



Original Article

## Evaluation of autonomic nervous system responses during isometric handgrip exercise using nonlinear analysis of heart rate variability

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**Abstract.** [Purpose] The purpose of this study was to examine, using a plethysmogram of the fingertips, autonomic responses at motor intensities of 30% or 50% of maximum voluntary contraction (MVC) during isometric handgrip exercise (IHG). [Participants and Methods] The participants of this study were 15 healthy persons. The finger volume pulse wave of each participant was measured continuously, using a BACS Advance equipment (TAOS Co.), for a total of 17 minutes: 5 minutes before IHG (Pre), 2 minutes during IHG (IHG), the first 5 minutes after IHG (Post 5), and then the second 5 minutes after IHG (Post 10). To evaluate autonomic nervous system activity, we used the Detrended fluctuation analysis (DFA) and Approximate Entropy (ApEn). [Results] During IHG, the pulse rate was significantly higher and the ApEn value was significantly lower than during the other periods of measurement. Compared to other analyzed parameters, ApEn decreased during IHG, but returned to its initial Pre period level during the Post 5 period. The  $\alpha_1$  value derived from the DFA analysis remained at a value of 1 during each measurement time point, indicating the absence of malfunctions in autonomic response. [Conclusion] Isometric handgrip exercise with 30% MVC seemed to be useful for the assessment of autonomic nervous system response.

**Key words:** Autonomic response, Nonlinear analysis, Chronic pain

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### INTRODUCTION

The International Association for the Study of Pain (IASP)<sup>1)</sup> defines chronic pain as that which persists despite apparent healing of tissue damage, or pain that occurs in response to minor stimuli not normally recognized as pain, despite the absence of tissue damage. According to the National Survey of Health and Welfare in Japan, patients with chronic pain in the musculoskeletal system, such as shoulder pain, back pain, and arthralgia, account for 15.4% of the population. The number of patients is estimated to be >20 million<sup>2)</sup>, with a decline in activities of daily living (ADL) and quality of life (QOL)<sup>3)</sup>.

Previous studies have reported that increased blood flow velocity associated with abnormal neovascularization is associated with pain in patients with chronic low back pain<sup>4, 5)</sup>, as well as, shoulder<sup>6, 7)</sup>, and knee osteoarthritis<sup>8)</sup>. It is believed that pain is caused by an increase in blood flow velocity leading to an influx of inflammatory cells<sup>8)</sup> or abnormal proliferation of nerves together with abnormally increased neovascularization<sup>9)</sup>. It has also been reported that when blood flow is restricted by administering vascular embolization agents to the abnormal vessels, they disappear, and the pain is relieved<sup>8)</sup>. Thus,

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chronic blood flow disorders may be one of the causes of chronic pain. Inflammation, malignant tumors, and arteriovenous malformations have been reported as mechanisms responsible for the increasing blood flow velocity<sup>10</sup>. However, in atherosclerosis, blood flow velocity increases when there is critical stenosis<sup>11</sup>, so narrowing of the vessel diameter is thought to increase blood flow velocity. The vessel diameter is regulated by local factors, endocrine substances, hormones, and autonomic nerves<sup>12</sup>. Therefore, abnormalities of autonomic nerves may be involved in the causation of blood flow velocity increases in patients with chronic pain and evaluation of the autonomic nervous system is thought to be important.

