Early proprioceptive stimulations in mechanically ventilated critically ill patients
Protocol **REA-MOUV – version 5 – 14/12/2022**
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Study sponsor:
Association MAPAR (Mise Au Point in Aesthesia Réanimation), Department of Anesthesia and Intensive Care, Centre Hospitalo-Universitaire de Bicêtre, 94275, Le Kremlin Bicêtre, France.

Study leaders, principal investigators:
Dr Bernard Vigué, MD, PhD, Surgical intensive care, Department of Anesthesia and Intensive Care, Centre Hospitalo-Universitaire de Bicêtre, 94275, Le Kremlin Bicêtre, France.
Florence Martinache, Physiotherapist, Université Paris-Saclay, CIAMS, 91405, Orsay, France

Investigators:
Dr Anne Claire de Crouy, MD, Post-intensive care rehabilitation unit, Department of Anesthesia and Intensive Care, CHU de Bicêtre, 94275, Le Kremlin Bicêtre, France.
Dr Aurore Rodrigues, MD, Surgical intensive care, Department of Anesthesia and Intensive Care, CHU de Bicêtre, 94275, Le Kremlin Bicêtre, France
François Radiguer. Neuropsychologist, Post-intensive care rehabilitation unit, Department of Anesthesia and Intensive Care, CHU de Bicêtre, 94275, Le Kremlin Bicêtre, France

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The funders played no role in the study design and will not participate in data collection and analysis.

Summary

List of abbreviations

FPS: Functional proprioceptive stimulations

CAM-ICU: Confusion assessment method for ICU

HADS: Hospital anxiety and depression scale

IMS: ICU mobility scale

MAS: Modified Ashworth scale

MoCA: Montreal cognitive assessment

MRC-SS: Medical research council-sum score

MTS : Modified Tardieu scale

PCL-5: PTSD Checklist for DSM-5

PFIT-s: Physical function ICU-test (scored)

PICS Post-intensive care syndrome

1. Context

The COVID-19 pandemic made the public aware of severe diseases and the medical community mindful of the importance of global management of critically ill patients. Beyond treating the initial illness, limiting the harmful consequences of the intense processes used by the body to survive is necessary. It is crucial to initiate the patients' rehabilitation as soon as they enter the intensive care unit (ICU) to counter the physical and psychological after-effects, which can be severe and sometimes permanent (1).

Indeed, ICU patients frequently suffer sequelae following their stay, even after their initial acute pathology has been controlled. The origin of these sequelae is multifactorial: oedema, disturbance of blood pressure control, cognitive disorders, deafferentation, and massive muscle wasting (2–6). These disorders may be linked to an initial neurologic pathology but also to acute inflammation, high doses of sedation, and prolonged bed rest and immobilization (7–10). The analysis of mortality causes encountered during the COVID-19 pandemic has extensively confirmed the deleterious effect of these complications (1). And a relationship between the extent of muscle wasting and mortality has been established (11).

Growing importance is thus given to early care in the ICU, not only to get patients out of their acute life situations but also to prepare them for discharge under the most optimal conditions. One way is to limit the sequelae linked to pathology and the ICU stay (12–17). The first step was to name the problem. These sequelae are grouped under the term Post-intensive care syndrome (PICS). This term includes the physical, psychological, and cognitive aspects. Whether one of these components predominates has not been determined, but the importance of their interactions has been acknowledged (18). The next step was to discuss which early intervention could help understand, counter, and limit these phenomena. Reflection on the consequences of intensive care opens new perspectives. It questions therapeutic attitudes with immediate positive effects but long-term harm (19,20). One aspect that has been discussed a lot is prolonged bed rest. Its consequences are so acute and severe that they are used to mimic and study the harmful effects of weightlessness during space travel (21–23). Breaking with this practice, studies on early mobilization in the ICU have demonstrated benefits: faster weaning from mechanical ventilation (17) or better glycemic control (24). Early mobilization combined with the cessation of sedation helps to significantly reduce delirium in ICU patients (17). The delirium duration has been associated with the severity of cognitive problems at three months and even one year after discharge from the ICU (25). These results show the close relationship between cognitive functions and movement.

