Povezanost spola i ejekcijske frakcije u bolesnika s akutnim koronarnim sindromom nakon reperfuzijske terapije

The Relationship Between Gender and Ejection Fraction in Patients with Acute Coronary Syndrome after Reperfusion Therapy

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SAŽETAK: Uvod: Prethodna istraživanja o povezanosti spola i ejekcijske frakcije (EF) odnosila su se samo na jednožilnu koronarnu bolest te su uzimala u obzir samo bolesnike s akutnim infarktom miokarda s elevacijom ST-segmenta (STEMI). U ovom smo radu istražili učinak spola na EF u akutnome koronarnom sindromu, uključujući STEMI i akutni infarkt miokarda bez elevacije ST-segmenta (NSTEMI) kod koronarne bolesti svih krvnih žila jer one mogu utjecati na funkciju lijeve klijetke.

Bolesnici i metode: U istraživanje je bilo uključeno 480 bolesnika s akutnim koronarnim sindromom (STEMI i NSTEMI). Zabilježene su sve početne karakteristike, kao i početna EF. Svi su bolesnici bili liječeni reperfuzijskom terapijom prema međunarodnim smjernicama. Nakon praćenja od godine dana EF je izmjerena ponovno.

Rezultati: Žene su bile statistički značajno starije od muškaraca (P < 0,05). Postojala je značajna razlika u EF-u između žena i muškaraca (P < 0,05). Tijekom razdoblja praćenja nije bilo značajnih promjena u EF-u u skupini žena (P > 0,05). Životna dob i ženski spol pokazali su se neovisnim prediktorima promjene EF-a.

Zaključak: Ženski je spol neovisan prediktor oporavka EF-a u bolesnika s akutnim koronarnim sindromom (STEMI i NSTEMI).

SUMMARY: Introduction: Previous gender-related studies on ejection fraction (EF) were single vessel specific and considered only patients with ST-segment elevation myocardial infarction (STEMI). This study evaluated the effect of gender on EF in acute coronary syndrome, including STEMI and non-ST-segment elevation myocardial infarction (NSTEMI) as well as all blood vessels, since they can affect left ventricular function.

Patients and Methods: 480 patients with acute coronary syndrome (STEMI and NSTEMI) were enrolled. All baseline characteristics along with EF were noted. All patients received reperfusion therapy as per international guidelines. Patients were followed up for one year, after which EF was reassessed.

Results: Women were significantly older than men (P<0.05). There was significant difference between EF the between female and male groups (P<0.05). No significant change was seen in EF in the female group during follow-up (P>0.05). Age and female gender were found to be independent predictors of change in EF.

Conclusion: Female gender is an independent predictor of recovery of EF in patients with acute coronary syndrome (STEMI and NSTEMI).

KLJUČNE RIJEČI: ejekcijska frakcija, žene, akutni koronarni sindrom, perkutana koronarna intervencija.

KEYWORDS: ejection fraction, women, acute coronary syndrome, percutaneous coronary intervention.

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Uvod

Infarkt miokarda (MI) jedan je od glavnih uzroka smrti i pobola u cijelome svijetu, a perkutana koronarna intervencija (PCI) ima ključnu ulogu

Introduction

Myocardial infarction (MI) is a major cause of morbidity and mortality worldwide, and percutaneous coronary intervention (PCI) plays a

u njegovu liječenju.[1,2] Usprkos činjenici da su žene rjeđe zahvaćene od muškaraca, njihova se stopa smrtnosti pokazala mnogo višom.[3]

Infarkt miokarda dovodi do nekroze koja je uzrokom dilatacije lijeve klijetke (LV) i njezinu disfunkciju. Dokazano je da je oslabljena sistolička funkcija LV povezana s lošim ishodima, pa se ejekcijska frakcija lijeve klijetke (EF) smatra važnim čimbenikom za kratkoročne i dugoročne ishode.[4-8]

Trenutačno je optimalna strategija liječenja bolesnika s MI-jem revaskularizacija zahvaćene žile s pomoću PCI-ja.[9,10] Usprkos dobro potvrđenoj ulozi PCI-ja u zaštiti vijabilnog tkiva miokarda i u poboljšanju opće funkcije LV-a, istraživanja su zabilježila različite ishode ovisno spolu.[11,12]

