The impact of a neuromuscular rehabilitation programme on the quality of life of patients with acute coronary syndrome and its relationship with sexual dysfunction: a randomised controlled trial

The impact of a neuromuscular rehabilitation programme on the quality of life of patients with acute coronary syndrome

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Abstract

Purpose: Many patients with acute coronary syndrome experience problematic or altered sexual function. This aspect of the disease is frequently ignored or overlooked by the healthcare community even though it can strongly influence health-related patient quality of life (HRQoL). Thus, the aim of this study was to compare the effects of a specific cardiac rehabilitation programme focused on aerobic and neuromuscular strength-resistance training to those of a classic rehabilitation programme, both in terms of HRQoL and erectile dysfunction in patients with acute coronary syndrome.

Methods: This study reports both secondary and unregistered outcomes from a double-blinded, randomised, and controlled clinical trial. The proposed intervention was based on the completion of a 20-session (10-week) cardiac rehabilitation programme for patients with cardiovascular disease. The patient cohort had been diagnosed with acute coronary syndrome and was recruited at the Cardiology Service of a private tertiary hospital. The outcomes assessed in this study were HRQoL and erectile disfunction assessed at baseline, after the intervention, and at a 6-month follow-up.

Results: A total of 30 participants were randomly allocated to each study arm. The results of the two-way mixed ANOVAs showed significant group × time interactions for all the outcome measures (EQ-5D_index, $p = 0.004$; EQ-5D_VAS, $p = 0.017$; QLMI-Q, $p \leq 0.001$; and IIEF-5, $p = 0.001$).

Conclusion: The neuromuscular strength training programme was more effective than the classic strength training programme in terms of increasing the HRQoL and improving erectile dysfunction in patients following acute coronary syndrome, with differences still remaining between these groups at the 6-month follow-up.

Key words: quality of life, acute coronary syndrome, sexual dysfunctions, cardiac rehabilitation.

Introduction

The WHO defines quality of life (QoL) as an individual's perception of their life situation in their cultural context and values, including goals, expectations, standards, and concerns [1,2].

One of the population groups in which pathology-related decreases in QoL have been most studied is that of patients with coronary heart disease, otherwise known as acute coronary syndrome (ACS) [3]. In these patients HRQoL is related to a lower capacity to carry out the activities of daily living because of a poor tolerance to exercise[3].

However, one aspect that is frequently ignored by the health community and which strongly influences the HRQoL of patients with ACS is that many of them experience problematic or altered sexual function. In this sense, the main results of a study by Mosack et al.[4] concluded that patients with ACS suffer alterations in their sexual relationships[5]. These may be in relation to pharmacological treatments and physical, emotional, or psychological symptoms such as the fear of triggering another heart attack[6].

The implementation of physical exercise programmes with comprehensive evaluation of cardiopulmonary function and response to physical activity is helpful in patients with ACS. Furthermore, cardiac rehabilitation programmes (CRPs) can be designed based on the outcomes of these evaluations, which can be very useful for assessing the clinical status and HRQoL of patients with ACS[7–9]. These CRPs are multifactorial interventions that have been recommended by the WHO since the 1960s and are defined as “the set of activities necessary to favourably influence the process of the clinical evolution of the disease, as well as to ensure patients the best physical, mental, and social condition possible so that they can, through their own efforts, preserve or recover as normal a position as possible in community life”[10–12].

In recent years, new types of CRPs have been gaining importance and have been replacing classic exercises with the aim of increasing the muscle groups used while also promoting a progressive increase in the complexity and intensity of the exercises. There has recently been notable interest in

the study of movement dysfunction and its influence on the efficiency of the daily activities of life and the quality of sports gestures, with this interest also crossing over into the field of rehabilitation. In fact, the studies by Myer et al.[13] and Mischiati et al.[14] highlight the importance of the neuromuscular control of both movement itself as well as movement quality in injury prevention. Motor control, which characterises neuromuscular training (NMT), is necessary for the performance of movement by allowing correct and varied muscle recruitment strategies while avoiding overloading structures. Indeed, exercises performed during patient rehabilitation could improve the ability to control movement during specific tasks[15,16]. Although NMT has mainly been applied in patients with musculoskeletal injuries[17-20], the authors working with these techniques have recommended its effects be explored in other populations with systemic disorders.

