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Patient views regarding the impact of hydrotherapy on critically ill ventilated patients: A qualitative exploration study

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ABSTRACT

Background: Intensive Care Unit Acquired Weakness can be mitigated by early activity and progressive mobilization. Hydrotherapy enables patients to work on their recovery in a very early stage. This may lead to higher levels of self-efficacy, subsequently higher activity-rates and faster functional recovery. Hydrotherapy might positively affect the regaining of control, hope and trust. Our aim is to explore patient perspective regarding the impact of hydrotherapy on critically ill ventilated patients.
Methods: This qualitative exploration study adopted an interpretative phenomenological approach using in-depth, face to face, semi-structured interviews. Questions covered: pre-admission physical activity, perception of hydrotherapy, affection to water, positive and negative experiences and feelings towards the recovery process. Interviews were analyzed using thematic analysis.
Results: Twelve patients were enrolled, of which eight could be interviewed. After analyzing, five main themes were found: experiencing consequences of critical illness, feeling safe in the water, being able to move, positive experiences relating to hydrotherapy and experiencing a turning point.
Conclusions: Hydrotherapy seemed to help patients regain control and belief in their recovery. Patients experienced exercising in water as a turning point in their recovery process. This study encourages to continue providing hydrotherapy to critically ill ventilated patients and may stimulate future research.

1. Background

>5.7 million patients are admitted annually to Intensive Care Units (ICU) in the United States [1]. Each year >85.000 adults are admitted to an ICU in the Netherlands [2]. ICU patients who have been mechanically ventilated for >48 h are at risk for (long-lasting) restrictions in physical, social and psychological functioning [3,4]. These problems are caused by an interaction between inactivity, inflammation, use of pharmacologic agents and the presence of neuromuscular syndromes associated with critical illness [5]. Skeletal muscle strength declines with approximately 2% per day of absolute bed rest [6]. Muscle weakness acquired at the ICU is defined as 'Intensive Care Unit Acquired Weakness' (ICUAW) [7,8]. Muscle wasting occurs early in critical illness following complex pathogenesis [9]. Functional decline can be prevented and decreased by early activity and progressive mobilization [10]. Physical therapy has an important role in the early progressive mobilization practice for mechanically ventilated patients [11-15]. However, clear proof for efficacy is not yet established and the optimal mobilization strategy has still not been defined [13].

Hydrotherapy is a commonly used therapy modality in rehabilitation centers because the upward force of water enables patients to train functional despite muscle weakness [16]. Additionally, water

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, Acute Respiratory Distress Syndrome; BMI, Body Mass Index; CABG, Coronary Artery Bypass Grafting; COPD, Chronic Obstructive Pulmonary Disease; ELD, External Lumbar Drain; EVD, External Ventricular Drain; GOLD, Global initiative for chronic Obstructive Lung Disease; HET, High Energetic Trauma; ICU, Intensive Care Unit; ICUAW, Intensive Care Unit Acquired Weakness; MV, Mechanical Ventilation; NIV, Non-Invasive Ventilation.

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immersion is known for its relaxing and pain modulating effects [16]. Furthermore, staying in (warm) water may reduce anxiety and increases perceived well-being [17].

In 2003, Taylor was the first to describe a mechanically ventilated patient mobilized in a pool [18]. In 2012 the Radboud university medical center (Radboudumc) in Nijmegen, the Netherlands opened a pool designed especially for the early mobilization of critically ill ventilated patients. It is located close to the ICU, has a movable floor, a maximum depth of 1.35 m and a water temperature of 30 degrees Celsius. The water is continuously filtered, and the total water content is cleaned at least every two hours.

In 2015 our research group showed that hydrotherapy can safely be applied to critically ill ventilated patients and emphasized the need for studies evaluating potential clinical benefits [19]. The effects of hydrotherapy have been studied in several different populations. Marinho-Buzelli et al. showed fair evidence supporting the use of hydrotherapy for improving mobility in adults with neurological diseases [20]. Hydrotherapy in patients with stable heart failure resulted in improved exercise capacity, muscle strength and quality of life similar to land-based training protocols [21]. Research in patients with knee and hip osteoarthritis showed small effects of hydrotherapy on patient-reported pain, disability and quality of life. However these patients are very different from our target population [22].

