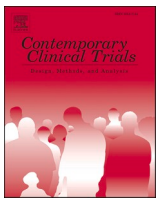
Contemporary Clinical Trials 138 (2024) 107463

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial



Improving adherence to rehabilitation for heart failure patients through immersive virtual reality (VIRTUAL-HF): A protocol for a randomized controlled trial

Valentina Micheluzzi [a,b,*], Gavino Casu [a,c], Giuseppe Damiano Sanna [a], Antonella Canu [a], Paolo Iovino [d], Gabriele Caggianelli [e], Ercole Vellone [b,f]

[a] Clinical and Interventional Cardiology, Sassari University Hospital, Sassari, Italy
[b] Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[c] Department of Medicine, and Pharmacy, University of Sassari, Sassari, Italy
[d] Health Sciences Department, University of Florence, Florence, Italy
[e] San Giovanni Addolorata Hospital, Rome, Italy
[f] Department of Nursing and Obstetrics, Wroclaw Medical University, Wroclaw, Poland

ARTICLE INFO

Keywords:
Heart failure
Cardiac rehabilitation
Virtual reality
Treatment adherence and compliance
Randomized controlled trial

ABSTRACT

Background: To improve symptoms and reduce poor outcomes related to heart failure (HF), international guidelines recommend cardiac rehabilitation (CR), particularly for those with a reduced ejection fraction. Unfortunately, patient adherence to rehabilitation programs remains suboptimal, with dropouts ranging from 15.4 to 63.3%. An innovative and promising intervention that could improve adherence to rehabilitation is virtual reality (VR). This study aims to evaluate the effects of VR in patients with HF who undergo CR using this technology in terms of adherence (primary outcome), functional capacity, perceived exertion, angina, quality of life, heart rate, oxygen saturation, blood pressure, maximum oxygen uptake, minute ventilation/carbon dioxide production slope, oxygen pulse, blood values of NT-proBNP and HF related rehospitalization rates (secondary outcomes).

Methods: A randomized controlled trial will be conducted in a sample of 80 patients referred to CR. Participants will be enrolled in a cardiological rehabilitation unit of a large university hospital in Italy and randomized (1:1) to the experimental intervention consisting of CR performed with high-quality immersive VR with PICO 4® Head Mounted Display headset and TREADMILL XR® software (Arm 1) or standard CR (Arm 2). Patients, according to guidelines, will perform 30-min of CR sessions with moderate intensity, twice a week for one month.

Results: Significant improvements in primary and secondary outcomes are expected in patients in the intervention group.

Conclusions: If proven to be effective, VR could be an innovative, safe, and easy digital health intervention to improve adherence to CR in patients with HF, as well as important clinical outcomes.

1. Introduction

Heart failure (HF) has been defined as a global pandemic, with 64 million people estimated to suffer worldwide [1]. The prevalence of HF in the general population in Europe and the United States ranges between 1% and 2%, with a higher prevalence in older adults [1]. Despite notable advancements in therapies, high hospitalization rates, morbidity, and mortality persist among HF patients, contributing to increased societal and healthcare system costs estimated at around $108 billion globally [2].

Patients with HF suffer from a plurality of physical and psychological symptoms, such as fatigue, anxiety, and depression, which can contribute to poor quality of life [3]. To improve HF-related outcomes, international guidelines recommend cardiac rehabilitation (CR) [4], a cornerstone of disease treatment, especially for those with a reduced ejection fraction [1]. CR is a multidisciplinary approach focused on reduction of symptoms, attenuated physiological responses to physical challenges, and improved psychosocial well-being through intervention

* Corresponding author at: Department of Biomedicine and Prevention, University of Rome Tor Vergata, Via Montpellier, 1-00133 Rome, Italy.
E-mail address: valentina.micheluzzi@gmail.com (V. Micheluzzi).

https://doi.org/10.1016/j.cct.2024.107463
Received 4 November 2023; Received in revised form 2 January 2024; Accepted 24 January 2024
Available online 30 January 2024

whose core is the supervised exercise training [3]. In fact, according to literature, CR programs for HF patients improve tolerance, exercise capacity, quality of life [5] and reduce rehospitalizations [6].

Although CR is crucial to improve outcomes in patients with HF, adherence to CR programs remains suboptimal [7]. A recent systematic review has shown a high dropout of CR in patients with HF ranging from 15.4 to 63.3% [7]. Multiple risk factors have been identified to increase dropout of CR including intrapersonal factors such as older age, female gender, lower education; clinical factors such as high body mass index, smoke, poor functional capacity; social factors such as being single, unemployed or retired, and organizational factors such as excessive distance from the rehabilitation center and lack of referrals from healthcare personnel. For these reasons, researchers are still looking for interventions to improve CR adherence in patients with HF [7].

An innovative and promising intervention that could improve adherence to CR in patients with HF is virtual reality (VR) [8]. VR can be divided into three distinct categories: non immersive, semi-immersive, and immersive. Non-immersive VR uses a screen that produces two-dimensional (2D) images, audio output, and joysticks for interaction, while semi-immersive VR also includes body sensors [8]. Both non-immersive and semi-immersive VR can be distracting for people due to potential environmental perturbations [9]. Immersive VR, on the other hand, offers high-quality three-dimensional (3D) images, delivered through an audiovisual head-mounted headset and controllers that allow full interaction with the virtual world [10].