To the best of our knowledge, this current work is the first time the effects of a NMT programme has been specifically tested in patients with ACS. However, a previous study by Ferrer-Sargues et al.[21] defined and designed a cardiac rehabilitation protocol based on NMT that was specifically adapted to patients with ACS. Nonetheless, to date, neither the benefit of this type of intervention in the different spheres related to patient HRQoL, nor its impact on their sexual function has been investigated. Thus, the objective of this present study was to compare the effects of a specific CRP focused on aerobic and neuromuscular strength-resistance training to those of a classic rehabilitation programme. Our hypothesis was that, compared to classic rehabilitation training, the CRP including NMT would achieve greater improvements in terms of HRQoL and erectile dysfunction in patients with ACS.

Methods

Study design and ethical considerations

This study reports secondary and unregistered outcomes from a double-blinded, randomised, and controlled clinical trial implemented in a university healthcare clinic. The design of this research conformed to the principles outlined in the Declaration of Helsinki and was approved by the Research

Ethics Committee at the University of [*Blinded for Review*] (with reference number CEI18/111). Participation in the study was voluntary and we obtained the written informed consent of every participant before starting this work. Eligible patients were informed about all the relevant aspects of this study before participating in the rehabilitation programme. The protocol was registered with the U.S. National Library of Medicine (ClinicalTrials.gov) with identifier NCT04246008 on 29 January 2020. Personal information was collected by clinical research coordinators and stored on a password-protected computer, making sure to always protect patient confidentiality.

Participants

The patient cohort was recruited at the Cardiology Service at a private tertiary hospital and participated in the intervention from February 2021 to January 2022. Regarding the patient eligibility criteria, the inclusion criteria were an age of 18–80 years with a diagnosis of ACS with or without ST-segment elevation, a moderate or low risk stratification according to both a cardiopulmonary exercise test (CPET) results and the guidelines published by the American Heart Association[(22)], and a medical prescription for cardiac rehabilitation. The exclusion criteria were the presence of any pathologies or acute conditions outlined in the American College of Sports Medicine guidelines for exercise testing and a prescription with an absolute contraindication for physical exercise. Other conditions leading to patient exclusion were CPET abnormalities, severe exercise-induced arrhythmia, ST-segment depression caused by exertion, excessive hypertensive responses, hypotension caused by exertion, thoracic pain, or the inability to complete the questionnaires because of cognitive impairment.

Intervention

The proposed intervention was based on the completion of a 20-session CRP for patients with cardiovascular disease following the criteria set forth by the American College of Sports Medicine[(23)] for the prescription of exercise in patients with cardiovascular disease. This includes parameters such as frequency, intensity, time, exercise types, volume, and progression. The interventions were

implemented twice a week and the intensity was adjusted according to the patient CPET results. Intensity was calculated so that the exercises produced an increase in the heart rate (HR) of 65% to 85% of the peak HR. Each training session lasted 60 minutes and comprised a 10-minute warm-up, 20 minutes of endurance training, 20 minutes of strength-resistance exercises, and finishing with 10 minutes of cooling down and stretching exercises. The CRP was led by two experienced physiotherapists, both present during the sessions. One physiotherapist was in charge of the warm-up, endurance phase, and cool-down, while the other one was responsible of the strength-resistance exercises in both groups of patients.

Both groups completed the same intervention type for the endurance phase of the CRP, which was performed on a treadmill (Ergosprint©, Ergoline GmbH) or a bicycle ergometer (Ergoselect200©, Ergoline GmbH). This work was either performed in a continuous harmonic or continuous variable modality, depending on the individual risk stratification of each patient. For the strength training, two groups of patients were established based on the type of intervention they would perform; both the groups spent the same amount of time engaged in the strength-resistance phase. On the one hand, the control group—the classic strength-resistance training (CRST) group—performed general upper and lower-limb strength training exercises which targeted all the large muscle groups and progressed from open-chain to closed-chain bodyweight exercises. On the other hand, the NMT group completed a battery of exercises designed to improve trunk stabilisation, upper-limb dissociation from the trunk, movement patterns, and muscle recruitment and control during a range of hip and knee motions. The strength intervention was designed to train the same muscle groups to avoid bias in upper and lower-limb performance.

All the participants were monitored during each session. Peripheral oxygen saturation (OXYM4000 pulse oximeter, Quirumed S.L.U., Spain) and HR (Polar Team H10©, Polar Electro OY) data were continuously acquired for each patient. The blood pressure (BP) of the participants was also recorded with an Omron M6 Comfort Blood Pressure Monitor (Omron Healthcare Europe B.V, Hoofddorp, The

Netherlands) at the beginning of the session, after the cardiorespiratory exercises, and after the strength-resistance training section of the intervention. All the participants maintained their pharmaceutical treatments for ACS throughout the entire study and no changes in these treatments were observed as the study progressed.