During the application of hydrotherapy to critically ill ventilated patients it struck treating physicians and therapists that the treatment had a particularly large influence on the mental state of patients although there are no studies present to substantiate these findings. Literature shows us that experiencing 'limited possibilities to act', lack of demands, and being dependent on others are pointed out by ICU-survivors to be the biggest challenges [23,24]. Hydrotherapy enables patients to actively contribute in the recovery process starting from a very early stage. This might help the patient believe in recovery and lead to higher levels of self-efficacy. High levels of self-efficacy result in higher activity rates [25], which might contribute to faster functional recovery. In this qualitative study we aimed to explore patient views on the impact of hydrotherapy in critically ill ventilated patients.

2. Methods

2.1. Study design

This qualitative study adopted a phenomenological approach in order to explore the common meaning and lived experiences related to 'the application of hydrotherapy on critically ill ventilated patients' [26]. This approach, based on Husserl's philosophy, enabled us to investigate patients' views on the phenomenon under study [27]. The researchers recognized their knowledge and experience treating critically ill ventilated patients, which could influence their interpretation of data, therefore they worked with a framework of interpretative phenomenology [28,29].

The study protocol was approved by the ethics committee of the Radboudumc (Number 2015-1552).

2.2. Setting, participants and recruitment

A purposive convenience sample of critically ill ventilated patients was included at the ICU of the Radboudumc, Nijmegen, the Netherlands. Ventilated patients admitted to the medical, surgical, or thoracic ICU were eligible for hydrotherapy if they were severely weak (unable to walk >5 m on land) and able to respond to verbal commands. Patients were excluded from hydrotherapy if they needed high ventilator support (fractional inspired oxygen > 0.6; positive end expiratory pressure > 10 cm H2O; inspiratory support > 15 cm H2O), were given vasopressive medication, had large wounds, displayed severe agitation or in case of colonization with multi-resistant bacteria. According to the Radboudumc hydrotherapy checklist the hydrotherapy sessions were prepared and subsequently performed (see Supplement 1).

To be eligible to participate in this study, patients had to partake in hydrotherapy at least once while being mechanically ventilated. Furthermore, they had to be able to communicate in Dutch. From January 2015 to April 2015 the list of patients who took part in hydrotherapy was screened weekly by the coordinating nurse (TH) and researcher (KF) to designate subjects eligible for participation in this study. The goal was to have a diverse sample consisting of patients with diversity in reason for admission, length of stay, gender, age and enthusiasm towards hydrotherapy. The researcher (RO) contacted all patients meeting the inclusion criteria and asked for permission to visit them (at home). This visit was planned 6 to 12 weeks after hospital discharge. Informed consent was signed prior to the interview.

2.3. Data collection

In semi-structured interviews with a maximal duration of 45 min, patients were asked about their experiences regarding hydrotherapy. The interview guide is displayed in Table 1. Core questions covered the following areas: pre-admission physical activity, pre-admission experiences with water/swimming, perception of hydrotherapy, positive and negative experiences related to hydrotherapy and feelings towards the recovery process. The interviewers (RO and KF) are experienced physical therapists who specialize in the field of intensive care medicine. Bracketing was trained during three test-interviews in order to ensure transcendental subjectivity [30].

Interviews were recorded on tape and transcribed verbatim. Only one interviewer was present during the interviews, patients were allowed to be accompanied by a close relative. There were no previous interactions between interviewer and respondent, except for the invitational phone call.

2.4. Data analysis

Data were open coded, axially coded, selectively coded and then thematized using an inductive approach [31]. To ensure trustworthiness and credibility two researchers (RO and KF) independently analyzed the data. In a consensus meeting, disagreements in coding and thematizing were discussed [32]. An independent researcher (RN) inspected the preliminary results for the effectuation of peer examination [33]. Analysis was performed using ATLAS.ti (Scientific Software Development

Table 1
Interview guide.

