Srce i krvni sudovi 2022; 41(2): 39-43

Review article

# The effects of cardiovascular rehabilitation in patients with reduced, mildly reduced, and preserved ejection fraction - do they benefit equally?

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**Abstract**

**Background.** Coronary artery disease (CAD) is the leading cause of heart failure (HF). The beneficial effects of cardiac rehabilitation (CR) in CAD patients are well known but whether they depend on ejection fraction (EF) is rather unknown.

**Aim.** To examine whether CAD pts with reduced, mildly reduced, and preserved EF benefit equally from comprehensive CR in terms of exercise tolerance.

**Methods.** 828 CAD pts attended a three-week CR program at the residential center. Before attending CR all patients underwent an echocardiographic exam after which pts were divided into three groups: heart failure with reduced (HFrEF≤40%), mildly reduced (HFmrEF 41-49%), and preserved EF (HFpEF≥50%). At baseline and at the end of CR exercise stress test (EST) was taken.

**Results**. There were 84 HFrEF pts (10.14%), 246 HFmrEF pts (29.71%), and 498 HFpEF pts (60.15%). At the first EST (EST1) and at the second EST (EST2) HFpEF and HFmrEF patients showed better strain tolerance compared to pts with HFrEF by reaching a higher strain levels and longer duration of EST. However, all three groups showed better strain tolerance at the EST2. Namely, they all reached higher strain level (for all three groups p=0.000) and longer duration of EST (for all three groups p=0.000). Also, in all three groups significantly higher percentage of patients reached submaximal heart rate at the EST2 compared to EST1 (p=0.001 for HFrEF, p=0.006 for HFmrEF, and p=0.000 for HFpEF). Pts with HFrEF had a significantly higher rate of arrhythmia at the EST2 compared to pts with HFmrEF and HFpEF (p=0.009). Improvement of physical strain level and duration of EST on EST2 compared with EST1 was more pronounced in pts with reduced (by 19,2% and 28,7%), than in pts with mildly reduced (by 13,9% and 17,5%) and pts with preserved LVEF (14,1% and 16,8%).

**Conclusion.** Results indicate that CR significantly improved physical strain tolerance in patients with coronary artery diseases independent of ejection fraction. In pts with HFmrEF and HFpEF CR resulted in higher level of strain tolerance than in pts with HFrEF. However, improvement in exercise capacity was more pronounced in pts with HFrEF.

**Kew words** coronary artery disease, heart failure, cardiovascular rehabilitation

## Introduction

Heart failure (HF) is a clinical syndrome consisting of clinical signs and symptoms caused by structural or functional heart abnormalities that lead to reduced cardiac output or elevated intracardiac pressure[1]. The prevalence of HF is 1-2%, but rises with age and appears to be higher than 10% in patients aged 70 years or older[2]. The most common causes of HF are coronary artery disease (CAD) and arterial hypertension (HTA)1.

HF is divided into three categories based on left ventricular ejection fraction (LVEF): HF with reduced EF (HFrEF) with EF ≤40%, HF with mildly reduced EF (HFmrEF) with EF 41-49%, and HF with preserved EF (HFpEF) with EF ≥50% ([1]). About 1/2 of HF patients have HFrEF, and the other half have HFmrEF or HFpEF[3]. It seems that patients with HFrEF have a worse prognosis compared to patients with HFmrEF or HFpEF[1]. However, in many cases HFpEF and HFmrEF progress to HFrEF[1].

A well-designed cardiovascular rehabilitation (CVR) is of tremendous importance in the treatment of cardiovascular diseases and secondary prevention of cardiovascular events. It improves the quality of life, reduces the risk of secondary cardiovascular events and prolongs life[4]. Moreover, in CAD patients CVR reduces inflammation and oxidative stress[5] and has a great impact on hemodynamics[6]. These positive effects are noted in both genders[7]. The latest European Association of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF give IA recommendation for exercise rehabilitation in all HF patients "who are able in

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order to improve exercise capacity, quality of life, and reduce HF hospitalization”[1]. These recommendation is given for all three classes of HF, although there is no date on beneficial effects of CVR on patients with HFmrEF.

