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Original Article

Non-invasive evaluation of autonomic responses in patients with rotator cuff tear-related nocturnal pain

Yusuke Fukumoto, PT, MSc[1, 2], Yoshihiro Tsuji, CE, PhD[1, 3, 4], Akihiro Kakuda, PT, MSc[1, 4], Ryuji Hori, PT, PhD[1, 4], Shintarou Kudo, PT, PhD[1, 4]*

[1] *Graduate School of Health Sciences, Morinomiya University of Medical Sciences: 1-26-16 Nankoukita Suminoe-ku, Osaka-shi, Osaka 559-8611, Japan*
[2] *Keimoto Orthopedic Rehabilitation and Osteoporosis Clinic, Japan*
[3] *Department of Clinical Engineering, Morinomiya University of Medical Sciences, Japan*
[4] *Inclusive Medical Science Research Institute, Morinomiya University of Medical Sciences, Japan*

Abstract. [Purpose] We aimed to determine the autonomic response in patients with rotator cuff tear-related nocturnal pain using nonlinear analysis of heart rate variability. [Participants and Methods] Twenty-eight patients with nocturnal pain who were diagnosed with a rotator cuff tear and received steroid injections, and whose nocturnal pain improved, were divided into a control group (14 patients) and a failure group (14 patients). Pulse wave was measured continuously using BACS Advance equipment (TAOS Co.) for a total of 17 min: 5 min before isometric hand grip, 2 min during isometric hand grip, 5 min after isometric hand grip, and 10 min after isometric hand grip. The autonomic nervous system activity was assessed using detrended fluctuation analysis and approximate entropy. [Results] The α_1 values obtained from the detrended fluctuation analysis were significantly higher in the failure group than in the control group at each measurement period. The approximate entropy was normal in 12 (85%) patients in the control group and six (42%) patients in the failure group; it was abnormal in two (15%) patients in the control group and eight (58%) patients in the failure group. [Conclusion] Among patients experiencing nocturnal pain, several have abnormal autonomic response during isometric hand grip.
Key words: Autonomic response, Nocturnal pain, Rotator cuff tear

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INTRODUCTION

Painful diseases of the shoulder joint, such as periarthritis and rotator cuff tear, affect approximately 2–5% of adults[1], which sometimes cause nocturnal pain. Nocturnal pain is closely associated with sleep disturbance; prolonged symptoms reportedly decrease the quality of life[2, 3]. Thus, it is crucial to control or reduce nocturnal pain to improve the patient's quality of life.

Although physiotherapy and pharmacotherapy[4] have traditionally been the treatment of choice for nocturnal pain, it has been ineffective in some patients. Recently, abnormal neovascularization in the anterior humeral circumflex artery (AHCA) and abnormal increase in blood flow have been reported in patients with nocturnal pain[5], suggesting the involvement of blood flow disturbance in the prolonged nocturnal pain. Furthermore, peripheral blood vessels are innervated by alpha-adrenergic nerve fibers[6], suggesting that the autonomic nervous system may be involved in blood flow disturbances that prolong nocturnal pain. However, abnormal autonomic response is yet to be studied in detail in patients with nocturnal pain.

*Corresponding author. Shintarou Kudo (E-mail: kudo@morinomiya-u.ac.jp)

Three types of heart rate variability analyses (time-domain, frequency, and nonlinear analyses)[7] are used to evaluate the autonomic nervous system. We focused on nonlinear analysis in this study, which is a temporal and spatial method for evaluating biological systems[8]. It did not need a long time to measure, and it could be quantitatively assessed without being affected by respiration or body movements[9], and has thus, been used in various diseases[10–12]. Fukumoto et al.[13] evaluated autonomic responses in 15 healthy individuals using nonlinear analysis and isometric hand grip exercises (IHG) at 30% of maximum voluntary muscle strength (MVC). They found that pulse wave fluctuations during exercise were constant and recovered to resting values on rest after exercise. Therefore, the involvement of the autonomic nervous system in prolonged nocturnal pain could be identified by evaluating the autonomic nervous system using nonlinear analysis. We hypothesized that the autonomic response may be disrupted in patients with prolonged nocturnal pain.