Question number	Question
1	How are you doing (nowadays)?
2	How have things been going since your hospital dismissal?
3	How do you spend your days now?
4	What do you think of your recovery since your hospital dismissal?
5	What do you remember of your ICU stay?
6	What kind of exercises did you perform during your hospital stay?
7	During your hospital stay you went into the water, can you tell about your experiences?
8	How did you feel about going into the water?
9	How did the caregivers initiate the practicing in water? How did you react?
10	What did you think of the practicing in water?
11	How was the communication with the therapists during the hydrotherapy?
12	What was the most important additional value of the hydrotherapy?
13	Was it nice to be away from the room and be washed? Is that why you enjoyed the hydrotherapy so much?
14	If you look back, would you choose to go into the water again?
15	Would you recommend the hydrotherapy to other patients?
16	Are you normally someone who likes to be in water?
17	In what way were you physically active before hospital admittance?

GmbH. Version 7, 2012). The results will be presented using direct quotes to provide for rich description of the themes.

3. Results

3.1. Patient characteristics

Table 2 shows the patient characteristics. Between January and April 2015 a total of 11 patients had an indication for hydrotherapy and fulfilled the study inclusion criteria. Of these 11 patients seven could be interviewed (see Fig. 1). These seven patients were all positive about hydrotherapy. Only after one year a patient could be included who expressed negative feelings towards hydrotherapy (patient no. 12). For detailed patient descriptions see Supplement 2.

3.2. Patient experiences

Five main themes were found to be important in the recovery process. Table 3 shows the main themes and related quotes.

3.2.1. Experiencing the consequences of critical illness

Experiencing the consequences of critical illness has a big impact on patients. They experience weakness in their arms and legs and realize the severity of their disease. For many activities in daily life they are dependent on their caregivers. Moreover, inability to communicate with people can be very frustrating. Muscle weakness can impair the possibilities to communicate with a letter board or by writing.

3.2.2. Feeling safe in the water

Some people display great enthusiasm when hydrotherapy is suggested. Most of them are experienced swimmers or relate swimming to holidays and happy memories. Others are scared by the idea of going into the water, especially when muscle strength is minimal. The strict protocol, presence of skilled staff and a high-tech swimming environment provide confidence. Patients lose their fear very quickly as they experience the warm water and the relaxation that comes with it. They trust the accompanying staff and follow their instructions.

3.2.3. Being able to move

In the water some people feel a certain kind of pressure on their body, which makes the body feel light. Other patients experience relaxation and pleasant sensations. Patients are able to move their arms and legs and in some cases they are able to stand and/or walk. When patients are able to move by themselves in the water, they experience they can actively contribute to their recovery.

3.2.4. Positive experiences relating to hydrotherapy

Patients often have no recollections of their stay in the ICU. Therefore, it was remarkable how many people had good memories relating to the hydrotherapy. Some people were looking forward to their next session and were disappointed when a session was cancelled. One patient said: "*when I was in hospital I went in the water twice a week. In the rehabilitation center they won't train me in the water for fear of my tracheal cannula. I really miss it*." Another patient said: "*Normally I never contribute to research projects, but in this case, I make an exception because the hydrotherapy was very important to me, and I want other patients to be able to get the same treatment*." People are positive about the skilled staff who care about them and the professional organization around the hydrotherapy sessions. The possibility for family to be present during the hydrotherapy sessions, and in some cases join the patient in the water, was also much appreciated. In several cases telling about the hydrotherapy affected patients so much, they got emotional.

3.2.5. Experiencing a turning point

Many patients experienced exercising in the water as an important turning point in their recovery process. During the sessions they regained confidence in their body and dared to look forward. One patient said: "*The nurses and doctors told me I would recover, but I did not believe them. Whenever I exercised in the water I felt that recovery was*

Table 2
Patient characteristics.

