



Heart rate variability responses to neuromuscular electrical stimulation in intensive care unit-acquired weakness patients: A pre-post observational study



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Received: 2025-11-20

Accepted: 2026-03-26

Published: 2026-07-13

ABSTRACT

Background: Intensive care unit-acquired weakness (ICU-AW) is common in critically ill patients, occurring in roughly 25–50% of mechanically ventilated ICU patients and limiting early mobilization. Neuromuscular electrical stimulation (NMES) may provide adjunctive rehabilitation and potentially modulate autonomic function. This study evaluated short-term changes in heart rate variability (HRV) after a five-day NMES course in ICU-AW patients.

Methods: One-group pre-post observational study in a tertiary ICU. Bilateral quadriceps NMES was delivered once daily for five consecutive days. Five-minute HRV recordings were obtained before the first session and after the intervention period and were analyzed using Kubios. Outcomes were the root mean square of successive differences (RMSSD), the standard deviation of normal-to-normal intervals (SDNN), and the low-frequency/high-frequency ratio (LF/HF); comparisons used Wilcoxon signed-rank tests.

Results: Seventeen patients completed the protocol, and no clinically significant NMES-related adverse events occurred. RMSSD increased from 22.49 ms (4.22–93.10) to 51.63 ms (3.81–92.88) ($p = 0.010$), and SDNN increased from 28.85 ms (11.03–93.54) to 47.70 ms (9.52–137.70) ($p = 0.040$). The LF/HF ratio showed no significant change (0.65 [0.19–8.24] vs 0.98 [0.18–7.71]; $p = 0.190$).

Conclusion: In ICU-AW patients, a five-day bilateral quadriceps NMES protocol was feasible and well-tolerated. The intervention period was accompanied by higher RMSSD and SDNN, indicating increased beat-to-beat and overall HRV that may reflect greater short-term autonomic adaptability during critical illness.

Keywords: heart rate variability, intensive care unit-acquired weakness, neuromuscular electrical stimulation, rehabilitation, sympathetic parasympathetic balance.

Cite This Article: Samosir, G.J., Poerwandari, D., Sari, D.I., Semedi, B.P., Atika. 2026. Heart rate variability responses to neuromuscular electrical stimulation in intensive care unit-acquired weakness patients: A pre-post observational study. *Physical Therapy Journal of Indonesia* 7(2): 214-218. DOI: 10.51559/ptji.v7i2.389

INTRODUCTION

Intensive care unit-acquired weakness (ICU-AW) is an important complication of critical illness, affecting approximately one-quarter to one-half of mechanically ventilated ICU survivors and being reported even more frequently in severe sepsis or multi-organ failure cohorts, and is associated with prolonged mechanical ventilation, longer ICU and hospital length of stay, and poorer long-term functional outcomes.¹⁻³ ICU-AW is often identified using the Medical Research Council (MRC) sum score; a total score <48/60 across six bilateral muscle groups indicates significant generalized weakness.^{1,4-7} ICU-AW encompasses a spectrum of

neuromuscular disorders, including critical illness polyneuropathy and myopathy, and is driven by multifactorial mechanisms such as systemic inflammation, prolonged immobilization, bioenergetic failure, and accelerated skeletal muscle catabolism. Rapid myofibrillar protein breakdown and the preferential loss of myosin during severe critical illness further contribute to weakness and delayed recovery.^{8,9}

Diagnosing ICU-AW in the ICU can be challenging because formal strength testing requires patient cooperation and adequate wakefulness. Clinical assessment commonly relies on structured manual muscle testing supported by standardized diagnostic recommendations.¹⁰ When such

assessment is not feasible, complementary approaches, including electrophysiological screening and prediction tools based on commonly recorded clinical variables, have been proposed to support early detection and risk stratification.^{11,12} These constraints also limit early mobilization in sedated or uncooperative patients, thereby highlighting the need for feasible bedside interventions. Neuromuscular electrical stimulation (NMES) may serve as an adjunct to mobilization, and its systemic physiological effects can be explored using early physiological markers such as heart rate variability (HRV).^{1,3,10}

Early mobilization is recommended whenever feasible; however, many ICU

patients cannot participate actively due to sedation, hemodynamic instability, or ongoing respiratory support.¹³ Post-ICU rehabilitation is also important, but may not fully address the early phase of muscle loss occurring during critical illness.^{14,15} NMES has therefore been explored as a practical adjunct when active exercise is limited. Studies in heterogeneous ICU cohorts, including mechanically ventilated and septic patients, suggest that NMES may attenuate muscle wasting and improve muscle-related outcomes in selected groups, with feasibility and acceptable safety reported across different protocols.¹⁶⁻²⁰ Nevertheless, evidence syntheses highlight substantial heterogeneity in stimulation parameters, populations, and endpoints, and many studies focus on general ICU cohorts rather than on patients with formally diagnosed ICU-AW.²¹⁻²⁴ In the present study, we applied NMES to the bilateral quadriceps because it targets a large, functionally critical lower-limb muscle group relevant to standing and ambulation and is readily accessible for bedside application.