Outcomes and metrics

Sociodemographic data from all the participants in this study were collected. Outcomes assessed in this study were HRQoL and erectile disfunction. HRQoL was quantified using the generic EuroQoL-5D questionnaire (EQ-5D)[24] and the specific HRQoL questionnaire for post-myocardial infarction patients (QLMI-Q)[25]. All the outcome measures were assessed at baseline (Time 0), after 20 rehabilitation sessions (Time 1), and at a 6-month follow-up (Time 2).

The EQ-5D is a self-reported questionnaire comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with each dimension subdivided into three levels: no problems, some problems, and extreme problems, indicating a patient's perceived level of function. Each level carries a weighted score which is combined across the five dimensions to reach an overall index score. The responses were converted into a utility index with the Spanish value set based on time trade-off to estimate values for all 243 possible health states, ranging from −0.5 to 1.0, with negative scores indicating states 'worse than death', 0 indicating no quality of life or 'death', and 1 indicating full health [24]. A 20-centimetre vertical visual analogue score (VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health) is also used to provide a score that is complementary to the patient's descriptive self-assessment of their health status. The patient is asked to mark the point on the vertical line of the VAS that best reflects their assessment of their global health status at the time. In this study, the Spanish version of EQ-5D was used[26,27]. The overall Cronbach's α value was 0.73 when tested in a population with coronary heart disease, which indicated that the internal consistency of the questionnaire was good[28].

The QLMI-Q is a specific questionnaire for cardiac patients comprising 44 items grouped into 9 dimensions as follows: health, sleep and rest, emotional behaviour, future projects, mobility, social relationships, alert behaviour, communication, leisure time, and work. There are no correct or incorrect answers for the QLMI-Q and each item is scored on a Likert-type scale with 5 response options where 5 corresponds to 'always true', 4 'almost always', 3 'sometimes', 2 'very rarely', and 1 'never'. Some patients did not answer some of the questions in which case, the mean value of the variable was used in place of the missing data value for that same variable. The total maximum score of the questionnaire is 220. The higher the QLMI-Q score, the worse the HRQoL[24]. The validated Spanish version of the questionnaire[25] was used in this work. The validity of the questionnaire was high (r = 0.81), as was its reproducibility (0.75) and reliability (0.90); the Cronbach alpha coefficient for all the items was 0.875[35].

Finally, the Spanish version of the International Index of Erectile Function (IIEF-5) was used to evaluate erectile dysfunction in male patients. The IIEF-5 questionnaire screens for this type of sexual dysfunction through 5 questions where the participant must provide the answer that best describes their situation in the 6 months prior. Each question has 5 response options with a score ranging from 1 to 5, with a cut-off score of 21 points (range = 5 ± 25)[29]. The Cronbach alpha coefficient for patients with heart failure was 0.84 and the test has been shown to be highly reliable[30].

Allocation concealment

A statistician from outside our research team used random number allocation software[31] to generate a random sequence which was concealed from all other study investigators throughout the entire study period. A block size of 6 participants was applied to determine patient assignment to the NMT or CRST groups. To obtain a balanced within-group distribution according to sex, this variable was blocked during the assignment. The patients were then referred to the University healthcare clinic where the physical therapist responsible for implementing the study obtained their written informed consent to participation and scheduled their programme sessions. Upon enrolment in the study and

after completing the primary and secondary outcome measures (baseline), the participants were randomly assigned either to the NMT or CRST group.

Each of the patient evaluation tests were identical and the physical therapist undertaking these tests was blinded to the patient allocation. In addition, the patients were also blinded to the rehabilitation type they had been assigned; they only knew that their sessions would comprise both cardiorespiratory fitness and strength training exercises. It was impossible to blind the physical therapists delivering the training programmes to the patient allocations because of their active role in administering these treatment sessions.

Statistical analysis

The sample size was calculated using G*Power software[32] (version 3.1.9.2) and was based on our previous pilot study which used *F*-tests and analysis of variance tests (ANOVAs) for repeated measures and within–between interactions, respectively. Statistical sample size power analysis for this analysis has been previously published[21] and was based on a functional outcome not included in the present study (the Incremental Shuttle Walking Test). This analysis indicated that a total of 30 patients (15 in each group) would be required. Two-way mixed ANOVA tests were used to compare the study effects on the sexual dysfunction and QoL results, using time (Time 0, 1, or 2) as the within-group factor and group (NMT or CRST) as the between-group factor. To further explore the effects of the interaction between the factors (time and group), post-hoc paired Student *t*-tests with a Bonferroni adjustment for alpha inflation were carried out. Effect sizes were estimated using the partial eta^2 and interpreted following the Cohen guidelines[33] for small effect sizes ($\eta 2_p$) = 0.01, moderate effect sizes ($\eta 2_p$ = 0.06), and large effect sizes ($\eta 2_p$ = 0.14). The statistical analyses were performed according to the intention-to-treat using SPSS software for Windows (v.24.0, IBM Corp., Armonk, NY). Finally, the statistical significance threshold was set to $p < 0.05$ for all the analyses.