Patient no.	Gender	Age	BMI	APACHE II –score	Reason for ICU-admission	ICU length of stay (in days)	MV duration (in days)	Hospital length of stay (in days)	Number of HT-sessions	Interview
1[a]	M	80	30	19	Coronary artery bypass grafting	42	42	75	8	−
2	M	70	28	24	Ventricular septal defect repair	29	29	44	2	+
3	F	44	30	17	Respiratory failure in alveolar lung pattern	20	20	49	3	+
4[a]	M	75	17	18	Complicated esophageal resection with gastric tube reconstruction	22	22	22	4	−
5	M	72	29	24	Surgery for Gastrointestinal rupture	38	38	49	3	+
6	F	33	23	9	Exacerbation asthma	40	36	56	3	+
7	F	49	30	28	Pneumonia in a patient with COPD GOLD 4	22	22	28	1	+
8	M	63	28	16	Chest/extremity trauma, surgery for HET with external fixation lower leg	33	32	74	11	+
9[a]	M	69	20	21	Out of hospital cardiac arrest, complicated with ARDS and lung fibrosis	85	69	85	9	−
10	F	70	22	28	Stem cell transplant in non-Hodgkin Lymphoma Complicated with pneumonia	39	32	34	3	−
11	M	65	25	26	Respiratory failure after cardiac surgery	53	29	72	8	+
12	F	73	25	#	Chest/extremity trauma, surgery for HET. Recovery complicated with ARDS, delirium, and severe ICUAW	98	17	119	8	+
Totals Mean (SD)	7 males 5 females	64 (14)	26 (4)	21 (6)	3 Cardiac surgery 3 Pulmonary disease 2 High energetic trauma 2 Gastro-intestinal surgery 1 Out of hospital cardiac arrest 1 Complicated stem cell transplant	38 (29)	27 (18)	59 (27)	5 (3)	8 + 4 -

BMI = Body Mass Index; APACHE = Acute Physiology and Chronic Health Evaluation; ICU=Intensive Care Unit; MV = Mechanical Ventilation; HT = hydrotherapy; M = Male; F=Female; − = not interviewed; + = interviewed; COPD = Chronic Obstructive Pulmonary Disease; GOLD = Global initiative for chronic Obstructive Lung Disease; HET = High Energetic Trauma ARDS = Acute Respiratory Distress Syndrome; ICUAW = Intensive Care Unit Acquired Weakness; # = missing.

[a] Patient died during hospital-stay.