1.1. Background

VR has been used in cardiovascular patients before, during, and after cardiac procedures such as coronary angiography, transcatheter aortic valve implantation, and atrial fibrillation ablations, showing positive effects in reducing anxiety and pain, as well as improving systolic blood pressure, respiratory rate, and heart rate [11–14]. VR has also been used prior to cardiac surgery procedures, resulting in reduced anxiety and improved procedural understanding through educational virtual content [15,16].

In the field of CR VR has been used in several studies to improve adherence and different systematic reviews and meta-analyses have also been conducted to understand its effectiveness [17–20]. Doumas et al. (2021) conducted a systematic review and meta-analysis of 42 RCTs (in total 1760 patients) on the effectiveness of immersive VR in improving upper limb rehabilitation adherence in post-stroke patients [20]. These authors found that VR was effective in improving rehabilitation adherence with a large effect size compared to conventional treatment.

In another systematic review, including five RCTs (147 patients in total), Meijer et al. (2018) examined the effectiveness of semi-immersive VR to improve rehabilitation adherence in patients with traumatic bone and soft tissue injuries. Adherence to CR appears to improve in the VR group but the poor number and high heterogeneity of the included trials led to inconclusive results [17].

In the narrative review by Alfieri et al. (2022), which included 17 studies conducted in patients with musculoskeletal diseases, semi-immersive VR was shown to improve motivation and adherence to exercise treatment compared to traditional rehabilitation [19]. Pacheco et al. (2020) conducted a systematic review and meta-analysis of 12 trials (1520 patients in total) on the effect of semi-immersive VR to improve mobility and balance in older adults, and found that this type of VR was effective on the variables considered and improved adherence to rehabilitation from 80% to 100% [18].

Although VR appears to be effective in improving adherence to rehabilitation, so far, we do not have evidence that VR also improves adherence in CR of patients with HF. Furthermore, immersive VR, which is characterized by a greater perceptive experience, appears to stimulate greater motivation to rehabilitation and consequently greater adherence [21] but we still do not have evidence in this regard. Therefore, the purpose of this trial will be to assess the effectiveness of immersive VR in improving adherence as well as improving other outcomes that, according with literature, are influenced from CR such as functional capacity, perceived exertion, angina, quality of life, heart rate, oxygen saturation, blood pressure, maximum oxygen uptake, minute ventilation/carbon dioxide production slope, oxygen pulse, blood values of NT-proBNP and HF related rehospitalization rates [5,22,23].

1.2. Conceptual framework

The design of the present study was guided by a conceptual framework, developed from the VREHAB framework by Campelo et al. (2017) [24], a more general theoretical framework in the field of rehabilitation in elderly patients. Our conceptual framework postulates a multisensory mechanism of action of immersive VR in patients with HF who undergo CR programs. According to our conceptual framework summarized in Fig. 1, visual, auditory, and tactile signals generated from the VR hardware and software system reach the brain [25] and simultaneously activate distraction, immersion, and presence [26]. Distraction occurs because the multisensory signals are processed as real in the brain, thus rapidly shifting the focus of attention from real to virtual environment [27].

Immersion generates cognitive, emotional, and perceptive processes similar to the real world [27]. Presence is activated because the person using VR really feels and interacts with the virtual space-time environment and detaches from the rehabilitation context which could be uncomfortable [27]. Distraction, immersion, and presence influence biological systems through the central nervous system, which sends signals to the physical system [24]. In this way, virtual contents produce greater motivation for the patient [28,29]. Consequently, enhancing motivation through VR during rehabilitation could represent a highly promising intervention for enhancing adherence and consequently, improving clinical outcomes influenced by CR [30].

1.3. Research hypotheses

Based on the available literature and the conceptual framework used in this study, we formulate the following hypotheses.

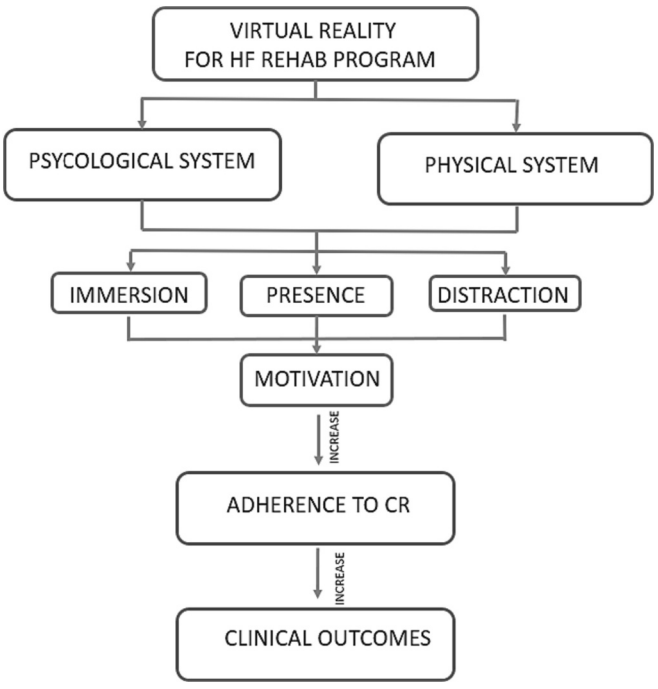


Fig. 1. Framework guiding the study.
VR = virtual reality; HF = heart failure; CR = Cardiac rehabilitation.