Prema istraživanjima, žene imaju višu smrtnost nakon PCI-ja u usporedbi s muškarcima. Moguće je da je to zbog višeg rizika u žena u trenutku liječenja PCI-jem.[13,14] No razlike na osnovi spola glede EF-a u bolesnika s akutnim infarktom miokarda s elevacijom ST-segmenta (STEMI) i infarktom miokarda bez elevacije ST-segmenta (NSTEMI) koji su bili liječeni primjenom PCI-ja nisu detaljno istražene, osim vrlo maloga broja studija koje su istraživale samo bolesnike sa STEMI-jem koji je zahvaćao prednju stijenku.

Lijeva se klijetka krvlju opskrbljuje prije svega preko lijeve prednje silazne grane.[15] Na EF utječu i drugi infarkti osim onih vezanih za tu arteriju, kao što je to infarkt desne klijetke i dominantne cirkumfleksne arterije i marginalne grane. Stoga smo u naše istraživanje uključili bolesnike sa STEMI-jem i NSTEMI-jem neovisno o zahvaćenoj krvnoj žili te istražili učinak spola na oporavak EF-a.

Bolesnici i metode

U istraživanje smo uključili bolesnike primljene u našu bolnicu koji su zadovoljavali sljedeće kriterije: (**a**) životna dob između 40 i 70 godina; (**b**) bolesnici s akutnim infarktom miokarda bez prethodnog anamnestičkog podatka o koronarnoj bolesti srca; (**c**) bolesnici koji su dali pisani informirani pristanak. Bolesnici koji nisu dali pristanak ili oni koji nisu mogli osigurati perkutanu revaskularizaciju zbog financijskih prepreka nisu uključeni u istraživanje.

Nakon uključenja u bolesnika su zabilježene sve početne karakteristike kao što su životna dob, spol, prisutnost čimbenika rizika (dijabetes, arterijska hipertenzija, pušenje, obiteljska anamneza koronarne bolesti srca /CAD/, EF te razdoblje od početka bolova u prsnom košu do PCI-ja). Troje kardiologa konzultanata obavilo je procjenu težine koronarne stenoze i TIMI protoka tijekom koronarne angiografije.

Na početku istraživanja (prije PCI-ja) i nakon jedne godine ehokardiografski pregled obavili su iskusni zdravstveni djelatnici koji nisu imali dostupne informacije o bolesniku. Izračun EF-a proveden je na *GE Vivid S5* uređaju primjenom metode po Simpsonu.[16]

Kontinuirane varijable opisane su kao srednja vrijednost ± SD (standardna devijacija), a Studentov t-test primjenjivan je za usporedbe. Kategoričke smo varijable opisali kao frekvencije i postotke, a Pearsonov hi-kvadrat test služio je za usporedbe. Test sume rangova i multivarijatna linearna regresijska analiza upotrebljeni su za procjenu učinka spola i raznih drugih varijabli na promjenu EF-a godinu dana nakon PCI-ja. P-vrijednost manja od 0,05 smatrala se statistički značajnom. Sve su analize provedene primjenom SPSS-a (verzija 20.0; SPSS, Chicago, Illinois, SAD).

vital role in its management.[1,2] Despite the fact that women are affected less often than men, their mortality rates have been shown to be much higher.[3]

Myocardial infarction resulting in necrosis causes left ventricular (LV) dilatation and dysfunction. Impaired LV systolic function has been proven to be associated with poor outcomes, so left ventricular ejection fraction (LVEF) is regarded as an important factor for short and long-term outcomes.[4-8]

Currently, the optimum strategy in treatment of patients with MI is revascularization of the culprit vessel with PCI.[9,10] In spite of the well-established role of PCI in protecting viable myocardium and improvement in the overall LV function, variable outcomes have been reported based on gender differences.[11,12]

As compared with men, women have been reported to have higher mortality after PCI. This may be due to higher risk in women at the time of PCI.[13,14] However, differences based on gender with regard to LVEF in patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) receiving PCI have not been extensively studied apart from very few studies that only examined patients with anterior wall MI (STEMI).

