RBFEx
ISSN Online: 2675-1372
ISSN Printed: 1677-8510

Brazilian Journal of Exercise Physiology

Literature Review

Exercise as early mobilization in patients using vasoactive drugs

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Amanda Mariano Morais[1], Daiane Naiara da Penha[1], Danila Gonçalves Costa[1], Vanessa Beatriz Aparecida Fontes Schweling[1], Jaqueline Aparecida Almeida Spadari[1], Giulliano Gardenghi[1,2].

1. Hospital e Maternidade São Cristóvão, São Paulo, SP, Brazil.
2. Hospital ENCORE, Aparecida de Goiânia, GO, Brazil.

ABSTRACT

Introduction: The functional benefits of early mobilization (EM) capable of minimizing limitations and deformities in the face of immobility are clear, but there are many barriers to conduct EM as a routine practice in the Intensive Care Unit (ICU), including the use of vasoactive drugs (VAD), since it is directly related to weakness acquired in the ICU, in addition to the resistance of the multidisciplinary team to mobilize the patient using VAD. **Objective:** The objective of this literature review is to raise a scientific basis in the management of critically ill patients using DVAs for EM in the ICU. **Methods:** It is an integrative review of the literature, with research in the databases: PEDro, Pubmed, Lilacs, with articles published between 2011 and 2018, in Portuguese and English, using the terms: vasoactive drugs, early mobility, exercise in UCI, vasopressor and its equivalents in Portuguese. **Results:** Nine studies were included that analyzed the EM intervention in patients using VAD, with or without ventilatory support. There was no homogeneous treatment among the researched works, varying between exercises in bed and outside, with passive and / or active action. However, regardless of the conduct, there was an improvement in the cardiovascular response without relevant changes regarding the use of VAD. **Conclusion:** EM is not contraindicated for patients in the ICU with the use of VAD, and it was shown to be effective and safe without promoting relevant hemodynamic and cardiorespiratory changes, which would determine its absolute contraindication

Key-words: Vasodilator agents, Early ambulation, Intensive care units, Physical therapy specialty.

RESUMO

Introdução: São claros os benefícios funcionais da mobilização precoce (MP) capaz de minimizar limitações e deformidades diante do imobilismo, porém são muitas as barreiras para conduzir a MP como prática de rotina na unidade de terapia intensiva (UTI), entre elas, o uso de drogas vasoativas (DVA), visto que está diretamente relacionada à fraqueza adquirida na UTI, além da presença da resistência da equipe multidisciplinar em mobilizar o paciente em uso de DVA. **Objetivo:** O objetivo desta revisão de literatura é levantar embasamento científico no manejo do paciente crítico em uso de DVA para MP em UTI. **Métodos:** É uma revisão integrativa da literatura, com pesquisa nas bases de dados: PEDro, Pubmed, Lilacs, com artigos publicados entre 2011 e 2018, em português e inglês, utilizando os termos: vasoactive drugs, early mobility, exercise in ICU, vasopressor e seus equivalentes em Português. **Resultados:** Foram incluídos nove trabalhos que analisaram a intervenção de MP em pacientes com uso de DVA, com ou sem suporte ventilatório. Não houve um tratamento homogêneo entre os trabalhos pesquisados, variando entre exercícios no leito e fora, de ação passiva e/ou ativa. Porém, independente da conduta, houve melhora da resposta cardiovascular sem alterações relevantes quanto ao uso da DVA. **Conclusão:** A MP não é contraindicada para pacientes em UTI com uso de DVA e mostrou-se eficaz e segura sem promover alterações hemodinâmicas e cardiorrespiratórias relevantes, que determinassem sua contraindicação absoluta.

Palavras-chave: Vasodilatadores, Deambulação precoce, Unidades de terapia intensiva, Fisioterapia.

Received on: July 5, 2020; Accepted on: August 10, 2020.

Correspondence: Giulliano Gardenghi, Rua Gurupi, Quadra 25, Lote 6 a 8 Vila Brasília,74905-350 Aparecida de Goiânia GO, Brazil. ggardenghi@encore.com.br

Introduction

Early mobilization (EM) is understood to mean physical therapy performed on the critical patient, in the first 48 hours of an installed disease, as a process of improving functionality and reducing time in Intensive Care Units (ICU) [1,2].