The link between intensive care and rehabilitation has been strengthened in many structures, and its development is recognized as essential (26,27). There is still a need to define methods and adaptations to common or specific problems of patients, despite confirmed successes (28). The timing, intensity, frequency, and type of management to be provided during the ICU stay are among the keys to success (29).

Among the therapies tested and easily achievable in the ICU, electrical stimulation of the motor nerves has been the subject of numerous clinical trials, demonstrating its protective effect on muscle atrophy in different situations: in control subjects with an immobilized limb (30) and ICU patients awake (31) or sedated (3). However, this technique has some limitations. The presence of oedema, sepsis or the administration of vasopressors is associated with a decrease in the muscular response to this stimulation (32,33).

Another promising non-invasive technique is emerging: vibration therapies. These therapies stimulate sensitive pathways through the neuromuscular spindles (34). Vibrations can be applied to the « whole body » (35) or to specific tendons (36). As for electrical stimulation,

tendon vibrations elicit muscle contractions, but indirectly, through the circuits of the central nervous system (37,38). In addition, a study conducted on mice and satellite cells cultured *in vitro* suggests that vibrations may positively affect muscle metabolism (39).

But above all, unlike electrical stimulation, which mainly has a peripheral effect, tendon vibrations involve the central nervous system, particularly sensory circuits. When applied to a specific muscle tendon and the tendon of the antagonist muscle, they can be synchronized in such a way as to cause illusions of movement (40,41) and even actual motor responses (37). Then, such vibrations help to maintain the levels of cortical activation associated with movements of an immobilized limb in healthy subjects (42).

These properties could make local vibrations a tool of great interest and easy to use for the prevention of muscle atrophy and its functional consequences in ICU patients (43). In addition, it could help preserve central circuits.

The present study aims at assessing the effect of early synchronized tendon vibrations of the lower limbs (called functional proprioceptive stimulations (FPS), Vibramoov® system) on critically ill patients mechanically ventilated for at least 48 hours. We hypothesize that early FPS will improve the functional status of patients at discharge from the ICU and will have a positive impact on the cognitive status of these patients.

2. Objectives

2.1. Primary objective:

To evaluate the effect of early functional proprioceptive stimulations (FPS) on the functional status of ICU patients whose severity is reflected by at least 48 hours of mechanical ventilation after admission.

2.2. Secondary objectives:

- To evaluate the effect of early FPS on cognitive function and study the correlation between changes in functional status and cognitive function.
- To evaluate the effect of early FPS on muscle strength.
- To evaluate the effect of early FPS on quadriceps muscle atrophy.
- To evaluate the effect of early FPS on spasticity (in patients with central neurological disorders).
- To evaluate the effect of early FPS on the occurrence of ICU delirium.
- To evaluate the effect of early FPS on the duration of mechanical ventilation.
- To evaluate the effect of early FPS on the incidence of critical illness neuromyopathies.
- To evaluate the effect of early FPS on ICU and hospital length of stay.
- To evaluate the effect of early FPS on in-hospital and 3- and 6-month mortality from ICU discharge.

3. Participants

All patients will be recruited in the intensive care unit of the Bicêtre hospital after written consent has been obtained from the trusted person as defined in article L.1111-6 of the Public Health Code, from a family member or, failing that, from one of the patient's relatives, in accordance with article L.1122-1-1 of the Public Health Code. The patient's consent will be obtained as soon as their condition allows it.

The inclusion of patients is carried out by one of the study's investigators (Dr Bernard Vigué, Dr Aurore Rodrigues, Dr Anne-Claire de Crouy), with the agreement of the patient's physician. A period of reflection is given to the person (patient or relative) after the information is provided and before the consent form is signed.

The participant (or their representative) receives a copy of the written information note summarizing the information about the research given orally.

After signing the consent form and before participating in the research, the participant receives a copy of the consent form.

The investigator keeps a copy of the dated and signed consent form.

The investigator also specifies participation in this research in the participant's medical record. Conscious patients who are able to express their consent are informed in detail orally, and their written consent is obtained if they are able to sign. Otherwise, their oral consent is obtained and attested by their trusted person, a family member, or, failing that, by a close relative who will sign the consent in the patient's place.