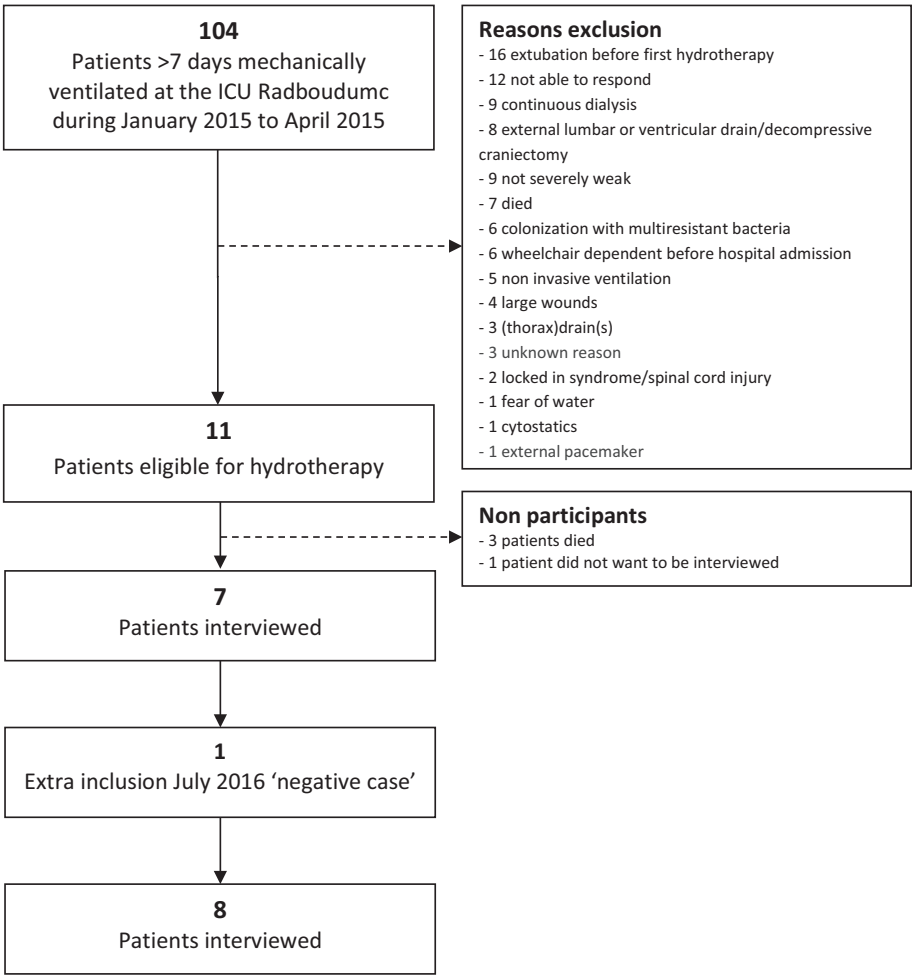

Fig. 1. is provided as a separated Microsoft Word file.

possible." Several patients pointed out that water exercising gave them a mental boost.

4. Discussion

In this small-scale interview study, we explored patient views regarding the impact of hydrotherapy on critically ill ventilated patients. Patients were remarkably positive about exercising in water and thought it to be of great value in the physical and mental recovery from critical illness. Hydrotherapy seemed to help patients regaining control and belief in their recovery. Patients experienced exercising in water as a turning point in their recovery process.

The hydrotherapy treatment was perceived to have strong influence on the recovery process, even by patients who exercised in the water only once. From a physiological perspective it is unlikely that one hydrotherapy session has an actual training effect. However, hydrotherapy treatment enables patients to discover their strength and actively contribute in functional training. It focuses on a person's strength rather than weakness. This could stimulate the individual self-efficacy. This is a major advantage compared to land-based exercise where the patient will continually face his inabilities. This approach fits with the new definition of health according to Huber et al. [34] They define health as "the ability to adapt and self-manage in the face of social, physical, and emotional challenges" [34]. It emphasizes that a person is more than his/her illness and still has potential for being healthy. Self-efficacy has been known for a long time as a strong predictor for activity levels and recovery [35,36]. The present study also indicates that self-efficacy, mood and belief in recovery are important factors during recovery from critical illness.

Earlier results from our research group stating that hydrotherapy is feasible and safe on critically ill ventilated patients [19], were confirmed in this study when viewed from a patients' perspective. Safety concerns seemed to be no issue for patients once they were in the water. Furthermore, in this study hydrotherapy was proven feasible in a diverse case mix. The case with an external fixation of the lower leg showed that open wounds are no contra-indication for hydrotherapy as long as wounds can be properly sealed. Based on our earlier study[19] and the results of Wegner et al. [37], these pools are even safe for critically vulnerable patients. This was confirmed in this study by a patient who underwent stem-cell transplantation. These patients have a higher infection-risk. Their treating physicians trusted the quality of the water to be sufficient and permitted this vulnerable patient to partake in hydrotherapy. No negative effects were seen afterwards. These findings implicate that the current safety-criteria may be adequate. As our group reported earlier, biochemical and microbiological analysis of pool water were performed to meet Dutch law standard criteria at any time [19].

Results from qualitative studies are assumed more valid when a deviant case is included [38]. After the inclusion period it was evaluated within the team, whether a patient had negative feelings towards hydrotherapy. Such a patient was admitted in July 2016. This person (patient no. 12) went into the water eight times. Especially the last couple of sessions were a negative experience because she found the hydrotherapy exhausting and the preparations and precautions overdone. During the interview she stated that she would have preferred to stop

Table 3
Themes exemplifying patient experiences.