Results

A total of 30 participants were randomly allocated to the NMT (n = 15) or CRST (n = 15) groups. Figure 1 shows the progression of the participants through the trial while the general characteristics and cardiovascular risk factors of the study population are shown in Table 1. There were no differences or small differences between the intervention and control groups for the majority of the study variables, at baseline. Only BMI showed moderate differences between the groups, although there were not large differences in obesity. According to WHO recommendations[34], as a cardiovascular risk factor, obesity was measured in these patients using waist circumference rather than BMI.

No dropouts were registered during the study at any of the time points and no significant adverse effects were reported during the intervention period by the participants in either group. This high adherence can be explained by the geographical proximity of the university healthcare clinic to both the hospital and patients' homes, and because the patients were either retired or were on sick leave from work at the time of the intervention and so their availability was greater. The results of the two-way mixed ANOVAs showed significant group × time interactions for all the outcome measures (EQ-5D_index, p = 0.004; EQ-5D_VAS, p = 0.017; total QLMI-Q score, $p \leq 0.001$; and IIEF-5, p = 0.001).

For the HRQoL, the between-group post-hoc analysis (Table 2) showed significant differences in the EQ-5D_index (NMT−CRST; 0.12, 95% CI [0.04 to 0.20]; p = 0.004), EQ-5D_VAS (NMT−CRST; 10.00, 95% CI [1.82 to 18.18]; p = 0.018), and total QLMI-Q score (NMT−CRST; −31.00, 95% CI [−48.73 to −13.27]; p = 0.001) with large effect sizes (η^2 p > 0.18) at the 6-month follow-up. Figure 2 shows the changes in EQ-5D in both groups over time. Erectile dysfunction was only recorded and analysed for men, according to the IIEF-5 questionnaire (n = 14 in each group). The post-hoc analysis showed significant between-group differences (NMT−CRST; 5.14, 95% CI [0.75 to 9.54]; p = 0.023) with a large effect size (η2 p = 0.18) at the 6-month follow-up.

After 20 rehabilitation sessions (Time 1), no differences between groups were found in any of the outcome measures. Additionally, the within-group post-hoc analysis (Table 3) showed a significant improvement in the NMT group for all the variables (p < 0.05), both post-treatment and at the 6-

month follow-up (Times 1 and 2). Nevertheless, only the EQ-5D_VAS (p = 0.042) showed a significant post-treatment improvement in the CRST group.

Discussion

The objective of this present study was to compare the effects of a specific NMT programme to those of a classic CRP on both HRQoL and erectile dysfunction reported by patients with ACS. Based on the HRQoL levels, our study showed that 6 months after the intervention, there had been a statistically significant improvement in the NMT group compared to the CRST group, both in terms of the generic questionnaire (EQ-5D) and the specific questionnaire (QLMI-Q) results. The fact that the observed difference in HRQoL between these groups occurred after 6 months (Time 1) and not immediately after completion of the 20-session (Time 2) intervention programme may be related to the very nature of the variables measured.

This concurs with previous studies[35] which have established that a mean period of 6–8 weeks is required by patients with ACS to normalise their lives from the time the original cardiovascular event had occurred. Along the same lines, Rumsfeld et al.[36] also showed that there were significant improvements in the physical role, general health, and vitality domains of the QoL score 3 months after the cardiovascular event, in addition to also observing greater patient adaptation to the disease condition during this time. However, it is also plausible that the training received by the patients in the NMT group was much more focused on the completion of functional exercises which would allow them to better apply said training in their daily activities and mobility, perhaps also somewhat improving their perception of their QoL.

Fear and anxiety are normal responses to a major life event like ACS. Thus, it is critical to consider how people manage and move toward the process of recovery following ACS. This transition is a psychological process with many stages in which people gradually come to terms with the new situation accompanying ACS. Neuromuscular rehabilitation may be more helpful in adapting to these

changes precisely because these exercises focus on the activities of daily living[37]. In this line, considering NMT as a functional activity could encourage patients to engage in these types of exercise, which would also imply greater therapeutic adherence[38,39]. Indeed, one of the key areas for improving the efficacy of CRPs is increasing patient adherence after completion of phase II of the programme which is then followed by the maintenance stage (phase III). This is because the effects achieved through the previous work will start to dissipate when adherence or maintenance in phase III is low[38].

