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Original Article

Influence of blood lactate variations and passive exercise on cardiac responses

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Abstract. [Purpose] This study aimed to investigate cardiovascular responses, including heart rate (HR) and heart rate variability (HRV), to various hyperlactatemia–passive exercise interactions. [Participants and Methods] Nine healthy male participants performed upper limb passive cycling movement, and their HR and HRV were assessed while their blood lactate levels were manipulated by sustained handgrip exercise at control, 15% maximum voluntary contraction (MVC), and 30% MVC, followed by postexercise circulatory occlusion. [Results] HR and root mean squared standard difference (rMSSD) of HRV response remained constant at all blood lactate levels during passive exercise (HR: control, 75.8 ± 3.4 bpm; 15% MVC, 76.9 ± 2.7 bpm; and 30% MVC, 77.0 ± 3.7 bpm; rMSSD: control, 33.2 ± 6.9 ms; 15% MVC, 36.3 ± 7.3 ms; and 30% MVC, 37.3 ± 8.9 ms). [Conclusion] Manipulating metaboreflex activation did not significantly alter HR or HRV during passive exercise. These results suggest that, in healthy participants, the interactions between mechanical and metabolic stimuli do not affect HR and HRV responses, implying that passive exercise may be safely implemented.
Key words: Passive exercise, Blood lactate, Heart rate

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INTRODUCTION

In skeletal muscle, group III fibers respond to mechanical stimuli, such as muscle stretch and contraction, while group IV fibers are activated by metabolic byproducts, such as lactic acid[1)]. These group III and IV fibers play a crucial role by transmitting afferent signals to the cardiovascular center located in the medulla oblongata, thereby modulating the autonomic nervous system (ANS)[2)]. This orchestration of the cardiovascular system by skeletal muscle is known as the exercise pressor reflex, which significantly contributes to the regulation of blood flow directed toward active muscles[1, 3)].

For critically ill patients who are unable to actively engage in exercise, passive exercise is a common early intervention aimed at activating mechanoreceptors within skeletal muscle[4, 5)]. Typically, such mechanoreceptor stimulation increases heart rate (HR) and alters heart rate variability (HRV), coupled with augmented blood flow responses within the exercised limb[6, 7)]. It was noted that metabolic byproducts, such as blood lactate (BLa), increased the sensitivity of mechanoreceptor reflexes and enhanced cardiovascular responses[8)]. Furthermore, excess lactate stimulates metabolic receptors, activating sympathetic nerve activity[9)]. As critically ill patients often present with elevated BLa levels, which have been associated with higher mortality rates[10)], implementation of passive exercise in critically ill patients necessitates vigilant monitoring of cardiovascular reactions, encompassing both mechanical and metabolic stimuli.

However, the intricate interplay between mechanical and metabolic stimuli in eliciting cardiovascular responses remains insufficiently understood. Investigating typical responses in critically ill patients is complicated by the use of ventilators, sedatives, or medications regulating HR. It is therefore imperative to obtain baseline data of normal cardiovascular responses

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to mechanical and metabolic stimulation to enhance our comprehension of cardiovascular responses, mediated through peripheral feedback mechanisms, in critically ill patients.

This study aimed to investigate the effect of mechanical and metabolic stimuli on HR and HRV in healthy participants, thereby contributing to a deeper understanding of how the cardiovascular system responds to combined mechanical and metabolic stimuli, with potential implications for future patient care and treatment strategies. Specifically, we compared HR and HRV responses to mechanical stimulation under different metabolic conditions, and hypothesized that the HR response during passive cycling movement (PCM) will exhibit an increasing trend with increasing metabolic stimulus intensity.

PARTICIPANTS AND METHODS

This cross-sectional included nine healthy adult males aged 20 years or older. The age, height, weight, and body mass index (BMI) of the participants were 21.8 ± 2.0 years, 167.8 ± 7.8 cm, 59.6 ± 6.8 kg, and 21.1 ± 1.7 kg/m^2, respectively (mean ± SD). Exclusion criteria included history of respiratory or cardiovascular diseases, smoking, motor system disorders that could impede voluntary movement, and history of neurological diseases. The participants did not perform any exercise for 24 hours or consume caffeine for 12 hours before the measurements. This study conformed to the principles of the Declaration of Helsinki and was conducted according to the protocol of the Ethics Committee of Seirei Christopher University (13006). Informed consent was obtained from all participants.