Homeostasis<sup>13</sup> is a classic conceptual model to explain how an organism maintains its internal environment in constant balance. The autonomic nervous system is intimately involved in the maintenance of homeostasis. Therefore, the concept of hemodynamics, which is referred to as the “buffering capacity” of an organism to respond, counteract, and adapt to internal and external stimuli to maintain homeostasis, is attracting attention<sup>14, 15</sup>. In other words, it is necessary to evaluate the autonomic nervous system’s response to stimulation from the viewpoint of hemodynamics. Previous studies have investigated autonomic nervous responses using micro neurograms and have reported that muscle sympathetic nerve activity increases during grip dynamometer grasping tasks (i.e. isometric hand grip, IHG)<sup>16–19</sup>. However, since muscle sympathetic nerve activity was measured at different intensities of 10%, 30%, 50%, and 60% of the maximal voluntary contraction (MVC) in these studies, direct comparison of the results was difficult. In addition, micro neurograms are invasive and difficult to use clinically. Frequency analysis is a common noninvasive autonomic nervous system assessment and has been performed in IHG<sup>20</sup>. However, it has the disadvantage that behavioral factors such as body movements, postural changes, and sleep/wake cycles<sup>21</sup> can affect the results. The detrended fluctuation analysis (DFA) is a nonlinear analysis, and its advantages include the mathematical elimination of behavioral factors, noninvasive analysis, and short recording time<sup>22</sup>. However, no study has examined IHG with different exercise intensities using nonlinear analysis. Therefore, the development of a simple and safe evaluation method for autonomic nervous system responses is required.

This study aimed to evaluate autonomic responses before and after IHG using nonlinear analysis and to examine the effects of different exercise intensities (30% and 50% of maximal voluntary muscle strength) on autonomic responses.

This study’s hypothesis is that different exercise intensities alter autonomic activity.

## PARTICIPANTS AND METHODS

Participants were 15 university students (6 males, 9 females, aged  $21 \pm 2$  years) attending Morinomiya University of Health Sciences, with no history of hypertension or heart disease, scoring less than 10 on the self-administered Anticipatory Depression Test (Hospital anxiety and depression scale; HAD) and less than 6 on the Athens Insomnia Scale (AIS). After obtaining approval from the Ethics Committee of their institution (approval number 2020-105), the study was conducted with the participants’ written informed consent. Morinomiya University of Health Sciences has granted ethical approval to conduct the study.

Pulse waves were recorded using a BACS Advance (TAOS Co., Ltd., Kanagawa, Japan) and sampled at a frequency of 200 Hz<sup>23</sup>. A probe was attached to the tip of the left second finger, and measurements were made in the sitting position. The participants were encouraged to refrain from alcohol intake on the day before the measurements, and to refrain from eating or drinking caffeine for three hours before measurement started. The room temperature of the site was standardized at 26–27°C, and care was taken not to talk during measurement.

In this study, we developed an experimental protocol to investigate autonomic responses before, during, and after IHG, referring to a study by Teixeira et al<sup>24</sup>. The participants rested in a sitting position for 5 minutes before the start of the measurement, and then pulse waves were continuously measured for a total of 17 minutes: 5 minutes before IHG (Pre), 2 minutes during IHG (IHG), the first 5 minutes after IHG (Post5), then the second 5 minutes (Post10). The IHG task was performed by all participants using a handgrip dynamometer (TOEI LIGHT Co., Ltd., Saitama, Japan) under two conditions: 30% MVC (2 minutes) and 50% MVC (2 minutes), with an interval of at least 1 day between them.

Pre, IHG, Post 5, and Post 10 pulse wave data were analyzed by Kubios HRV software for pulse rate analysis (Kuopio, Finland) and by nonlinear analysis, namely the detrended fluctuation analysis (DFA) and Approximate Entropy (ApEn) analysis. DFA is used for heart rate variability analysis as a method to detect long term correlations in non-steady time series data<sup>25, 26</sup>. It is also applied to various object groups and disease groups, and it has been reported that it can predict disease prognosis or vital prognosis<sup>22</sup>. In DFA analysis,  $1/f$  fluctuation is considered to occur when  $\alpha_1=1$ ;  $1/f$  fluctuation in heart rate variability is considered to be a basic bodily rhythm<sup>27</sup>. The greater the degree of deviation from  $\alpha_1=1$ , the more difficult it is to respond or compensate for the disturbance. ApEn analysis is a method<sup>28</sup> that detects whether periodicity exists in time varying data, and evaluates the regularity of pulse wave time series data. The more regular and predictable the time series data, the lower the value of ApEn, while irregular time series data are difficult to predict and thus have higher values.