Regarding erectile dysfunction, our study showed a statistically significant improvement in this issue in the NMT group compared to the CRST group, as measured through the IIEF-5 questionnaire 6 months after the intervention. Erectile dysfunction has negative consequences on the QoL of men and can cause psychological symptoms such as anxiety and depression[40]. This problem, which to date has been investigated very little in patients with ACS, has a multifactorial aetiology that may be caused by medication, fear of provoking another ischemic episode, and by other psychological, neurogenic, vascular, and endocrine pathologies, among others[41].

Despite mainly focusing on physical training and increasing functional capacities, CRPs also have an impact on emotional state[42]. The systematic review carried out by Khan et al.[43] showed that cardiac rehabilitation had a positive influence on the depressive symptoms of patients with ACS, with the prevalence of depression being 14% pre-cardiac rehabilitation and 3% post-cardiac rehabilitation. Constant monitoring of patients during the intervention, together with the presence of health professionals in the sessions and the group work involved in these programmes, promotes engagement in these physical pursuits and can positively impact patient activities, including their sexual lives[44]. In our intervention, an improvement was observed at 6 months in the NMT CRP group compared to the CRST group. However, the intragroup comparison showed an improvement both at the end of the 20-session (10-week) intervention and after 6 months of NMT rehabilitation. Nevertheless, these results must be interpreted carefully since this study was underpowered and because it was only possible to assess erectile dysfunction in the male participants.

Moderate-to-vigorous intensity exercise seemed to be the most effective intervention for improving erectile dysfunction because it resulted in higher cardiac output[45,46], as shown in the research by Lange et al.[45]. Given that sexual activity implies an energy consumption of at least 3–5 METS, for people without angina, excessive dyspnoea, or ischemic ST-segment changes, it seems plausible that the training that produced more cardiac output (e.g., NMT involving more muscle groups in the functional exercises) in patients with cardiovascular disease could also increase erection quality in this type of patient[47]. In addition, NMT treatment also influenced exercise tolerance, a parameter that has been related to sexual condition in ischemic patients[48].

The training programmes developed in this study responded to the need to implement early educational interventions in patients with cardiovascular disease[49]. Of note, this study compared the performance of a NMT programme specifically designed by an expert research team to that of a conventional strength training programme whose effectiveness had previously been demonstrated in patients with ACS. Thus, it is likely that the differences found between these groups, both in terms of HRQoL and in erectile dysfunction, was suitably assessed. However, despite the above, this work was not without limitations.

First, the overall sample size was somewhat small, even though it was consistent with the required sample size calculated before starting the work. The reduced cohort size was because of the specific disease we were investigating. Although NMT has been studied in a different population group, until now it has never been explored in patients with cardiovascular disease. Using a reduced sample size in this current work allowed us to maintain adequate patient training in terms of personalisation and safety. NMT is a type of whole-body training protocol that is more demanding than classic strength training in terms of coordination and movement because of its employment of global and functional movement patterns. NMT also allows progression in terms of the movement complexity of the exercises performed without abruptly increasing patient heart rates or fatigue. Therefore, by

considering the characteristics of the study population, applying this type of training makes sense to ensure the proper functioning of the intervention as well as patient safety.

Another limitation was that it was impossible to evaluate the erectile dysfunction questionnaire for the entire sample because it was only applicable to participants with male genitalia. Among the different types of possible sexual dysfunction, we focused on this outcome because erectile dysfunction is a specific type of sexual dysfunction that is strongly related to other cardiovascular risk factors such as diabetes mellitus, hypertension, and metabolic syndrome, among others[50]. Furthermore, although several studies have observed sexual impairment effects in terms of lubrication and reaching orgasm in both in men and women as a result of ACS, erectile dysfunction still appears as the most prevalent sexual dysfunction. The latter develops in up to 46% of men with cardiovascular disease and of these, 75% have problems getting erections and 67% have problems maintaining erections[51]. Future studies could focus on how a cardiac rehabilitation programme could impact other subgroups of sexual dysfunction such as sexual desire disorders, orgasm dysfunctions, or sexual pain, to help improve the HRQoL in all patients, regardless of gender.

Conclusion

This work presents evidence for the effectiveness of a neuromuscular strength training programme, as compared to a classic strength training programme, 6 months after their completion, to increase the HRQoL and improve the erectile dysfunction of patients following ACS. Future studies with a larger sample sizes will be required to confirm the potential benefits of this type of training, which focuses on patient functionality, with the ultimate goal of improving factors related to biopsychosocial domains.

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Conflicts of interest: None

Funding: none

Author contributions:

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All the authors read and approved the final version of this manuscript.