The functional benefits of EM are clear [3], capable of minimizing limitations and deformities [3-5]. It has better results when started early [4], with a positive effect on improving quality of life and longevity after discharge [6].

The prolonged stay in the ICU is associated with bed immobilization, which is responsible for the development of weakness acquired in the ICU due to the loss of skeletal muscle of 1-1.5% per day at rest [3,7] this loss may reach 3% [8] and still last for five years after hospital discharge [5,7]. Even with these data, immobility is considered a public health problem, since less than 10% of critical patients in Brazil are mobilized in a hospital environment, which impacts on the increase comorbidities and mortality [3,9].

Because it is little practiced, there are few national studies that demonstrate such a practice [9-11], however we know that patients who are most commonly mobilized early, are on mechanical ventilation [1,2,4-6,8,10-13], and a part, under the effect of several medications, due to the severity of the clinical scenario. In agreement with this data, in the United States of America it was observed that non-mechanically ventilated patients were less likely to be mobilized and, in addition, the exercises performed were limited to the bed [14].

There are many barriers to conduct EM as a routine practice in the ICU, ranging from the poorly prepared and untrained multiprofessional team, lack of equipment, instability of the patient's clinical condition, sedation and use of vasoactive drugs (VADs), and it is also necessary constant monitoring of hemodynamic repercussions. [7,15]

The literature states that VADs are among the most widely used drugs in all intensive care centers [16]. Many critically ill patients use these to optimize cardiac output and systemic and pulmonary vascular tone, due to their peripheral, pulmonary, cardiac and renal effects, with vasoconstriction, inotropism, chronotropism, bronchodilation and others. They are able to reestablish blood flow in vital organs in states of circulatory shock [17-19] for having fast and powerful action, improving the prognosis and survival of patients. However, the use of VADs is associated with weakness acquired in the ICU regardless of other factors, so that this loss of muscle strength will be more pronounced when associated with bed immobilization. Therefore, it should be used with caution and with hemodynamic and laboratory monitoring [20,21] because the response in alpha and beta receptors is directly related to the dose applied [19,21].

Resistance is perceived among physicians regarding the mobilization of patients using mechanical ventilation and drugs (sedation and vasoactive), which we fear often extends to the multidisciplinary team [5,22,23]. They use the risk of changes as a justification to the risk of cardiovascular criteria (mean arterial pressure, cardiac output and blood flow), since during EM there is an increase in oxygen consumption due to muscle activation, which can result in adverse events, especially if the team is not adequately prepared to perform this procedure [23].

A better understanding of the risks when mobilizing patients who are using VADs can reduce the distance between research and clinical practice. Having knowledge of the barriers that imply in performing EM and the concomitant use of VADs, the purpose of this literature review is to raise scientific basis in the management of critically ill patients using VADs for EM in the ICU.

Methods

This study is an integrative literature review and research was carried out through the databases: PEDro, Pubmed, Lilacs, with articles published between 2011 and 2018, in Portuguese and English, using the terms: vasoactive drugs, early mobility, exercise in ICU, vasopressor and its equivalents in Portuguese. The articles were evaluated according to the recommendation of "Oxford Center for Evidence-Based Medicine": A) Systematic review (with homogeneity) of controlled and randomized clinical trials. Controlled and randomized clinical trial with narrow confidence interval. Therapeutic results of the "all or nothing" type; B) Systematic review (with homogeneity) of cohort studies. Cohort study (including randomized trial of lower quality). Observation of therapeutic results / Ecological study. Systematic review (with homogeneity) of case-control studies. Case-control study; C) Case reports (including lower quality cohort or case-control); D) Expert opinion without critical evaluation or based on basic subjects (physiological study or study with animals). In all the databases consulted, 63 articles were found and only nine were selected that fit the inclusion criteria, who underwent motor physiotherapeutic intervention in patients using VADs. Narrative / integrative or systematic review articles and studies that did not make clear the use of VADs were excluded. The selection flowchart follows below, in figure 1.