In the case of unconscious patients or those unable to give their consent, the patient is informed as soon as possible, and their consent is sought to continue the research in the same way described in the previous paragraph. If the patient agrees, the research is continued. If the patient refuses to participate in the research, their participation in the study is immediately suspended. If the patient also refuses the processing of the data collected up to that point, these data are deleted immediately.

3.1. Inclusion criteria:

- Adult (≥ 18 years old)
- Hospitalised in the intensive care unit
- Mechanically ventilated for at least 48 hours
- Functionally independent two weeks before admission to the ICU (Barthel score ≥ 70, estimated by the interrogation of relatives (17,44))

3.2. Non-inclusion criteria:

- Admitted in the intensive care unit for more than 5 days
- Hyperacute phase (absence of hemodynamic balance...)
- Orthopedic injury preventing the implementation of the protocol
- Severe psychiatric or cognitive history
- Irreversible disorder with a 6-month mortality greater than 50% (17,44) or patient with probable fatal outcome in the ICU

- Rapidly developing neuromuscular disease
- Spinal cord injury
- Severe head injury (Glasgow Coma Scale score ≤ 8)
- Known pregnancy
- Patients with phlebitis
- Patients with active devices such as pacemakers, defibrillators, insulin pumps, neurostimulators, etc.
- Patients with cardiac arrhythmia
- Epileptic patients
- Patients with fragile skin or open wounds
- Not affiliated to the French social security system
- Patients who do not speak French or English
- Persons deprived of liberty and under the protection of a conservator

The inclusion period will last for 1.5 years or until the required number of subjects (calculated below) is reached.

Patients may withdraw from the study at any time if they wish, and the number of patients who do so will be recorded.

4. Study design and randomization

This study is a controlled, randomized, single-blinded study (blinded evaluations except for muscle ultrasound). The physical and cognitive examinations will be carried out respectively by a physiotherapist and a neuropsychologist unaware of the patients' allocation. The muscle ultrasound will be performed by the therapist delivering the FPS.

Patients will be randomized into the two groups (intervention and control groups) using blocked randomization in a 1:1 ratio.

In addition, patients will be stratified into two groups according to the presence or absence of a central nervous system lesion.

Randomization lists will be generated using the Randomization.com website.

Data will be collected using Goupile, an online editor of eCRF (https://goupile.fr/), and hosted on a certified HDS (*Hébergeur de données de santé* (Health data host)) server.

5. Intervention

Patients in the control group will receive the standard care usually provided in the intensive care unit. The motor physiotherapy sessions will be standardized according to the protocol described by Schweickert et al. (17), adapted to the intensive care unit of the Bicêtre hospital (detailed protocol in Appendix 1).

Patients in the intervention group will receive the same standard of care and, in addition, will receive 30-minute FPS sessions on the lower limbs, 4 times per week, from inclusion until

discharge. Discharge from the ICU is defined as the time when the patient is deemed fit to be transferred to another department or facility. It can therefore occur before the actual discharge if the patient remains in intensive care due to a lack of space at the destination. A trained physiotherapist will deliver the treatment with the Vibramoov® system (Techno Concept, Manosque, France). This system consists of twelve wireless vibrators (two for each of the joints of the lower limbs), attached to the patient with the help of orthoses and controlled by a computer via Bluetooth.

The intervention will start as soon as the physician in charge of the patient considers the patient clinically stable, i.e., out of the initial hyperacute phase (48 to 72 hours after admission in the intensive care unit). At this time, the hemodynamic situation will be controlled (stability of the mean arterial pressure without modification of the treatment for at least 4 hours) whether they are ventilated or not.

5.1. Criteria for discontinuation or suspension of treatment:

In agreement with the patient's physician, the therapist must stop the session if they observe an endangerment of the patient according to any of the following criteria: mean arterial pressure (MAP) < 60 mmHg; systolic blood pressure (SBP) > 200 mmHg; heart rate (HR) > 130 or < 40; respiratory rate (RR) < 5 (non-ventilated patients) or >35; intracranial pressure (ICP) ≥ 30 mmHg; pulsed oxygen saturation (SpO_2) < 90%). The protocol will be stopped if this event occurs more than twice consecutively.

