Very early mobilization following acute stroke: Controversies, the unknowns, and a way forward

Julie Bernhardt
National Stroke Research Institute, Melbourne, Australia and School of Physiotherapy, La Trobe University, Melbourne, Australia

Abstract

Evidence that organized stroke-unit care results in better outcome has led to positive changes in stroke service delivery around the world. It is well accepted that stroke rehabilitation should commence as early as possible for optimal recovery to be achieved. Exactly how early rehabilitation should start is controversial. Early mobilization (getting up out of bed within 24 h of stroke onset) is a well-established feature of acute stroke care in many Scandinavian hospitals. Elsewhere in the world, stroke protocols enforce bed rest for the first few days or foster long periods of bed rest after stroke. This paper aims to provide an overview of the topic of very early mobilization (VEM). It is divided into three sections: section 1 reviews the effects of bed rest and outlines arguments both for and against enforced bed rest after stroke; in section 2, VEM as a treatment for stroke and the limitations of existing literature in the field are described; and section 3 outlines the systematic approach that has been taken by our team of clinical researchers to the study the effect of VEM after stroke. Conclusion: VEM represents a simple, easy-to-deliver intervention, requiring little or no equipment. It is potentially deliverable to 85% of the acute stroke population and, if proven to be effective, may help reduce the significant personal and community burden of stroke. As current opinion about when mobilization should begin is divided, one way to move forward is through the conduct of a large high-quality clinical trial (such as A Very Early Rehabilitation Trial (AVERT)). Although some inroads have been made, further research in this field is clearly warranted.

Keywords

Cerebral venous thrombosis, intracranial hypertension, stroke

For correspondence:
Assoc Prof. Julie Bernhardt, Director AVERT Very Early Rehabilitation Research Program, National Stroke Research Institute, 300 Waterdale Rd, Heidelberg Heights, 3081, Victoria, Australia. E-mail: j.bernhardt@unimelb.edu.au

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this review paper is divided into three main sections. In the first section, the effects of inactivity associated with bed rest are reviewed and the current arguments for and against enforced bed rest after stroke are discussed. In the second section, current physiotherapy practices in the acute phase of care are briefly reviewed along with very early mobilization (VEM) as a treatment for stroke. The limitations of existing literature in the field are briefly described here. In the final section, the systematic approach taken by our clinical research team to the study of VEM after stroke is outlined.

Section 1: Bed rest

Intuitively, early mobilization after a stroke makes sense. For many years, the negative effects of bed rest have been expounded. Bed rest is believed to have a potentially negative effect on the cardiovascular, respiratory, renal, gastrointestinal, musculoskeletal, and neurological systems and is also said to be associated with increased adverse events such as deep-vein thrombosis, bedsores, osteoporosis, pneumonia, and functional decline. However, relatively little direct study of the effects of bed rest on these systems has been undertaken. A recent study by Kortebein et al. examined the effect of 10 days of bed rest in 12 healthy elderly men and women (mean age 67 years) on skeletal muscle protein synthesis, nitrogen balance, lean tissue mass, and lower extremity strength. This study, though small, found significant reduction in all measures post-bed rest, when compared to pre-bed rest. The authors reported a pronounced loss of lower extremity skeletal muscle strength as a result of only 10 days of bed rest and point out that the loss was greater than that found in younger individuals after 28 days of bed rest. Loss of strength of as much as 40% has been reported within the first week of immobilization, and the antigravity muscles of the calf and back, needed for standing up, appear to atrophy at a faster rate than non-antigravity muscles. As expected, bone density is also affected with bed rest. Bloomfield reported 6-40% decrease in bone density in just 4 to 6 weeks as a result of bed rest. The cardiovascular consequences of bed rest may also be significant, with reduction in VO2max occurring early in healthy individuals, independent of age or gender. Orthostatic intolerance can begin to appear within 3-4 days of commencing bed rest and is likely to appear more rapidly in individuals with underlying cardiovascular disease and in the elderly. The research indicates that even those with good general health are affected by a period of bed rest. Although the impact of bed rest on individuals with diseases has also been examined, the specific physiological responses of these individuals to bed rest has received less attention. The systematic review by Allen et al. concluded that research to date gives little support for the use of bed rest in the treatment of a wide range of conditions and suggests that bed rest may delay recovery and even result in harm. They observed that ‘ideas about bed rest seem so entrenched that medical practice has been slow to change—even when faced with evidence of ineffectiveness’ (p.1232). In a more recent cohort study of 498 elderly hospitalized patients (aged > 70 years), Brown et al. reported that 33% of patients were placed on bed rest ‘on admission and remained there, often without valid medical reasons’ and that decreased mobility was independently associated with adverse outcomes. Little is known about the physiological and functional effects of bed rest on patients with stroke.

