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WHAT'S NEW IN INTENSIVE CARE

Neuromodulation in the intensive care unit

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Neuromodulation, through various forms of invasive and noninvasive stimulations at the central or peripheral level, can enhance or suppress neural activities, offering the potential for therapeutic intervention. Studies of neuromodulation have reported intriguing clinical outcomes and promising application prospects across various disciplines, particularly in the realm of novel therapeutic modalities. Critically ill patients are commonly susceptible to intractable systematic dysfunctions due to sedation, immobility, and controlled ventilation. In recent years, the application of neuromodulation in the intensive care unit (ICU) has increased, and its efficacy has been tested in multiple scenarios across critical stages of the disease process (Fig. 1).

Critical illness polyneuromyopathy (CIPNM) is a common complication of patients presenting with muscle weakness in the ICU. CIPNM is associated with a prolonged duration of mechanical ventilation and increased mortality in the ICU population. A few preventive tools or specific treatments have been proposed for CIPNM. The pathophysiological mechanisms of transcutaneous electrical muscle stimulation (TEMS) may involve an anabolic stimulus to the muscle and reversal of the catabolic effects of critical illness and immobilization; TEMS has been employed as an ancillary treatment in patients with severe chronic heart failure and chronic obstructive pulmonary disease [1]. Acute systemic effects on peripheral microcirculation have also been identified [2]. Moreover, metabolism-reflex activation during TEMS may increase sympathetic excitability and contribute to changes in heart rate, systolic blood pressure, blood volume, and cardiac output, thereby affecting muscle metabolism. Neuromuscular electrical stimulation can be used to maintain muscle thickness and strength in patients with critical illness. A randomized-controlled trial including 140 critically ill patients revealed that daily TEMS sessions prevent the development of CIPNM and result in a shorter duration of ventilation in the experimental group compared to the control group [1 (0–10) day vs. 3 (0–44) days, median (range), $p=0.003$] [3]. However, some systematic reviews reported no beneficial effects of TEMS with low-quality evidence and suggested that further randomized-controlled trials (RCTs) are needed to determine the role of TEMS as an adjuvant treatment to support patients with muscle weakness in the ICU [1, 4].

Diaphragmatic dysfunction, which is caused by the suppression of respiratory muscle activity by sedative agents and passive mechanical ventilation, together with multiple inflammatory mechanisms, is now widely described in patients undergoing mechanical ventilation in the ICU. Transcutaneous electrical diaphragmatic stimulation (TEDS) provides noninvasive stimulation through surface electrodes placed bilaterally on the thorax over the diaphragm apposition zone. Several teams have studied the effects of TEDS, showing that the use of TEDS can decrease diaphragmatic dysfunction and improve respiratory muscle strength in patients in the ICU [5, 6]. However, a recently published controlled trial with 66 patients assessed the impact of daily active electrical stimulation versus sham stimulation on the prevention of diaphragm dysfunction during the mechanical ventilation weaning process [7]. The diaphragm thickening fraction (odds ratio [OR] 1.55, 95% confidence interval [CI] 0.47–5.1; $p=0.47$), maximal inspiratory muscle pressure (35.5 ± 11.9 vs. 29.7 ± 11.7 cmH_2O; $p=0.469$), and peak cough flow (83.2 ± 39.5 vs. 75.3 ± 34.08 L/min; $p=0.83$) were similar in the TEDS and sham groups. Further studies are warranted to explore the effectiveness of these treatments in ICU settings.

Vagal nerve stimulation (VNS) has proven beneficial for patients with refractory epilepsy as a potential adjunct

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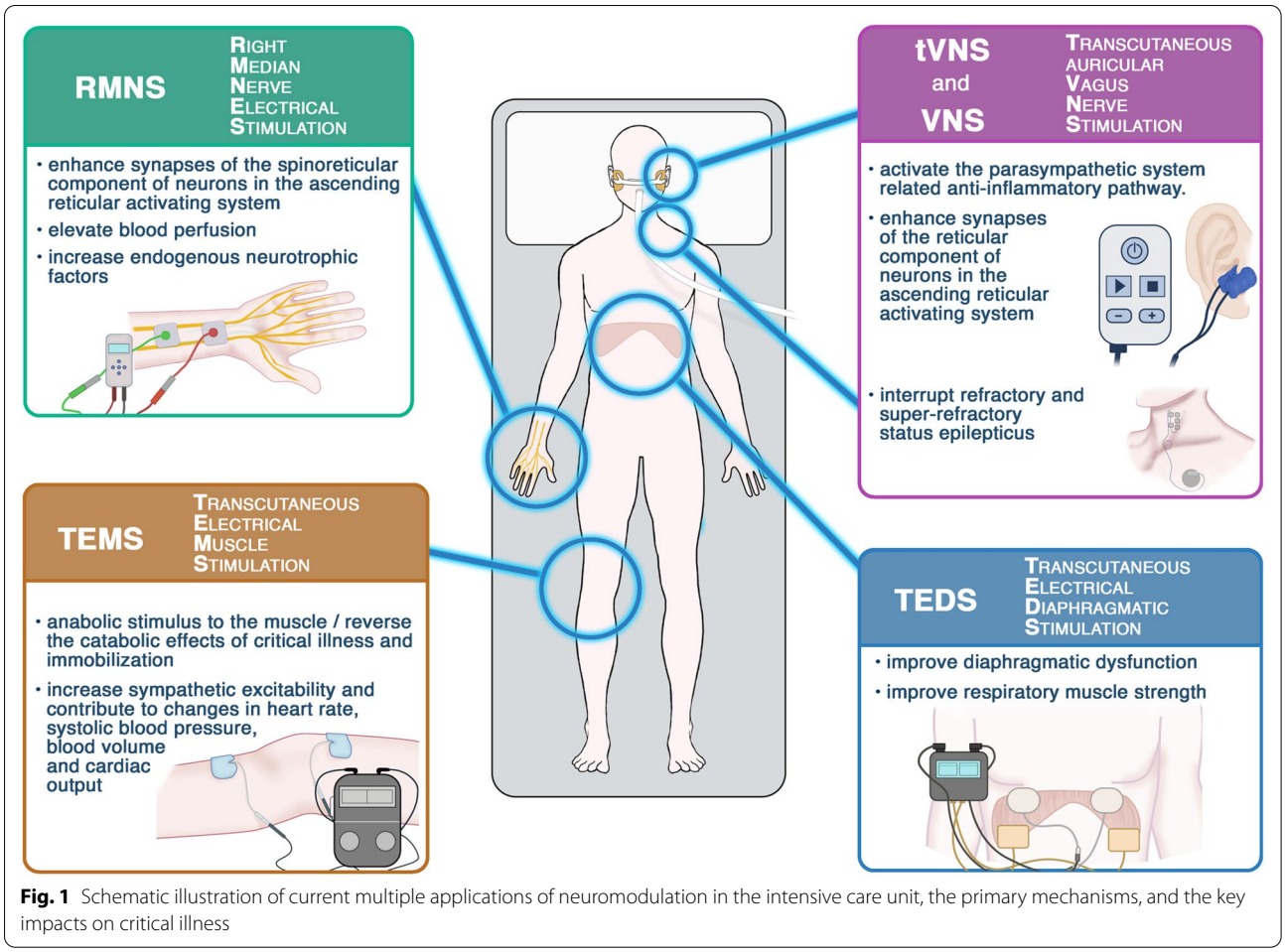