For statistical analysis, R. 3.6. 1 was used, and pulse rate,  $\alpha_1$ , and ApEn were compared and examined by two-way analysis of variance of repeated measurements with pulse wave analysis times of Pre, IHG, Post 5, Post 10, and exercise intensity of 30% MVC or 50% MVC as variables. Multiple comparisons were made using Shaffer’s modified t-test for post hoc testing, with a cutoff at a significance level of less than 5%.

## RESULTS

The pulse rate,  $\alpha_1$  and ApEn at each exercise intensity are shown in Table 1. The results of the two-way analysis of variance of pulse rate and ApEn data indicated that the main effect was seen for the time factor ( $p < 0.01$ ), but there was no effect of the exercise intensity factor (pulse rate,  $p = 0.3$ ; ApEn,  $p = 0.4$ ), and no interaction between timing and exercise intensity (pulse rate,  $p = 0.09$ ; ApEn,  $p = 0.3$ ). For  $\alpha_1$ , there was no main effect for the time factor ( $p = 0.4$ ) or exercise intensity ( $p = 0.5$ ) and again no interactions between timing and exercise intensity ( $p = 0.8$ ). When multiple comparisons were made for pulse rate and ApEn in which the main effect was recognized for the timing factor, the IHG pulse rate was significantly higher than the Pre, Post 5, and Post 10 pulse rate ( $p < 0.05$ ). Furthermore, ApEn at IHG was significantly decreased compared with Pre, Post 5, and Post 10 ( $p < 0.05$ ).

## DISCUSSION

The purpose of this study was to noninvasively evaluate autonomic responses during isometric hand grip at 30% MVC and 50% MVC exercise intensities. We hypothesized that the autonomic responses would differ depending on the exercise intensity. Contrary to this prediction, the results showed that the pulse rate increased and ApEn decreased, but  $\alpha_1$  was maintained at 1 and remained unchanged during isometric hand grip at both 30% MVC and 50% MVC; there was no significant difference in exercise intensity between the two groups. Thus, during IHG, sympathetic nervous activity was augmented regardless of exercise intensity, and the pulse wave was regular and maintained at 1/f fluctuation.

Traditionally, micro neurograms have been used to evaluate autonomic responses during exercise, and there have been reports of muscle sympathetic nervous activity at both a low intensity of 10% and 30% MVC in IHG<sup>16, 19</sup>) and at a high intensity of 50% and 60% MVC<sup>17, 18</sup>). However, there is also a report that muscle sympathetic nervous activity does not increase at 30% MVC<sup>18</sup>), and there is no consensus on autonomic nervous system responses to exercise intensity. In the present study, we found that sympathetic nerves were active regardless of exercise intensity, whether 30% MVC or 50% MVC. In addition, as a new finding, it became clear that the pulse wave response during IHG was regular and maintained 1/f fluctuation in healthy individuals.

IHG is widely used to augment sympathetic nerve activity and induce a pressor response, and is one of the main tests of autonomic nervous system function. Cardiovascular responses such as increased heart rate and increased blood pressure are generated during exercise, and it is considered that multiple peripheral reflexes such as the muscle metabolizing receptor reflex, muscle mechanoreceptor reflex, arterial baroreflex, and cardiopulmonary baroreflex act in combination with central command<sup>29</sup>). Of these peripheral reflexes, the muscle metabolizing receptor reflex is stimulated by the accumulation of metabolic products such as lactate, hydrogen ions, bradykinin, prostaglandins, and potassium ions associated with exercise in the active muscle, and it is known that sympathetic nervous activity is increased through the Central nervous system (CNS) to increase heart rate and blood pressure<sup>30</sup>). Therefore, increasing the pulse rate led to the muscle metabolic reflex with IHG.