The purpose of this study was to clarify the autonomic responses of patients with nocturnal pain using nonlinear analysis.

PARTICIPANTS AND METHODS

Of the 38 patients with nocturnal pain who had a rotator cuff tear diagnosed by ultrasound or magnetic resonance imaging at their center between March 2021 and August 2021, 28 were included, excluding 10 patients who had pain for <3 months (two patients), were male (five patients), no steroid injection (one patient), and no consent for participation in the study (two patients). Lindelon, a synthetic corticosteroid, was administered to the participants, and 14 patients who complained of persistent nocturnal pain were classified in the Failure group (age: 52.4 ± 3.8 years) and 14 patients whose nocturnal pain improved in the Good group (age: 51.8 ± 6.1 years) after a 1–2 week interview (Table 1). The timing of post-injection autonomic evaluation was not standardized. Joint range of motion, muscle strengthening, and physical therapy were conducted during the rehabilitation period. The study was approved by the ethics committee of Morinomiya University of Medical Sciences (No: 2020-105). Written informed consent was obtained from the participants after explaining the purpose of this study.

Pulse waves were recorded using a BACS Advance (TAOS Co., Ltd., Kanagawa, Japan) and sampled at a frequency of 200 Hz[14]. A probe was attached to the tip of the left second finger, and measurements were made in the sitting position. The participants was 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 during measurement was maintained at 24–26°C, and the participants were asked not to talk during the measurements.

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[15]. 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 hand grip dynamometer (TOEI LIGHT Co., Ltd., Saitama, Japan), which was used at 30% MVC.

Pre, IHG, Post 5, and Post 10 pulse wave data were analyzed by Kubios HRV software for pulse rate analysis (Eastern Finland Kuopio) 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[16, 17]. 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[18]. In DFA analysis, 1/f fluctuation is considered to occur when α_1=1; 1/f fluctuation in heart rate variability is considered to be a basic bodily rhythm[19]. The greater the degree of deviation from α_1=1, the more difficult it is to respond or compensate for the disturbance. ApEn analysis is a method[20] 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. In addition, we used a predefined normal value of change from Pre to Post10[13], and its normal range was defined as ± 2SD[21, 22].

The blood flow velocity in the AHCA was measured in pulsed Doppler mode using an ultrasound imaging system (LOGIQ S8 XDclear2.0+, GE Health Care, Tokyo, Japan) with a 4–12 Mhz variable linear probe, referring to the measurement

Table 1. Patient information

	Failure group (n=14)	Good group (n=14)
Age (years)	52.4 ± 3.8	51.8 ± 6.1
Injured parts		
SSP	8	9
ISP	4	3
SSP + SSC	2	2
Affected part		
Right	11	12
Left	3	2

SSP: Supraspinatus; ISP: Infraspinatus; SSC: subscapularis.

methods of previous studies. A cut-off of 20.5 cm/s was used[23]. Pain DETECT[24] comprised of nine questions (scored as 0–38 points) was used to assess neuropathic pain. A cut-off score of 19 points was sufficient to determine neuropathic pain with 85% sensitivity and 80% specificity; its reliability and validity have been previously confirmed[25]. Sleep status was evaluated using the self-assessed Athens Insomnia Scale (AIS), which was developed by the World Project on Sleep and Health, established by the World Health Organization (WHO), and verified to be highly reliable and valid[26]. The scale consists of eight items: five items evaluating nighttime sleep difficulties including "falling asleep", "nocturnal awakenings", "early morning awakenings", "total sleep time satisfaction", and "sleep quality satisfaction"; three items evaluating daytime dysfunction including "daytime mood", "daytime activity (physical and mental)", and "daytime sleepiness". The three items evaluating daytime dysfunction were evaluated using a 4-point scale; the scores were summed up.