In 1944, Dock argued that ‘the physician must always consider complete bed rest as a highly unphysiologic and definitely hazardous form of therapy, to be ordered only for specific indications and discontinued as early as possible.’

Certainly, there has been a radical shift in thinking about the amount of rest that is helpful after acute myocardial infarction. Over the past 60 years, treatment has changed from prescription of complete bed rest for 6-8 weeks, to bed rest for 12 or more hours. Theoretically, it appeared sensible to keep patients with acute myocardial infarction in bed so as to allow sufficient time for the affected organ, the heart, to heal and for scar formation to be completed. Although a change in the accepted practice was slow in coming, it was the realization that the detrimental effects of bed rest on multiple body systems outweighed the benefits to the heart that ultimately led to change.

Bed rest after stroke

What is the current thinking about bed rest following stroke? Opinions vary widely about the timing of first out-of-bed activity after stroke. A recent survey of 99 Scottish doctors, nurses, and physiotherapists found little agreement among them about who should be mobilized, when mobilization should begin, and who should be responsible to help the patient with mobilization. In Scandinavia, activity out of bed within 24 h is widely practiced. However in other parts of the world, a period of enforced bed rest lasting between 1-3 days post stroke is recommended. In 2006, Diserens et al. proposed a ‘rapid out of bed’ treatment protocol for acute stroke that requires the patient to lie flat for the first 24 h after stroke onset; the head of the bed is then raised to 45° on the second day post stroke in the absence of intracranial hypertension or worsening neurological status. On day three (i.e., after 48 h) the patient is allowed to have the head of the bed elevated to 90° for at least 4 h, all the while keeping a watch for aggravation of symptoms and signs. If 4 h in the head-up position is well tolerated,
the patient is allowed to sit out of bed in a chair (or to stand, if tolerated). The Swiss team acknowledges that this protocol requires testing in a prospective randomized study. What is interesting to note is the reasoning behind the development of this protocol. While Diserens et al. acknowledged that the limited research into VEM has produced mixed results and that some studies support the practice, they argue that the Scandinavian practice of VEM is considered ‘too abrupt by most specialists, fearing diminished cerebral blood flow by mobilization out of bed.’ In short, it is clinical opinion that has driven the protocol because of the limited evidence currently available.

The stroke protocol adopted by Wojner-Alexandrov and colleagues also employs 24 h of bed rest. This was developed largely on the basis of preliminary research examining residual blood flow velocity in middle cerebral artery ischemic stroke. In a study of 20 patients, the head of the bed was positioned at 30°, 15° and 0°. In each position, transcranial Doppler was used to measure mean flow velocity at the site of the occlusion. The researchers found a 12% increase in mean flow velocity with lowering of the head of the bed from 30° to 15°. A further 8% improvement was found as patients were placed in a flat (0°) position. Although transcranial Doppler assessment of mean flow velocity cannot be used to calculate cerebral blood flow, a relationship can be reasonably assumed. In the face of these results, Wojner-Alexandrov and colleagues suggest that 0° head positioning may improve residual flow in the affected middle cerebral artery and thus improve brain perfusion. The authors acknowledge that not all patients can tolerate 0° positioning for extended periods and that the risk of aspiration is likely to increase in this position. They also acknowledge that the extent of any long-term benefit in being managed resting flat is currently unknown. In this hypothesis-generating study, functional outcome was not examined. Nevertheless, they have adopted a ‘24-h rest flat’ policy for many of their patients despite some concerns about the safety of the practice. The underlying argument for this treatment approach is that maintenance of cerebral blood flow will help support the vulnerable ischemic penumbra. It appears likely, however, that in most cases the penumbra is probably present only during the first 3-16 h, and at most for 48 h, after the stroke event. Although harm to a possible long-lasting penumbral zone might be hypothesized, there is currently no evidence that mobilization affects levels of perfusion or, importantly, alters clinical outcome.