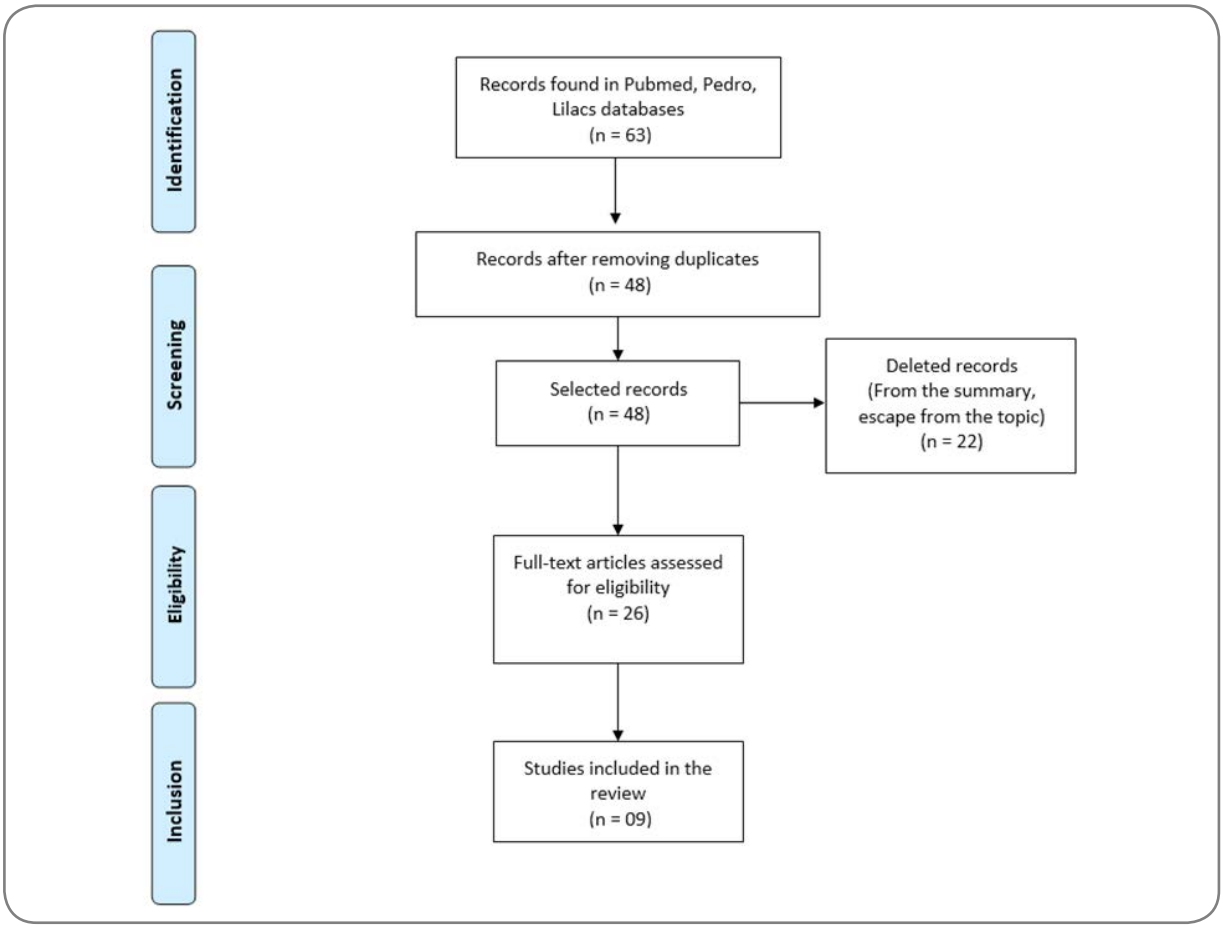

Figure 1 - Flowchart for selecting articles.

Results

Nine articles were included, where patients were submitted to physical therapy intervention, with or without the use of VADs, with constant hemodynamic monitoring.

The results obtained through the selected studies are shown in tables I and II. Table I shows the name of the author, year of publication, the degree of evidence, the objective of the study and the conclusion obtained through the observed results. Table II shows the name of the author, year of publication, the sample of patients with their respective distribution and the physiotherapeutic intervention. It is important to note that the interventions described in Table II were different, but all were performed in a hospital environment. The results show that the use of VADs was not an obstacle to the performance of EM, as they did not cause hemodynamic instability, in addition to potentially improving the cardiovascular response to muscle activation. In addition, there were no adverse events that required an increase in the dose of VADs, showing, therefore, that their presence is not a contraindication for physical therapy interventions.

