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If Muscle Works, Use It! Potential Therapeutic Effects of Early Muscle Stimulation Through Exercise or Neuromuscular Electrical Stimulation in The Acute Phase of Endotoxic Shock

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About the Study

This is a Short Commentary on our article entitled "Neuromuscular Electrical Stimulation Improves Energy Substrate Metabolism and Survival in Mice with Acute Endotoxic Shock," which was recently published in SHOCK (PMID: 31935202) [1].

In this study, we demonstrated that neuromuscular electrical stimulation (NMES) exerts therapeutic effects under conditions, stimulation applied once at low frequency and low voltage or applied twice at low frequency and high voltage, that induce a mild switch in energy metabolism from glucose into lipid predominance through peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) upregulation and suppression of inflammation and may be an effective early intervention even in hemodynamically unstable patients. In a previous study, we investigated changes in energy substrate utilization during sepsis and found that it changed from glucose to predominantly lipid utilization, with protein catabolism also increasing, as a function of sepsis severity [2]. We had also demonstrated that low-intensity exercise in the acute phase of endotoxic shock has beneficial effects similar to those of NMES [3]. These results suggest that upregulation of PGC-1α following exercise or NMES causes a metabolic switch from glucose to lipid utilization and suppresses inflammation, thereby improving the nutritional state and leading to a better outcome.

In the field of critical care nutrition, the importance of early enteral nutrition is emphasized by the well-known slogan, "If gut works, use it!" In the same way, we would like to offer another slogan, "If muscle works, use it!" to underscore the therapeutic benefits of early muscle stimulation through exercise or NMES in the acute phase of endotoxic shock.

However, as we mentioned in the limitations paragraph of our article, the protein levels of PGC-1α, the enzyme levels for carbohydrate or lipid metabolism, and the indicators of inflammation other than interleukin-6 were not measured. Therefore, there remained some unclear points about the mechanism of the effect of NMES for improving metabolism and survival. Further studies will clarify the precise mechanism and confirm the effect of early muscle stimulation.

Furthermore, the appropriate conditions of NMES for human patients to exert the same effects as observed in this animal study remain to be determined. Various studies have demonstrated the therapeutic potential of NMES for preventing muscle atrophy and preserving muscle mass and avoiding post-intensive care syndrome or intensive care unit-acquired weakness [4-6]; however, the difficulty in applying NMES effectively in critically ill patients has also been reported [7-9]. Moreover, the appropriate conditions to exert beneficial effects on metabolism and inflammation are thought to be different from those mentioned above; from the findings of our studies, it will be considerably weaker than that for maintaining muscle strength. There are some real problems. In attaching the NMES device to patients experiencing trauma or burns, we have to identify safe body parts, and the potential influence of NMES on the patient's hemodynamic state or electrical monitoring devices should be considered. Further studies are necessary to investigate how to safely apply NMES to unstable human patients and take advantage of the beneficial effects on metabolism, inflammation, and survival.

Currently, based on the concept that lipid metabolism-oriented therapeutic intervention can improve the outcome of critically ill patients, we are planning to start the following new studies. First, to test a model that more closely resembles human patients, we intend to apply the commercial NMES

device to large animals such as pigs to obtain precise data and investigate the appropriate NMES conditions to achieve therapeutic effects on metabolism and inflammation in humans. Second, we intend to investigate the effect of specific nutrients such as epigallocatechin gallate or resveratrol on metabolism and inflammation because these nutrients are reported to upregulate PGC-1α [10,11], and we expect they may have effects similar to those of exercise or NMES when used as nutritional intervention.

Although in a clinical setting it may be unsafe for patients to exercise in the acute phase of endotoxic shock, NMES and some specific nutrients may become breakthrough candidates for clinical application in critically ill patients, and we intend to continue to pursue challenging research in the future.

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