Evaluation of the effectiveness of rehabilitation patients after cardiac surgery: Meta-analysis

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1. SUMMARY

Author name: Hamza Khalid

Title: Evaluation of the effectiveness of rehabilitation patients after cardiac surgery: Meta-analysis.

Aim: To evaluate the effectiveness of rehabilitation patients after cardiac surgery by investigating changes in peak VO2 and 6MWD.

Objectives:

1. To analyse the changes of 6MWD for patients who underwent rehabilitation after cardiac surgery.

2. To analyse the changes of peak VO2 for patients who underwent rehabilitation after cardiac surgery.

Methods: The search was conducted on databases MEDLINE (via PubMed) from 2000 to 2019. All studies were eligible that evaluated the effectiveness of a post-interventional cardiac rehabilitation programme in patients after cardiac surgery (CABG or TAVI). In order to assess the methodological quality of studies, PEDro scale was used. The walked distance during the six-minute walk test (6MWD) and peak VO2 were evaluated. The statistical analysis was conducted in Review Manager Version 5.3.

Results: 13 studies were included (548CABG and 425TAVI patients). The meta-analysis showed that a cardiac rehabilitation programme was associated with a significant improvement in peak VO2 as 0.98 (0.63, 1.33; p<0.00001) after CABG and 6MWD as (0.51 (0.35, 0.67); p<0.00001) after TAVI involving one group. In addition, the studies where we compared control and interventional group after TAVI or CABG surgery the meta-analysis showed that the cardiac rehabilitation programme is not statistically significant in peak VO2 (0.30 (0.05, 0.55); p=0.02 and 6MWD (0.86 (-0.69, 2.41); p=0.28)

Conclusion: Rehabilitation performed after cardiac surgery (CABG or TAVI) significantly improves 6MWD as p<0.00001. When we compare results of 6MWD between control and interventional group it proves to be not statistically significant as p=0.28. Rehabilitation performed after cardiac surgery (CABG or TAVI) significantly improves peak VO2 as p<0.00001. When we compare results of peak VO2 between control and interventional group it proves to be not statistically significant as p=0.02.
2. SANTRAUKA

Autorius vardas: Hamza Khalid

Pavadinimas: Pacientų po širdies operacijų reabilitacijo efektyvumo vertinimas: Meta-analyzė

Tikslas: Įvertinti pacientų po širdies operacijų reabilitacijos efektyvumą, analizuojant šešių minučių ėjimo testo ir pasiekto max deguonies sunaudojimo rezultatus.

Tikslai:

1. Išanalizuoti pacientų po širdies operacijų šešių minučių ėjimo testo rezultatų pokyčius reabilitacijoje

2. Išanalizuoti pacientų po širdies operacijų pasiekto max deguonies sunaudojimo rezultatų pokyčius reabilitacijoje


Rezultatai: Į analizę įtraukėme 13 straipsnių (548CABG ir 425TAVI pacientai). Meta analizė parodė, kad po reabilitacijos programos ligonių po CABG operacijų pagerėjo peak VO2 0,98 (0,63, 1,33); p <0,00001) ,o po TAVI operacijų pacientams pagerėjo 6MĖT (0,51 (0,35, 0,67); p <0,00001). Be to, meta analizės tyrimai, kuriuose buvo kontrolinės tiriamųjų grupės po TAVI ir CABG operacijų, parodė, kad taikytos reabilitacijos programos skatino didėjimą peak VO2(0,30 (0,05, 0,55) p = 0.02 ir 6MĖT tačiau skirtumas tarp grupių nepatikimas., (0.86 (-0.69, 2.41); p = 0.28.

Išvada: Pacientams po širdies operacijų (CABG ir TAVI), taikytos reabilitacijos programos pagerino 6MĖT rezultatus p <0.00001. Lyginant kontrolinės ir tiriamųjų grupių 6MĖT rezultatus patikimas skirtumas negautas p=0.28. Pacientams po širdies operacijų (CABG ir TAVI), taikytos reabilitacijos programos pagerino pasiektą max deguonies sunaudojimą <0.00001. Lyginant kontrolinės ir tiriamųjų grupių pasiektą max deguonies sunaudojimą patikimas skirtumas tarp grupių negautas p=0.02.
3. ACKNOWLEDGEMENTS

Above all, I would like to thank to the Great Almighty, the author of knowledge and wisdom for his countless blessings. The completion of this undertaking could not have been possible without the physical and financial support of my family. Their contributions are sincerely appreciated and gratefully acknowledged.

However, I would like to express my deep appreciation and indebtedness particularly to my supervisor Dr. Juratė Samėnienė for her guidance and encouragement in carrying out this project. Her timely advice, meticulous scrutiny, scientific approach and scholarly advice have guided me a lot to accomplish this task.

4. CONFLICT OF INTEREST

The author reports no conflicts of interest.
5. ABBREVIATIONS LIST

CABG - Coronary artery bypass grafting

TAVI - Transcatheter aortic valve implantation

CVD - Cardiovascular disease

UK - United Kingdom

MI - Myocardial infarction

Peak VO2 - Peak oxygen consumption

6MWD - Six-minute walk distance

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

CR - Cardiac rehabilitation

CRP - Cardiac rehabilitation program

PEDro scale - Physiotherapy Evidence Database

SMD - Standard mean difference

CPET - Cardio pulmonary Exercise Testing

CAD - Coronary artery disease

6MWT - Six minute walk test
6. INTRODUCTION

The medical complexity and average age of patients undergoing cardiac surgery increases so the functional capacity has become an important indicator as both a pre-operative assessment and postoperative outcome measure. Functional capacity is the term ascribed to the physiologic reserve required to complete activities in a variety of circumstances during everyday living without undue fatigue and has been represented as an independent characteristic that can influence outcomes following cardiac surgery [1–3]. A reduction in functional capacity indicates a loss of physiological reserve, which shows the early sensation of fatigue [4]. In the early postoperative recovery following cardiac surgery patients experience a loss of physiologic and therefore functional capacity, particularly elderly and those patients with pre-existing reduced physiologic reserve [4]. Recent studies have expressed this functional reduction as well as the negative impact this can ultimately have on postoperative outcomes [1,2,5]. In preventing postoperative pulmonary complications early mobilization and respiratory based exercises may provide some benefits; however, improvements in functional capacity have not been consistently represented [6-8].