Any discontinuation of treatment and its cause will be documented. Tout arrêt de traitement ainsi que sa cause sera documenté.

6. Outcomes

6.1. Primary outcome:

Functional status assessed by the Physical function ICU-test (scored) (**PFIT-s, score range out of 10**, Appendix 2) (45,46) **at discharge from the ICU**.

The PFIT-s requires less than 20 minutes to complete (46).

6.2. Secondary endpoints:

1. Cognitive impairments assessed using the Montreal cognitive assessment (**MoCA**, Appendix 3) (47), the Hospital anxiety and depression scale (**HADS**, Appendix 3) (48), and the PTSD Checklist for DSM-5 (**PCL-5**, Appendix 3) (49) at discharge from the ICU and 3 months after discharge from the ICU (during a visit or by phone).
2. Functional status assessed by the **PFIT-s** 8 to 10 days from admission in the ICU and upon awakening. The definition of awakening is that used by De Jonghe et al. (50). It is the first day in which the patient is able to follow at least 3 out of the 5 following orders (on two consecutive evaluations at a 6-hour interval): “Open (close) your eyes,” “Look at me,” “Open your mouth and put out your tongue,” “Nod your head” and “Raise your eyebrows when I have counted up to 5”.
   These intermediate tests will be used to assess recovery kinetics.
3. Functional status assessed by the ICU mobility scale (**IMS**, Appendix 4) (51) upon awakening and discharge from the ICU.
4. Evolution of the functional status evaluated by **the Barthel index** (Appendix 5) (52) at discharge from the ICU and 3 months after discharge from the ICU (during a visit or by phone).
5. **Correlations** between functional tests (PFIT-s, IMS, Barthel Index) and cognitive tests (MoCA, HAD, PCL-5) at discharge from the ICU.
6. Muscular strength assessed by the Medical research council-sum score (**MRC-SS**, Appendix 6) (53) and with a dynamometric measure of quadriceps strength. Evaluation upon awakening and then once a week until discharge from the ICU.
7. Muscle atrophy assessed by **ultrasound measurement** of rectus femoris and vastus intermedius thickness, rectus femoris cross-sectional area, and rectus femoris echogenicity. Measures at inclusion (D_0), D_4, D_{10}, then once a week until discharge from the ICU.
8. Spasticity at discharge from the ICU assessed by the modified Ashworth scale (**MAS**, Appendix 7) (54) and the modified Tardieu scale (**MTS**, Appendix 7) (55) (only for patients with central nervous system lesions).
9. Number of delirium days in ICU assessed with the Confusion assessment method for ICU (**CAM-ICU**, Appendix 8) (56).
10. Number of days ventilation-free in the first 28 days in the hospital.
11. Incidence of ICU-Acquired Weakness (ICU-AW), diagnosed by an MRC-SS < 48/60 (50).
12. Length of ICU stay.
13. Length of hospital stay.
14. Mortality rate in hospital, at 3 months and 6 months.

7. Vigilance

7.1. Definitions

Adverse event: any unintended harmful event, illness, injury, or untoward clinical sign, including an abnormal laboratory finding, in participants, users, or others in a clinical investigation, whether or not related to the device under clinical investigation.

Serious adverse event: any adverse event that results in a) death; b) a severe deterioration of the health status of the participant that results in (i) a life-threatening illness or injury; (ii) a permanent impairment of an anatomical structure or function; (iii) hospitalization or prolongation of hospitalization of the patient; (iv) medical or surgical intervention to prevent any life-threatening illness or injury or permanent impairment of an anatomical structure or function; or (v) a chronic illness.

Device defect: any defect in the identity, quality, durability, reliability, safety, or performance of a device under investigation, including any malfunction, error in use, or defect in the information provided by the manufacturer.

Incident: any malfunction or alteration in the characteristics or performance of a device made available on the market, including an error in use due to ergonomic features or any defect in the information provided by the manufacturer and any adverse side effect.