In the face of limited research into the effect of positioning after stroke, it appears that research indicating a potential negative effect of being upright early after stroke has led to the development of stroke protocols that require a period of enforced bed rest. It is interesting to reflect that a similar argument (potential negative effects of activity on myocardial healing) formed the basis of the development of the ‘rest in bed’ protocols following acute myocardial infarction that dominated hospital care in the 1940s. Thinking has, of course, radically shifted in this field and early cardiac rehabilitation programs are now common. More research is needed before early mobilization in stroke can be guided by evidence.

Stroke patients as a group are at very high risk of developing complications, with an estimated 85% experiencing complications such as infections, pressure sores, contractures, deep venous thrombosis, pulmonary embolism, and pain during their hospital stay. Complications resulting from immobility may account for up to 51% of the deaths in the first 30 days after ischaemic stroke, with over 62% of complications occurring in the first week. The true contribution of immobility to poor outcome is difficult to quantify. We do not know how much immobility (bed rest) predisposes patients to a greater number of, or more severe, complications; however, we do know that the complications of immobility occur within the first few days following stroke. There is also evidence that in many conditions bed rest does more harm than good. Bed rest may of course be a highly suitable form of management for some stroke patients very early after stroke. However, it is important to consider both the harms and the benefits to the individual as a whole of protocols that promote periods of enforced bed rest after stroke. The physiological responses of patients to sitting and standing early after stroke are reviewed in the next section and in Table 1.

Section 2: Physiotherapy and VEM

Early rehabilitation by a multidisciplinary team is well accepted as part of good stroke care. Physiotherapy

<table>
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<tr>
<th>Table 1: Key points from bed rest review</th>
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<tr>
<td><strong>Summary: Bed rest</strong></td>
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<tr>
<td>● Bed rest is associated with increased complications in hospitalized patients</td>
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<tr>
<td>● Negative effects with bed rest assumed on cardiovascular, respiratory, renal, gastrointestinal, musculoskeletal, and neurological systems</td>
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<tr>
<td>● Muscle loss, reduced strength, reduced bone density and VO2max, and orthostatic intolerance all found early even in healthy subjects</td>
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<td>● Little support for bed rest as a treatment for patients with disease</td>
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<td>● ‘Head-up’ position may decrease cerebral blood flow but functional outcome not studied</td>
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<td>● 51% deaths in the first month after stroke may be due to immobility-related complications</td>
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input soon after a patient is admitted with stroke is generally directed at early identification of mobility limitations so that safe bed transfers and measures for restoration of functional mobility can be commenced as soon as possible. Falls risk is also commonly assessed by the physiotherapist who will implement a multidisciplinary treatment plan to reduce the likelihood of a patient falling. Such a plan is likely to include some system for easy recognition of those most at risk of falls through use of prominent notices above beds and/or colored stickers on walking aids. Pressure devices on chairs that set off an alarm when a patient at high risk of falls stands up without supervision may also be used. Very low beds and chairs (bean bags) or mattresses laid on the floor may be used for high-risk patients who are agitated. Restraints are never used to prevent falls, with many hospitals legislating against their use. Physiotherapists also address recovery of sensorimotor function in the upper and lower limbs and assist with the treatment of musculoskeletal problems or complications (eg, painful shoulders) and respiratory problems. Much of the research, and therefore the evidence base for the benefits of physiotherapy, comes from the post-acute period. Evidence to support specific physiotherapy interventions in the first few weeks after stroke is scarce. For this reason, a common approach is to apply proven interventions from the rehabilitation period into the acute stroke period. Physiotherapy interventions may be beneficial or harmful.