Aerobic exercise is proved to be a major component of cardiac rehabilitation for patients who have undergone cardiac surgery. In the modern era, exercise based cardiac rehabilitation aims to improve aerobic and functional capacity through the use of aerobic based exercise which includes walking and stationary cycling, providing benefits of symptom improvement, attenuation of cardiac disease progression and reduced mortality and hospital admission [9-13]. The majority of cardiac rehabilitation research has focused primarily on outpatient programmes which typically last several weeks following surgery [9-14].

A cardiac rehabilitation programme may promote a positive impact in relevant clinical outcomes so it is strongly recommended for patients after cardiac surgery, especially in the elderly because of the high prevalence of comorbidities and frailty [15].

In the literature there are several studies that determine the effectiveness of rehabilitation. In an overall view, some treatment options proved to be more effective than others but duration of the treatments also varied among studies as some were as short as few weeks while others were for several months. Currently, there is a paucity of literature evaluating the outcomes of patients commencing cardiac rehabilitation after cardiac surgery. This systematic review and meta-analysis aims to assess the clinical outcomes of rehabilitation commenced after cardiac surgery.
7. AIM AND OBJECTIVES

The aim of the study is to evaluate the effectiveness of rehabilitation patients after cardiac surgery by investigating changes in Peak VO2 and 6MWD.

Objectives:

1. To analyse the changes of 6MWD for patients who underwent rehabilitation after cardiac surgery.

2. To analyse the changes of Peak VO2 for patients who underwent rehabilitation after cardiac surgery.
8. LITERATURE REVIEW

Cardiovascular disease (CVD) is one of the leading causes of death worldwide and in United States [16, 17]. Thus it is considered as the number one cause of death globally with an estimated 17.7 million related mortalities in 2015 and 85 million people are living with CVD in Europe [18]. For CVD patient’s cardiac rehabilitation is proved to be one of the most recognised and well evidenced treatments. Therefore in the modern era Cardiac rehabilitation remains effective and this is evident due to reduction in re-admissions and cardiovascular mortality in trial populations and in observational studies a reduced overall mortality [19, 20].

8.1 Coronary artery bypass grafting

CABG is defined as open-heart surgery in which a section of a blood vessel is grafted from the aorta to the coronary artery thus redirects blood around a section of a blocked or partially blocked coronary artery in heart to improve blood flow to heart muscle. In 1876, Adam Hammer established the pathophysiology of coronary artery disease when he proposed that angina which is due to imbalance of coronary perfusion supply and demand was caused by blockage of coronary blood supply and myocardial infarction occurred after the occlusion of at least one coronary artery [21].

Over the last decade an STS (Society of thoracic Surgeons) data base analysis demonstrated an average risk-adjusted decline in mortality of 27% on the outcomes of coronary surgery [22]. So does the annual rate of CABG and it continue to drop to 1081 CABGs per 1 million adults in 2007 to 2008 in the United States [23]. However, the annual mortality of CVD still exceeds 4 million (47% of all deaths) in Europe and 1.9 million (40% of all deaths) in the European Union according to the latest figures of the European Heart Network [24]. Indeed, cardiac rehabilitation is conducted by an interdisciplinary team in order to decrease the cardiovascular risk factors and slow the progression of CVDs [25].

For patients with extensive coronary artery disease coronary artery bypass grafting (CABG) is proved to be an effective treatment [26, 27]. It is one of the most frequently performed operation worldwide and is most commonly performed using cardiopulmonary bypass called on-pump CABG which enables coronary anastomoses to be carried out on the arrested heart [28, 29]. However, to reduce complications associated with cardiopulmonary bypass and manipulation of the aorta techniques were
developed to perform CABG on the beating heart without cardiopulmonary bypass by the process called off-pump CABG [30].

8.2 Heart valve surgeries

More than 4% of North American and European individuals older than 75 years are affected by Aortic stenosis which is the most commonly acquired valvular heart disease [31, 32]. Moreover, aortic stenosis causes higher morbidity and mortality rates than other diseases that involves cardiac valves [33]. Thus, the survival in the symptomatic phase is approximately 2–3 years [34]. It causes decrease in functional independence and quality of life of patients. The main symptoms related to this disease are weakness, chest pain, dyspnoea or syncope during and/or after performing basic activities of daily living [35]. For patients with symptomatic aortic stenosis the procedure of choice is surgical aortic valve replacement (sAVR). However, due to high level of frailty in a significant proportion of these patients that increases risk of complications and perioperative mortality. Trans-catheter aortic valve implantation (TAVI) has robust therapeutic potential [36]. Cardiac rehabilitation programs improve functional capacity and quality of life in patients who undergo a surgery of aortic valve replacement [40]. For patients with severe aortic stenosis the development of transcatheter aortic valve implantation (TAVI) has provided an alternative to open heart surgery who are at high risk for periprocedural mortality. Over the last few years mortality after TAVI continues to decrease and equals that of surgical aortic valve replacement in selected number of patients [41].