Figure 1 provides an overview of the experimental testing sessions in the current study. Prior to the experiment, the maximum voluntary contraction (MVC) of the right forearm (dominant arm in all participants) was measured as the maximum value squeezed three times with maximal effort using a handgrip dynamometer. We also employed an intensity control condition (CTL), which did not involve handgrip exercises. Additionally, we calculated intensities at 15% and 30% of maximal voluntary contraction (MVC). Handgrip exercises (HGE) at CTL, 15% MVC, and 30% MVC were subsequently used to activate the metaboreflex. An experimental session started with 5 min of rest, followed by HGEs performed under the various MVC conditions and continuous muscle contraction for 3 min. Postexercise circulatory occlusion (PECO) was then performed on the contracting right upper arm for 3 min using a blood pressure manchette (DS44, Welch Allyn, Chicago, IL, USA) pressurized at 220 mmHg. PECO is used to examine the response of metabolites, such as lactate, produced during continuous exercise and accumulated in the muscle due to arterial occlusion[11, 12]. Following PECO, and 1 min before PCM, both palms were strapped to the pedals of the PCM device (Room March Pro, Yubun Corporation, Tokyo, Japan). Upper extremities were placed within the range of motion defined by elbow flexion angles of 0° and 90°, and the shoulder flexion angle was maintained near 90° at a pedal cadence of 60 rpm. Participants were encouraged to remain passive and not actively move their upper extremities prior to the start of PCM and throughout the protocol, and participants were observed to avoid voluntary contraction of the upper arm throughout the protocol. Participants had a recovery period of at least 30 min between each MVC condition.

Electrocardiography (ECG) was performed using one lead in a standard CM5 configuration with three silver chloride monitoring electrodes placed on the chest. Traces were recorded using an ECG monitor (BSM-2400, Nihon Kohden, Tokyo, Japan) at a sampling frequency of 1,000 Hz (PowerLab and LabChart 5 software, AD Instruments, Dunedin, New Zealand). Mean arterial pressure (MAP), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured noninvasively from the left upper arm wrapped in a manchette with an automated sphygmomanometer (HEM-770A, Omron, Kyoto, Japan). BLa was measured 3 min after the start of rest, 1 min after the start of PECO, and immediately after PCM using a blood lactate meter (Lactate Pro, arkray, Kyoto, Japan) that measures BLa by drawing blood directly from the fingertips of the right hand. Respiratory rate was monitored using an expiratory gas analyzer (AE-300S, MINATO Medical Science CO., LTD., Osaka, Japan) maintained at 0.25 Hz with 2-s expiration and 2-s inspiration to exclude the influence of respiratory sinus arrhythmia[13]. Respiratory rate was controlled by an electronic metronome set at 60 bpm as auditory feedback and respiratory rate was adjusted accordingly if the mean respiratory rate error was greater than 15 ± 2 breaths/min. HRV was analyzed as root mean squared standard difference (rMSSD) between adjacent R-R intervals using measures in the

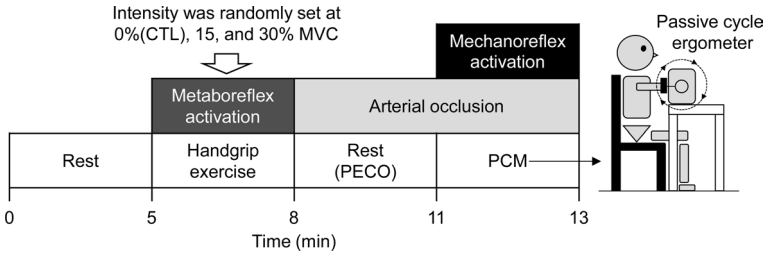

Fig. 1. Overview of the experimental testing sessions.
CTL: control; MVC: maximum voluntary contraction; PECO: postexercise circulatory occlusion; PCM: passive cycling movement.

time domain (LabChart 5). The rMSSD of HRV provides information regarding parasympathetic heart modulation and an estimate of short-term high-frequency variations in HR as an index of vagal tone[14].

