

Infarkt miokarda i fibrilacija atrijske: postoje li razlike između žena i muškaraca?

Myocardial Infarction and Atrial Fibrillation: Are there Differences between Men and Women?

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SAŽETAK: Žene s akutnim infarktomiokarda s elevacijom ST-segmenta primaju još uvijek suboptimalnu skrb i imaju lošiji ishod nakon infarkta miokarda (IM) nego muški spol. Američka udruga *American Heart Association* osvijestila je razlike u zbrinjavanju akutnog infarkta miokarda između muškaraca i žena te je postavila medicinsko zbrinjavanje žena s IM-om kao prioritet zdravstvene usluge. Fibrilacija atrijske (FA) u žena danas se još uvijek ne liječi adekvatno oralnim antikoagulantnim lijekovima, a povezana je s češćim moždanim udarom. U liječenju FA-a u žena češće se primjenjuje kontrola frekvencije, a rjeđe kontrola ritma. Žene se rjeđe podvrgavaju invazivnim kardiovaskularnim procedurama. Prevencija moždanog udara odrednica je liječenja FA-a.

SUMMARY: Today, women with ST-elevation myocardial infarction receive suboptimal management and have worse outcomes than men, with higher rates of in-hospital adverse events and higher mortality. In 2017, the American Heart Association identified "closing knowledge gaps on acute myocardial infarction and treatments for women" as a public health priority. There are sex-specific differences in the management of atrial fibrillation (AF). Women with AF receive suboptimal management and are significantly less likely to receive therapeutic anticoagulation, attempt rhythm control, or undergo invasive cardiovascular procedures. Stroke prevention still remains central to the management of AF.

KLJUČNE RIJEČI: žene, infarkt miokarda, fibrilacija atrijske.

KEYWORDS: women, myocardial infarction, atrial fibrillation.

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Danas, unatoč bitnim napredcima u prevenciji bolesti i zdravstvenoj zaštiti, kao i produženom očekivanom trajanju života, sve se više se navodi potrebnost kvalitete zdravstvene usluge te je nevjerojatno da još uvijek ima razlika između muškaraca i žena u dijagnostičkoj zbrinjavanju fibrilacije atrijske ili infarkta miokarda¹⁻³. To se očituje u lošijem kliničkom ishodu s višom stopom neželjenih ishoda tijekom hospitalizacije i višom smrtnošću žena⁴. *American Heart Association* uočila je potrebu osvješćivanja problema razlike u zbrinjavanju akutnog infarkta miokarda između muškaraca i žena te je kao prioritet postavila jednakost medicinskoga zbrinjavanja žena (i muškaraca) s infarktom miokarda (IM)⁵.

S obzirom na to da postoje fiziološke razlike u samom elektrokardiogramu (EKG) između muškaraca i žena te da žene imaju vrlo često atipičnu

The necessity for quality health services has been increasingly emphasized recently despite significant advances in disease prevention and health care as well as an increase in expected lifespan. It is incredible there are still differences between men and women in diagnostic management of atrial fibrillation or myocardial infarction¹⁻³. These differences also manifest in higher mortality and poorer clinical outcomes in women, with higher rates of unwanted outcomes during hospitalization⁴. The American Heart Association emphasized the need to raise awareness of the differences in the management of acute myocardial infarction between men and women and prioritized achieving equality in medical management for women (and men) with myocardial infarction (MI)⁵.

Given that there are physiological differences in the electrocardiograms (ECG) themselves be-

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kliničku sliku IM-a i mnogo češće mikrovaskularnu bolest, smatramo da je iznimno važno u svakodnevnom radu provoditi jednaki pristup zdravstvene zaštite žena s IM-om i fibrilacijom atrijske (FA).

Fiziološke razlike u elektrokardiogramu između muškaraca i žena

Ono što se može uočiti kao „ženski EKG“ jest J-točka niža od 0,1 mV u prekordijalnim odvodima uz naglu tranziciju od QRS-kompleksa prema ST-segmentu u prekordijalnim odvodima. „Muški oblik“ EKG-a ima J-točku višu od 0,1 mV u najmanje jednom od četiriju odvoda i ST-kut je ≥ 20 stupnjeva u najmanje jednom od tih odvoda. Često nalazimo tzv. juvenilni oblik EKG-a (negativni T-val u odvodu V1) kao normalnu varijaciju „ženskog EKG-a“ pa stoga posebno mjesto u analizi EKG-a ima T-val⁶. Repolarizacija je pod utjecajem ženskih hormona, posebice funkcioniranje kalijevih kanala. Stoga je QTc interval mnogo duži u žena nego u muškaraca u svim dobnim skupinama (promatrano od 17 do 75 godina)⁷. Jednake promjene repolarizacije u žena uočene su i pri mjerenju T-alternansa.