8.3 Cardiac rehabilitation

Cardiac rehabilitation and prevention are mainly the coordinated sum of efforts needed to establish the best possible physical, psychological, and social conditions that help limit or reverse the progression of the underlying medical condition and as a result enable patients to keep or reclaim their familiar place in society [37]. Indeed, cardiac rehabilitation is conducted by an interdisciplinary team that works in order to cause reduction in cardiovascular risk factors to stabilize or even slow the progression of CVDs [38]. The goal of Cardiac rehabilitation programs is to limit the psychological and physiological stresses of CVD, reduce the risk of mortality secondary to CVD and improve cardiovascular function so that patients can achieve their highest quality of life [39].
8.4 Risk factors for cardiovascular disease

In all modes the aims of cardiac rehabilitation are to reduce risk factors and facilitate optimal recovery. According to the World Heart Federation, four of the highest associated risk factors for CVD are smoking, Obesity, hypertension, and physical inactivity [42]. Smoking cessation is key to the British Association of Cardiovascular Prevention and Rehabilitation (BACPR) standards and it includes programmes to encourage smoking cessation supported by skilled staff [43]. According to the UK data 6.4% of patients qualifying for cardiac rehabilitation were smoking and one-fifth of this group had successfully quit by post assessment, which equated to over 300 patients [44].

According to Chief Medical Officer Guidelines, patients with <150 min of moderate activity per week are considered physically inactive and that make up 58.4% of patients entering cardiac rehabilitation services [45]. But by the end of cardiac rehabilitation on average 28.1% of patients (4448) had move into the higher physically active group, thus setting a trend associated with reduced mortality [46]. Hypertension being a major risk factor for CVD, defined in the CVD population as >140/90 (>130/80 for South Asians) [42]. This study categorised the South Asians as >130/80 and suggesting that there are differences in risk associated with blood pressure and this particular group [47]. A reduction in systolic blood pressure by 5 mmHg can reduce cardiovascular mortality by 20–40%. However, by the time they finish cardiac rehabilitation through successful titration of drugs from the cardiac rehabilitation staff and increase in physical activity, 6% of previously high blood pressure patients move into category of <140/90 [46]. In the recent EUROSPIRE IV, it was found that after attending cardiac rehabilitation approximately 60% of hypertensive patients were <140/90 [48].

According to recent statistics more than 400 million adults throughout the world are obese and approximately 30% of patients qualifying for cardiac rehabilitation have a BMI higher than 30 [44]. However, evidence suggests that patients moving from being overweight to normal BMI have a reduction in risk of cancer and CVD [49].

8.5 Indication of Cardiac rehabilitation

Inclusion and re-inclusion to cardiac rehabilitation also apply following any stepwise alteration in any of the conditions like heart valve repair/replacement, CABG, acute MI within 12 months, stable angina, heart or heart-lung transplant, percutaneous coronary intervention with or without stenting, chronic systolic heart failure and other atherosclerotic diseases like peripheral arterial disease. It is recognized that people, including those with diabetes, pulmonary artery hypertension, compensated congestive heart failure, heart transplant recipients, heart failure with preserved ejection
fraction, and congenital heart disease require cardiac rehabilitation or secondary prevention programs [40].

8.6 Contraindications of Cardiac rehabilitation

Cardiac rehabilitation only applies to the exercise aspect. Thus it is contraindicated in selected patients that include patients with recent thrombophlebitis with or without pulmonary embolism, unstable angina, intracavitary thrombus, severe obstructive cardiomyopathies, acute decompensated congestive heart failure or any musculoskeletal condition that prevents adequate participation in exercise and uncontrolled inflammatory or infectious pathology [41].

8.7 Technique of Cardiac rehabilitation

Phase I: Inpatient phase

This phase begins in the inpatient setting after completion of an intervention so it starts by assessing the patient's physical ability and motivation to tolerate rehabilitation. Therapists and nurses may start by guiding patients through non-strenuous exercises in the bed or at the bedside, focusing on a range of motion and limiting hospital deconditioning. The rehabilitation team may also focus on activities of daily living and educate the patient on avoiding excessive stress. Patients are encouraged to remain relatively rested until completion of treatment of comorbid conditions, or post-operative complications. The rehabilitation team assesses patient needs such as assistive devices, patient and family education, as well as discharge planning [41, 50].

Phase II: Outpatient CR

Once a patient is stable and after being cleared by cardiology, outpatient cardiac rehabilitation may begin. Phase II typically lasts 3-6 weeks though some may last up to up to 12 weeks. Initially, patients are evaluated for limitations in physical function, restrictions of participation secondary to comorbidities, and limitations to activities. A more rigorous patient-centred therapy plan is designed, comprising three modalities: information/advice, tailored training program, and a relaxation program. The treatment phase intends to promote independence and lifestyle changes to prepare patients to return to their lives at home [41, 50].
Phase III: Post-CR

This phase involves more self-monitoring. Phase III centres on increasing flexibility, strengthening, and aerobic conditioning. Patients receive encouragement towards maintaining an active lifestyle and continue exercise. Outpatient visits to physician specialists are recommended to monitor cardiovascular health and medications regimens, promote healthy lifestyle changes and intervene when necessary to prevent relapse [41, 50].

8.8 Characteristics of exercise interventions

Aerobic exercise training

The most common modes of exercise are cycling, jogging, walking and swimming that demonstrates aerobic activity when carried out at moderate intensity. In order to achieve a safe exercise training effect the appropriate duration, intensity and frequency of exercise should be chosen. Aerobic exercise training can either be interval or continuous. But there is also strong evidence which demonstrates the benefits of interval-type training. The interval design enables the individuals to complete short work periods at high intensities that turn out to challenge the pumping ability of the heart [52, 53].