Table I - Degree of recommendation, objective of the study and the conclusion of the articles of early mobilization in patients using VAD.

Author / Year	DR	Objective	Conclusion
Hodgson C *et al.* **2015 [12]**	C	Investigate current mobilization practices, strength at discharge from the ICU and functional recovery at 6 months in patients admitted to the ICU, under mechanical ventilation.	The use of vasopressors and deep sedation were common. The main barriers reported in patients who did not receive early mobilization were intubation and sedation. The MRC-SS score was higher in patients who mobilized under mechanical ventilation.
Garzon-Serrano J *et al.* **2011 [7]**	C	Assess the level of mobilization achieved and the barriers to progress to the next level of mobilization, performed by physiotherapists and nurses.	To ensure cardiovascular stability during mobilization, administration of vasopressors, volume, vasodilators and analgesics was maintained, as indicated in the safety studies. There were no adverse events associated with mobilization in this study.
Liu K *et al.* **2018 [15]**	B	Determine the safety of early mobilization by assessing the incidence of adverse events, when performed by professionals who are not specialists in mobilization, and the degree of mobility evolves.	They found that early mobilization is safe, did not demonstrate significant adverse effects that required additional treatment and / or an increase in the dose of vasoactive drugs.
Wolfe KS *et al.* **2018 [20]**	B	Evaluate the relationship between the use of vasoactive drugs and the result of weakness acquired in the ICU.	A total of 80 of the 172 patients demonstrated ICU Acquired Weakness (ICU-AW). In the multivariate analysis, the use of vasoactive drugs was associated with an increase of more than three times the chance of developing ICU-AW at hospital discharge, regardless of other risk factors established for ICU-AW.

Table I – Continuation

Author / Year	DR	Objective	Conclusion
Gardenghi G *et al.* **2017 [24]**	C	To investigate the cardiorespiratory behavior of patients in the postoperative period of cardiac surgery receiving or not VADs during the cycle for upper limb, verifying the safety of the same regarding the eventual loss of radial arterial catheter.	The adoption of the upper limbs cycle was safe in the PO of cardiac surgery, without causing unfavorable changes in the studied cardiorespiratory parameters, even in individuals using VADs.
Boyd J *et al.* **2018.[25]**	C	Investigate the safety of exercise rehabilitation in patients on mechanical ventilation and evaluate the recommendations of the ICU mobilization scale	In 809 mobilization opportunities, 260 did not occur due to hemodynamic instability, in 101 patients performed exercise in bed and in 448 out of bed. And in 299 care patients were using vasopressor support, there was an adverse event in a patient who was using moderate dose norepinephrine when placed on the tilt table. The article concludes that addiction to vasoactive medication should not be considered a reason to withhold exercise rehabilitation.
Pires-Neto R *et al.* **2013 [26]**	C	To verify the physiological changes and the safety of an early intervention on the cycle ergometer (<72h of mechanical ventilation) in critically ill patients.	The very early passive cycle ergometer exercise in sedated, critical, mechanically ventilated patients was considered safe and was not associated with significant changes in hemodynamic, respiratory conditions or metabolic variables, even in those who used vasoactive agents.
Hodgson C *et al.* **2016 [27]**	A	Determine whether a specific intervention (EGDM) would result in a higher dose of early mobilization in the ICU and whether it could prevent ICU-AW and improve the function of patients.	Early mobilization with a goal was safe and feasible, resulting in an increase in active exercises and in the mobility milestones achieved in patients admitted to the ICU.
Genc A *et al.* **2014 [28]**	C	To compare the effects of passive limb mobilization on hemodynamic and ventilatory parameters in patients without or with low doses of vasopressor.	There was an increase in preload due to increased venous return induced by mobilization. No significant changes between groups. An increase of more than 20% in heart rate was detected in three patients and an increase in mean arterial pressure in six patients.

DR = Degree of recommendation. ICU = Intensive Care Unit; MRC-SS = Medical Research Council Sum-Score; ICU-AW = Weakness acquired in the ICU; VAD = vasoactive drug; PO= Postoperative; EGDM = Early mobilization at the highest level of activity.