Postoji hipoteza da razlika u EKG-u između žena i muškaraca nastaje zbog utjecaja razine testosterona, a tomu pridonosi i analiza EKG-a u muškaraca koji su orhidektomirani. U žena koje se koriste hormonskim nadomjesnim liječenjem nisu utvrđene znatne promjene QT-interval, no moguća je prolongacija QT-a u žena u drugoj fazi menstrualnog ciklusa^{6,7}. Stoga treba biti oprezan pri primjeni lijekova u žena koji produljuju QT-interval.

Razlike u dijagnostici i zbrinjavanju koronarne bolesti srca

Metaanaliza 74 studije koja je uključila 13 331 ženu i 11 511 muškaraca pokazala je da je atipična angina 11 – 27 % češća u žena mlađih od 65 godina nego u žena starijih od 75 godina kao i u muškaraca⁸. Angiografski je više od 50 % takvih ispitanica imalo suženje koronarnih žila koje je bilo manje od 50 %, dok su ostale imale minimalnu stenozu ili uopće nisu imale koronarnu bolest srca (KBS). Neopstruktivna KBS češće se dijagnosticira u mlađih žena koje se prezentiraju akutnim koronarnim sindromom⁹. Žene s akutnim infarktom miokarda s elevacijom ST-segmenta (STEMI) imale su češće neopstruktivnu KBS u usporedbi s muškarcima (10 – 25 % prema 6 – 10 %). Neopstruktivna KBS i atipična bol pridonosi dvostruko većem riziku od nefatalnog IM-a u usporedbi s asimptomatskim ženama¹⁰. Problem u neprepoznavanju i neadekvatnom zbrinjavanju žena s KBS-om najčešće je u dijagnostičkom postupku: najčešće je primjenjivani test opterećenja. Međutim, u žena je senzitivnost testa 61 %, a specifičnost 70 %. U muškaraca je senzitivnost 72 %, a specifičnost 77 %. Osim toga, do 14 % žena ima lažno pozitivan nalaz. Stoga je nužno u dijagnostičkom postupku u žena koristiti se drugim metodama.

Preporučuje se stoga pri sumnji na KBS i nejasnom nalažu ergometrije koristiti se stres-ehokardiografijom ili jednom od perfuzijskih metoda. Pozitronska emisijska tomografija (SPECT) neinvazivna je metoda s visokom senzitivnošću (95 %) i nešto manjom specifičnošću, a u praksi se vrlo dobrim pokazala i primjena vazodilatatora (dipiridamola) u stres-testu (senzitivnost 95 do 100 %, a specifičnost do 89 %)¹¹.

tween men and women and that women often have a very atypical clinical picture for MI as well as a much higher prevalence of microvascular diseases, we believe it is extremely important to apply the same health care approach in the protection of women with MI and atrial fibrillation (AF) in everyday practice.

Physiological differences in electrocardiograms between men and women

What can be identified as the “female ECG” is a J point lower than 0.1 mV in the precordial leads with a sudden transition from QRS complex to ST segment in precordial leads. The “male form” of ECG has a J point higher than 0.1 mV in at least one of the four leads and an ST angle of ≥ 20 in at least one of those leads. We often find the so-called juvenile form of ECG (negative T-wave in the V1 lead) as a normal variation of “female ECG”; consequently, T-waves have a special role in ECG analysis⁶. Repolarization is under the influence of female hormones, especially the function of calcium channels, causing the QTc interval to be significantly longer in women than in men in all age groups (studied for ages 17-75)⁷. The same repolarization changes in women were also found when measuring T-wave alternans.

According to one hypothesis, the ECG difference between men and women is caused by the influence of testosterone levels, which is corroborated by ECG analysis in men who underwent orchiectomy. No significant changes in QT intervals were found in women receiving hormone supplement treatment, but QT prolongation is possible in women who are in the second phase of the menstrual cycle^{6,7}. One must thus be careful in applying medication in women with prolonged QT intervals.