Table 1: Training prescription of exercise generally applicable [54]

<table>
<thead>
<tr>
<th>Mode</th>
<th>Continuous endurance: walking, jogging, cycling, swimming, stair climbing, and aerobic dancing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>At least 20–30 min (most preferably 45–60 min)</td>
</tr>
<tr>
<td>Frequency</td>
<td>Most days (at least 3 days/week and preferably 6–7 days/week)</td>
</tr>
<tr>
<td>Intensity</td>
<td>50–80% of peak oxygen consumption (close to anaerobic threshold) or of peak heart rate or 40–60% of heart rate reserve</td>
</tr>
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</table>

A progressive increasing training regimen prescription with regular follow-up controls every 3 to 6 months in order to adjust the duration and the level of the exercise according to the level of tolerance. Peak VO2 done by cardiopulmonary exercise testing is the ideal physiologic marker of intensity [54].
Exercise intensity

In maintaining aerobic fitness and reversion of risk factors exercise intensity is proved to be an important factor [56, 57]. Absolute intensity is the rate of energy expenditure during exercise and is represented in kcal/min or metabolic equivalent tasks (METs) [57, 58].

Exercise training zone

Nowadays it is suggested that in order to enhance cardiorespiratory fitness, exercise should be sufficiently intense to overload the aerobic system. As the aerobic fitness is improved when exercise intensity is above the aerobic threshold [59]. Within the aerobic training zone, the boundaries of which are indicated in Table 2. For primary and secondary cardiovascular disease prevention the target intensity is suggested to be close to the second anaerobic threshold [60, 61].

| Table 2: Relationship among indices of exercise intensity and training zone [87] |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Intensity                      | METs            | VO2max (%)      | HRR (%)         | HR max (%)      | Training zone   |
| Low intensity                  | 2–4             | 28–39           | 30–39           | 45–54           | Aerobic         |
| Moderate intensity             | 4–6             | 40–59           | 40–59           | 55–69           | Aerobic         |
| High intensity                 | 6–8             | 60–79           | 60–84           | 70–89           | Lactate, aerobic, anaerobic |
| Very hard effort               | 8–10            | >80             | >84             | >89             | Lactate, aerobic, anaerobic |

HR max: maximum heart rate, HRR: heart rate reserve, METs: metabolic equivalents, 1 MET: individual metabolic resting demand, when sitting quiet about 3.5 ml oxygen/kg/min in general population.
Maximal Oxygen Uptake

Functional capacity is the ability of an individual to perform aerobic work according to the maximal oxygen uptake (V̇o2max), which is calculated by this formula $\text{V̇o2max}=(\text{HRxSV})\times \text{a–V̇o2}$ that represents the product of cardiac output and arteriovenous oxygen (a–V̇o2) difference at physical exhaustion, where HR means heart rate and SV indicates stroke volume. V̇o2max generally is achieved by exercise but it involves only half of the body musculature so it is believed that V̇o2max is limited by maximal cardiac output rather than peripheral factors [62]. V̇o2max is related to conditioning status, gender, age and other morbidities or medications that influence its components. V̇o2max can exceed 80 mL O2/kg/min for a young male endurance athlete. However, within the 50th percentile for a sedentary, but healthy 80-year-old woman a value of 15 mL O2/kg/min falls. Aerobic capacity typically declines an average of 10% per decade in nonathletic subjects [63,64].

Exercise Mode

Functional capacity generally is performed on a motorized treadmill or a stationary cycle ergometer. However, in United States treadmill exercise is typically the preferred modality. Furthermore, untrained individuals usually terminate cycle exercise due to quadriceps fatigue at a work rate 10% to 20% below their treadmill peak VO2 [65]. Cycle ergometry usually requires cooperation with the individual in maintaining pedal speed at the desired level, mostly about 60 rpm. However, modern ergometers that are electronically braked maintain a steady workload at various speeds. Many studies showed a consistent relationship between aerobic capacity determined with a treadmill and a cycle ergometer and the latter mode of exercise tends to produce a lower peak VO2[66,67].

Furthermore, cycle ergometry is usually preferred in subjects with gait or balance instability, severe obesity, or orthopedic limitations or in cases when simultaneous cardiac imaging is planned. In addition, arm ergometry is usually used to assess the aerobic capacity of wheelchair athletes or other individuals with lower-limb disabilities. As most persons cannot achieve work rates comparable to those achieved with leg exercise because of the smaller and often deconditioned muscle mass [68].

Exercise capacity, functional capacity and exercise tolerance are considered synonymous and imply that a maximal effort has been given by the individual and maximal exercise test has been performed. However, these terms are used occasionally to represent an individual’s capacity to perform submaximal activities using one of a variety of tests; therefore in order to avoid confusion, the type of exercise evaluation should be described specifically [69].
Six-minute walk test (6MWT)

The 6MWT should be performed on a flat surface with a known distance measured and marked off. Patients are asked to walk self-paced for 6 minutes back and forth between the two marked points. Rests are allowed and in the meanwhile during and at the end of test administrators are able to provide feedback. Patients are permitted to use an assistive device but the person investigating should not walk with the patient during the test [88]. The laps are finally counted and a distance walked in 6 minutes is noted [88]. Mostly in clinical situations the 6MWT provides information that represents a better index of the patient's ability to perform daily activities than is peak oxygen uptake; for example, 6MWD correlates much better with formal measures of quality of life [89]. In a recent study, cardiac rehabilitation in patients referred with various heart diseases increased 6MWD by a mean of 170 m (15%) [90].

8.9 Clinical significance and effectiveness of cardiac rehabilitation

Overall cardiac rehabilitation decreases health care costs and increases the quality of life [51]. Due to the exercise component, cardiac rehabilitation has many physiologic benefits. A British cardiac rehabilitation program reported a drastic improvement in 6-min walk distance (6MWD) from 1032 ± 249 to 1238 ± 258 ft. over 6 weeks of training (two exercise sessions per week) but did not specifically indicate what proportion of their patients improved [91]. Furthermore, exercise training has been shown to increase maximal oxygen uptake (VO2max). As it improve endothelial function, and improve myocardial reserve flow. Moreover, cardiac rehabilitation can reduce smoking, body weight, serum lipids, and blood pressure [41].
9. RESEARCH METHODOLOGY AND METHODS

9.1 Study design

A meta-analysis of studies comparing the effects of a CR in patients after cardiac bypass and heart valve surgery called TAVI. This followed the recommendations of the preferred reporting items for meta-analyses (PRISMA) [70].