**Effective interventions for stroke**

- Task-specific training for targeted activities (eg, sitting, standing, walking, reaching, and manipulation of objects), including the use of constraint of the nonaffect ed hand to promote use of the hemiplegic upper limb
- Strength training, including use of electrical stimulation and/or progressive resistance training
- Training for cardiovascular fitness to improve walking capacity
- Intensive training, typically sessions of 20-45 min, twice per day, 3-5 days per week for 4-6 weeks, is superior to less intensive regimes
- Functional electrical stimulation for patients with severe weakness around the shoulder to reduce subluxation and pain, plus use of firm supportive devices for the hemiplegic upper limb

Use of standard treadmills and body weight-supported treadmills is becoming increasingly common; however, at present there is no evidence to indicate that their use leads to better outcomes than simple walking exercises on the ground.

**Harmful interventions**

- Overhead arm pulleys to exercise the hemiplegic upper limb
- Aggressive passive movements/stretching of the upper limb

Both of these interventions are associated with the onset of shoulder pain.

As discussed earlier, the organization of the setup in which the stroke patient is managed will strongly influence the physiotherapy care provided. Staffing levels vary according to whether a service is focused on providing acute or rehabilitative care. For those services with an acute stroke management focus, the role of the physiotherapist may be restricted to providing early mobility advice, falls risk assessment, prevention of post-stroke complications where physical means are effective and, where possible, commencement of rehabilitation. Protocols have been developed to improve care of the hemiplegic upper limb in the acute stroke environment and have shown promising results.

More research is needed however to underpin the benefits of physiotherapy and other multidisciplinary interventions delivered in the first few weeks after stroke.

Early mobilization is recommended in a number of clinical guidelines for acute stroke but it is not supported by high-level evidence. There are no universally accepted definitions of what constitutes ‘early rehabilitation.’ Before discussing VEM however, the terms ‘very early’ and ‘mobilization’ need to be defined. A surprising number of definitions exist for these terms. Within our research program, ‘early’ is defined as the first week after onset of stroke symptoms and ‘very early’ as within the first 24 h after symptom onset. ‘Mobilization’ is defined as out-of-bed activity; in-bed activities are called ‘bed rest.’

A Cochrane systematic review to answer the specific question of whether commencing out-of-bed activities (mobilization) within 48 h is better than delayed onset of mobilization in improving outcomes in stroke patients is currently underway. The results of this review will not be preempted. However, several observations about the state of the literature in this field are relevant here. When examining the literature for stroke trials with an ‘early’ onset of a rehabilitation intervention that include a mobilization component, the absence of unconfounded, high-quality trials is clear [Figure 1]. Trials of physiotherapy interventions after stroke, largely comparing two different forms of mobility-based interventions, are few and often have small sample sizes. The timing and type of intervention delivered is often poorly defined and few studies have considered the possible harms associated with the intervention. Few trials could be found that commenced physiotherapy within 24 h of stroke onset, and while
there are a few that report some differences in outcome with change in the timing of the intervention, generally this was not the main focus of the study. Trials that compare stroke-unit care with general medical ward care and specify that an early rehabilitation approach was a feature of the stroke unit are also shown in Figure 1. Treatment in these units is often described as commencing within 24 h of stroke onset and patient outcomes in the majority of these studies have been better (often markedly so) than those of patients treated within a general medical ward. Stroke-unit trials have generally been designed with greater rigor and have larger sample sizes. The main difficulty encountered in evaluating these studies, however, is that early rehabilitation forms only one component of care within the organized stroke unit setting. It is therefore not possible to determine the independent effect of early rehabilitation (or mobilization) on patient outcome. Furthermore, the rehabilitation intervention itself often poorly defined. The very early mobilization provided as part of care in the Trondheim stroke unit in Norway is a notable exception.\[4,51\] Patients randomized to this stroke unit, which featured very early (≤ 24 h) and frequent mobilizations as part of the total care package, were less likely to die, more likely to return home, and had a shorter length of hospital stay compared to general ward care patients. Stroke unit patients’ odds of being dead or dependent were reduced by 64% (OR 0.36, 95% CI: 0.21 to 0.61; \( P = 0.01\)).\[1\] Of the factors that distinguished stroke-unit care from general medical care, the same group found VEM to be the strongest predictor of improved outcome.\[52\] They argued that early initiation of mobilization has a powerful effect on the outcome of patients managed in the stroke-unit environment. However, these studies provide only indirect evidence of the benefits of VEM; the true benefit (or harm) of very early mobilization can only be tested in a carefully controlled randomized trial.