The aim of the study was to examine whether patients with coronary artery disease and reduced, mildly reduced, and preserved EF benefit equally from comprehensive cardiovascular rehabilitation in terms of exercise tolerance.

## Methods

The study involved eight hundred twenty-eight CAD patients, 202 (24.4%) women and 626 (75.6%) men. All patients participated in a three-week CVR program at the Institute for Treatment and Rehabilitation “Niska Banja” after surviving myocardial infarction (MI), percutaneous coronary intervention or coronary artery bypass grafting (CABG). Before the beginning of CVR an echocardiographic exam was performed and all patients were divided into three groups: patients with HFrEF (84 patients, 10.14%), HFmrEF (246 patients, 29.71%), and PFpEF (498 patients, 60.15%). All patients belonged to New York Heart Association (NYHA) I-II class.

During a three-week CVR all patients underwent a dosed and individualized physical training which included bicycle riding, walking and cardiovascular exercise programs. At baseline and at the end of CVR exercise stress test (EST) was done. ESTs were performed on the treadmill (3017 Full Vision Drive, Newton, Kansas, USA) according to the Bruce protocol. Tests were limited by symptoms and signs like chest pain, lack of air, dizziness, etc., complex heart rhythm disorders, pathological changes on the electrocardiogram (ECG), or submaximal heart rate (calculated as 85% from 220-age equation). Pathological changes on ECG were defined as the occurrence of horizontal and/or down-sloping ST depression ≥ 01 mm. Complex heart rhythm disorders were defined as long-term episodes of bigeminy of ventricular premature complex (VPC), couplets of VPC, and ventricular tachycardia. All data were collected, compared, and analyzed based on EF values.

Statistical analysis was performed using SPSS for Windows (Version 20; SPSS, Chicago, IL, USA). Frequencies and percentages were used for the description of the patient’s characteristics. Numerical data were expressed as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used to test the normality of data. Statistical significance for nominal data was tested with the χ2 test and, where appropriate, the Fisher exact test. The Student’s t- test was used to assess the statistical significance of parametric continuous data, and Mann–Whitney U-test and Wilcoxon Signed Ranks Test were for nonparametric continuous variables. The Pearson’s correlation was used to determine the correlation between variables. Statistical significance was set to a level of $p < 0.05$.

## Results

Women were more present in the group with HFpEF compared to the other two groups (27.51% vs. 19.51 HFmrEF, and 20.24% HFrEF), with statistically significant difference noted between HFmrEF and HFpEF (p=0.37). The age structure was similar in all three groups. Smokers were more present in group with HFmrEF (58.54%) compared to the group with HFpEF (48.19%) and HFpEF (52.38%), with statistically significant difference noted between HFmrEF and HFpEF (p=0.033). Other risk factors for cardiovascular diseases (hyperlipidemia, diabetes mellitus, arterial hypertension, heredity) did not differ between the groups (Table 1).

At the beginning of CVR, the first exercise stress tests (EST1) were performed. Patients with HFpEF showed better strain tolerance compared to HFrEF and HFmrEF as they achieved higher strain level. Also, EST1 lasted the longest in patients with HFpEF. On the other hand, patients with HFrEF showed the worse strain tolerance. For both parameter statistically significant differences