Serious incident: any incident that has directly or indirectly resulted, may have resulted or may result in a) the death of a patient, user, or any other person; b) a severe temporary or permanent impairment of the health status of a patient, user, or any other person; c) a severe threat to public health.

7.2. Documentation of adverse events

All adverse events, including serious adverse events, as defined above, will be collected, reviewed, and documented throughout the clinical investigation period. Documentation of these includes:

- Description of the adverse event
- The date of the adverse event and, if applicable, its resolution
- The severity of the adverse event (mild, moderate, or severe)
    - Mild: symptoms that are barely noticeable to the subject or do not cause discomfort.
    - Moderate: symptoms of sufficient severity to cause discomfort to the subject. Treatment of symptoms may be required.
    - Severe: symptoms of sufficient severity to cause severe discomfort to the subject. Treatment of symptoms may be required
- Serious (yes/no)
- Related to the investigation procedure? (not related, possibly related, related)
- Related to the medical device? (not related, possibly related, related)
- Administration of treatment or implementation of action (discontinuation of the procedure, exclusion from the study, no action)
- Anticipated (yes/no)

In accordance with article R1123-49 of the Public Health Code, the investigator will notify the sponsor without delay from the day they become aware of all serious adverse events and all adverse reactions and serious incidents occurring during the research. This notification will be the subject of a written report by e-mail to the MAPAR office (the sponsor), e-mail: contact@mapar.org, regardless of its causal relationship with the trial device or the research.

7.3. Procedures for reporting serious adverse events related to the investigation procedure

In the event of a serious adverse event related to the investigation procedure, the investigators will inform the sponsor without delay according to the procedure described above.
The sponsor will then inform the ANSM (Agence nationale de sécurité du medicament) by e-mail to EC.DM-COS@ansm.sante.fr.
For serious adverse events and defects that have resulted in death or imminent risk of death, serious injury, or illness and that require prompt corrective action for patients, users, or others, or any new information relating to such events: the ANSM will be informed without delay (immediately), and no later than 2 calendar days from the day on which the sponsor becomes aware of the reportable event or new information concerning a previously reported event.
For other serious adverse events and defects or any new information/update concerning them: the ANSM will be informed without delay (immediately) and no later than 7 calendar days from the day the sponsor becomes aware of the reportable event or of new information concerning a previously reported event.

7.4. Procedures for reporting serious incidents related to the medical device

In the event of a serious incident related to the medical device, the investigators will inform the sponsor without delay according to the procedure described above.
The sponsor will then inform the ANSM by e-mail to EC.DM-COS@ansm.sante.fr. For serious incidents and defects that have resulted in death or imminent risk of death, serious injury, or illness and that require prompt corrective action for patients, users, or others, or any new information relating to such events: the ANSM will be informed without delay (immediately), and no later than 2 calendar days from the day the sponsor becomes aware of the reportable event or new information concerning a previously reported event.
For other serious incidents and defects or any new information/update concerning them: the ANSM will be informed without delay (immediately) and no later than 7 calendar days from the day the sponsor became aware of the reportable event or of new information concerning a previously reported event.

8. Monitoring

A physician independent from the investigation site will monitor the study (Pr Karim Tazarourte, head of the SAMU 69 - Emergency - hyperbaric medicine department, Groupement Hospitalier Edouard Herriot). A remote contact will be made when the research is set up; then, the monitor will come on-site twice during the study: halfway through and at the end of the inclusions. He will ensure that good clinical research practices are respected. In particular, he will verify the conformity of the consents, the respect of the eligibility criteria, as well as the collection and transmission to the sponsor of the adverse events within the time limits defined

above. All visits will be the subject of a written monitoring report. A copy will be sent to the principal investigator.