VEM in the Trondheim unit has been usual practice for over 10 years. Indredavik and colleagues argue that the intervention is safe and that, with adequate hydration and careful observation, drops in blood pressure or signs of clinical worsening (temporary or permanent) has been rare.\[53\] In this unit VEM commences within 24 h of stroke onset (mean 17 h).\[4\] It is delivered by nurses and physiotherapists who work closely together throughout the day. The multidisciplinary team is small in this unit, consisting of doctors, nurses and nursing assistants, and physiotherapists. Occupational therapists and speech therapists are involved later in the program as part of the early supported discharge team.\[53\] The emphasis is not on patients sitting out of bed for long periods of time. Within this programme, having a low level of consciousness post stroke is not considered to be a contraindication for early mobilization. Over time, Indredavik and colleagues have provided further evidence in support of the long-term benefits of both their stroke-unit care (which includes VEM)\[54\] and early supported discharge programmes.\[55\]

**Physiological impact of VEM**

Recently, the Norwegian team presented the preliminary results of a cohort study of 100 patients with moderate or severe stroke admitted to their stroke unit within 24 h of stroke onset.\[56\] They recorded mean blood pressure, heart rate, oxygen saturation, and consciousness before, during, and after an early mobilization procedure. In this sample, the median time to first mobilization was 22 h after stroke symptom onset. Fourteen patients were unable to complete the full early mobilization procedure due to dizziness/vomiting, high or low blood pressure, or temporary reduction in consciousness. The majority (86%) of patients tolerated the early mobilization procedure well and completed the protocol. These patients experienced a small transient increase in mean blood pressure on being made to sit up in bed for 1 min; this reduced after 5 min of sitting and disappeared by the end of the mobilization procedure 55 min later. There was an increase in heart rate, which peaked at 5 min of
sitting out in a chair (increasing from approximately 70 to 81 beats per minute), but dropped to close to pre-mobilization levels after sitting for 55 min. The group also experienced sustained improvements in consciousness and oxygen saturation.

This is an important study. Through studying the changes in physiological variables at selected intervals over the first 55 min of mobilization, Indredavik and colleagues have provided information about what can be expected when patients are mobilized for the first time. Furthermore, it is clear from these data that 14% of patients with moderate and severe stroke may be unable to complete mobilization within 24 h of symptom onset. Although they do not provide details about the characteristics of those who failed first mobilization, further information is likely to follow. Most importantly, they show that the majority of patients were able to be sat out of bed for 55 min on the first day of stroke, with arguably small and transient increases in blood pressure and heart rate and positive effects on consciousness and oxygen saturation.

Oxygen saturation has also been shown to improve in patients sat out of bed early after stroke (median 72 h post stroke) in the study by Rowat and colleagues when compared with patients kept lying. Interestingly, in this study, only 55% (65/129) of patients were able to sit in a chair, with the remainder being considered ‘too ill’ to do so (p.68). A more recent systematic review of the effect of positioning on oxygen saturation after stroke indicates that evidence of benefit is equivocal for all but those patients who have respiratory comorbidities; for these patients, sitting as upright as possible is recommended.