We analyzed HR, rMSSD of HRV, BLa, SBP, DBP, and MAP using two-way analysis of variance with repeated measures of linear mixed models with time (REST, HGE, PECO, PCM) and by condition (CTL, 15%, and 30% MVC) to evaluate interactions between time and conditions. Post-hoc analysis with Bonferroni correction was used to evaluate interactions within each parameter. Participants were entered as a random effect. Sequential Bonferroni correction was used to adjust for multiple comparisons and BMI. All statistical analyses were performed using the SPSS version 26 statistical software package for Windows (IBM Corp, Armonk, NY, USA). Data are expressed as mean ± standard error of the mean (SEM). Statistical significance was set at $p<0.05$.

RESULTS

Table 1 summarizes HR, rMSSD of HRV, BLa, and blood pressure responses at REST, HGE, PECO, and PCM under each MVC condition. HR changed over time, but these changes were not affected by MVC condition. HR during PCM was increased compared with that at REST or HGE under all MVC conditions. In addition, HR during PCM was similar under all MVC conditions. The rMSSD of HRV exhibited significant differences over time and under different MVC conditions. Post-hoc analysis showed a significant increase in rMSSD of HRV from HGE to PECO at CTL and 30% MVC. Under all MVC conditions, rMSSD of HRV significantly decreased during PCM compared with REST, HE, and PECO. The rMSSD of HRV during PCM was similar under all MVC conditions. BLa, SBP, DBP, and MAP exhibited significant changes over time and under different MVC conditions. Post hoc analysis showed that BLa was significantly increased under all condi-

Table 1. Summary of HR, rMSSD of HRV, BLa, and blood pressure responses at RES5T, HGE, PECO, and PCM