The Hospital Anxiety and Depression Scale (HAD) for general outpatients was used to evaluate quality of life in terms of mental and psychological aspects. The questionnaire consists of 14 items, with odd-numbered questions for anxiety (HADS-A) and even-numbered questions for depression (HADS-D). Each item is scored from 0 to 3. Based on a previous study[27], a score of ≥8 on odd-numbered items was defined as anxiety, and ≥11 on even-numbered items was defined as depression.

For the primary outcome, the pulse rate and α_1 were compared using two-way ANOVA; the four levels of pulse wave (Pre, IHG, Post5, and Post10) and patient groups (failure and, good groups) as factors. The Mann–Whitney U test was used for the post-hoc analysis. Fisher's exact probability test was used to compare the ApEn. For the secondary outcome, each item in the failure and good groups were analyzed using an uncorrelated t-test. In addition, Fisher's exact probability test was used to compare the number of persons who exceeded the cut-off for each item. Statistical analysis was conducted using R (version 3.6.1), and a p-value <5% was considered statistically significant.

RESULTS

The pulse wave and α_1 values in the failure and good groups are listed in Table 2. For α_1, no main effect was observed for the timing factors (Pre, IHG, Post5, Post10), but the failure group deviated from α_1=1 in the Pre, IHG, and Post5 stages compared to the good group (Table 3). Twelve patients (85%) in the good group and six patients (42%) in the failure group demonstrated ApEn within the normal range of the healthy individuals. Meanwhile, two patients (15%) in the good group and eight patients (58%) in the failure group demonstrated it without a normal range of the healthy individuals. There was a

Table 2. Changes in pulse rate, α_1 during exercise

	Measurement time			
	Pre	IHG	Post 5	Post 10
Pulse rate (beats/min)				
Good group	72 ± 9	76 ± 9	72 ± 9	71 ± 8
Failure group	78 ± 6	82 ± 6	76 ± 6	74 ± 5
α_1				
Good group	0.14 ± 0.12	0.10 ± 0.09	0.13 ± 0.13	0.19 ± 0.1
Failure group	0.27 ± 0.14*	0.25 ± 0.14*	0.25 ± 0.17*	0.27 ± 0.12*

Values for each indicator are expressed as mean ± SD.
n=14.
*p<0.05 vs. Pre.
Pre: 5 min before isometric handgrip exercise (IHG); IHG: 2 min during IHG; Post 5: 5 min after IHG; Post 10: 6 to 10 min after IHG.
SD: standard deviation.

Table 3. Changes in α_1 during exercise

	Measurement time			
	Pre	IHG	Post 5	Post 10
α_1				
Good group	1.12 ± 0.14	1.05 ± 0.12	1.13 ± 0.13	1.12 ± 0.17
Failure group	1.19 ± 0.22*	1.23 ± 0.17*	1.24 ± 0.18*	1.25 ± 0.16*

Values for each indicator are expressed as mean ± SD.
n=14.
*p<0.05 vs. Pre.
Pre: 5 min before isometric handgrip exercise (IHG); IHG: 2 min during IHG; Post 5: 5 min after IHG; Post 10: 6 to 10 min after IHG.
SD: standard deviation.

significant difference in the proportion of participants in the Good and Failure groups who were within or without the normal range of ApEn ($p<0.05$). The pulse rate did not have a main or interaction effect on the timing or patient factors.

The NRS, AHCA, Pain DETECT, AIS, HADS-A, and HADS-D scores in the failure and good groups and the number of patients who exceeded the cut-off are shown in Table 4.

The NRS ($p<0.01$), Pain DETECT ($p<0.01$), and AIS ($p<0.05$) scores were significantly higher in the failure group than in the good group. No significant differences were observed in the other parameters.