**Table 1.** Baseline characteristic of patients

| EF ≤40% | | Groups | | | Total | χ2 | p |
|---|---|---|---|---|---|---|---|
| | | 41%-49% | ≥50% | | | | |
| Gender n (%) | Women | 17 (20.24%) | **48 (19.51%)** | **137 (27.51%)** | 202 (24.4%) | 6.587 | **.037** |
| | Men | 67 (79.76%) | **198 (80.49%)** | **361 (72.49%)** | 626 (75.6%) | | |
| Hyperlipidaemia n (%) | No | 9 (10.71%) | 29 (11.79%) | 46 (9.24%) | 84 (10.14%) | 1.209 | .546 |
| | Yes | 75 (89.29%) | 217 (88.21%) | 452 (90.76%) | 744 (89.86%) | | |
| Hypertension n (%) | No | 13 (15.48%) | 32 (13.01%) | 69 (13.86%) | 114 (13.77%) | .329 | .848 |
| | Yes | 71 (84.52%) | 214 (86.99%) | 429 (86.14%) | 714 (86.23%) | | |
| Diabetes mellitus n (%) | No | 63 (75%) | 184 (74.8%) | 371 (74.5%) | 618 (74.64%) | .014 | .993 |
| | Yes | 21 (25%) | 62 (25.2%) | 127 (25.5%) | 210 (25.36%) | | |
| Heredity n (%) | No | 57 (67.86%) | 148 (60.41%) | 294 (59.04%) | 499 (60.34%) | 2.338 | .311 |
| | Yes | 27 (32.14%) | 97 (39.59%) | 204 (40.96%) | 328 (39.66%) | | |
| Smoking n (%) | No | 40 (47.62%) | **102 (41.46%)** | **257 (51.61%)** | 399 (48.19%) | 6.797 | **.033** |
| | Yes | 44 (52.38%) | **144 (58.54%)** | **241 (48.39%)** | 429 (51.81%) | | |
| Age (m±sd) | | 61.93±10.01 | 59.78±9.75 | 60.79±9.6 | 60.61±9.69 | 3.856 | .145 |

**Table 2.** The first exercise stress test (EST1)

| EF ≤40% | | Groups | | | Total | χ2 | p |
|---|---|---|---|---|---|---|---|
| | | 41%-49% | ≥50% | | | | |
| Level | | 1.98±0.86 | 2.3±0.91 | 2.34±0.99 | 2.29±0.96 | 10.066 | **.007** |
| Duration (min) | | 4.32±2.43 | 5.42±2.48 | 5.52±2.69 | 5.37±2.63 | 15.086 | **.001** |
| DP before | | 9704.29±2030.22 | 10113.58±5310.56 | 9926.81±6664.13 | 9959.73±5955.86 | 2.620 | .270 |
| DP after | | 19109.35±4272.01 | 22233.87±13138.37 | 21681.51±4005.08 | 21584.67±7960.08 | 24.689 | **.000** |
| SHR achieved n (%) | No | 47 (55.95%) | 103 (41.87%) | 209 (41.97%) | 359 (43.36%) | 6.039 | **.049** |
| | Yes | 37 (44.05%) | 143 (58.13%) | 289 (58.03%) | 469 (56.64%) | | |
| Arrhythmia n (%) | No | 51 (89.47%) | 143 (89.38%) | 308 (91.12%) | 502 (90.45%) | .455 | .797 |
| | Yes | 6 (10.53%) | 17 (10.63%) | 30 (8.88%) | 53 (9.55%) | | |
| Ischemic changes n (%) | No | 80 (95.24%) | 219 (89.39%) | 434 (87.15%) | 733 (88.63%) | 4.865 | .088 |
| | Yes | 4 (4.76%) | 26 (10.61%) | 64 (12.85%) | 94 (11.37%) | | |

DP – double product; SHR – submaximal heart rate.

were noted between HFmrEF and HFpEF on one hand, and HFrEF on the other (p=0.007 for level, and p=0.001 for duration). Also, a significantly greater percentage of patients with HFmrEF and HFpEF achieved submaximal heart rate at the end of EST1 compared to HFrEF (p=0.049, Table 2).

After three weeks of CVR the second EST (EST2) was performed. Results were similar to EST1. Namely, patients with mildly reduced and preserved LVEF showed better strain tolerance compared to patients with reduced LVEF by reaching a higher strain levels and longer duration of EST. On the other hand, arrhythmias were more present in HFrEF compared to HFpEF and HFmrEF (Table 3).