Beyond neuromuscular effects, NMES may influence autonomic regulation through afferent stimulation and cardiovascular reflex pathways. Autonomic regulation can be assessed noninvasively using HRV, which reflects beat-to-beat variability and has been proposed as a physiological marker relevant to stress response and recovery trajectories.²⁶⁻²⁸ Clinically, HRV reflects autonomic responsiveness, which is often impaired during critical illness and may relate to physiological stress and recovery processes.²⁶⁻²⁸ Because ICU care frequently involves respiratory failure management and dynamic ventilatory support, careful interpretation of HRV measurements is warranted in this setting.²⁹ However, HRV responses to NMES specifically in ICU-AW patients remain insufficiently characterized. We hypothesized that quadriceps NMES would be associated with increases in time-domain HRV indices, the root mean square of successive differences (RMSSD), and the standard deviation of normal-to-normal intervals (SDNN) and changes in the low-frequency/high-frequency (LF/HF) ratio in ICU-AW patients. Therefore,

this study aimed to evaluate short-term HRV changes following a five-day course of quadriceps NMES in ICU-AW patients using a pre-post observational design.

METHODS

Study Design and Setting

This study used a one-group pretest-posttest (pre-post) observational design conducted in the adult ICU of a tertiary referral hospital. This approach was chosen for feasibility and hypothesis generation because of rapid ICU turnover and fluctuating clinical conditions, which made the implementation of a control or sham group less practical; therefore, causal inference is limited.

Participants

Adult ICU patients were enrolled consecutively according to the following eligibility criteria: age 18–60 years, ICU stay >48 hours, mechanical ventilation >24 hours, and fulfillment of the clinical diagnostic criteria for ICU-AW.⁸ The upper age limit (60 years) was used to reduce heterogeneity related to age-associated autonomic variability and comorbidity burden, which can substantially influence HRV measures; therefore, the findings may be less representative of older ICU-AW populations. ICU-AW diagnosis was established by the study investigators (ICU physicians) using standardized clinical criteria and MRC sum score assessment when patients were awake and able to follow commands, before baseline HRV recording and initiation of NMES. Delirium was assessed using the CAM-ICU at the time of assessment, and patients with delirium precluding reliable strength testing were excluded. Exclusion criteria also included pre-existing neuromuscular disease, stroke or brain injury, spinal cord injury, peripheral vascular disease affecting the lower limbs (including deep vein thrombosis), prior significant arrhythmia, pre-ICU motor paralysis, lower-limb fracture or fixation, skin conditions or edema preventing electrode placement, end-stage malignancy, an implanted pacemaker, ongoing sedation at assessment time, a history of heart failure, and recent use (<24 hours) of norepinephrine, inotropes, or beta-blockers before intervention. A total

of 20 patients were screened, and all met the inclusion criteria. Of these, three were excluded from the analysis because they were transferred out of the ICU before completing the five-day intervention and HRV measurements. The final cohort comprised 17 participants.

Intervention

Neuromuscular electrical stimulation (NMES) was delivered once daily for five consecutive days with patients in a 30-degree supine position. Surface electrodes (2.5 cm) were placed bilaterally over the vastus medialis and vastus lateralis, positioned on the proximal and distal muscle bellies. Stimulation was applied simultaneously to both legs using a symmetrical biphasic waveform at 50–80 Hz with a pulse width of 300 μ s, a duty cycle of 2–5 s on and 4–10 s off (1:2 ratio), and 1-s ramp up/down, for 30 minutes per session. Stimulation intensity was titrated to patient tolerance until a palpable motor contraction was achieved. HRV recordings were obtained in the morning at rest, with minimal concurrent procedures and no mobilization, both before and after the intervention period. Safety monitoring during each session included pain or intolerance, skin irritation or burn, oxygen desaturation, arrhythmia, and hemodynamic instability; NMES was discontinued if any of these events occurred. The five-day regimen was selected as a pragmatic, feasible ICU-based intervention window to examine short-term physiological responses and tolerability with repeated sessions.¹⁶⁻²⁰