DISCUSSION

The study results showed that the failure group deviated from $\alpha_1=1$ in the Pre, IHG, and Post5 stages compared to the good group. Furthermore, ApEn deviation was identified in more patients in the failure group than in the good group. Thus, the failure group was considered to have 1/f fluctuation failure and lack of recovery by rest.

Nocturnal pain is closely associated with sleep disturbances, and the persistence of symptoms decreases the quality of life[2, 3]. Furthermore, sleep disorders reportedly cause autonomic nervous system dysfunction, such as decreased parasympathetic activity and increased sympathetic activity[28]. Therefore, abnormal autonomic responses may exist in patients with nocturnal pain. However, this has not been investigated and thus remains unknown. In the present study, the failure group showed failure of the autonomic responses, such as an inability to maintain 1/f fluctuation and a lack of recovery by rest.

Fukumoto et al.[13] examined the IHG of 30% MVC in healthy individuals using non-linear analysis. They reported that $\alpha_1=1$ was maintained before and after IHG in healthy individuals and ApEn recovered to the resting value after the task ended. The ApEn level in cardiac patients with abnormal autonomic response reportedly decreases significantly[29]; the greater the deviation from $\alpha_1=1$, the more difficult it is for patients to respond and compensate for the disturbance. Furthermore, a study of patients with chronic kidney disease, revealed that the increase in ApEn even after rest reportedly occurs due to a breakdown of the autonomic nervous response[12]. The deviations from $\alpha_1=1$ in the failure group and the overall large number of deviations from the normal range in the present study suggest that an abnormal autonomic response occurs.

Several factors affect the autonomic nervous system, including chronic pain[30], neuropathic pain[31], sleep disorders[28], stress[32], and mood disorders[33], each of which can be evaluated using questionnaires and indices. In this study, we determined that the NRS, Pain DETECT, and AIS scores were higher in the failure group than in the good group. However, there was no significant difference in the number of participants who exceeded the cut-off value. Therefore, the reason for the autonomic response failure could not be determined. This indicates that the factors influencing the autonomic nervous system are complex and cannot be sufficiently assessed using a single questionnaire. It is important to evaluate autonomic responses, as was done in the present study.

In this study, it was clarified that abnormal autonomic nerve response was concerned in the prolongation of the nocturnal pain. However, it is considered that the evaluation using only the conventional question index is insufficient for the evaluation of autonomic nervous system. It is considered that the evaluation of autonomic nervous response by nonlinear analysis used in this study is non-invasive and useful for clinical use.

Table 4. Outcome measure

	Failure group (n=14)	Good group (n=14)
NRS	6.5 ± 1.7**	4.4 ± 1.5
AHCA (cm/s)	21.5 ± 5.2	18.5 ± 3.1
	(8/14)[a]	(3/14)[a]
Pain DETECT	6.6 ± 1.0**	4.4 ± 1.5
	(0/14)[a]	(0/14)[a]
AIS	4.3 ± 1.4*	2.9 ± 0.9
	(9/14)[a]	(5/14)[a]
HADS-A	9.8 ± 2.6	7.5 ± 2.5
	(6/14)[a]	(3/14)[a]
HADS-D	7.3 ± 2.5	6.8 ± 1.8
	(2/14)[a]	(1/14)[a]

[a]The number of people who have exceeded the cut off.
*$p<0.05$ vs. Good.
**$p<0.01$ vs. Good.
NRS: numeric rating scale; AHCA: anterior humeral circumflex artery; AIS: Athens insomnia scale; HADS: hospital anxiety and depression scale.

This study has two limitations. First, it is not clear whether the changes in the autonomic response of the good group were caused by the injection. If nocturnal pain improves with injections, it is possible that the autonomic nervous system may be affected. Further studies examining the changes in autonomic responses before and after injections are required. Second, the sample size of this study was small. Further studies with larger sample sizes are required.

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Conflict of interest

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

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