Fig. 1 Schematic illustration of current multiple applications of neuromodulation in the intensive care unit, the primary mechanisms, and the key impacts on critical illness

treatment modality in the ICU, although there are lack of specific guidelines and controlled studies. In a systematic review including single case-reports and small case series, VNS can interrupt refractory and super-refractory status epilepticus in 74% (28/38) of patients within duration ranges from 3 to 84 days with a mean of 8 days after acute implantation [8]. It may offer rapid responses in the acute phase of the disease and potentially reduce the pharmacological load [9]. More evidence from prospective studies is needed to investigate the role of acute VNS implantation in patients with refractory status epilepticus and its potential risk and cost-effectiveness in the ICU.

The potential of noninvasive transcutaneous electrical stimulation to enhance arousal and emergence from coma or a disorder of consciousness has been the subject of increasing interest. In this setting, transcutaneous VNS (tVNS) and right median nerve electrical stimulation (RMNS) were recently suggested. A RCT demonstrated that the Coma Recovery Scale-Revised (CRS-R) and Glasgow Coma Scale (GCS) scores improved more in patients in a minimally conscious state over a 4-week course of tVNS treatment, compared to the sham group (CRS-R: $Z = -2.267$, $p = 0.023$; GCS: $Z = -1.990$, $p = 0.047$) [10]. In addition to tVNS, RMNS has been proposed to be a safe and effective treatment for promoting the recovery of coma patients in the early phase of traumatic brain injury. In a recent controlled study of RMNS for accelerating emergence from coma in acute traumatic brain injury patients, a greater proportion of patients in the RMNS group regained consciousness compared with the control group (72.5%, $n = 121$, 95% CI 65.2–78.7% vs. 56.8%, $n = 92$, 95% CI 49.1–64.2%, $p = 0.004$), and neurological function outcomes were significantly increased in the RMNS group [11]. Preclinical studies have indicated that tVNS or RMNS may improve unconsciousness through various mechanisms, including enhancing synapses of the spinoreticular component of neurons in the ascending reticular activating system, elevating blood perfusion, and increasing endogenous neurotrophic factors to increase the survival of a greater number of neurons [12]. However, confirmatory studies are needed to provide more definitive evidence and

a plausible mechanism for coma treatment prior to the adoption of tVNS or RMNS as routine practice in critical care. Moreover, tVNS has shown promising results in significantly modulating serum inflammatory cytokines in sepsis patients in a recent study [13]. tVNS and RMNS have also been tested to effectively reduce stress-induced sympathetic arousal in young healthy participants [14]. To date, there are few effective treatments for modulating sympathetic–parasympathetic functions in the early stage of critical care. Although clinical evidence on this topic is limited, preclinical studies open avenues for further investigation. These findings may provide a promising novel strategy for relieving the stress response, normalizing vital signs, and stabilizing circadian rhythm and homeostasis in the ICU.

Given the complexity of conditions in critically ill patients, it should be noted that introducing neuromodulation in ICU will present considerable practical challenges related to patient tolerance, treatment programs, and the range of indications and contraindications. Transcutaneous electrical stimulation may cause local effects such as skin reddening and pricking. It should not be approved in patients with history of severe conditions, including heart arrhythmias, lung abnormalities, dysautonomias, progressive neurological diseases, psychiatric disorders, and ulcers. Moreover, the stimulators may interfere with pacemaker and other electrical medical devices such as monitors and infusion pumps. More trials are needed to determine the safety of interventions and potential interference with concurrent treatment in the future. With the therapeutic potential of neuromodulation for ICU populations, the scarcity of clinical evidence opens a window of clinical availability and preclinical mechanism exploration to generate robust evidence to translate the concept of neuromodulation to clinical applications in the ICU.

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Declarations

Conflict of interest
All authors reported no possible competing interests.

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