1. Patients with HF enrolled in a CR program with VR will show improved adherence to the scheduled sessions (primary endpoint) compared to those enrolled in a standard CR program
2. Patients with HF enrolled in a CR program with VR will exhibit better outcomes influenced by CR such as functional capacity, perceived exertion, angina, quality of life, heart rate, oxygen saturation, blood pressure, maximum oxygen uptake, minute ventilation/carbon dioxide production slope, oxygen pulse, blood values of NT-proBNP and HF related rehospitalization rates (secondary endpoints) than those enrolled in a standard CR program.

2. Methods

VIRTUAL-HF is a single-center, parallel randomized controlled trial of patients attending a CR program in a large university hospital in Italy. The VIRTUAL-HF protocol is registered on ClinicalTrials.gov (identifier: NCT06115928) and was written according to the SPIRIT 2013 guidelines [31].

2.1. Eligibility Criteria

The target population will be outpatients with HF who undergo CR programs and who provide their signed consent to participate in this study. HF is a clinical syndrome characterized by significant heterogeneity in phenotypic profiles [1,32]. For instance, patients with HFrEF are more frequently male, younger, and affected with ischemic heart disease, whereas patients with heart failure and preserved ejection fraction (HFpEF) tend to be older and more often female [1,32]. In HFpEF patients, atrial fibrillation, obesity, chronic kidney disease, orthopedic disorders, and non-cardiovascular comorbidities are more common due to their older age compared to those with HFrEF. Furthermore, we are aware of significant differences in medical treatments between these two groups [33]. Therefore, considering the sample size of our study ($n = 80$ [40 + 40]), in order to reduce heterogeneity, we decided to test our hypothesis in the HFrEF group. For these reasons participants will have to meet the following criteria: i) age over 18 years; ii) a clinically stable chronic HF diagnosis and iii) left ventricular ejection fraction (LVEF) $< 40\%$. Exclusion criteria will be: i) conditions that exclude exercise training (e.g., bone fractures); ii) conditions that exclude VR use of VR (e.g., blindness and deafness); iii) severe cognitive impairment, documented with a score of 0–4 on the Six-item Screener [34,35] iv) end-stage renal disease requiring dialysis; v) ascertained advanced pneumopathies; vi) active neoplasms and vii) rheumatic diseases.

2.2. Intervention

According to guidelines, the intervention of this trial will consist, of a total of eight 30-min CR sessions on the treadmill, supervised by healthcare personnel, twice a week for four weeks [3]. The exercise intensity will be moderate, ranging from 12/20–14/20 on the Borg scale [3,36]. During these sessions, participants will perform CR with a VR headset with hardware-type technology consisting of a PICO 4® head mounted display (HMD) headset and the software TREADMILL XR®. We will use the latest generation of high-quality immersive VR technology equipment, with built-in high computing power, self-contained, with sophisticated software and excellent optical components, producing low latency, a large field of view, and greatly improving the VR experience. Based on these characteristics, the PICO 4® head-mounted display was chosen. This equipment will allow participants to observe specific natural environments, characterized by multimedia content in 4 K+ by video definition and 360° spherical video. To increase the immersive experience, it is also important to stimulate the auditory sensory modality [27]. The audio content of the app will provide natural sounds as a background, which will be heard directly through the viewer in high-definition stereo mode to ensure an immersive audiovisual experience. TREADMILL XR® app was chosen for its natural content because engaging with such environments has been shown to create a highly effective distraction, leading to a significant redirection of attention [37]. VR will be administered throughout the 30-min CR session with the help of a qualified healthcare professional. Participants will be able to move their eyes and head freely, adjust the volume to their preferred level, and stop the VR session at any time for any reason. Ten minutes before the first session begins, a VR trained healthcare professional will provide instruction and demonstrations on using the technology. They will ensure the patient is well-versed and proficient in handling the virtual equipment. Moreover, they will offer continuous support to the patient throughout and after each session, by promptly resolving any arising issues. Furthermore, for safety reasons, the healthcare professional through a tablet will view and potentially stop the patient's virtual reality contents, as well as halt the treadmill.

2.3. Control group

The control group will perform CR on a treadmill, supervised by healthcare professionals, following the same guidelines [3] as the intervention group in terms of number of sessions, duration, and intensity, but without the use of VR.

2.4. Baseline and follow-up assessments

Participants considered eligible for this study will be evaluated at baseline (T0) for sociodemographic and clinical characteristics (e.g., age, sex, comorbidity, distance to reach the rehabilitation center, pharmacological therapy) and for primary and secondary outcomes. Data at T1 will be collected after the last of the eight scheduled CR session; data at T2 will be collected during a specific follow-up, one month after the end of the CR program at the rehabilitation center. At T2, we will assess patient satisfaction with rehabilitation using the visual analog scale (VAS), rating from 0 (indicating 'no satisfaction') to 10 ('full satisfaction'). The selection of VAS is due to its simplicity, clarity, and intuitive nature, enabling participants to express satisfaction levels rapidly [38].