Table II - Sample of patients with respective distribution in groups and type of intervention performed on a patient using VAD.

Author/ Year	No. of patients and distribution	Treatment
Hodgson C *et al.* **2015**	N: 192 VAD: 127 (68%)	Mobilization was performed with exercises in bed, standing beside the bed or walking. On the third day, all mobilized patients were mechanically ventilated by an endotracheal tube.
Garzon-Serrano J, *et al.* **2011**	N: 63 patients; 179 interventions; 131 interventions performed by nurses (50% of these patients with VADs), 48 interventions performed by physiotherapists (65% of these patients with VADs)	**Level 1:** Passive ROM for upper limbs and lower limbs, globally, and sitting on the bed. **Level 2:** includes transferring the patient to a chair via a mechanical lift and / or sitting by the bed. **Level 3:** standing by the chair or side of the bed. **Level 4:** activities include walking the patient.
Liu K *et al.* **2018**	Patients admitted to the ICU: 839 selected patients: 232. 587 sessions were conducted. The incidence of adverse events, among all rehabilitation sessions, was 2.2%.	**Level 1:** No mobilization or exercises in bed. **Level 2:** Patient with elevated SP, including cycle ergometer and active mobilization. **Level 3:** Bedside sedestation. **Level 4:** Active transfer to the chair. **Level 5:** Static or walking gait.
Wolfe KS *et al.* **2018**	Sample of 172 patients	The patients included in the study received physical and early occupational therapy within 72 hours of MV (early mobilization) or standard care as requested by the physician.
Gardenghi G *et al.* **2017**	N: 26 patients Control group without VAD: 13 patients VAD group: 13 patients All submitted to CS (myocardial revascularization and / or valve replacement) by median sternotomy.	It was performed in the 1st PO, cycle ergometer for upper limbs for 5 minutes, with parameters evaluated during the activity: HR, SPO_2, dyspnea, upper limbs effort (Borg) and perfusion pressure (MAP).
Boyd J *et al.* **2018**	Sample of 91 patients	Exercises in or out of bed, evolving in the mobility scale according to the patient's clinical condition.
Pires-Neto R *et al.* **2013**	19 patients on mechanical ventilation, 13 patients using VADs	They performed only passive lower limbs cycle ergometer exercise for 20 minutes using a cycleelectric ergometer, evaluating the following variables: MAP, SBP, HR and SPO_2.
Hodgson C *et al.* **2016**	There were 50 patients enrolled in the study, 21 patients in the control group and 29 patients in the intervention group.	The EGDM protocol included active functional activities, including walking, standing, sedestation and rolling. The patient could receive assistance from the team or equipment, but actively participated in the exercise at the highest functional level. EGDM starts at the highest level of activity that a patient can sustain and work to maximize activity.
Genc A *et al.* **2014**	Total patients: 120. GROUP 1 did not receive vasopressor (38 patients) GROUP 2 received vasopressor dopamine <10 µg / kg / min, noradrenaline / adrenaline <0.1 µg / kg / min (82 patients).	1 daily session of 10 repetitions of flexion-extension in each joint, both of upper and lower limbs.

VAD = Vasoactive Drug; ROM = Range of Motion; ICU = Intensive Care Unit; SP = supine position; MV = Mechanical Ventilation; CS = Cardiac Surgery; PO = Postoperative; HR = Heart Rate; SPO_2 = Peripheral Oxygen Saturation; MAP = Mean Arterial Pressure; SBP = Systolic Blood Pressure; EGDM = Early mobilization at the highest level of activity.

Discussion

The literary survey carried out and demonstrated in the results provided evidence that EM in the ICU, in the presence of VADs, can be a safe alternative in the care of critical patients, seeking to minimize the negative repercussions of bed immobilization.

The consensus of experts published in 2014 by Hodgson *et al.* [29] was unable to reach an agreement regarding the dose of VADs that can be considered safe to initiate early mobilization. However, Boyd *et al.* [25] evaluated the safety limits for exercise in intensive care units in patients using VADs, based on the same system of signs and colors as the consensus mentioned above, in which green means low risk of adverse events, yellow, when there are risks for mobilization, but the benefits overlap risks as long as the team is qualified and trained in the processes and red, when there is a potential risk of adverse events with serious consequences. In this prospective cohort study, there were 91 patients, and the authors recorded the most advanced form of exercise (that is, the exercise with the greatest muscle activation) used each day, defining active exercises performed in or out of bed as rehabilitation exercises. VADs were categorized, according to individual dose, into low, moderate and high doses. Patients who used more than one VAD were categorized according to the highest level of one of the medications [25].