Variable	Testing time	Condition			Two way ANOVA	Between-condition differences		
		CTL	15% MVC	30% MVC	p-value	CTL vs. 15%	CTL vs. 30%	15% vs. 30%
HR	REST	71.0 ± 3.4	68.8 ± 2.7	70.5 ± 3.7	0.70	−1.2 ± 1.3	−0.5 ± 1.3	0.7 ± 1.3
(bpm)	HGE	72.5 ± 3.4	71.4 ± 2.7	75.9 ± 3.7		−1.1 ± 2.8	3.4 ± 2.8	4.6 ± 2.8
	PECO	71.8 ± 3.4	71.4 ± 2.7	70.8 ± 3.7		−0.4 ± 1.7	0.6 ± 1.7	− 0.6 ± 1.7
	PCM	75.8 ± 3.4[a]	76.9 ± 2.7[a,b,c]	77.0 ± 3.7[a]		1.1 ± 3.1	1.1 ± 3.1	0.0 ± 3.1
BLa	REST	1.2 ± 0.2	1.3 ± 0.4	1.2 ± 0.8	0.02	0.1 ± 0.1	0.0 ± 0.1	0.2 ± 0.1
(mg/dl)	HGE	–	–	–		–	–	–
	PECO	1.7 ± 0.2	2.3 ± 0.4	2.7 ± 0.8		−0.6 ± 0.3	0.9 ± 0.3*	−0.4 ± 0.3
	PCM	2.0 ± 0.2[a]	2.8 ± 0.4[a]	5.1 ± 0.8[a]		0.1 ± 0.6	2.4 ± 0.6*	2.3 ± 0.6*
rMSSD	REST	50.8 ± 6.9	44.6 ± 7.3	49.1 ± 8.9	0.02	−6.2 ± 5.7	−1.7 ± 5.7	4.5 ± 5.7
(ms)	HGE	44.7 ± 6.9	48.5 ± 7.3	43.9 ± 8.9		3.9 ± 6.9	−0.8 ± 6.9	−4.7 ± 6.9
	PECO	37.6 ± 6.9	45.5 ± 7.3	66.1 ± 8.9[b]		7.9 ± 8.0	28.5 ± 8.0*	20.6 ± 8.0
	PCM	33.2 ± 6.9[a]	36.3 ± 7.3[b]	37.3 ± 8.9[c]		3.1 ± 5.6	4.0 ± 5.6	1.0 ± 5.6
SBP	REST	118.7 ± 2.2	120.1 ± 2.1	120.0 ± 2.5	<0.01	1.4 ± 2.2	1.1 ± 2.2	−0.1 ± 2.2
(mmHg)	HGE	117.2 ± 2.2	126.6 ± 2.1[a]	141.1 ± 2.5[a]		9.3 ± 2.2*	23.9 ± 2.2*	14.6 ± 2.2*
	PECO	119.6 ± 2.2	123.1 ± 2.1	131.0 ± 2.5[a, b]		3.6 ± 2.4	11.4 ± 2.4*	7.9 ± 2.4*
	PCM	–	–	–		–	–	–
DBP	REST	83.6 ± 2.1	84.0 ± 1.6	84.0 ± 1.8	<0.01	0.4 ± 1.7	0.4 ± 1.7	0.0 ± 1.7
(mmHg)	HGE	83.1 ± 2.1	88.9 ± 1.6[a]	99.0 ± 1.8[a]		5.8 ± 1.6*	15.9 ± 1.6*	10.1 ± 1.6*
	PECO	82.1 ± 2.1	85.8 ± 1.6	95.7 ± 1.8[a]		3.7 ± 2.6	13.6 ± 2.6*	9.9 ± 2.6*
	PCM	–	–	–		–	–	–
MAP	REST	95.3 ± 1.7	96.0 ± 1.6	96.0 ± 1.6	<0.01	0.8 ± 1.7	0.7 ± 1.7	−0.1 ± 1.7
(mmHg)	HGE	94.5 ± 1.7	101.4 ± 1.6[a]	113.0 ± 1.6[a]		7.0 ± 1.5*	18.6 ± 1.5*	11.6 ± 1.5*
	PECO	94.6 ± 1.7	98.2 ± 1.6	107.4 ± 1.6[a]		3.6 ± 2.2	12.9 ± 2.2*	9.22 ± 2.2*
	PCM	–	–	–		–	–	–

Values reported as the mean ± SE.

The post-hoc tests involved multiple comparisons using the Bonferroni correction to assess differences in time or condition. Footnote symbols were defined as follows: 'a' indicated $p<0.05$ compared with the REST condition, 'b' indicated $p<0.05$ compared with HGE, 'c' indicated $p<0.05$ compared with PECO, and '*' indicated $p<0.05$ for comparisons between conditions (CTL vs. 15%, CTL vs. 30%, or 15% vs. 30%).

HR: heart rate; Bla: blood lactate; rMSSD: root mean square of standard division; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HGE: handgrip exercise; PECO: postexercise circulatory occlusion; PCM: passive cycling movement; CTL: control; MVC: maximum voluntary contraction; SE: standard error; ANOVA: analysis of variance.

tions compared with REST, with the greatest increase observed at 30% MVC during PCM. At 30% MVC, HGE and PECO increased the blood pressure parameters compared with REST. In addition, HGE led to greater increases in blood pressure parameters at 30% MVC than under the other MVC conditions.

DISCUSSION

We aimed to investigate the effects of changes in BLa during passive exercise on HR and HRV in healthy young males. Contrary to our hypothesis, our results showed that HR response during PCM remained unchanged despite elevated BLa. Furthermore, we only observed an interaction between the rMSSD of HRV and MAP during PECO at 30% MVC, whereas there was no difference in HR response. These findings are the first to demonstrate that rhythmic mechanical stimulation by PCM increases HR, regardless of metabolic stimulation, in healthy young males. Furthermore, enhanced rMSSD of HRV at 30% MVC showed an antagonistic vagal response to sympathetic nervous activity elevated by metabolic stimulation. Our results suggest that these cardiovascular responses are important for the correct interpretation of HR response to simultaneous metabolic and mechanical stimulation.