Technology exposure can cause adverse effects like cybersickness, a form of visually induced motion sickness in virtual environments, leading to symptoms such as nausea, dizziness, fatigue, and oculomotor disorders [39]. Despite its reported rarity in patients in existing literature, we will evaluate this potential issue at the end of every session in the intervention group utilizing the Virtual Reality Symptom Questionnaire [39]. Moreover, we plan to include this potential confounding in each statistical model, pending assessment of its prevalence.

2.5. Primary outcome

The primary outcome will be adherence to CR measured as the number of sessions performed, compared to the scheduled sessions expressed as a percentage. This endpoint will be measured at T1.

2.6. Secondary outcomes

Functional capacity will be measured at T0, T1 and T2 with the 6-min walk test (6MWT), which is a valid and reliable test to monitor the course of mild to moderate chronic HF disease and to assess the efficacy of the intervention considering its prognostic value. The patients will be instructed to walk at their own pace for 6 min while trying to cover the greatest distance possible on a flat and hard surface. The distance traveled in meters corresponds to the test value. A 6MWT $<$ 300 m is associated with a higher 1-year mortality, while a 6MWD $<$ 468 m is associated with an increased hospitalization rate [40].

Perceived exertion will be measured at T0, T1 and T2 using the Borg scale which captures physical activity intensity levels related to heart rate during exercise [36]. The rate is multiplied by 10 to determine the

ideal heart rate during aerobic exercise. The Borg scale score ranges from 6 to 20 corresponding to "no effort" and "maximum effort", respectively, equating a minimum of 20% to a max of 100% effort. The Borg scale has been shown to be valid and reliable with an intraclass correlation coefficient of 0.88 [41].

Angina will be measured at T0, T1 and T2 with the Canadian Cardiovascular Society classification of angina pectoris (CCS) [42]. The CCS classification system employs four grades ranging from I (no physical activity limitation) to IV (inability to perform any physical activity without discomfort). This scale demonstrated satisfactory consistency and diagnostic precision for the evaluation of angina in populations with HF [43].

Quality of life will be measured at T0, T1 and T2 with the Kansas City Cardiomyopathy Questionnaire (KCCQ) [44], which consists of 23 items to assess physical function, symptoms, social function, self-efficacy and quality of life of HF. KCCQ scores range from 0 to 100 and the scores represent health status as follows: from 0 to 24, very poor to poor; 25 to 49, poor to fair; 50 to 74, fair to good; and 75 to 100, good to excellent. The internal consistency reliability (Cronbach's alpha) of KCCQ dimensions ranges between 0.63 and 0.92 [45].

Heart rate, oxygen saturation, and blood pressure will be measured at T0, T1 and T2 through a digital monitor. Maximal oxygen uptake (VO2max), minute ventilation/carbon dioxide production slope (Ve/VCO2) and oxygen pulse will be measured at T0 and T2 with the cardiopulmonary exercise test (CPET) and NT-proBNP values at T0 and T2 with blood samples. Rehospitalization related to HF will be measured with the frequency of rehospitalization from the beginning of rehabilitation at T2. In Table 1, all outcomes, the instruments used, and the measurement timings are summarized.

2.7. Recruitment and consent

Participants will be recruited during regular outpatient clinic visits. Eligible patients will receive a detailed and written explanation of the study procedures and objectives. Written informed consent will be obtained prior to enrollment in the study by trained research assistants. To ensure sufficient enrollment, the study will be advertised to all patients referred to CR.

Table 1
Outcomes, instruments and timings of measurement.

Activity/Assessment	Instruments	T0 Baseline	T1 Eighth session end of the CR program	T2 One month after the end of the CR program
Adherence to CR program	Case Report Form		X	
Functional capacity	6MWT	X	X	X
Perceived exertion	Borg Scale	X	X	X
Angina	CCS grading of angina	X	X	X
Quality of life	KCCQ	X	X	X
Heart rate	Digital monitor	X (min and max)	X (min and max)	X (min and max)
Oxygen saturation	Digital monitor	X	X	X
Blood pressure	Digital monitor	X	X	X
Maximal oxygen uptake	CPET	X		X
Minute ventilation/carbon dioxide production slope	CPET	X		X
Oxygen pulse	CPET	X		X
NT- proBNP	Biochemical analysis	X		X
HF-related rehospitalization	Case Report Form			X

CCS = Canadian Cardiovascular Society; KCCQ = Kansas City Cardiomyopathy Questionnaire; 6MWT = 6-min walk test.

2.8. Randomization and allocation concealment

The allocation sequence, randomized with allocation 1:1, will be generated with random numbers by an online software (www.randomizer.org/), with a simple randomization approach, where number 1 is the code for the intervention group and number 2 is the code for the control group. The mechanism for implementing the allocation sequence will be performed by sequentially numbered, opaque, and sealed envelopes. Numbers 1 and 2 will be entered into envelopes, which will be opened by the research assistant in front of the patients. The allocation sequence will be generated by an independent statistician, blinded to the study coordinator.

2.9. Blinding

Participants' assignments to the randomization groups will be blinded to the study coordinator and data analyst. The research assistants who will conduct the measurements in both groups will also be blinded, as the patients will be instructed not to disclose their group assignment. The healthcare professional supervising the patients during the CR cannot be blinded, but will not be involved in data collection. Due to the nature of the intervention, blinding of the patients is not possible.