9.2 Eligibility criteria

All eligible studies evaluating the effects of Cardiac rehabilitation in patients after cardiac bypass and TAVI were considered. In order to estimate the effectiveness of CR, functional capacity or exercise tolerance was assessed in all studies by investigating outcomes like Peak VO2 and 6MWD. Thus, studies comprising of these outcomes were included. There was no limitation concerning sample size, age of patients or study design. Studies published between 2009 and 2019 were included, Hence no trial was excluded based on the presence of any comorbidities at baseline. Furthermore, CR was done under the supervision and responsibility of a rehabilitation centre and all publications were limited to those involving human subjects and written in English.

9.3 Exclusion criteria

Studies that were not relevant and involved other cardiac surgeries than CABG and TAVI were excluded. Furthermore, the studies administrating different outcomes were not included as well as illustrated in Fig. 1. Other than this, articles older than 2009 were excluded and the ones which were not in English language. Studies consisting of less than 10 patients in an intervention cohort were also excluded.

9.4 Search Strategy

The studies were found using a systematic search in the databases MEDLINE (via PubMed). The search included studies published from 2000 to 2019. Relevant studies were identified using the following MeSH terms "cardiac rehabilitation OR ("cardiac"[All Fields] AND
"rehabilitation"[All Fields]) OR "cardiac rehabilitation"[All Fields]) AND after[All Fields] AND ("heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND ("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgeries"[All Fields]).

The study flow diagram according to PRISMA statement is shown in Fig. 1.

9.5 Data extraction and quality assessment

The data was extracted independently. I sought to extract information on: (a) sample size; (b) characteristics of individuals, including mean age, gender; (c) surgery through which the patient undergone CABG or TAVI; (d) cardiac rehabilitation characteristics which includes modality of exercise, times per week, intensity and duration; (e) Outcomes featuring Peak VO2 to assess functional capacity and 6MWD. After extraction, the data were summarized in table 4.

The methodological quality of studies was assessed using the PEDro scale which indicates the presence or absence of 11 quality measures. Criterion 1 was not included to calculate the scores of the sum of others have led to a maximum score of 10 points. Studies with a score ≥6 points were classified as high-quality trials while those with a score ≤5 points were classified as poor quality trials [71].

9.6 Statistical analysis

The meta-analysis included the studies in which the description of Peak VO2 and 6MWD was measured before and after a CRP in order to estimate the effect size of a CR after CABG and TAVI surgeries. This was done separately based on studies with control trails and studies without control trials. In control trials, treatment effect size that represent the standardized mean difference with a 95% confidence interval is calculated by dividing the difference in changes before and after treatment between groups, by the pooled standard deviation of clinical outcomes. Another meta-analysis without control group comprised of studies in which description of the peak VO2 and 6MWD was recorded before and after a CR in one group and was used to utilize the standard mean difference with a 95% confidence interval by using fixed and random-effects models.

A random effect model was used if a case of heterogeneity (P less than 0.05 or I2 more than 50%) is noticed. Statistical I2 was used to estimate the heterogeneity of the studies included. Thus, 0% indicates no evidence of heterogeneity and ones with 25%, 50% and 75% represent low, moderate and high heterogeneity. P value of overall effect ≤ 0.05 represents statistically significant difference.
Standardized mean difference which is higher than 0.5 is considered as a moderate clinically relevant effect size and a SMD which is higher than 0.8 is considered as a large clinically relevant effect size [72]. Statistical analysis was conducted and analyzed using Review Manager Version 5.3.
10. RESULTS

In the initial electronic search, 793 potentially relevant studies were identified in the databases MEDLINE (via PubMed). After reading their titles, 672 articles were excluded due to irrelevance with the search topic. Then, after reading the abstracts of the remaining studies, 38 relevant studies were potentially identified. According to the selection criteria 13 clinical trials were selected for qualitative analysis, which are published in English and the rest were excluded as they not meet the selection criteria of this study. Figure 1 shows the summary of the search and selection process.

**Fig 1: Flowchart of the selection of trials included in this study.**
10.1 Study characteristics

The characteristics of the studies are illustrated in Table 4. There were 630 participants included, who were undergone CABG or TAVI surgeries. These participants were selected and allocated to a cardiac rehabilitation programme. In another study 169 individuals were allocated in interventional group who underwent CR after CABG or TAVI surgery and 174 individuals in control group after CABG or TAVI surgery. In general, according to studies patients after TAVI surgery were older than patients who had CABG surgery. The minimum age of patient is 49 and the maximum age of participant included in this study is 83 years old. It included more percentage of men however in the article by shabani et al [83], 100% female patients were investigated.