Outcomes

Short-term HRV recordings were obtained in the morning at rest, with patients in a 30° supine position whenever feasible, with minimal concurrent procedures and no mobilization. Recordings were performed at baseline (before the first NMES session) and after completion of the NMES course (post-intervention). RR-interval data were recorded using a chest-strap heart rate sensor (Polar H10) and analyzed using Kubios HRV Standard software. Signal segments with excessive artifacts were excluded; standard artifact correction procedures were applied, and a clean 5-minute segment without ectopic

beats was selected for analysis following recommended approaches for short-term HRV reporting.²⁷ The primary HRV indices were RMSSD and SDNN (time-domain) and the LF/HF ratio (frequency-domain).²⁶⁻²⁸

Data analysis

Continuous variables were summarized as medians (minimum–maximum). Pre–post comparisons of HRV indices were analyzed using the Wilcoxon signed-rank test. Analyses were conducted using a two-sided significance threshold of $p < 0.05$.

RESULTS

A total of 20 patients initiated the NMES protocol. Three patients were excluded from the final analysis because they were transferred out of the ICU before completing the five-day intervention and HRV measurements. Thus, 17 participants completed all five sessions and were included in the analysis, and their baseline characteristics are summarized in **Table 1**. The median age was 49 years (18–60), and 10 participants (58.8%) were female. The median SOFA score was 7 (2–12). The median duration of sedation was 2 days (2–4), the median duration of mechanical ventilation was 3 days (2–11), and the median ICU length of stay was 6.5 days (4–14). Common comorbidities included hypertension (35.3%) and chronic lung disease (47.1%).

No adverse events were observed during the NMES sessions. Specifically, no participant experienced pain or intolerance requiring dose reduction, skin irritation or burns, oxygen desaturation, arrhythmia, or hemodynamic instability, and no session needed to be interrupted or discontinued. The exclusions were due to transfer out of the ICU rather than NMES-related intolerance or complications.

Pre– and post-HRV comparisons are presented in **Table 2**. RMSSD increased from a median of 22.49 ms (4.22–93.10) at baseline to 51.63 ms (3.81–92.88) after NMES ($p = 0.010$), corresponding to an absolute median increase of 29.14 ms (approximately +130% relative to the baseline median). SDNN increased from 28.85 ms (11.03–93.54) to 47.70 ms (9.52–137.70) ($p = 0.040$), an absolute median increase of 18.85 ms (approximately +65%

Table 1. Baseline characteristics of 17 participants

Variable	Median (min-max) or n (%)
Age, years	49 (18–60)
Body mass index, kg/m ²	22.30 (15.22–30.47)
SOFA score	7 (2–12)
Sedation duration, days	2 (2–4)
Mechanical ventilation duration, days	3 (2–11)
ICU length of stay, days	6.5 (4–14)
Sex, male	7 (41.2)
Sex, female	10 (58.8)
Hypertension, yes	6 (35.3)
Diabetes mellitus, yes	2 (11.8)
Kidney disease, yes	3 (17.6)
Chronic lung disease, yes	8 (47.1)
Post-elective surgery, yes	4 (23.5)
Post emergency surgery, yes	7 (41.2)

%, percent; ICU, intensive care unit, min-max, minimum–maximum; n, frequency; SOFA, sequential organ failure assessment.

Table 2. Heart rate variability parameters before and after neuromuscular electrical stimulation of 17 participants

Variable	Pre-intervention Median (min-max)	Post-intervention Median (min-max)	P-value*
RMSSD, ms	22.49 (4.22–93.10)	51.63 (3.81–92.88)	0.010
SDNN, ms	28.85 (11.03–93.54)	47.70 (9.52–137.70)	0.040
LF/HF ratio	0.65 (0.19–8.24)	0.98 (0.18–7.71)	0.190

*Wilcoxon signed-rank test.

LF/HF, low-frequency/high-frequency; Min-max, minimum–maximum; RMSSD, root mean square of successive differences; SDNN, standard deviation of normal-to-normal intervals.

relative to the baseline median). The LF/HF ratio changed from 0.65 (0.19–8.24) to 0.98 (0.18–7.71) without a statistically significant difference ($p = 0.190$). Notably, both pre- and post-intervention values showed wide ranges, indicating substantial interindividual variability; individual trajectories suggested heterogeneous response patterns across participants. Analyses were exploratory across multiple HRV indices, and the p -values were not adjusted for multiple comparisons.

Time-domain HRV indices increased after NMES; however, clinically meaningful thresholds for short-term RMSSD and SDNN in ICU-AW populations are not well established. Accordingly, these findings are reported as physiological modulation and should

be interpreted in conjunction with clinical outcomes in future studies.