However, all three groups showed better strain tolerance at the EST2. Namely, they all reached higher strain level (for all three groups p=0.000) and longer duration of EST (for all three groups p=0.000). Also, in all three groups significantly higher percentage of patients reached submaximal heart rate at the EST2 compared to EST1 (p=0.001 for HFrEF, p=0.006 for HFmrEF, and p=0.000 for HFpEF), but only patinets with HFrEF had higher values of double product at the end of EST2 compared to the end of EST1 (0.031). On the other hand, patients with HFrEF had a significantly higher rate of arrhythmia at the EST2 compared to patients with mildly reduced and preserved LVEF (p=0.009) (Table 4). Improvement of physical strain level and duration of EST2 compared with EST1 was more pronounced in patients with reduced (by 19,2% and 28,7%), than in patients with mildly reduced (by 13,9% and 17,5%) and patients with preserved LVEF (14,1% and 16,8%).

## Discussion

A well-designed CVR includes exercise training, dietary advices, psychosocial support, patient education, control of modifiable cardiovascular and non-cardiovascular risk factors and adequate medication therapy[8]. It is known that personalized and well-organized CVR may lead to the better lipid profile, anxiety and depression reduction, better blood pressure control, reduction in hospitalization and mortality rate[9]. These positive effects of CVR are shown in patients with arterial hypertension, valvular heart diseases, coronary artery disease, and heart failure. This is why all recent and relevant Guidelines advice CVR in secondary prevention of cardiovascular diseases giving it a IA recommendation[1,10-13].

Interestingly, the first Guideline which emphasized the importance of CVR in secondary cardiovascular

**Table 3.** The second exercise stress test (EST2)

| EF ≤40% | | Groups | | | Total | χ2 | P |
|---|---|---|---|---|---|---|---|
| | | 41%-49% | ≥50% | | | | |
| Level | | 2.36±0.82 | 2.62±0.99 | 2.67±0.96 | 2.62±0.96 | 8.427 | **.015** |
| Duration (min) | | 5.56±2.28 | 6.35±2.78 | 6.45±2.74 | 6.33±2.72 | 8.055 | **.018** |
| DP before | | 9409.94±2122.07 | 9717.66±1804.27 | 9641.4±2091.13 | 9640.57±2012.82 | 1.713 | .425 |
| DP after | | 20112.86±3554.76 | 21835.98±3807.56 | 21929.65±3690.82 | 21717.51±3747.32 | 16.521 | **.000** |
| SHR achieved n (%) | No | 31 (36.9%) | 83 (33.74%) | 153 (30.72%) | 267 (32.25%) | 1.615 | 0.446 |
| | Yes | 53 (63.1%) | 163 (66.26%) | 345 (69.28%) | 561 (67.75%) | | |
| Arrhythmia n (%) | No | 47 (81.03%) | 140 (86.42%) | 310 (92.54%) | 497 (89.55%) | 9.385 | **.009** |
| | Yes | 11 (18.97%) | 22 (13.58%) | 25 (7.46%) | 58 (10.45%) | | |
| Ischemic changes n (%) | No | 77 (91.67%) | 213 (86.59%) | 427 (85.74%) | 717 (86.59%) | 2.173 | .337 |
| | Yes | 7 (8.33%) | 33 (13.41%) | 71 (14.26%) | 111 (13.41%) | | |

DP – double product; SHR – submaximal heart rate.