10.2 Cardiac rehabilitation programme

The CRP was performed in patients mostly during the early phase after the CABAG or TAVI surgeries. In five studies the CRP duration was around 3 weeks [73,76,80,81,84]. In three studies the patients underwent 6 months of cardiac rehabilitation [74,75,82]. However, in the rest 4 studies different CRP lengths were noticed 30 days 6, 8 and 12 weeks [78,85,77,82]. Training frequency ranged from five to seven times per week [74,78,81,84]. In three studies it was up to 1-3 times per week [75,77,85]. Other studies did not address the intensity prescription. Generally, all studies included aerobic training except Rogers et al [79] that includes cardiovascular training, resistance training and functional training such as sit to stand. Furthermore resistance training was also found in much studies [73,75,77,79,80,81,82,83]. Gymnastic was added as well in just two studies [78,84]. A summary of exercise intervention protocols is presented in Table 4.
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<td>Fauchere et al(2014)</td>
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<td>Rogers et al(2018)</td>
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<td>Busch et al (2012)</td>
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<td>Zanettini et(2014)</td>
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<td>Shabani et(2010)</td>
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<td>Tomoonishi et al (2009)</td>
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<td>Sarah et(2017)</td>
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<td>Savage et. (2015)</td>
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</table>

Criteria: (2) randomly allocated; (3) concealed allocation; (4) baseline comparability; (5) blinding subjects; (6) blinding therapists; (7) blinding assessors; (8) sample loss >15%; (9) intention to treat; (10) statistical analysis; (11) treatment effect
Table 4: Characteristics of studies included in the methodological analysis

<table>
<thead>
<tr>
<th>Author, year, study</th>
<th>Sample size</th>
<th>Age, gender (M/F), years</th>
<th>Surgery</th>
<th>Intervention</th>
<th>Duration</th>
<th>Ejection fraction %</th>
<th>Peak VO2% change ml/kg/min</th>
<th>6MWT outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savage et al. (2015) prospective study</td>
<td>N=394</td>
<td>63.6±9.4</td>
<td>CABG</td>
<td>AT, Weight training exercise</td>
<td>22.8 ± 11.8 days</td>
<td>54.3±11.5</td>
<td>Pre CR: 17.7±4.1 Post CR: 21.1±5.2</td>
<td>NR Improvement in peak VO2 is observed for patients who attended the cardiac rehabilitation</td>
</tr>
<tr>
<td>Spiroski et al. (2016)</td>
<td>N=54</td>
<td>57.72±7.6</td>
<td>CABG</td>
<td>AT in manner of CT and IT. The outpatient programme includes cycling as well.</td>
<td>Inpatient: 3 weeks (7k/week) 45 minutes duration Outpatient: 6 months (5k/week)</td>
<td>Pre CR: 55±5.81 Post CR: 59.30±4.26</td>
<td>Pre CR: 16.35±3.83 Post CR: 21.54±3.61</td>
<td>NR Short-term exercise training is safe and improves functional capacity.</td>
</tr>
<tr>
<td>Marzolini et al. (2015) retrospective study</td>
<td>N=25</td>
<td>49.4±10.7</td>
<td>CABG</td>
<td>AT Resistance training</td>
<td>6 months session. 90 min exercise classes 1k/week</td>
<td>NR</td>
<td>Pre CR: 20.2±5.6 Post CR: 25.7±8.4</td>
<td>NR Improvement in VO2peak and sufficient improvement in functional capacity.</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Age (±)</td>
<td>Intervention</td>
<td>Duration</td>
<td>Pre CR</td>
<td>Post CR</td>
<td>Findings</td>
<td></td>
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<tr>
<td>Russo et al. (2013)</td>
<td>78</td>
<td>83.3±3.6</td>
<td>Respiratory workout.</td>
<td>16.6±4.7</td>
<td>NR</td>
<td>NR</td>
<td>Short term, supervised CR is safe, feasible and effective.</td>
<td></td>
</tr>
<tr>
<td>Pressler et al. (2016)</td>
<td></td>
<td>81±6</td>
<td>IG receive combined endurance and resistance exercise</td>
<td>2 session first week and 3 sessions per week during weeks 2 to 8</td>
<td>IG</td>
<td>IG</td>
<td>CR improved the exercise capacity.</td>
<td></td>
</tr>
<tr>
<td>Fauchere et al. (2014)</td>
<td>34</td>
<td>82±5</td>
<td>Gymnastics, aerobic and respiratory workout sessions</td>
<td>(2–3/day, 6 days/week) in 30 days</td>
<td>NR</td>
<td>NR</td>
<td>The improvement in the 6-MWT was significant after CR</td>
<td></td>
</tr>
<tr>
<td>Rogers et al. (2018)</td>
<td></td>
<td>82</td>
<td>Cardiovascular training and resistance training Functional exercise such as ‘sit to stand</td>
<td>7.5 sessions in 1k/week in 6 weeks</td>
<td>CG:85.7%</td>
<td>IG:69.2%</td>
<td>There is not much improvements at 6 months in 6-MWT</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Exercise Details</td>
<td>CR Duration</td>
<td>Pre CR Metric</td>
<td>Post CR Metric</td>
<td>Improvement</td>
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<tr>
<td>Busch et al (2012)</td>
<td>IG N=84</td>
<td>CG N= 89</td>
<td>CG participated in the usual CR exercise program, including walks, calisthenics and cycle ergometer. IG undergo usual CR and daily resistance and balance training.</td>
<td>3-week long</td>
<td>78.5 ± 3.2 y</td>
<td>54.0 ± 10.4 y</td>
<td>IC PreCR:11 ± 2.7 PostCR:13.5 ± 2.9 IG PreCR:296 ± 84 PostCR:363 ± 86 CG PreCR:311 ± 80 PostCR:352 ± 82 There is significantly greater improvement in functional capacity measured as 6-MWD in the IG than in the CG.</td>
<td></td>
</tr>
<tr>
<td>Zanettini et al (2014)</td>
<td>N=60</td>
<td>83.5 ± 5.0 yrs F:53%</td>
<td>Resistance training, bed and sitting exercises, calisthenics and ambulatory training and aerobic training.</td>
<td>3 weeks</td>
<td>NR</td>
<td>NR</td>
<td>Pre CR:210 ± 87 Post CR:275 ± 97 There is significantly greater improvement in functional capacity measured as 6-MWD</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Age (years)</td>
<td>Intervention</td>
<td>Duration</td>
<td>Pre CR</td>
<td>Post CR</td>
<td>Improvement</td>
<td></td>
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<tr>
<td>Tomooshi et al, 2009</td>
<td>N:32 M:97%</td>
<td>66 ± 10</td>
<td>CABG training</td>
<td>6 months</td>
<td>NR</td>
<td>NR</td>
<td>A significant improvement in Peak VO2 after CRP</td>
<td></td>
</tr>
<tr>
<td>Sarah et al, 2017</td>
<td>N:136 M:52.2%</td>
<td>80.6 ± 5</td>
<td>TAVI ergometer endurance training</td>
<td>3 weeks</td>
<td>56.1±9.7%</td>
<td>NR</td>
<td>An improvement in 6MWD</td>
<td></td>
</tr>
<tr>
<td>Bilińska et al, 2013</td>
<td>CG N=50 IG N=50</td>
<td>56 ± 6 IG:57 ± 6</td>
<td>CABG AT 60-min bicycle ergometer exercise sessions in an interval manner</td>
<td>3 times per week in 6-week</td>
<td>CG:56.3 ± 8.8% IG:57.1 ± 8.9%</td>
<td>CG PreCR:24.3 ± 4.0 PostCR:25.7 ± 4.9</td>
<td>After CR a significant improvement is found in Peak VO2.</td>
<td></td>
</tr>
</tbody>
</table>