The effect of early body positioning on postural hypotension has been studied by a number of authors. In 1999, Panayiotou et al. examined the response of patients with mild and moderate stroke severity to sitting up and standing within 48 h of stroke onset. Patients exhibited increases in mean arterial blood pressure on moving from the supine to the sitting and standing positions, but persistent postural hypotension (defined as ≥ 20 mmHg fall in systolic blood pressure) occurred in fewer than 10% of patients. Consistent with the findings of Indredavik et al., heart rates were significantly faster in sitting and standing positions than in the supine position. A study as Asberg, in which stroke patients with cerebral infarction commenced standing up every hour 24-48 h after stroke onset, found marked improvements in orthostatic tolerance in this group compared with a similar group who were not encouraged to stand up early. The authors of both studies concluded that they could see no reason why early standing activities should not form part of acute stroke management.

**Impact of early exercise on brain injury and reorganization**

Very few studies have examined the impact of early initiation of mobilization in particular or exercise, in general, on brain reorganization or injury. It is important to briefly review this topic here. Particularly in light of the fact that the results of a number of animal studies published in the late 90s suggested that early activity after stroke was associated with significant harm. The interest of these studies, animals with recent stroke were forced to use their affected forelimb for many hundreds of repetitions over 7-15 days post-lesion. After some days, the animals were killed and their lesion volume determined. In these studies, early forced activation resulted in greater increase in lesion volume as compared to that in animals that commenced training later. These findings resulted in the publication of a caution from Aldous about the potential harms of early exercise after stroke. Anecdotally, these papers appear to have had a significant impact, making clinicians question the safety of commencing activity early after stroke and, indeed, to ask whether it is safe to subject patients to the intervention for the purposes of research. However, the temperature of the rats was poorly monitored or controlled in these studies. Hyperthermia alone can lead to significant harms to ischemic brain tissue and therefore it is not possible to say with any certainty that exercise was the cause of increased lesion volume. It should also be noted that increased tissue loss does not necessarily equate to poorer outcome. Early training led to improved functional outcome in one of the studies, despite increases in lesion volume. Finally, even the authors in these studies called the forced exercise ‘extreme’ and such extreme exercise would not be acceptable in humans. In 2003, Yang and colleagues compared the effect of commencing exercise early (<24 h) post stroke with that of later (2 weeks) commencement of exercise in a rat model of ischemic stroke. The group that commenced training early was found to have better neurological function and reduced infarct volume compared with spontaneously recovered rats. Temperature was monitored in this study.

Activity is believed to be a powerful modulator of brain reorganization. The literature is still unclear about the optimal timing of physical activity after stroke in animal models. There is a dearth of literature examining the impact of early vs late training on brain reorganization in humans after stroke [Table 2].

**Further research needed**

There is much that remains unknown about VEM [Figure 2]. The evidence in favor of VEM is indirect.
Bernhardt: Very early mobilisation

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and concerns about the practice exist. Even assuming that VEM may produce more benefits than harms, we know little about the optimal timing, dose, duration, frequency, and scheduling of the intervention itself. Furthermore, the type of patient who may benefit most (or be harmed) by VEM is also unknown. For example, is it safe to mobilize patients with intracerebral hemorrhage? Should patients who have been given tPA be allowed to mobilize and, if so, how soon after tPA? Who should be responsible for delivering the intervention is also uncertain, although most nurses and physiotherapists believe they have a role to play here. Finally the cost-effectiveness of the intervention needs to be considered.

An obvious way to advance understanding in this field was to develop and test a VEM protocol in a randomized controlled trial (RCT).