**Table 4.** Comparison between the first and the second exercise stress test in men

| EF | | ≤40% | | | 41%-49% | | | ≥50% | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | M±SD | Z/ χ2 | P | M±SD | Z/ χ2 | p | M±SD | Z/ χ2 | p |
| EST1 Level | | 1.98±0.86 | -4.326$^{c}$ | **.000** | 2.3±0.91 | -6.404$^{c}$ | **.000** | 2.34±0.99 | -9.366$^{c}$ | **.000** |
| EST2 Level | | 2.36±0.82 | | | 2.62±0.99 | | | 2.67±0.96 | | |
| EST1 duration | | 4.32±2.43 | -5.818$^{c}$ | **.000** | 5.42±2.48 | -8.959$^{c}$ | **.000** | 5.52±2.69 | -11.584$^{c}$ | **.000** |
| EST2 duration | | 5.56±2.28 | | | 6.35±2.78 | | | 6.45±2.74 | | |
| EST1 DP before | | 9704.29±2030.22 | -1.066$^{d}$ | .286 | 10113.58±5310.56 | -.701$^{d}$ | .483 | 9926.81±6664.13 | -.266$^{c}$ | .790 |
| EST2 DP before | | 9409.94±2122.07 | | | 9717.66±1804.27 | | | 9641.4±2091.13 | | |
| EST1 DP after | | 19109.35±4272.01 | -2.163$^{c}$ | **.031** | 22233.87±13138.37 | -1.715$^{c}$ | .086 | 21681.51±4005.08 | -1.184$^{c}$ | .236 |
| EST2 DP after | | 20112.86±3554.76 | | | 21835.98±3807.56 | | | 21929.65±3690.82 | | |
| SHR | EST1 | 37 (44.05%) | 6.126 | **0.013** | 143 (58.13%) | 3.458 | 0.063 | 289 (58.03%) | 13.609 | 0.000 |
| | EST2 | 53 (63.1%) | | | 163 (66.26%) | | | 345 (69.28%) | | |
| Arrhythmia n (%) | EST1 | 6 (10.53%) | 1.625 | 0.202 | 17 (10.63%) | 0.660 | 0.416 | 30 (8.88%) | 0.448 | 0.503 |
| | EST2 | 11 (18.97%) | | | 22 (13.58%) | | | 25 (7.46%) | | |
| ST depression n (%) | EST1 | 4 (4.76%) | 0.876 | 0.349 | 26 (10.61%) | 0.912 | 0.340 | 64 (12.85%) | 0.420 | 0.517 |
| | EST2 | 7 (8.33%) | | | 33 (13.41%) | | | 71 (14.26%) | | |

prevention was the one about the diagnosis and treatment of chronic heart failure back in 2008[14]. Cardiac rehabilitation is of tremendous importance in HF patients as it may improve the quality of life, functional capacity and cardiac function. These beneficial effects are recognized in center-based, home-based and hybrid (short term center-based and then home-based) cardiac rehabilitation[15]. It seems that high-intensity interval training in HF leads to better exercise capacity. A meta-analysis which included 24 studies with CAD, HFrEF or HFpEF patients showed a significantly greater improvement in VO2 peak after high-intensity exercise compared to moderate-intensity continuous training (by 1.40 mL/min/kg; 95% confidence interval (CI) 0.69–2.11; P ≤0.001)[16]. However, in the SMARTEX-HF study which included 261 NYHA II-III HFrEF patients, high-intensity training wasn't superior to moderate-intensity continuous training[17]. Nevertheless, both types of exercise training did lead to better strain tolerance in HF patients.

Although beneficial effect of CVR are well-known, patients with HF seldom attend cardiac rehabilitation programs. Even in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial, which was the largest trial of CVR in patients with HFrEF, the long-term adherence was below 30% ([18]). There are many factors that led to these disappointing results. One of the most important was physician inertia ([9]). There is no doubt that stronger physician endorsement can significantly increase the participation of HF patients in CVR programs.

Both, HFrEF and HFpEF, are characterized by reduced physical tolerance and chronic fatigue. HFpEF patients suffer from exercise intolerance due to vascular, skeletal muscle, and cardiac abnormalities[19]. A personalized moderate to high-intensity training in these patients can increase $VO_2$ peak, quality of life and exercise stress tolerance[19]. Many studies have shown the beneficial effects of well-designed CVR on physical strain tolerance in patients with HFpEF and HFrEF. These positive effects CVR was shown regardless of age, sex, comorbidities, and frailty[20]. However, there is no study which investigated the effects of CVR on patients with HFmrEF.