Theme	Quotes
Experiencing the consequences of critical illness	"I was laying there and I couldn't lift my arm. I could not even operate the television remote. (…) A board with letters on it was given to me, but I couldn't even point at the board. That was so weird, I never realized laying in bed and being held in a coma would make you this weak." (Patient no. 6) "There was so much going on around me. I was having renal dialysis. I was carrying 40 l of fluid in me, I felt like an inflatable doll. (Patient no. 11) "Only when the cannula was in the right place I could talk, otherwise I couldn't. You see, when they slid the cannula up I couldn't say anything. That was incredibly annoying. But, well it was probably necessary. At one point, I thought I was choking, so I pulled the cannula out so I was able to get some air, but then they immediately put it in place. What I also remember is that they tied up my hands for some time, apparently I was too much trouble." (Patient no. 5) "Your body has failed you, that is how you feel at that point." (Patient no. 7)
Feeling safe in the water	"The first time I was afraid, because I was not capable of doing anything. I've never been a good swimmer, so I was frightened at the beginning. But when we started the fear was gone within a couple of minutes." (Patient no. 8) "They brought everything. If something happened to me, they could immediately give me oxygen or start mechanical ventilation etcetera, but fortunately that was not necessary. There were always nurses and physical therapists nearby." (Patient no. 11) "My wife also went into the water. And the therapist. That really gave me a safe feeling." (Patient no. 8) "The warm water, the swimming in it (…) it was a kind of relaxation. It was lovely and joyful." (Patient no. 3) "I had a lot of trust that it would go well. I know I'm a good swimmer. Despite the fact that you've no strength at all, you don't realize that. You think like: if I'm in the water I can just swim away." (Patient no. 5)
Being able to move	"I remember at first that I couldn't lift my arms. Swimming is just so nice, after that I was just capable of doing a lot more. I really felt the difference." (Patient no. 6) "I was so weak and unable to stand upright, and in the pool that was not the case at all, I was able to stand and walk." (Patient no. 7) "In the beginning I was unable to move at all and I was thinking and worrying all the time. When you're in the water all those thoughts are gone, it all goes so smooth and easy. It goes by itself. It's all so very light, whatever you do, and that's wonderful." (Patient no. 8) "In the water you can do so much more. Muscles are incredibly more relaxed. You can move in ways you would never be able to do on land." (Patient no. 11) "That pool just made miracles happen. After swimming I could raise my arm and turn my head. Just all these normal things." (Patient no. 6)
Positive experiences relating to hydrotherapy	"For me it was of great value, even though I went in the water only once." (Patient no. 7) "Thought the experience in the water was fantastic." (Patient no. 2) "I would do it every day. It really makes you fresh, and the freshness was missing a lot of times. I really made a mess with food and stuff." (Patient no. 5) "In the Radboudumc I went in the water twice a week. Later on even three times a week. I was really looking forward to the swimming sessions." (Patient no. 8) "I think we should go swimming every day." (Patient no. 6)
Experiencing a turning point	"I just had the feeling that I could not walk anymore, not move anymore. Then in the swimming pool they put you on your feet and then you start walking through the pool. Then I thought: if I can walk here, I can do it outside of the pool as well later on." (Patient no. 7) "It was good for body and soul. The swimming really gave me a boost." (Patient no. 6) "I would really recommend to start walking again in the water. It gives you a boost, like: hey I can walk again. The strength is actually there, that's what you experience at that point." (Patient no. 2) "After the swimming session(s) my recovery took a leap forward. That was truly amazing. Everybody was amazed. Yes, then it went really fast." (Patient no. 2) "It did so much for me, I can't tell you how much. It gave me back my confidence, that I could indeed recover the way I wanted. I cried in that pool. It was just fantastic. Yes, for me it was a real turning point." (Patient no. 7)

the hydrotherapy treatment earlier. Our treatment protocol for hydrotherapy demands caregivers to extensively inform patients and relatives about the intended hydrotherapy. Patients are specifically asked whether they want to undergo hydrotherapy treatment or not. However, based on these results we will evaluate patient experiences with hydrotherapy more often, in order to check whether the patient really wants to continue.