### Section 3: The VEM research program

In this final section, the results of research conducted as part of the development of a large, phase III RCT of VEM are presented. The systematic approach that our clinical research team have taken in the study of VEM has, by and large, followed the common phase I, II, and III stages of clinical trial development.\[70\]

#### Phase I

The fact that this simple intervention had been used for over 10 years in a number of Scandinavian hospitals without signs of undue harm and with potential benefits suggested that it was sensible to quickly move to trial development. Therefore, a proof-of-concept study was not needed for phase I of the trial. However, it was important in this phase to determine whether VEM was already established practice in Australia (as many clinicians believed) and to gather baseline information about the ‘dose’ of mobilization that was typically delivered early after stroke. Furthermore, given that different models of stroke-unit care exist around the world, it was necessary to determine who, within the multidisciplinary team, was most responsible for patient mobilization, as these clinicians would be asked to deliver the interventions within the clinical trial.

An audit of 155 consecutive admissions to a large teaching hospital stroke unit determined that only 69.7% of patients received treatment by a physiotherapist during their hospital stay (unpublished data). Of those who were seen by a therapist, only 7% were seen within the first 24 h of stroke onset. A further 46.3% of patients were seen by 48 h and 9.3% were not seen until 96 h (4 days) had passed after symptom onset. A study by Cadhilac et al.\[71\] of nine Australian hospitals, and including 511 acute stroke patients, confirmed that patients were seen by a physiotherapist within 24 h on only 43% of occasions. From these data it was impossible to determine whether mobilization took place or if the focus of the first visit was on assessment. If physiotherapists were, as is to be expected, the main drivers of mobilization practices early after stroke, then these data indicated that VEM was at best being delivered to fewer than half of all stroke admissions. The acquisition of prospective data that could detail activity patterns in acute stroke patients was needed.

### Table 2: Key points from review of very early mobilization literature

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<th>Summary: Very early mobilization</th>
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<td>• Defining the terms ‘very early’ (&lt; 24 h of symptom onset) and ‘mobilization’ (out-of-bed activity) is vital</td>
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<tr>
<td>• Current evidence for very early mobilization is indirect, with strongest evidence from a stroke unit in Trondheim, Norway[4,49]</td>
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<tr>
<td>• Many rehabilitation trials are confounded and therapy trials are often small, with poorly defined interventions</td>
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<td>• 86% of patients may be able to mobilize within 24 h of stroke onset, with a transient increase in blood pressure and improved consciousness and O 2sat[56]</td>
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<tr>
<td>• Sitting and standing within 48-72 h of stroke onset is associated with improved orthostatic tolerance and O 2sat, and postural hypotension is uncommon[54,56,57]</td>
</tr>
<tr>
<td>• Extreme forced exercise in animal models of stroke appears harmful [61-63], but very early modest exercise is better than late exercise[67]</td>
</tr>
<tr>
<td>• Activity is a powerful modulator of brain reorganization[65,66]</td>
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![Figure 2: Current unknowns about very early mobilization](http://www.annalsofian.org)
An observational study of patient activity in the first 2 weeks after stroke was therefore conducted across five acute stroke units in Melbourne, Australia.[72] In this study, behavioral mapping (structured observation) was employed for 9 h (0800-1700) on two consecutive days in each of the units. From November 2001 to March 2003, 64 patients admitted within 2 weeks of stroke (mean time to observation 5.6 days) were observed at 10-min intervals throughout the active day. Fifty-eight patients (mean age 71.3 years) with mild to severe stroke completed the study. As a proportion of the therapeutically active day, patients spent over 50% of their time resting in bed, 28% sitting out of bed, and only 13% engaged in activities with the potential to prevent complications and improve recovery of mobility. Over 60% of the time the patients were alone.[72] Physiotherapists were found to be important drivers of mobility in the acute units, however they were present for only 3% of the active day, did not see all patients, and treatment generally lasted for an average of 24 min per day. Nurses were equally responsible for helping patients to mobilize and spent more time with patients.[73]

The main finding from this study was that patients in the acute phase of care were not mobilizing often and that physiotherapists and nurses helped most with out-of-bed activity. It therefore appeared feasible to add into current care an earlier start and higher dose of mobilization as part of a clinical trial, with both nurses and physiotherapists delivering the intervention [Figure 3].