In our study, CAD patients with HFpEF had the best strain tolerance on the first and on the second EST. The worst exercise strain tolerance was noted in CAD patients with HFrEF. These findings were somewhat expected. However, in our study all three classes of HF showed a significant improvement of exercise stress tolerance after finishing a three-week rehabilitation program. Moreover, the greatest improvement was noted in CAD patients with HFrEF. These results, once again, emphasize the importance of CVR in patients with HF.

## Conclusion

Results indicate that cardiovascular rehabilitation significantly improves physical strain tolerance in patients with coronary artery diseases independent of ejection fraction. In patients with HFmrEF and patients with HFpEF cardiovascular rehabilitation resulted in higher level of strain tolerance than in patients with HFrEF. However, improvement in exercise capacity was more pronounced in patients with HFrEF.

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## Sažetak

### *Efekti kardiovaskularne rehabilitacije kod pacijenata sa smanjenom , blago smanjenom I očuvanom ejekcionom frakcijom – da li je korist ista za sve?*

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***Uvod.*** *Koronarna arterijska bolest (KAB) je vodeći uzrok srčane insuficijencije (SI). Pozitivni efekti kardiovaskularne rehabilitacije (KVR) kod pacijenata sa KAB su dobro poznati, ali je nepoznato da li zavise od ejekcione frakcije (EF). Cilj ovog rada je biod a se ispita da li bolesnici sa KAB i redukovanom, blago redukovanom i očuvanom EF imaju jednaku korist od KVR u smislu tolerancije napora.*
***Metode.*** *828 pacijenata sa KB je pohađalo tronedeljni program KVR. Pre započinjanja KVR svi pacijenti su podvrgnuti ehokardiografskom pregledu nakon* ***čega*** *su bolesnici podeljeni u tri grupe: srčana insuficijencija sa smanjenom (engl. HFrEF≤40%), blago smanjenom (engl. HFmrEF 41-49%) i očuvanom EF (engl. HFpEF≥50%). Na početku i na kraju KVR urađen je test fizičkim opterećenjem (TFO).*
***Rezultati.*** *Bilo je 84 HFrEF (10,14%), 246 HFmrEF (29,71%) i 498 HFpEF (60,15%). Na prvom TFO (TFO1) i na drugom TFO (TFO2) HFpEF i HFmrEF pacijenti su pokazali bolju toleranciju fizičkog napora u poređenju sa bolesnicima sa HFrEF dostizanjem viših nivoa opterećanja i dužim trajanjem TFO. Međutim, sve tri grupe su pokazale bolju toleranciju napora na TFO2. Naime, svi su dostigli viši nivo opterećenja (za sve tri grupe p=0,000) i duže trajanje TFO2 (za sve tri grupe p=0,000). Takođe, u sve tri grupe značajno veći procenat pacijenata je dostigao submaksimalnu srčanu frekvencu na TFO2 u odnosu na TFO1 (p=0,001 za HFrEF, p=0,006 za HFmrEF i p=0,000 za HFpEF). Bolesnici sa HFrEF su imali* ***češće*** *aritmije na TFO2 u poređenju sa bolesnicima sa HFmrEF i HFpEF (p=0,009).*
***Zaključak.*** *Rezultati pokazuju da je KVR značajno poboljšala toleranciju fizičkog napora kod pacijenata sa oboljenjem koronarnih arterija nezavisno od ejekcione frakcije. Kod pacijenata sa HFmrEF i HFpEF KVR je doprinela višem nivu tolerancije napora u poređenju sa HFrEF bolesnicima. Međutim, sveukupno poboljšanje tolerancije napora bilo je izraženije kod pacijenata sa HFrEF.*

*Ključne reči: koronarna bolest, srčana slabost, kardiovaskularna rehabilitacija*