DISCUSSION

In this pre–post observational study of ICU-AW patients, a five-day course of quadriceps NMES was feasible and was not associated with observed adverse events. The main finding was an increase in time-domain HRV indices (RMSSD and SDNN) following the intervention period, indicating short-term changes consistent with greater beat-to-beat variability. RMSSD is commonly interpreted as reflecting short-term variability predominantly influenced by parasympathetic activity, while SDNN represents overall variability across the

recording window.²⁶⁻²⁸ Collectively, these findings suggest that NMES may be accompanied by measurable short-term autonomic modulation during critical illness, rather than representing evidence of autonomic recovery or improved clinical outcomes. Importantly, the wide pre- and post-intervention ranges indicate substantial interindividual variability, suggesting that HRV responses to NMES may not be uniform across ICU-AW patients and should be interpreted cautiously in this small cohort.

The observed HRV changes are biologically plausible. Electrically evoked muscle contractions may activate group III/IV skeletal muscle afferents and engage cardiovascular reflex pathways (e.g., muscle metaboreflex and baroreflex modulation), which could influence autonomic outflow and beat-to-beat variability; however, these mechanisms remain hypothetical in the present study because reflex engagement and related mediators were not measured directly. Given the short intervention window, the findings are best interpreted as short-term physiological modulation rather than longer-term autonomic adaptation or recovery. In critically ill populations where early active mobilization is frequently limited,¹³ NMES can serve as an adjunct strategy to deliver “passive exercise-like” stimulation. Prior ICU studies have reported that NMES may reduce muscle wasting and weakness or improve muscle-related outcomes in selected groups,^{16,17} and that trial protocols and pilot work have supported feasibility and safety in mechanically ventilated patients, including stimulation of large lower-limb muscle groups and, in some settings, the diaphragm.¹⁸⁻²⁰ Systematic reviews and meta-analyses also suggest potential benefits of NMES on muscle outcomes and ICU-related endpoints, although heterogeneity in stimulation protocols and patient populations remains a key limitation.²¹⁻²⁴ Our findings add a physiological perspective by indicating that HRV can change measurably after a short NMES course in ICU-AW patients.

In contrast to time-domain indices, the LF/HF ratio did not show a consistent change after NMES. Interpretation of the LF/HF ratio is complex and may be influenced by respiration, recording conditions, and broader limitations of

mapping frequency-domain components to sympathovagal balance in heterogeneous clinical settings.²⁸ Moreover, ICU patients have multiple dynamic confounders, including sedation exposure, ventilatory support, concurrent medications, and fluctuating illness severity that can affect HRV signals and may blunt or obscure frequency-domain changes.²⁹ Short-term recordings can still be informative when collected and reported with standardized approaches, but careful attention to artifacts and measurement conditions remains essential.²⁷

This study has several limitations. Given the within-subject pre-post design, the results describe changes in HRV from baseline to post-intervention during the study period, while acknowledging that concurrent time-varying ICU factors may also have influenced HRV. Although eligibility criteria were designed to reduce key HRV confounders by excluding patients with significant arrhythmia, ongoing sedation at assessment time, heart failure, and recent exposure to norepinephrine, inotropes, or beta-blockers (<24 hours) residual influences from dynamic ICU factors (e.g., fluctuations in illness severity, ventilatory parameters, analgesia or sedation adjustments outside the assessment window, and other concurrent medications) may still have affected HRV. The five-day protocol was intended to capture early physiological responsiveness to NMES. Although the observed HRV changes provide a physiological signal of autonomic modulation, their clinical significance has not yet been established and should not be assumed to represent meaningful clinical benefit. Future controlled studies should evaluate dose-response effects of NMES, incorporate standardized capture of sedation/ventilation parameters and medication covariates, and link autonomic responses to clinically meaningful endpoints. Work on NMES tolerability and physiological monitoring within guided protocols may also support scalable implementation in ICU rehabilitation pathways.²⁵

CONCLUSION

In ICU-AW patients, a five-day bilateral quadriceps NMES protocol was feasible and well tolerated. The intervention

period was accompanied by higher RMSSD and SDNN values, indicating increased beat-to-beat and overall heart rate variability that may reflect greater short-term autonomic adaptability during critical illness.

ETHICAL CONSIDERATION

The study protocol was approved by the institutional ethics committee (Approval No. 0800/KEPK/X/2023). Written informed consent was obtained from participants or their legal representatives as applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

GJS, DP, and DIS conceptualized the study design, searched the literature, collected and analyzed the data, and prepared and edited the manuscript; BPS conceptualized the study design, searched the literature, collected the data, and prepared the manuscript; AA performed the data analysis and edited the manuscript.

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