Differences in diagnostics and treatment of coronary artery disease

A meta-analysis of 74 studies which included 13,331 women and 11,511 men showed that atypical angina is 11-27% more common in women under 65 years of age than in men and women older than 75⁸. Angiographically, more than 50% of these female subjects had coronary vessel constriction that was lower than 50%, while the rest had minimal stenosis or no coronary artery disease (CAD) at all. Non-obstructive CAD is more often diagnosed in younger women who present with acute coronary syndrome⁹. Women with acute myocardial infarction with ST segment elevation (STEMI) had non-obstructive CAD more frequently compared with men (10-25% vs. 6-10%, respectively). Non-obstructive CAD and atypical pain contribute to a risk of non-fatal MI that is twice as high than that of asymptomatic women¹⁰. The failure to recognize and adequately treat women with CAD usually lies in the diagnostic procedure: the stress test is the one that is most frequently used. However, the sensitivity and specificity of this test in women is 61% and 70%, respectively. In men, the sensitivity and specificity are 72% and 77%, respectively. In addition, up to 14% of women have a false-positive result. It is thus necessary to apply different methods in the diagnostic procedure for women.

The use of stress echocardiography or one of the perfusion methods is thus recommended when suspecting CAD and in case of unclear stress test results. Positron emission tomography (SPECT) is a non-invasive method with high sensitivity (95%) and somewhat lower specificity, and the use of vasodila-

Uspoređujući dostupnost transradijalnoga pristupa perkutanoj koronarnoj intervenciji (PCI) za zbrinjavanje STEMI-ja u žena u odnosu prema muškarcima tijekom 2017./2018. godine, u američkim je istraživanjima uočena njegova nedostatnost. Iako najveću korist od primarnog PCI-ija imaju upravo žene s transradijalnim pristupom (kojim se smanjuju komplikacije poput krvarenja), isti se primjenjuje mnogo rjeđe nego u muškaraca^{12,13}. Neovisni čimbenici rizika od krvarenja nakon PCI-ja upravo su prezentacija STEMI-ja i ženski spol koji su povezani s povišenom smrtnošću nakon STEMI-ja. Upravo je u žena sa STEMI-jem izazov uskladiti i postići ravnotežu lijekovima koji omogućuju potrebnu antitrombotičnu/agregacijsku zaštitu bez povišenog rizika od krvarenja. Huded *et al.* u istraživanju iz 2018. godine navode mogućnost smanjenja rizika od krvarenja za 5,4 % i smanjenja broja transfuzija eritrocita za 3,9 % u žena sa STEMI-jem ako se primijeni jedinstveni dijagnostički sustav (*4-step STEMI protocol*) uz farmakološku terapiju temeljenu na smjernicama (*guideline-directed medical therapy; GDMT*)¹³. U istraživanju je bio uspoređivan prethodni dijagnostički postupak zbrinjavanja s novopredloženim: obuhvaćena su ukupno 1272 ispitanika sa STEMI-jem (68 % muškaraca, 32 % žena), a žene su bile starije i imale više pridruženih kroničnih bolesti. Ispitanici su bili podijeljeni u dvije skupine: skupinu u kojoj se novopredloženi postupnik GDMT redovito primjenjivao i kontrolnu skupinu u kojoj se GDMT prije PCI-ja manje primjenjivao. Žene u kontrolnoj skupini imale su višu učestalost moždanog udara u bolnici, vaskularne komplikacije, krvarenje, transfuzije i smrtnost. U skupini s novopredloženim postupnikom postignuto je sniženje 30-dnevne smrtnosti žena (3,2 % viša u žena nego u muškaraca; $p = 0,090$) u usporedbi s kontrolnom skupinom (6,1% viša u žena nego u muškaraca; $p = 0,002$)¹³.

Fibrilacija atrijsa u žena

Procjenjuje se da je 2010. godine u svijetu 20,9 milijuna muškaraca i 12,6 milijuna žena bolovalo od fibrilacije atrijsa (FA)¹⁴. Smatra se da će do 2030. godine Europska unija imati 14 do 17 milijuna bolesnika s FA-om, tj. da se svake godine dijagnosticira 120 000 do 250 000 novih bolesnika. Prevalencija FA-a u muškaraca iznosi 596 na 100 000 osoba, a u žena je niža: 373 na 100 000 osoba. Kako populacija stari, prevalencija i troškovi vezani za zbrinjavanje FA-a neprekidno rastu.

