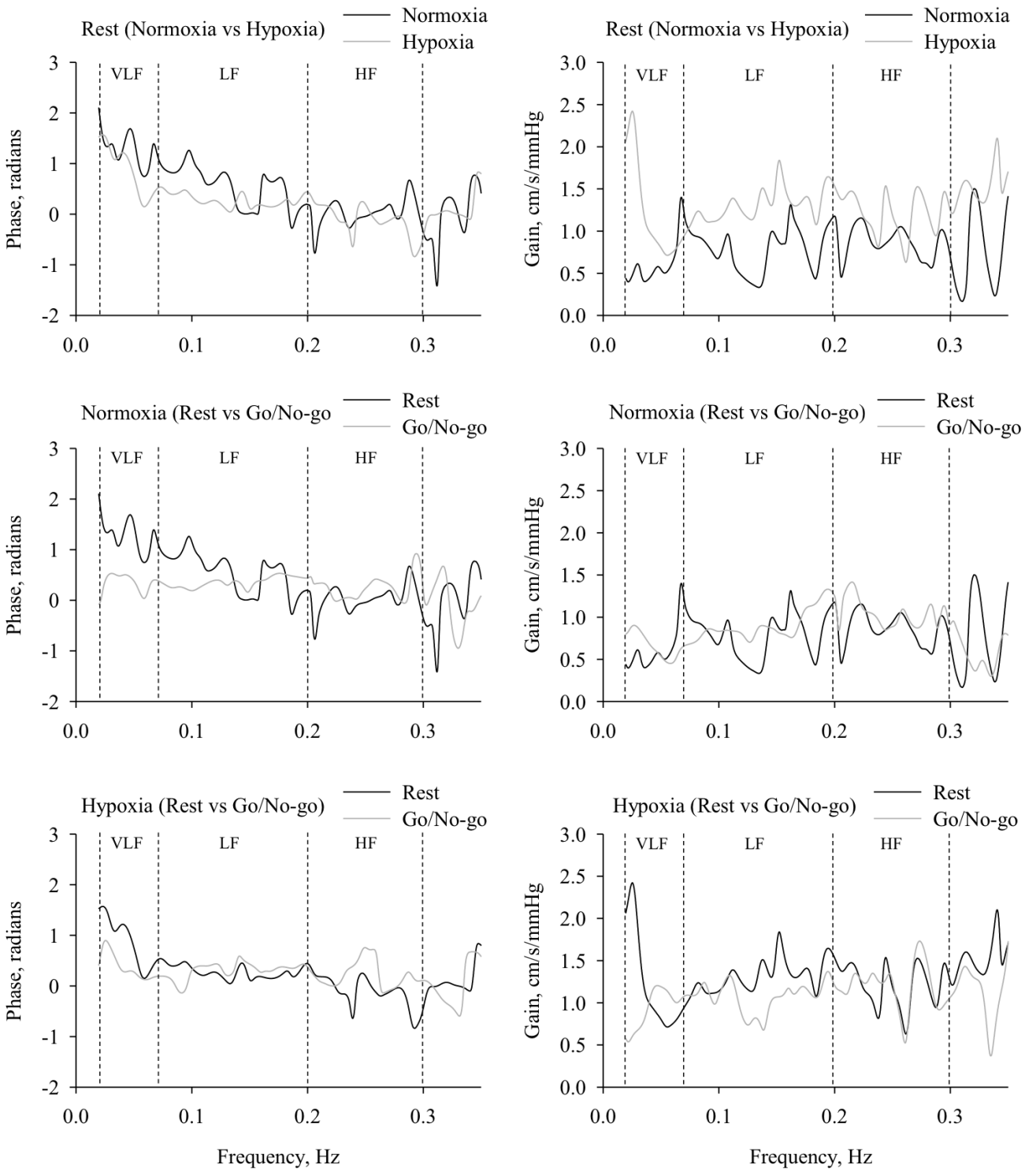


Figure 2


Rest (Normoxia vs Hypoxia)
Normoxia
Hypoxia
VLF
LF
HF
Phase, radians
Gain, cm/s/mmHg
Normoxia (Rest vs Go/No-go)
Rest
Go/No-go
Hypoxia (Rest vs Go/No-go)
Frequency, Hz