For the trial, it was important to ensure that mobilization commenced within 24 h of stroke onset. This would match the protocol used within the stroke unit in Trondheim, Norway, from where so much of the published literature on this topic has emerged. Furthermore, given the concerns expressed by some authors about potential harms, careful study of the safety of the intervention was also planned. To better define the dose of intervention, behavioral mapping was also conducted within the Trondheim unit.[74,75] As expected, marked differences in physical activity patterns were found, with notably higher activity in patients with severe stroke in the Trondheim unit. Importantly, this study helped to define the dose of mobilization for the trial.

Phase II
In 2004, the multicenter phase II safety and feasibility RCT of early rehabilitation (with a focus on mobilization) vs standard stroke care commenced. A key objective in developing the trial was to ensure that all possible quality criteria were met. In A Very Early Rehabilitation Trial (AVERT), patients with either infarct or hemorrhage who were randomized to the VEM group commenced mobilization out of bed within 24 h of stroke onset. The intervention was delivered by a nurse/physiotherapist team, 6 days a week for a maximum of 14 days or until discharge (whichever was sooner). While the detail of the intervention will not be described here, the focus of the intervention was on patients being assisted to achieve both early and frequent functional out-of-bed activities. In phase II the aim was to recruit equal numbers of stroke patients with mild, moderate, and severe stroke. This was particularly important, given that a key objective of the study was to examine safety outcomes such as death, early deterioration, serious adverse events, and perceived exertion following interventions. Blinded assessment of outcome was carried out at 7 and 14 days, and at 3, 6, and 12 months.

Recruitment closed in March 2006. Seventy one patients were recruited (58% with moderate and severe stroke) and randomized, with only two patients lost to follow-up at 12 months post stroke. The primary results of this study indicated that the trial protocol was both safe (no significant differences in safety outcomes) and feasible (early start and higher dose achieved).[76]

Phase III
The phase III trial protocol is largely unchanged from phase II and is detailed elsewhere.[77,78] The aim of phase III is to determine both the efficacy and cost-effectiveness of the intervention with a planned sample size of 2104 patients to be recruited over 5 years. The
study includes patients over 18 years with confirmed stroke admitted to hospital within 24 h of onset of stroke symptoms. According to the inclusion criteria, patients must be rouseable and the physiological variables (eg, heart rate, blood pressure, O₂ saturation) must fall within broad safety limits. Patients who are moderately to severely disabled prior to stroke (modified Rankin Scale ≥ 3) are excluded. In addition, those showing rapid early deterioration of symptoms or with a concurrent diagnosis of rapidly deteriorating disease (eg, terminal cancer) are excluded, as are patients with unstable coronary disease or other hazardous medical conditions.

The study is powered to detect a 7% or greater absolute difference in death and disability (modified Rankin Scale primary outcome) at 3 months. Secondary measures include complications after stroke, quality of life, mood, Barthel index, and time to achieve unassisted walking post stroke. Phase III commenced in July 2006 at nine hospitals around Australia. Throughout 2007 the emphasis has been on recruiting new centers into the trial, with the aim of having over 30 participating hospitals from Australia and internationally. Trialists consist of nurses, physiotherapists, and doctors working in acute stroke care units. Through the conduct of a large, high-quality, multicenter RCT, the AVERT collaboration hope to contribute to the body of evidence around VEM after stroke.

Conclusion

VEM is a simple, easy-to-deliver intervention, which requires little or no equipment. It is potentially deliverable to 85% of the acute stroke population and, if proven to be effective, may reduce the significant personal and community burden associated with stroke. However, current opinion about when mobilization should start is divided, and one way to move forward is through the conduct of high-quality clinical trials (such as AVERT). Further research in this field is clearly warranted.

Acknowledgments

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Conflict of Interest: Nil