Three of the patients included in this study died. These patients all showed prolonged ICU stay, weaning failure, and there was no hope for recovery. Treatment was terminated, resulting in their deaths. These three patients underwent a relatively large amount of hydrotherapy sessions, however hydrotherapy treatment stopped at least seven days before they died. The patients who died could not be interviewed, though it would have been of interest because we know at least one of these patients had negative feelings towards hydrotherapy. It could have been of additive value to have a second divergent case included whereas the majority of the patients was positive about hydrotherapy.

Not only patients suffer from their stay at ICU, the people around them suffer as well. Several studies have reported the importance of providing care to relatives and family of ICU patients [39,40]. In 2007 Davidson et al. published a practice guideline for support of the family in the patient-centered ICU, recommending a flexible and open policy regarding the visits of family and loved ones [39]. In our hospital family is invited to be present during hydrotherapy sessions and, if possible, to join the patient in the water. In this study, family members participated in the water in one third of the cases. Corresponding to the cited literature, this study shows that family and relatives highly appreciated the possibility to participate during hydrotherapy.

Currently, patients can only go for hydrotherapy when admitted to the ICU and being unable to walk more than five meters on land. Patients reported it to be disappointing that hydrotherapy could not be continued in other departments or other healthcare facilities. It is understandable patients want to continue hydrotherapy treatment, certainly when experience an improvement in their recovery. However, the Radboudumc is the only facility providing hydrotherapy to this population and the capacity of the pool is limited to a maximum of five treatments a day. In this context it is very important to manage patient expectations from an early stage, to be able to prevent disappointments. In the ideal situation hydrotherapy is continued on the ward and in other facilities until the patient is able to train on land. Future studies should evaluate cost-effectiveness of hydrotherapy, because it is a time-consuming and labor-intensive therapy demanding a high-tech pool with high structural costs. With more insight in the costs and

effects of hydrotherapy, other institutions can determine whether it is eligible and profitable to build their own pool for this population.

Limitations of this study include the lack of triangulation. The use of other methods than taped interviews, for example participant observations or taking field notes, could have enriched the data [33]. In addition, we have not included quantitative functional outcome measures in this study although this could have provided more insight in our sample. We could not include this data because the outcomes were not sufficiently reported in the patient files. Furthermore, patients' memories and cognition were not investigated prior to the interview. During the interviews, several patients declared they had limited memory of their stay in ICU, which might have caused recall bias. Furthermore, we cannot rule out patients might have felt pressured by the one on one interviews. Therefore, they might have given socially desirable answers, despite informed consent procedure and the emphasis on transparency.

Findings from this study encourage to continue providing hydrotherapy to critically ill ventilated patients. We gained insight in patients' views and experiences regarding hydrotherapy. These results can be used to design quantitative research. In order to obtain more thorough understanding of treatment effects and determinants of recovery, we recommend including measurements of self-efficacy, belief in recovery, mood and depression. When there is more clarity on the effects of hydrotherapy in this population it might be easier to select the patients who are more likely to benefit from hydrotherapy treatment. To investigate the effect of hydrotherapy a controlled intervention study should be designed. Since the ICU population is heterogeneous and they receive multiple interventions at the same time it might be complicated to perform a randomized controlled trial. To predict recovery in critically ill ventilated patients, we recommend a cohort design using repeated measurements to compare patient recovery curves and show the influence hydrotherapy has on the recovery process.

5. Conclusions

This study gives insight in the views and experiences of eight critically ill ventilated patients who went for hydrotherapy. Hydrotherapy seems to help patients regain control and belief in their recovery. Patients experienced exercising in water as a turning point in their recovery process. Results from this study are an encouragement to continue providing hydrotherapy to critically ill ventilated patients and can be used in designing evaluative research.

Ethics approval and consent to participate

The study protocol was assessed by the ethics committee of the Radboudumc (Number 2015–1552).

The Medical Research Involving Human Subjects Act (WMO) does not apply to the present study and an official approval by the committee was not required.

Consent for publication

All interviewed patients signed informed consent for publication. The original signed consent forms are retained by the corresponding author.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KF and RO designed the study. TH and KF screened and included the patients. RO approached the included patients. KF and RO interviewed the patients. KF, RO and RN analyzed the data. KF and RO wrote the paper with input from all authors. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

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