At BLa levels induced by CTL, 15%, and 30% MVC, an increase in HR was observed in response to PCM. Therefore, in healthy adult males, passive exercise may induce a consistent HR response regardless of metabolic status. Moreover, PCM, which was utilized in this study, represents a more dynamic form of exercise than electrically-induced movements[15]. Passive exercise of skeletal muscle sends input signals to the medulla oblongata via group III fibers and the ANS, increasing HR due to vagal withdrawal[16, 17]. The metaboreflex is a feedback response in which metabolite accumulation activates group IV fibers, thus increasing sympathetic nerve activity, which, in turn, increases peripheral vascular resistance and blood flow to the muscle[1, 18]. Both of these reflexes therefore increase muscle perfusion during exercise[8, 19], albeit via different pathways. Fisher et al.[11] reported that HR response to mechanical stimulation was unaffected by varying metaboreflex activation. In addition, Kaufman and Rybicki[20] showed that while ischemia increased the response in 47% of the group IV afferents recorded during exercise, only 13% of the group III afferents exhibited increased activity. This result indicates that group III fibers are less responsive to metabolic stimuli. Therefore, the observed lack of interaction between mechanical and metabolic stimuli in HR response may be attributed to independent responses to different signals.

Our results revealed no difference in rMSSD of HRV during PCM under different MVC conditions. As mechanical stimulation causes vagal withdrawal[21, 22], our results suggest that mechanical stimulation is independent of metabolic stimulation-induced increases in sympathetic activity. Specifically, while HR responses remained constant with varying metabolic intensity, PECO at 30% MVC exhibited an interaction between MAP and rMSSD of HRV. The changes in MAP may be attributed to the metaboreflex, as it responds to increased pressure with increasing metabolic stimulus intensity. In contrast, rMSSD of HRV was enhanced only at 30% MVC. Parasympathetic reactivation and increased rMSSD of HRV were only observed at 40% MVC when PECO was applied following 25% and 40% MVC[12]. We found that metaboreflex activation at 30% MVC antagonistically induced parasympathetic reactivation when sympathetic activity increased, and sympathetic and vagal activity increased before PCM onset. This response may offset the effects of increased sympathetic activity[12, 23]. However, reactivation of vagal activity, which was characteristic of 30% MVC, may have affected HR reactivity during mechanical stimulation, and pharmacological autonomic blockade experiments are therefore warranted in further studies.

Although passive exercise can be harmful if not performed carefully, it offers benefits for bedridden patients[24] and further studies to validate the safety and maximize the benefits of exercise therapy for critically ill patients will require a detailed analysis of ANS and cardiovascular dynamics in this population. As this study enrolled only healthy male participants, the applicability of the results is limited as the findings may not be relevant to patients with severe diseases. Future studies with larger sample sizes involving critically ill patients are therefore required to validate our results. Furthermore, it was difficult to measure blood pressure while performing PCM because metabolic and mechanical stimuli were applied simultaneously. Therefore, it is not certain whether the metaboreflex was maintained during PCM. However, BLa was increased after PCM compared with PECO, suggesting that the metaboreflex was likely maintained during PCM.

In healthy participants, comparable changes in HR were induced by combined metabolic and mechanical stimulation. Furthermore, the antagonistic increase in vagal activity in response to sympathetic activity induced by metabolic stimulation may be related to HR regulation via the interaction between metabolic and mechanical stimulation. Our findings provide insight into the mechanism of circulatory regulation by passive exercise. However, because critically ill patients have impaired autonomic function[25, 26], the effect of mechanical stimulation by passive exercise on HR and rMSSD of HRV requires further investigation to guide appropriate exercise interventions for critically ill patients, minimizing the harmful effects and maximizing the benefits of exercise in bedridden patients.

Conflict of interest

None.

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