AT = Aerobic training, CT = continuous training, IT = interval training, WT = weight training, CR = Cardiac rehabilitation, TAVI = Transcatheter aortic valve implantation, NR = Not reported, CG = control group, IG = Intervention group, M = male, F = female, CABG = Coronary artery bypass grafting, 6MWT = 6-minute walk test.
Four studies were included in a meta-analysis that shows 322 patients undergone rehabilitation and the results of peak VO2 were recorded before and after rehabilitation [73,74,75,83]. These studies include the patient who underwent CRP after CABG surgery. In the pooled analysis, CRP after CABG was associated with a significant peak VO2 standardised mean improvement 0.98 [0.63, 1.33]; p < 0.00001) suggesting a large, clinically relevant effect size [74]. There was evidence for significant moderate heterogeneity between studies (I2 = 66%; p = 0.03) that lead to perform a random-effects model meta-analysis. This meta-analysis represent p value ≤ 0.05, thus it shows statistically significant increase between two groups.

Four studies were included in a meta-analysis that shows 308 patients undergone rehabilitation and the results of 6MWD were recorded before and after rehabilitation [78,76,84,81]. These studies include the patient who underwent CRP after TAVI surgery. In the pooled analysis, CRP after TAVI was associated with a significant 6MWD standardised mean improvement (0.51 (0.35, 0.67); p < 0.00001) suggesting a moderate, clinically relevant effect size. Furthermore there is no evidence of heterogeneity between studies (I2 = 0%; p = 0.52) that lead to perform a Fixed-effects model meta-analysis. This meta-analysis represent p value ≤ 0.05, thus it shows statistically significant difference between two groups.
The data for the Peak VO2 were available for three trials with control groups, which included post cardiac surgery CABG and TAVI [85, 80, 77]. They reported data for 126 patients in experimental group and 130 patients in a control group. In the pooled analysis, a CRP after cardiac surgeries (CABG or TAVI) was associated with a significant Peak VO2 standardised mean improvement (0.30 (0.05, 0.55); p = 0.02). There was low evidence for significant heterogeneity between studies (I2 = 37%; p=0.20), leading to perform a fixed-effects model meta-analysis. This meta-analysis represent p value ≤ 0.05, thus it shows there was no statistically significant difference in the peak oxygen consumption for patients who underwent CRP following cardiac surgery compared with the control group patients.

The figure shows the forest plot of the standardised mean improvement on a 6MWD (meters) in post-TAVI patients after a CRP. TAVI: transcatheter aortic valve implantation; CRP: cardiac rehabilitation programme.

Figure: 3 Forest plot of the standardised mean improvement on a 6MWD (meters) in post-TAVI patients after a CRP. TAVI: transcatheter aortic valve implantation; CRP: cardiac rehabilitation programme.

Fig: 4 Peak oxygen consumption (ml·kg⁻¹·min⁻¹) after CRP compared with control group following TAVI and CABG surgery.
The data for the 6MWD were available for four trials with control groups, which included post cardiac surgery CABG and other studies after TAVI [80,77,79,82]. They reported data for 126 patients in experimental group and 132 patients in a control group. In the pooled analysis, a CRP after cardiac surgeries (CABG or TAVI) was associated with a significant 6MWD standardised mean improvement (0.86 (-0.69, 2.41); p = 0.28). There was evidence for high significant heterogeneity between studies (I² = 96%; p<0.00001), leading to perform a random-effects model meta-analysis. This meta-analysis represent p value 0.28 that is more than 0.05, thus it shows there was no statistically significant difference between two groups.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Busch et al 2012</td>
<td>67</td>
<td>85</td>
<td>88</td>
<td>41</td>
</tr>
<tr>
<td>Pressler 2016</td>
<td>26</td>
<td>96.5</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Rogers et al 2018</td>
<td>-59.1</td>
<td>23.8</td>
<td>13</td>
<td>-15.5</td>
</tr>
<tr>
<td>Shalani et al 2010</td>
<td>103.8</td>
<td>50.7</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>126</td>
<td></td>
<td>132</td>
<td>100.0%</td>
</tr>
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</table>

Heterogeneity Test: τ² = 2.38, Ch² = 70.45, df = 3 (p < 0.00001), I² = 96%
Test for overall effect: Z = 1.09 (p = 0.28)

Fig.5 6MWD after CRP compared with control group following TAVI and CABG surgery.
11. DISCUSSION OF THE RESULTS

This is the first meta-analysis investigating CRP effects in patients after cardiac surgery (CABG or TAVI) as most of them investigate effectiveness of rehabilitation after coronary artery disease. This current meta-analysis describes four evident findings. First the positive effect of CRP in patients after CABG surgery which is measured by comparing peak Vo2 before and after CRP. Second the significant improvement in 6MWD after CRP in patient after TAVI, by comparing the results of before and after cardiac rehabilitation following cardiac surgery. Third and fourth includes the meta-analysis of patients in interventional and control groups investigating the significant difference and improvement in two outcomes (peak VO2 and 6MWD) after CRP following cardiac surgery (CABG or TAVI).