The LV is mainly supplied by the left anterior descending (LAD) branch of the left main coronary vessel.[15] Ejection fraction is also affected by infarctions other than the ones associated with the LAD artery such as right ventricular infarction and the dominant circumflex artery with the major obtuse marginal branch. Therefore, in this study we enrolled patients (STEMI and NSTEMI) irrespective of the vessel involved and assessed the effect of gender on recovery of LVEF.

Patients and Methods

Patients admitted to our hospital who fulfilled the following criteria were enrolled in the study: (**a**) age between 40 and 70 years; (**b**) patients with acute myocardial infarction and no previous history of ischemic heart disease; (**c**) patients giving written and informed consent. Patients who did not give consent or who could not afford to undergo percutaneous revascularization due to financial constraints were excluded from the study.

At presentation, all baseline characteristics such as age, gender, diabetes, hypertension, smoking, LVEF, family history of coronary artery disease (CAD), and interval from onset of chest pain to PCI were noted. During coronary angiography, assessment of severity of coronary stenosis and TIMI flow was performed by three consultant cardiologists.

Echocardiography was carried out at baseline (before PCI) and after one year by experienced operators who were blinded to patient information. Ejection fraction was estimated with biplane Simpson's rule using GE Vivid S5 system.[16]

Continuous variables were described as mean ± SD (standard deviation) and Student t-test was used for comparison. Categorical variables were described as frequencies and percentages, and Pearson's chi square test was used for comparisons. Rank-sum test and multiple linear regression analysis were used to assess the effect of gender and various other variables on the change in LVEF one year after PCI. A P value of less than 0.05 was considered significant. All analyses were carried out using SPSS (version 20.0; SPSS, Chicago, Illinois, USA).

Svi sudionici u istraživanju dali su informirani pristanak. Protokol istraživanja odobrio je Etički odbor Rehman medicinskog instituta, a istraživanje se pridržavalo Helsinške deklaracije.

Rezultati

U istraživanje je bilo uključeno ukupno 480 bolesnika, od kojih su 280 (58,3 %) bili muškarci, a 200 (42,6 %) žene. Početne su karakteristike prikazane u **tablici 1**. Žene su bile statistički značajno starije u usporedbi s muškarcima (65,9 ± 8,01 prema 55 ± 9,38, P < 0,05). Ostale karakteristike, koje su uključivale pušenje, dijabetes, arterijsku hipertenziju, hiperlipidemiju, bubrežno oštećenje i pretilost na početku istraživanja nisu bile različite u skupinama ovisno o spolu (P > 0,05). Bolesnici su u objema skupinama, nakon primitka u bolnicu, primali slične lijekove, koji su uključivali acetilsalicilatnu kiselinu, klopidogrel, beta-blokatore, inhibitore angiotenzin konvertirajućih enzima ili blokatore angiotenzinskih receptora te statine. Ovisno o indikaciji, primijenjeni su i diuretici.

Koronarna angiografija i revaskularizacija metodom PCI-ja izvedene su u svih bolesnika. Učestalost višežilne koronarne bolesti i zahvaćenost pojedinih koronarnih krvnih žila bile

Informed consent was obtained from all subjects included in the study. The study protocol was approved by the Ethics Committee of Rehman Medical Institute and the study abided by the Declaration of Helsinki.

Results

A total of 480 patients were enrolled in this study, out of which 280 (58.3%) were men and 200 (42.6%) were women. The baseline characteristics of the study group are shown in **Table 1**. Women were significantly older compared with men (65.9±8.01 vs. 55±9.38, P<0.05). Other indices including smoking, diabetes, hypertension, hyperlipidemia, renal failure, and obesity did not show any significant difference in male and female groups at baseline (P>0.05). Patients in the male and female groups received similar medications at admission, which included aspirin, clopidogrel, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and statins. Patients were given diuretics when indicated.

Coronary angiography followed by a revascularization procedure (PCI) were performed in all patients. Multi-vessel disease as well as the type of vessel involved were similar in both

TABLE 1. Baseline characteristics of study groups.