2.10. Data management

To promote data quality, all research assistants will be trained prior to starting the study. Data stored securely in a password-protected cloud system will undergo thorough scrutiny by an independent researcher for errors or missing information.

Patient identification will be anonymized by assigning them a unique number, ensuring privacy protection. Only the principal investigator will have access to the correct linkage between the assigned numbers and respective patients. To promote participant retention at baseline and follow-ups, patients will be informed of each measurement that will be performed and the relative clinical significance of each outcome.

The research assistant will also collect data on adverse events such as cybersickness and other undesirable effects of interventions. Assessment and management of adverse events and evaluation of the need to conduct auditing trials will be the responsibility of the principal investigator.

2.11. Ethical considerations

The VIRTUAL-HF protocol has been approved by the Ethics Committee of the Cagliari University Hospital (number 0531/22) and will be carried out according to the principles of the Declaration of Helsinki [46]. The conduct of the study and the storage of data will take place in accordance with the General Data Protection Regulation Rules (GDPR). Any amendment to the study will be re-submitted for evaluation by the ethics committee.

2.12. Sample size

Assuming 80% power and a significance level of 0.05, 76 patients are needed to detect a medium effect size (Cohen's d = 0.66) [20,47] of the intervention on the primary outcome. Expecting a possible 5% drop out, a total sample of 80 subjects (40 for each arm) is required. The sample size calculation for the present trial was calculated with GPower v. 3.1.9.7 [48].

2.13. Statistical analysis

Data will be analyzed with an intention-to-treat approach. Baseline

sociodemographic characteristics will be compared between the randomization groups, using the independent sample's *t*-test or Wilcoxon's rank sum test for continuous variables and chi-square, or Fisher's exact test, for categorical variables.

Adherence to CR will be expressed as a percentage of non-adherence (100%-percentage of adherence) to obtain a right-skewed distribution. Differences in nonadherence will be examined with an independent sample t-test. Changes over time in nonadherence will be analyzed with a generalized linear model using a gamma distribution and log-link function. However, if the distribution has an excess of zeros, we will use the zero-inflated Poisson or negative-binomial models. We will include the percentage of nonadherence from baseline to T1, for each patient in the respective arms. Covariates will be time, randomization group, and the interaction between group and time.

Secondary outcomes involving continuous variables will be reported as the difference (delta) in scores between each follow-up and baseline. Changes in scores over time will be analyzed with longitudinal linear mixed models to account for missing values and drop out. We will include the scores of each variable from baseline to T2, for each patient in the respective arms. Covariates will be time, randomization group, and the interaction between group and time.

The frequency of hospitalization rates will be reported as absolute numbers and percentages and compared between the groups at each follow-up. To determine the effect of the randomization group on hospitalization rates, we will implement the zero-inflated negative binomial regression, because we hypothesize that, given the short follow-up period, at least one-half of the patients will not be hospitalized (thus the data will display an excess of zero and will be over dispersed). Conversely, we will implement the zero-inflated Poisson regression. The count variable will be taken at the T2 follow-up, and the covariate will be the randomization group. If hospitalization events occurred no more than once for patients at the end of the study period, we will model the variable as binary and perform a binary logistic regression with the randomization group as covariate. The statistical significance level is established at $p < 0.05$ (two-tailed). Statistical analyses will be performed using SPSS® v.25 [49] and STATA v.14 [50].

3. Conclusion

This research protocol aims to evaluate the effect of immersive VR on adherence to CR in patients with HF compared to conventional CR. Our hypotheses are that the use of VR will improve adherence and other outcomes influenced from CR such as functional capacity, perceived exertion, angina, quality of life, heart rate, oxygen saturation, blood pressure, maximum oxygen uptake, minute ventilation/carbon dioxide production slope, oxygen pulse, blood values of NT-proBNP and HF related rehospitalization rates. CR is strongly recommended by the international guidelines to improve the outcomes of patients with HF [1], however, the low adherence rates that characterize CR programs remain a challenge for clinicians and researchers [7]. VR can offer a good solution to this problem because it's a promising complementary intervention, synergistic with conventional CR [51]. VR is the result of multidisciplinary evidence-based practices aimed at a holistic treatment that allows adaptation to the subject's capabilities and desired level of intensity [52].VR could be an intervention where the cost-benefit ratio appears favorable, but further research will be needed to confirm this [53].

Our study has several strengths. First, immersive VR is easy to implement into standard care due to its intuitive features [54]. Second, this study will also evaluate long-term effects since patients will perform immersive VR during the eight CR sessions and measurements will be performed at the end of the four-week program and after other four weeks. By doing this last follow-up (T2) we will have the possibility to evaluate if VR continues its effect even after the program has finished.

We also acknowledge a few limitations. First, VIRTUAL-HF is focused on patients with HF, limiting generalizability to all CVD patients. Second, blinding of the intervention is not possible due to the nature of immersive VR; Ultimately, immersive VR technology might cause slight discomfort, which will be managed by healthcare professionals assisting patients with any issues, along with monitoring through cybersickness assessment.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Valentina Micheluzzi: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Gavino Casu:** Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing – review & editing. **Giuseppe Damiano Sanna:** Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – review & editing. **Antonella Canu:** Investigation. **Paolo Iovino:** Data curation, Formal analysis, Writing – review & editing. **Gabriele Caggianelli:** Methodology, Visualization, Writing – review & editing. **Ercole Vellone:** Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

None declared.