In summary, there were 809 mobilization opportunities, with the physiotherapist who made the decision on the indication of mobilization, in 260 (32.1%) of these opportunities rehabilitation did not occur because passive mobilizations were performed, which for the authors was not considered a rehabilitation intervention. In the total of mobilizations performed, on 299 occasions the patients were using inotropes or vasopressors, in 144 (48.16%) of these occasions the exercise was not performed. The exercises in bed occurred in 41 (13.71%) of these sessions, and in 114 (38.12%) occasions they were performed out of bed. Of all these occasions, only one adverse event occurred when patients were on VAD support. This adverse event was defined as cardiovascular instability and occurred when using the tilt table in a patient who was classified as receiving a moderate level of inotropic support (0.15 mcg / kg / min noradrenaline). At the conclusion of the study, they suggest that addiction to vasoactive medication should not be considered a reason to retain exercise rehabilitation [25].

Camargo *et al.* [2] performed a single passive cycle ergometer exercise for lower limbs for 20 minutes in 19 hemodynamically stable patients, deeply sedated and mechanically ventilated. Among those evaluated, 13 (68%) were using noradrenaline. The hemodynamic, respiratory and metabolic variables were evaluated minute by minute before, during and after exercise. The variables analyzed included: cardiac output, systemic vascular resistance, central venous oxygen saturation in the blood, respiratory rate and tidal volume, oxygen consumption, carbon dioxide, blood lactate production and levels. In conclusion, exercise was considered safe, not being associated with significant changes in hemodynamic, respiratory conditions or metabolic variables, even in those that required vasoactive agents.

Passive exercises (PE) are widely used in the treatment of unconscious patients and an early start is recommended. Genc *et al.* [28] aimed to determine the effects of PE on hemodynamic and respiratory parameters in critically ill patients receiving vasopressor or inotropic support at a low dose. The medical records of 120 patients were evaluated and were retrospectively grouped into two groups in which thirty-eight patients did not receive vasopressor / inotropic support (group 1) and 82

patients received low-dose vasopressor / inotropic support (group 2). Central venous pressure, heart rate, mean arterial pressure, and oxygen saturation were recorded before and immediately after PE. No statistically significant difference was observed in the rate of change in hemodynamic or respiratory parameters between the two groups after PE. This retrospective study confirmed that PE results in similar hemodynamic and respiratory changes in critically ill patients who received low doses of vasopressor / inotropic support compared to those who did not.

In a recent study by Gardenghi *et al.* [24], 26 patients underwent cardiac surgery for myocardial revascularization or valve replacement, performed with median sternotomy, and half were using dobutamine and norepinephrine with doses at medical discretion. They were submitted to active exercises on the 1st PO day using a cycle ergometer for upper limbs for 5 minutes with intensity assessed by effort and dyspnea (4 and 5 on the Borg scale), and by the parameters of HR, SpO_2 and MAP. Gardenghi *et al.* were able to demonstrate that EM in this group was safe, as there were no related adverse events, and mainly, there were no abnormal hemodynamic changes even in patients using VADs.

Liu *et al.* showed that EM is safe, even when performed by professionals who are not specialized in EM, in a hospital without a culture of mobilization, performing basic training for only one month. They determined the safety of mobilization by assessing the incidence rate of adverse events in rehabilitation sessions. During 587 sessions there were 13 adverse events that included seven episodes of patient intolerance and six of orthostatic hypotension, and activity was stopped. There were no serious adverse events that required additional treatment such as increasing the dose of VAD [15]. In addition, it was observed that patients who received therapy for about 20 minutes, the real time being determined according to the case of each patient, took an average time of 1.2 days to get out of bed.