9. Statistical analysis

- **Calculation of the number of subjects needed:** the minimum clinically important difference (MCID) of the PFIT-s is 1.5 points, and in a population comparable to ours, the standard deviation is 3.06 (45). For a statistical significance threshold $\alpha = 0.05$ and a statistical power $1-\beta = 0.8$, the number of subjects needed is 67 subjects per group (calculation performed with GPower). Considering a 10% loss of subjects, the number of subjects needed is **75 subjects per group**.
- **Patient characteristics** will be reported using descriptive statistical analysis. Continuous variables following a normal distribution will be expressed as mean ± standard deviation. Continuous variables following a non-normal distribution will be expressed as median and interquartile range.
- **Between-group comparisons :**
    - For continuous variables, comparisons between groups will be made using independent samples t-test or Wilcoxon rank sum test (if the conditions for performing the t-test are not met).
    - For categorical variables, comparisons between groups will be made using χ^2 tests or Fisher's exact tests (if the conditions for performing the χ^2 test are not met)
- **Within-group comparisons:** changes in variables over time within groups will be assessed using statistical tests for repeated measures.
- **Correlations between functional and cognitive scores:** correlations between quantitative variables will be assessed using Pearson or Spearman correlation coefficients.
- Logistic regression will be used to determine the factors involved in the persistence of cognitive impairment at 3 months.
- Missing data will be replaced by multiple or single imputation as appropriate (57).
- Any treatment interruptions and their causes will be documented.
- Patients for whom the experimental treatment will be stopped will not be excluded from the study; their data will be used in an initial intention-to-treat analysis. Another analysis will be performed afterwards to consider only patients who have followed the treatment.
- The threshold for statistical significance is set at $\alpha = 0.05$.
- A correction for multiple comparisons will be applied.
- Statistical analyses will be performed with the R software.

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Appendix 1: protocol of motor physiotherapy sessions

- 1 session per day, 5 days a week
- In unresponsive or nonawake patients:
    - **Passive movements** of each limb to maintain joint amplitudes: **10 movements** (back and forth) according to each axis of mobility of the joint
    - **Cycloergometer 2 times a week**
- In patients who are awake and responsive to commands:
    - By increasing difficulty :
        - **Active movements** to maintain joint amplitudes, with or without assistance, in bed, lying on the back
        - **Mobility** exercises **in bed**, including transfers from lying to sitting at the edge of the bed and sitting balance at the edge of the bed, with or without assistance
        - **Sit-to-stand transfers**, bed-to-chair transfers, with or without assistance
        - **Standing balance**, walking on the spot
        - **Walking** in the unit
    - The progression from one stage to the next is decided by the physiotherapist in agreement with the multidisciplinary team
    - **Cycloergometer 2 times a week**
    - In the presence of an external ventricular drain (EVD), walking is possible by clamping the EVD in stable patients, in agreement with the patient's physician
- Chair-sitting is initiated as early as possible on medical prescription.

Appendix 2: Physical function ICU-test (scored) (PFIT-s)

Four items are assessed: assistance in transferring from sitting to standing, cadence of walking on the spot, shoulder flexion strength, and knee extension strength.

Classification of Component Scores Used in the Physical Function ICU Test (Scored) (PFIT-s) Ordinal Score

PFIT-s Components			
Assistance	**Cadence (steps/min)**	**Shoulder Strength[a]**	**Knee Strength[b]**
0=unable	0=unable	0=grade 0, 1, or 2	0=grade 0, 1, or 2
1=assist × 2	1=>0–49	1=grade 3	1=grade 3
2=assist × 1	2=50–<80	2=grade 4	2=grade 4
3=no assistance	3=80+	3=grade 5	3=grade 5

[a] Maximum strength of left or right shoulder flexion using the Oxford grading system.
[b] Maximum strength of left or right knee extension using the Oxford grading system.

Ordinal Scores and Equivalent Interval Scores for the Physical Function ICU Test (Scored) (PFIT-s)[a]

Scale	PFIT-s Score												
Ordinal	0	1	2	3	4	5	6	7	8	9	10	11	12
Interval	0	2	3.2	3.9	4.4	4.9	5.4	5.9	6.4	7.1	7.9	8.8	10

[a] Algorithm for conversion from ordinal to interval score=5.418 + (1.068 × logit location of ordinal score).

Source : Denehy L, de Morton NA, Skinner EH, Edbrooke L, Haines K, Warrillow S, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). Phys Ther. déc 2013;93(12):1636-45.