Variable	Women (n=200)	Men (n=280)
Age (years)	65±8.01	55±9.38*
Left ventricular ejection fraction (%)	40.26±9.09	47.85±10.73*
Diabetes	64 (32%)	81 (29%)
Hypertension	62 (31%)	84 (30%)
Family history of CAD[a]	26 (13%)	42 (15%)
Hyperlipidemia	42 (21%)	70 (25%)
Renal failure	18 (9%)	28 (10%)
Obesity[b]	44 (22%)	70 (25%)
Smoking	34 (17%)	59 (21%)
Aspirin	200 (100%)	280 (100%)
Clopidogrel	198 (99%)	280 (100%)
Beta blocker	194 (97%)	266 (95%)
ACEI[c] / ARB[d]	180 (90%)	260 (93%)
Nitrates	196 (98%)	269 (96%)
Diuretics	70 (35%)	84 (30%)
Lipid lowering agents	140 (70%)	210 (75%)

[a] Coronary Artery Disease
[b] Obesity is BMI above 30
[c] Angiotensin Converting Enzyme Inhibitor
[d] Angiotensin Receptor Blocker
*P ≤ 0.05

su slične u žena i u muškaraca (P > 0,05). Nije bilo značajne razlike između dviju skupina glede učestalosti reinfarkta i smrtnosti (**tablica 2**).

Na početku istraživanja EF u skupini žena bila je niža nego u skupini muškaraca, a razlika je bila statistički značajna (40,26 ± 9,07 prema 47,85 ± 10,73, P < 0,05). Nakon jedne godine EF se znatno poboljšala u usporedbi s početnim vrijednostima u muškaraca (47,85 ± 10,73 prema 53,01±9,10, P<0,05), dok u žena promjena EF-a nije bila statistički značajna (40,26 ± 9,07 prema 41,73±8,85, P > 0,05) (**tablica 3**). Na kraju razdoblja praćenja EF je bila mnogo niža u skupini žena u usporedbi s muškarcima, što je analizirano s pomoću testa sume rangova (prosječni rang 65,62 prema 115,18, P < 0,05).

Multivarijatne linearne regresijske analize služile su za procjenu učinka spola na EF. U analitički su model uključene varijable kao što su spol, životna dob, pušenje, dijabetes, arterijska hipertenzija, ukupni kolesterol, indeks tjelesne mase (ITM), kreatinin, obiteljska anamneza CAD, višežilna koronarna bolest, početna EF, razdoblje od početka bola do reperfuzije i vrijednost troponina. Regresijska je analiza pokazala da su ženski spol i životna dob neovisni prediktori oporavka EF-a (P < 0,001) (**tablica 4**).

men and women (P>0.05). There was no significant difference between the two groups as far as re-infarction and mortality were concerned (**Table 2**).

At baseline the LVEF in the female group was found to be lower than in the male group, and the difference was statistically significant (40.26±9.07 vs. 47.85±10.73, P<0.05). After one year, LVEF improved significantly in men as compared with baseline (47.85±10.73 vs. 53.01±9.10, P<0.05), while in women the change in EF was not significant (40.26±9.07 vs. 41.73±8.85, P>0.05) (**Table 3**). At follow-up, LVEF was significantly lower in women as compared with men, which was analyzed with a rank sum test (mean rank 65.62 vs. 115.18, P<0.05).

Multivariable linear regression analyses was used for assessment of the effect of gender on LVEF. Indices such as gender, age, smoking, diabetes, hypertension, total cholesterol, body mass index (BMI), creatinine, family history of CAD, multi-vessel disease, baseline LVEF, time interval from pain onset to reperfusion, and troponin were included in the model for analysis. The regression analysis showed that female gender and age were independent predictors of LVEF recovery (P<0.001) (**Table 4**).

TABLE 2. Angiographic variables and procedural outcomes based on gender.