Heart rate variability (HRV) represents the time difference between successive heartbeats and is evaluated by measuring the RR interval of the electrocardiogram<sup>31</sup>). HRV is used to noninvasively evaluate the effect of the autonomic nervous system on cardiac function<sup>32, 33</sup>). There are 3 analytical methods: time domain analysis, frequency analysis, and nonlinear analysis<sup>31</sup>). In a previous study using  $\alpha_1$ , Gronwald et al.<sup>34</sup>) reported that  $\alpha_1$  does not change at exercise intensities lower

**Table 1.** Changes in pulse rate,  $\alpha_1$ , and ApEn during exercise (n=15)

	Measurement time			
	Pre	IHG	Post 5	Post 10
Pulse rate (beats/min)				
30%MVC	73.1 ± 7.2	78.6 ± 8.2*	72.3 ± 7.1	72.5 ± 6.5
50%MVC	70.4 ± 5.4	79.9 ± 8.6*	68.1 ± 4.9*	67.9 ± 5.9*
$\alpha_1$				
30%MVC	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.2	1.1 ± 0.2
50%MVC	1.1 ± 0.2	1.0 ± 0.4	1.0 ± 0.2	1.0 ± 0.2
ApEn				
30%MVC	1.1 ± 0.1	0.7 ± 0.1*	1.1 ± 0.1	1.0 ± 0.1
50%MVC	1.1 ± 0.1	0.7 ± 0.1*	1.0 ± 0.2	1.0 ± 0.2

Values for each indicator are expressed as mean ± SD.

MVC: maximum voluntary contraction; ApEn: Approximate Entropy; Pre: 5 min before isometric handgrip exercise (IHG); IHG: 2 min during IHG; Post5: 5 min after IHG; Post10: 6 to 10 min after IHG.

\* $p < 0.05$  vs. Pre.

than the anaerobic metabolic threshold. Therefore, the intensity of exercise in this study was predicted to be lower than the anaerobic metabolic threshold, and  $\alpha_1$  in 30% and 50% of IHG would not have changed. In a study of ApEn in patients with chronic kidney disease, the increase in ApEn was considered to be due to the failure of the autonomic nervous response<sup>35</sup>. Based on these findings, the present study with healthy participants is expected to show regular changes while maintaining 1/f fluctuation as a response before and after IHG. The results of this study are therefore as hypothesized.

In healthy participants, the sympathetic nervous system was active regardless of whether exercise intensity was 30% MVC or 50% MVC; additionally, the pulse wave was regular and 1/f fluctuation was maintained. High intensity exercise such as 50% MVC may cause pain and be unfeasible in some participants due to excessive load. However, since there is no difference in these measurements at different exercise intensities, it is possible to evaluate autonomic nervous responses employing an exercise intensity of 30% MVC. In addition, fingertip blood flow is a simple and noninvasive method for monitoring peripheral circulation<sup>36</sup>, as peripheral blood vessels are innervated by the  $\alpha$ -adrenergic nerve fibers, and it is thus considered to reflect autonomic nervous system activity<sup>37–39</sup>. Noninvasive measurement has the advantage of being easy to use in the clinical setting. For this reason, noninvasive analysis during IHG at an exercise intensity of 30% MVC can be easily used in the clinical setting and is considered to be a useful method for the evaluation of autonomic responses.

There are several limitations to this research. The first is that the autonomic nervous system response in older adults remains unknown because we studied only healthy young participants. Atherosclerosis associated with aging may decrease the distensibility of blood vessels and change the pulse wave form. The relationship between the effect of aging and the autonomic nervous system response needs to be examined in future. A second limitation is that the autonomic response in patients with chronic pain cannot be determined in healthy subjects who do not complain of pain. In the future, it will be necessary to investigate the autonomic nervous system responses in patients with chronic pain. Third, the present study included 15 participants; a larger sample size is required to establish a standard. Fourth, it has been reported that sex influences cardiovascular response<sup>40, 41</sup>, but this study was not able to investigate the menstrual cycle. Finally, the amount of activity, diet, and BMI of the participants was not fully investigated; therefore, it remains unclear whether these factors affect the autonomic response.

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### *Conflict of interest*

The authors have no conflicts of interest to declare, pertaining to this study.

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