Garzon-Serrano *et al.* [7] evaluated the level of mobilization performed by physiotherapists and nurses in patients admitted to the ICU, on a scale of 0 to 4, where 4 was the highest level of mobilization. Activities were carried out at the bedside, transfers from bed to chair and gait training, so mobilization was considered a process of improving mobility in the ICU. The use of VADs was not a predictor of exclusion for mobilization, and they were used to maintain stable hemodynamic parameters, and their use did not promote adverse effects on patients. The level of patient mobilization achieved by physical therapists was higher than that achieved by nurses. Among the professionals, different mobilization barriers were identified, such as hemodynamic instability and renal replacement therapy, which were barriers more considered by nurses, while neurological impairment was classified as a higher barrier by physical therapists. Due to a direct relationship between the level of mobilization and the beneficial effects of it, initiatives to standardize this intervention among intensivists become important.

In the prospective multicenter cohort study carried out by Hodgson *et al.* [12], developed in 12 ICUs in Australia and New Zealand, with 192 patients, the practice of EM, strength at discharge from the ICU and functional recovery of patients on mechanical ventilation were investigated. As barriers to EM, sedation and intubation were identified. Activities were performed in bed, bedside and out of bed, with sedation, orthostasis, ambulation and active movements for upper limbs and lower limbs in flexion and extension, after an average of 5 days of hospitalization. Ambulation was performed after day 7 of hospitalization. 209 mobilizations were recorded, and there were no serious adverse events, except for 6 records where interruption due to cardiovascular or respiratory instability occurred, without the need for medi-

cal intervention. The use of VAD was present in 66% of the patients and was not an impediment to treatment. Thus, the MRC-SS score was higher in patients who were mobilized on MV (50.0 ± 11.2 versus 42.0 ± 10.8, P = 0.003). And yet, more than 50% of patients discharged from the ICU developed weakness acquired in the ICU associated with death after discharge.

In the study by Wolfe *et al.* [20], which consists of a secondary analysis of patients who were selected to receive early mobilization within 72 hours of MV, patients were subjected to tests of muscle strength by the bed by a blind therapist, to assess whether had developed muscle weakness acquired in the ICU (ICU-AW). Of the 172 patients analyzed, 80 demonstrated ICU-AW at hospital discharge. The authors reported that the use of VADs was associated with a three-fold increase in the chances of developing ICU-AW, regardless of other established risk factors. They mention that this effect is directly associated with the duration of vasoactive medication and the cumulative dose of norepinephrine, which is not seen in vasopressin and phenylephrine. They also observed that only the β-adrenergic groups of VADs (noradrenaline, epinephrine, dopamine and dobutamine) were significantly linked to the development of ICU-AW [20].

In 2016 Hodgson [27] followed an EM protocol, where patients performed activities at the highest level they could, aiming to maximize the safety of the mobilization. Patients were not excluded because they were using VAD, they were only excluded from early mobilization if they had a norepinephrine dose> 0.2ug / kg / min or a 25% increase in the dose of any VAD in the last 6 hours. It resulted in an increase in mobility minutes performed by patients in the ICU, reaching a higher level of activity after discharge. On the other hand, four adverse events were reported, namely agitation and transient hypotension and only one was necessary to interrupt the therapy, none of which required complementary drug therapy.

This article has limitations that should be noted. As it is a literature review, it is not possible through it to specify that all literature on the subject has been included, no matter how much the authors have tried to do so. It also includes different populations, which can interfere with the conclusion.

Conclusion

In the search to reduce the distance between scientific research and clinical practice, this literature review showed that early mobilization for ICU patients using vasoactive drugs proved to be effective and safe without promoting relevant hemodynamic and cardiorespiratory changes, which would determine their absolute contraindication. Thus, in view of the beneficial responses, early mobilization can and should be used as a resource in intensive care, as long as there is a monitoring of risks by the multidisciplinary team.

Conflict of interest statement
No conflicts of interest with potential potential for this article have been reported.

Financing source
There was no external funding source for this study.

Authors' contributions
Conception and design of the study: Gardenghi G and Spadari JAA. Data acquisition: Morais AM, Penha DN, Costa DG and Schweling VBAF. Analysis and interpretation of data: Gardenghi G and JAAS. Writing of the manuscript: Morais AM, Penha DN, Costa DG and Schweling VBAF. Critical review: Gardenghi G and Spadari JAA.

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