Variable	Women (n/%)	Men (n/%)
Multi-vessel disease	76 / (38%)	98 / (35%)
LAD[a]	120 / (60%)	140 / (50%)
LCX[b]	98 / (49%)	122 / (43%)
RCA[c]	80 / (40%)	98 / (35%)
STEMI[d]	80 / (40%)	120 / (43%)
NSTEMI[e]	120 / (60%)	160 / (57%)
Pain onset to reperfusion time (hours)	14.56±10.05	12±14.30
Re-Infarction	3 / (1.50%)	5 / (1.78%)
Decompensated Cardiac Failure	8 / (4.0%)	7 / (2.5%)
Mortality	4 / (2.00%)	6 / (2.14%)
PCI Procedure		
Single (Culprit) Vessel	198 (99%)	277
Multi-vessel	2 (1%)	3 (1%)
TIMI flow	3	3
Complications – No Flow	3 (1.5%)	4 (2.0%)
Dissection	2 (1%)	3 (1%)

[a] Left Anterior Descending artery
[b] Left Circumflex Artery
[c] Right Coronary artery
[d] ST-segment Elevation Myocardial Infarction
[e] Non-ST-segment Elevation Myocardial Infarction.

TABLE 3. Left ventricular ejection fraction in study groups at baseline and follow-up.

Variable	Female	Male
Baseline LVEF (%)	40.26±9.07	47.85±10.73*
Follow-up LVEF (%)	41.73±8.85	53.01±9.10*

* P ≤ 0.05

LVEF = left ventricular ejection fraction.

TABLE 4. Multivariable regression analysis for predictors of change in left ventricular ejection fraction.

	Multivariable analysis	
	HR (95% CI)	P value
Gender	1.121 (1.102-1.251)	**0.04**
Age	1.299 (1.102-1.611)	**0.03**
Diabetes Mellitus	0.125 (0.101-1.812)	0.15
Hypertension	2.556 (0.112-56.497)	0.59
Body Mass Index	0.691 (0.359-1.299)	0.30
Smoking	1.894 (0.061-65.155)	0.69
Left Ventricular Ejection Fraction	1.112 (0.723-1.587)	0.59
Creatinine	0.892 (0.791-1.056)	0.10
Family History of Coronary Artery Disease	0.985 (0.899-1.010)	0.49
Chest Pain (Time of Onset)	2.451(0.103-13.638)	0.45
Total Cholesterol	1.165 (0.186-6.383)	0.79
Multi Vessel Disease	0.198 (0.010-69.442)	0.59
Troponins	0.114 (0.015-1.895)	0.13

Rasprava

Rezultati ovog istraživanja pokazuju da je oporavak EF-a jednu godinu nakon akutnog MI-ja liječenog primjenom PCI-ja bio lošiji u žena nego u muškaraca. Ovakav učinak na EF može se objasniti na temelju našeg istraživanja zajedno s rezultatima još jedne studije koja je uključivala bolesnike sa STEMI-jem koji je zahvatio prednju stijenku.[4] Više čimbenika može biti odgovorno za ovakve rezultate, uključujući stariju dob u trenutku primitka u bolnicu te viši pobol pri nastupu bolesti u žena. Važnost takvih čimbenika može se potkrijepiti raznim drugim istraživanjima.[4,13,14]

Žene su bile starije dobi u usporedbi s muškarcima. Na temelju postojećih podataka znamo da je kardioprotektivni učinak estrogena odgovoran za kasniji nastup kardiovaskularnih bolesti u žena, što dovodi do činjenice da CAD u žena nastupa u starijoj dobi.[17] Budući da su komorbiditetna stanja češća u starijoj dobi, žene s nastupom bolesti u starijoj dobi pretežno imaju i višu učestalost pridruženih bolesti. Nadalje, dokazano je da je zastupljenost drugih bolesti, kao što je dijabetes, veća u žena, a on se na koronarnoj angiografiji može

Discussion

The results of this study showed that the recovery of LVEF one year after PCI for acute MI was worse in women than men. This effect on LVEF can be explained on the basis of our study in conjunction with another study which considered patients with anterior wall myocardial infarction (STEMI) only.[4] Multiple factors may be responsible for such results, which include older age at the time of presentation and more comorbidities at the time of presentation in women. The importance of such factors can be supported by various other studies.[4,13,14]

Women were of older age as compared to men. Based on established facts, the cardio-protective effect of estrogen is responsible for the delay in the onset of cardiovascular disease in women, which translates into the fact that CAD would present at an older age in women.[17] As comorbidities are more common in old age, women with onset at an older age tend to have higher incidence of comorbidities. Moreover, the prevalence of other diseases such as diabetes has been established to be more common in women, which can present as multivessel disease on coronary angiography.[11,18-23] Findings in the

očitovati kao višežilna bolest.[11,18-23] Podatci iz ovog istraživanja nisu pokazali takvu tendenciju u višežilnoj bolesti u žena, što se može pripisati činjenici da je broj bolesnika s dijabetesom bio podjednak u objema skupinama.