Data availability

No data was used for the research described in the article.

References

[1] T.A. McDonagh, M. Metra, M. Adamo, et al., 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur. Heart J. 42 (36) (2021) 3599–3726, https://doi.org/10.1093/eurheartj/ehab368.
[2] G. Savarese, P.M. Becher, L.H. Lund, P. Seferovic, G.M.C. Rosano, A.J.S. Coats, Global burden of heart failure: a comprehensive and updated review of epidemiology, Cardiovasc. Res. 118 (17) (2023) 3272–3287, https://doi.org/10.1093/cvr/cvac013.
[3] M. Ambrosetti, A. Abreu, U. Corrà, et al., Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the secondary prevention and rehabilitation section of the European Association of Preventive Cardiology, Eur. J. Prev. Cardiol. 28 (5) (2021) 460–495, https://doi.org/10.1177/2047487320913379.
[4] P.A. Heidenreich, B. Bozkurt, D. Aguilar, et al., 2022 AHA/ACC/HFSA guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines, Circulation 145 (18) (2022) e895–e1032, https://doi.org/10.1161/CIR.0000000000001063.
[5] R.S. Taylor, S. Walker, N.A. Smart, et al., Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis, J. Am. Coll. Cardiol. 73 (12) (2019) 1430–1443, https://doi.org/10.1016/j.jacc.2018.12.072.
[6] Y. Meng, W. Zhuge, H. Huang, T. Zhang, X. Ge, The effects of early exercise on cardiac rehabilitation-related outcome in acute heart failure patients: a systematic review and meta-analysis, Int. J. Nurs. Stud. 130 (2022) 104237, https://doi.org/10.1016/j.ijnurstu.2022.104237.
[7] D.M. Resurrección, P. Moreno-Peral, M. Gómez-Herranz, et al., Factors associated with non-participation in and dropout from cardiac rehabilitation programmes: a systematic review of prospective cohort studies, Eur. J. Cardiovasc. Nurs. 18 (1) (2019) 38–47, https://doi.org/10.1177/1474515118783157.
[8] A. Hamad, B. Jia, How virtual reality technology has changed our lives: an overview of the current and potential applications and limitations, Int. J. Environ. Res. Public Health 19 (18) (2022), https://doi.org/10.3390/ijerph191811278.
[9] F. Burrai, M.G. De Marinis, M. Piredda, Virtual reality during chemotherapy infusion, Holist. Nurs. Pract. (2023), https://doi.org/10.1097/HNP.0000000000000616. Published online August 15.
[10] F. Burrai, S. Othman, E. Brioni, et al., Effects of virtual reality in patients undergoing Dialysis, Holist. Nurs. Pract. 33 (6) (2019) 327–337, https://doi.org/10.1097/HNP.0000000000000330.
[11] M. Keshvari, M.R. Yeganeh, E. Paryad, Z.A. Roushan, M. Pouralizadeh, The effect of virtual reality distraction on reducing patients' anxiety before coronary