The data showed a similar gain in exercise tolerance after TAVI, assessed by the 6MWD. In all trials after CR a significant increase in walked distance was observed 0.51 (0.35, 0.67); p < 0.00001. Thus shows improvement in the group before and after CR. The improvement is seen in both studies with and without control trials. However, in studies including control trials an improvement is observed in all studies except Rogers et al [79], which include really old patients of mean age of 83 years old and BMI more than 25 who attended just 7.5 session of CR in six weeks and the left ventricular ejection fraction is greater in control group as compared to interventional group. Thus, there were baseline imbalances in 6-min walk test and left ventricular function between the groups which perhaps have affected the results of outcomes. According to another article by shabani et al [82], there is a great improvement in the results of 6MWD after cardiac rehabilitation, as it included much younger patients of mean age 59 years old and who have undergone 36 CR sessions in a period of 12 weeks. However, there is no significant difference observed between interventional group and control groups. The group of patients participating in the control group also underwent few exercises that result to be effective as well in increasing exercise tolerance among patients in a control group. According to study of Busch et al [80], it’s clearly mentioned that the exercises control group undergone include walking, calisthenics and cycle ergometer.

CRP also improved peak aerobic capacity after cardiac surgery measured by peakVO2. In addition, the meta-analysis results that include control trial studies showed that patients undergoing CABG or TAVI had similar benefits in improvement of peak oxygen consumption. A significant improvement in peak VO2 is observed after CRP comparing to the baseline results before undergoing cardiac rehabilitation (0.98 (0.63, 1.33); p<0.00001. However, there was substantial heterogeneity in the studies measuring
peak VO2 after CRP (I² = 66%). This variation might be due to the time of exercise commencement, modality and intensity of exercise and duration of the intervention.

The CRP consisted low/medium intensity exercise or activities aiming at improving aerobic capacity by walking or cycling, an arm ergometer was also used in those patients who were not able to cycle Russo et al [76] and resistance training. The routine varies from 1 time per week to daily and the duration varies from 3 weeks to 6 months under supervision of physiotherapists. Most of the studies included resistance and callisthenic exercises. However, two studies included gymnastics as well [74, 84]. The greatest contribution was from Russo et al [76], who completely described that the aerobic training started with 10-minute sessions and progressively increased 5 minutes per session up to reach target of 30 minutes. But the intensity did not exceed 70% of the predicted maximal heart rate which was monitored by a digital telemetry system. In the other study of Marzolini et al [75], the initial walking distance of approximately 1.6 km/d and an intensity of 60% to 80% of VO2 peak was set but every 2 week prescriptions were progressed, thus increasing distance to a maximum of 6.4 km and then increasing intensity to a maximum of 80% of VO2 peak. The training intensity was aimed to be 60% to 80% of peak VO2 as assessed by Cardiopulmonary exercise testing (CPET) in the study carried out by Spiroski et al [74].

CPET is increasingly being used in a wide spectrum in order to evaluate undiagnosed exercise intolerance and also for the objective determination of functional capacity and impairment. CPET provides complete assessment of the exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems. As it provides with the understanding that resting pulmonary and cardiac function testing cannot reliably predict exercise performance and functional capacity and that overall health status correlates better with exercise tolerance than with resting measurements so its use in patient management is seen increasing [86].

There are few limitations to this review. Studies included are powered for outcome improvements rather than just formal safety analysis comprised of patients who undergone CABG or TAVI surgery. Then the Patients included in most studies were also very low risk, with mean left ventricular ejection fraction over 50%. The poor methodological quality was observed in few studies that are usually attributed to experimental design, namely offering treatment to all patients who hence prevented the blinding and randomisation in few studies. In order to rate the methodological quality of randomised controlled trials which differ from most of the studies included, (PEDro scale) was developed. Concerning the methodological quality even though it is difficult to randomly assign patients as well as therapists after cardiac surgery but it’s recommended to have a group matching and the blinding of the assessors to the outcomes. This improvement is observed independently of age, sex, comorbid
conditions and the duration or intensity of intervention. The interventions comprising appropriately prescribed and supervised CRP should be further investigated consisting of more randomized trials considering safety outcomes and higher-risk patient groups. However, the results of this review should allow future high-quality randomized trials and non-randomized trials to further investigate the efficacy and safety of cardiac rehabilitation in higher risk cardiac surgery cohorts.

12. CONCLUSIONS

1. Rehabilitation performed after cardiac surgery (CABG or TAVI) significantly improves 6MWD as p < 0.00001. When we compare results of 6MWD between control and interventional group it proves to be not statistically significant as p=0.28.

2. Rehabilitation performed after cardiac surgery (CABG or TAVI) significantly improves Peak VO2 as p < 0.00001. When we compare results of Peak VO2 between control and interventional group it proves to be not statistically significant as p=0.02
13. LITERATURE LIST


37. Niebauer J. Is There a Role for Cardiac Rehabilitation After Coronary Artery Bypass Grafting? Circulation. 2016; 133(24):2529-2537. Available from: https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.116.021348?fbclid=IwAR3_n4cL1oqxd6HS41shP7vYw-1m35RJHw1HeqTma2hBjG5XVqiSYo84uAI