Ovo je istraživanje uključivala bolesnike sa STEMI-jem i s NSTEMI-jem. Razlog za uključivanje bolesnika s NSTEMI-jem bila je činjenica da je EF važan prediktor smrtnosti i u toj skupini. Dodatni je razlog bio u tome što su prethodne studije koje su istraživale utjecaj MI-ja na EF uključivale samo bolesnike sa STEMI-jem. Nema podataka o istraživanjima u bolesnika s NSTEMI-jem.[24]

Dreyer *i sur.*[17] također su pokazali da je vrijeme od početka bolova u prsnom košu do primitka u bolnicu dulje u žena nego u muškaraca. Jedan od glavnih razloga ponuđenih kao objašnjenje jest nedostatak informiranosti o simptomima MI-ja u žena.[19] Produžetak razdoblja od početka simptoma do javljanja u bolnicu uzrokuje teška oštećenja miokarda te posljedično oštećenje funkcije. U ovom je istraživanju uloga takvih zbunjujućih varijabli isključena uključivanjem bolesnika sa sličnim trajanjem bola u prsnom košu. Istraživanja su pokazala da je ženski spol neovisni prediktor pobola i smrtnosti u bolesnika s PCI-ijem nakon MI-ja,[13,14,25,26] što je slučaj i u rezultatima ovog istraživanja.

Ovo je istraživanje imalo nekoliko ograničenja. Prvo, uzorak je bio umjerene veličine, što je posljedica više čimbenika kao što su odbijanje davanja pristanka za uključenje u istraživanje i financijska ograničenja. Drugo, razdoblje praćenja bilo je razmjerno kratko. Smatramo da bi rezultati bili izraženiji u većem uzorku i s duljim razdobljem praćenja.

Zaključak

Prema rezultatima ovog istraživanja, žene nakon MI-ja i izvedenog PCI-ja imale su lošiji oporavak EF-a u usporedbi s muškarcima. Učinak spola očitovao se i u bolesnika sa STEMI-jem i NSTEMI-jem te nije povezan s lokalizacijom promjene u zahvaćenoj koronarnoj žili.

current study did not show such a trend in multi-vessel disease in women, which can be attributed the fact that the number of patients with diabetes was similar in both groups.

This study included patients with STEMI as well as NSTEMI. The reason for the inclusion of NSTEMI patients was that LVEF is an important predictor of mortality in NSTEMI patients as well. Moreover, previous studies of the role of gender in LVEF included only patients with STEMI in the study samples. There is no data of such studies in patients with NSTEMI.[24]

Dreyer *et al.*[17] also demonstrated that the time from onset of chest pain to hospital admission was longer in women as compared with men. One of the main reasons suggested is that women have a lack of awareness of MI symptoms.[19] A prolonged time interval from onset of symptoms to presentation at a hospital leads to severe myocardial damage and hence impaired function. In this study, the role of such confounding variables was ruled out by including patients presenting with similar duration of chest pain. Studies have demonstrated that being female is an independent predictor of morbidity and mortality in patients with MI after PCI,[13,14,25,26] which was also reflected in the results from our study.

The present study had a few limitations. First, the sample size was moderate, which is due to a number of factors such as not giving consent for inclusion in the study and financial constraints. Second, the follow-up period was relatively short. We believe that the results would be more pronounced with a larger sample and longer follow-up period.

Conclusion

In this study, we found that women had a poorer recovery of LVEF as compared with men after PCI. This gender-specific effect was present in both STEMI and NSTEMI patients and is not related to the coronary vessel involved.

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