angiography: a randomized clinical trial study, Egypt. Heart J. 73 (1) (2021) 98, https://doi.org/10.1186/s43044-021-00224-y.
[12] H. Morgan, M. Nana, D. Phillips, S. Gallagher, The effect of a VIrtual RealiTy immersive experience upon anxiety levels, procedural understanding, and satisfaction in patients undergoing CArdiac CaTHeterization: the VIRTUAL CATH trial, J. Invasive Cardiol. 33 (9) (2021) E681–E686.
[13] R.R. Bruno, Y. Lin, G. Wolff, et al., Virtual reality-assisted conscious sedation during transcatheter aortic valve implantation: a randomised pilot study, EuroIntervention 16 (12) (2020) e1014–e1020, https://doi.org/10.4244/EIJ-D-20-00269.
[14] A.N.L. Hermans, K. Betz, D.V.M. Verhaert, et al., 360° virtual reality to improve patient education and reduce anxiety towards atrial fibrillation ablation, Europace 25 (3) (2023) 855–862, https://doi.org/10.1093/europace/euac246.
[15] M. Grab, F. Hundertmark, N. Thierfelder, et al., New perspectives in patient education for cardiac surgery using 3D-printing and virtual reality, Front. Cardiovasc. Med. 10 (2023) 1092007, https://doi.org/10.3389/fcvm.2023.1092007.
[16] T.M. Hendricks, C.N. Gutierrez, J.M. Stulak, J.A. Dearani, J.D. Miller, The use of virtual reality to reduce preoperative anxiety in first-time sternotomy patients: a randomized controlled pilot trial, Mayo Clin. Proc. 95 (6) (2020) 1148–1157, https://doi.org/10.1016/j.mayocp.2020.02.032.
[17] H.A. Meijer, M. Graafland, J.C. Goslings, M.P. Schijven, Systematic review on the effects of serious games and wearable technology used in rehabilitation of patients with traumatic bone and soft tissue injuries, Arch. Phys. Med. Rehabil. 99 (9) (2018) 1890–1899, https://doi.org/10.1016/j.apmr.2017.10.018.
[18] T.B.F. Pacheco, C.S.P. de Medeiros, V.H.B. de Oliveira, E.R. Vieira, F.A.C. de Cavalcanti, Effectiveness of exergames for improving mobility and balance in older adults: a systematic review and meta-analysis, Syst. Rev. 9 (1) (2020) 163, https://doi.org/10.1186/s13643-020-01421-7.
[19] F.M. Alfieri, Dias C. da Silva, N.C. de Oliveira, L.R. Battistella, Gamification in musculoskeletal rehabilitation, Curr. Rev. Musculoskelet. Med. 15 (6) (2022) 629–636, https://doi.org/10.1007/s12178-022-09797-w.
[20] I. Doumas, G. Everard, S. Dehem, T. Lejeune, Serious games for upper limb rehabilitation after stroke: a meta-analysis, J. Neuroeng. Rehabil. 18 (1) (2021) 100, https://doi.org/10.1186/s12984-021-00889-1.
[21] I. Cikajlo, Potisk K. Peterlin, Advantages of using 3D virtual reality based training in persons with Parkinson's disease: a parallel study, J. Neuroeng. Rehabil. 16 (1) (2019) 119, https://doi.org/10.1186/s12984-019-0601-1.
[22] R.S. Taylor, S. Walker, N.A. Smart, et al., Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials, Eur. J. Heart Fail. 20 (12) (2018) 1735–1743, https://doi.org/10.1002/ejhf.1311.
[23] Y. Wang, J. Cao, X. Kong, S. Wang, L. Meng, Y. Wang, The effects of CPET-guided cardiac rehabilitation on the cardiopulmonary function, the exercise endurance, and the NT-proBNP and hscTnT levels in CHF patients, Am. J. Transl. Res. 13 (6) (2021) 7104–7114.
[24] A.M. Campelo, J.A. Hashim, A. Weisberg, L. Katz, Virtual Rehabilitation in the elderly: Benefits, issues, and considerations, in: 2017 International conference on virtual rehabilitation (ICVR), IEEE, 2017, pp. 1–2, https://doi.org/10.1109/ICVR.2017.8007485.
[25] J. Radianti, T.A. Majchrzak, J. Fromm, I. Wohlgenannt, A systematic review of immersive virtual reality applications for higher education: design elements, lessons learned, and research agenda, Comput. Educ. 147 (2020) 103778, https://doi.org/10.1016/j.compedu.2019.103778.
[26] D. Freeman, S. Reeve, A. Robinson, et al., Virtual reality in the assessment, understanding, and treatment of mental health disorders, Psychol. Med. 47 (14) (2017) 2393–2400, https://doi.org/10.1017/S003329171700040X.
[27] J.J. Cummings, J.N. Bailenson, How immersive is enough? A Meta-analysis of the effect of immersive technology on user presence, Media Psychol. 19 (2) (2016) 272–309, https://doi.org/10.1080/15213269.2015.1015740.
[28] D. Scates, J.I. Dickinson, K. Sullivan, H. Cline, R. Balaraman, Using nature-inspired virtual reality as a distraction to reduce stress and pain among Cancer patients, Environ. Behav. 52 (8) (2020) 895–918, https://doi.org/10.1177/0013916520916259.
[29] B. Mouatt, A.E. Smith, M.L. Mellow, G. Parfitt, R.T. Smith, T.R. Stanton, The use of virtual reality to influence motivation, affect, enjoyment, and engagement during exercise: a scoping review, Front. Virtual Real. (2020) 1, https://doi.org/10.3389/frvir.2020.564664.
[30] M.K. Pishkhani, A. Dalvandi, A. Ebadi, M.A. Hosseini, Adherence to a rehabilitation regimen in stroke patients: a concept analysis, Iran. J. Nurs. Midwifery Res. 25 (2) (2020) 139–145, https://doi.org/10.4103/ijnmr.IJNMR_170_18.
[31] A.W. Chan, J.M. Tetzlaff, P.C. Gøtzsche, et al., SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials, BMJ. 346 (2013) e7586, https://doi.org/10.1136/bmj.e7586.
[32] R.S. Taylor, H.M. Dalal, A.D. Zwisler, Cardiac rehabilitation for heart failure: "Cinderella" or evidence-based pillar of care? Eur. Heart J. 44 (17) (2023) 1511–1518, https://doi.org/10.1093/eurheartj/ehad118.
[33] C.J. Kapelios, M. Canepa, L. Benson, et al., Non-cardiology vs. cardiology care of patients with heart failure and reduced ejection fraction is associated with lower use of guideline-based care and higher mortality: observations from the Swedish heart failure registry, Int. J. Cardiol. 343 (2021) 63–72, https://doi.org/10.1016/j.ijcard.2021.09.013.
[34] C.M. Callahan, F.W. Unverzagt, S.L. Hui, A.J. Perkins, H.C. Hendrie, Six-item screener to identify cognitive impairment among potential subjects for clinical research, Med. Care 40 (9) (2002) 771–781, https://doi.org/10.1097/00005650-200209000-00007.
[35] J. Xue, H.F.K. Chiu, J. Liang, T. Zhu, Y. Jiang, S. Chen, Validation of the six-item screener to screen for cognitive impairment in primary care settings in China, Aging Ment. Health 22 (4) (2018) 453–457, https://doi.org/10.1080/13607863.2017.1280768.
[36] G.A. Borg, Psychophysical bases of perceived exertion, Med. Sci. Sports Exerc. 14 (5) (1982) 377–381.
[37] M. Castro-Sánchez, F. Zurita-Ortega, J.A. Pérez-Turpin, et al., Physical activity in natural environments is associated with motivational climate and the prevention of harmful habits: structural equation analysis, Front. Psychol. 10 (2019) 1113, https://doi.org/10.3389/fpsyg.2019.01113.
[38] A. Voutilainen, T. Pitkäaho, T. Kvist, K. Vehviläinen-Julkunen, How to ask about patient satisfaction? The visual analogue scale is less vulnerable to confounding factors and ceiling effect than a symmetric Likert scale, J. Adv. Nurs. 72 (4) (2016) 946–957, https://doi.org/10.1111/jan.12875.
[39] S.L. Ames, J.S. Wolffsohn, N.A. McBrien, The development of a symptom questionnaire for assessing virtual reality viewing using a head-mounted display, Optom. Vis. Sci. 82 (3) (2005) 168–176, https://doi.org/10.1097/01.opx.0000156307.95086.6.
[40] N.H.M.K. Uszko-Lencer, R. Mesquita, E. Janssen, et al., Reliability, construct validity and determinants of 6-minute walk test performance in patients with chronic heart failure, Int. J. Cardiol. 240 (2017) 285–290, https://doi.org/10.1016/j.ijcard.2017.02.109.
[41] M.L. Day, M.R. McGuigan, G. Brice, C. Foster, Monitoring exercise intensity during resistance training using the session RPE scale, J. Strength Cond. Res. 18 (2) (2004) 353–358, https://doi.org/10.1519/R-13113.1.
[42] L. Campeau, The Canadian cardiovascular society grading of angina pectoris revisited 30 years later, Can. J. Cardiol. 18 (4) (2002) 371–379.
[43] L. Long, L. Anderson, A.M. Dewhirst, et al., Exercise-based cardiac rehabilitation for adults with stable angina, Cochrane Database Syst. Rev. 2 (2) (2018) CD012786, https://doi.org/10.1002/14651858.CD012786.pub2.
[44] C.P. Green, C.B. Porter, D.R. Bresnahan, J.A. Spertus, Development and evaluation of the Kansas City cardiomyopathy questionnaire: a new health status measure for heart failure, J. Am. Coll. Cardiol. 35 (5) (2000) 1245–1255, https://doi.org/10.1016/s0735-1097(00)00531-3.
[45] R. Masterson Creber, R. Polomano, J. Farrar, B. Riegel, Psychometric properties of the Kansas City cardiomyopathy questionnaire (KCCQ), Eur. J. Cardiovasc. Nurs. 11 (2) (2012) 197–206, https://doi.org/10.1177/1474515111435605.
[46] World Medical Association, World medical association declaration of Helsinki: ethical principles for medical research involving human subjects, JAMA 310 (20) (2013) 2191–2194, https://doi.org/10.1001/jama.2013.281053.
[47] M.M.A. da Cruz, A.L. Ricci-Vitor, G.L.B. Borges, et al., A randomized, controlled, crossover trial of virtual reality in maintenance cardiovascular rehabilitation in a low-resource setting: impact on adherence, motivation, and engagement, Phys. Ther. 101 (5) (2021), https://doi.org/10.1093/ptj/pzab071.
[48] F. Faul, E. Erdfelder, A.G. Lang, A. Buchner, G*power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences, Behav. Res. Methods 39 (2) (2007) 175–191, https://doi.org/10.3758/BF03193146.
[49] D. George, P. Mallery, IBM SPSS statistics 27 step by step, Routledge, 2021, https://doi.org/10.4324/9781003205333.
[50] William Gould, Stata Statistical Software. Release 16, Published online, 2019.
[51] A. Ruano-Ravina, C. Pena-Gil, E. Abu-Assi, et al., Participation and adherence to cardiac rehabilitation programs. A systematic review, Int. J. Cardiol. 223 (2016) 436–443, https://doi.org/10.1016/j.ijcard.2016.08.120.
[52] F. Burrai, S. Othman, E. Brioni, et al., Virtual reality in dialysis: a new perspective on care, J. Ren. Care 44 (4) (2018) 195–196, https://doi.org/10.1111/jorc.12264.
[53] Y.Y. Jia, J.P. Song, L. Yang, Can virtual reality have effects on cardiac rehabilitation? An overview of systematic reviews, Curr. Probl. Cardiol. 49 (2) (2024) 102231, https://doi.org/10.1016/j.cpcardiol.2023.102231.
[54] F. Burrai, S. Ortu, M. Marinucci, M.G. De Marinis, M. Piredda, Effectiveness of immersive virtual reality in people with Cancer undergoing Antiblastic therapy: a randomized controlled trial, Semin. Oncol. Nurs. (2023) 151470, https://doi.org/10.1016/j.soncn.2023.151470. Published online July.