Rizični čimbenici za FA najčešće su šećerna bolest, arterijska hipertenzija, povećani indeks tjelesne mase (ITM), porast životne dobi, pušenje, kao i KBS¹⁴. Tijekom prošlih desetljeća spomenuti su se čimbenici promijenili i u muškaraca i u žena: na prvo mjesto izbili su povećan ITM, neregulirana arterijska hipertenzija, tj. metabolički sindrom koji čine neke od rizičnih čimbenika nastanka i kronične bubrežne bolesti¹⁵. Dosašnje studije nisu pokazale utjecaj hormonske terapije na pojavu FA-a, posebno ne hormonskoga nadomjesnog liječenja u postmenopauzi. Međutim, najveće su se razlike pokazale u liječenju žena s FA-om i povećanim rizikom za dobivanje moždanog udara¹⁶.

Najviše podataka pružaju studije o antikoagulantnim lijekovima, iako su i u njima žene uključene u manjem broju (35 do 40 % svih ispitanika). U svim do sada provedenim studijama uočeno je povećani rizik za dobivanje moždanog udara u žena s FA-om, posebice u žena koje imaju srčano popuštanje s očuvanom sistoličkom funkcijom (HFpEF). Ženski je spol neovisni čimbenik rizika za moždani udar prouzročen FA-om i za

tors (dipyridamole) during stress tests has also been shown to be effective (sensitivity 95% to 100%, specificity 89%)¹¹.

American studies conducted in 2017/2018 that compared the availability of the transradial approach in percutaneous coronary intervention (PCI) for the treatment of STEMI in women compared with men found that it was unsatisfactory for women. Although it is women with transradial approach who benefit most from primary PCI (reducing complications such as bleeding), it is applied far more rarely than in men^{12,13}. Independent risk factors for bleeding after PCI are STEMI presentation and the female sex, which are associated with higher mortality after STEMI. The challenge in women with STEMI is to coordinate and balance medications that allow for the necessary antithrombotic/aggregation protection without increased risk of bleeding. Huded *et al.* in a study from 2018 on women with STEMI found a reduction in bleeding risk and the number of erythrocyte transfusions of 5.4% and 3.9%, respectively, as a result of the application of a unique diagnostic system (4-step STEMI protocol) in addition to guideline-directed medical therapy (GDMT)¹³. The study compared the previous diagnostic management procedure with the newly suggested one: there was a total of 1,272 participants with STEMI (68% men, 32% women); the women were older and had more comorbid chronic diseases. The participants were divided into two groups: the group in which the new GDMT was applied regularly and the control group where the GDMT was applied less regularly before PCI. The women in the control group had a higher incidence of in-hospital stroke, vascular complications, bleeding, transfusion, and mortality. The group using the new GDMT approach achieved a reduction in 30-day mortality in women (3.2% higher in women in comparison with men, $p = 0.090$) in comparison with the control group (6.1% higher in women than in men, $p = 0.002$)¹³.

Atrial fibrillation in women

It is estimated that in 2010 20.9 million men and 12.6 million women suffered from atrial fibrillation (AF) globally¹⁴. It is believed that by 2030 the European Union will have 14 to 17 million patients with AF, i.e. that approximately 120,000 to 250,000 new patients are diagnosed every year. The prevalence of AF in men is 596 per 100,000 persons and is lower in women: 373 per 100,000 persons. As the overall population ages, the prevalence and financial burden associated with AF management are constantly increasing.

The risk factors for AF are usually diabetes, arterial hypertension, increased body-mass index (BMI), advanced age, smoking, and CAD¹⁴. Over the past decades, these factors have changed both in women and in men: the first places were taken by increased BMI, unregulated arterial hypertension, and metabolic syndrome, which also represent some of the risk factors for the development of chronic renal disease¹⁵. Current studies have not found an influence of hormone therapy on the manifestation of AF, especially not for postmenopausal hormone supplementation. However, the most significant differences were observed in the treatment of women with AF and increased risk of stroke¹⁶.

Most of the data comes from anticoagulant medication studies, although they also include women in smaller numbers (35-40% of total participants). All studies to date found increased risk of suffering stroke in women with AF, especially with women who had heart failure with preserved ejection

sustavnu tromboemboliju. To je uvršteno i u CHA₂DS₂-VASc bodovni sustav (kongestivno zatajivanje srca / sistolička disfunkcija, hipertenzija, dob >65, diabetes mellitus, moždani udar /TIA/ tromboembolizam, vaskularna bolest, ženski spol). Svaki navedeni parametar pridonosi ukupnome broju (0 – 9) koji upućuje na stupanj rizika od moždanog udara¹⁷. Ženski je spol uvršten i za procjenu rizika od krvarenja u tzv. HAS-BLED bodovni sustav (hipertenzija, poremećaj funkcije bubrega ili jetre, prethodni moždani udar, kao i anamnestički podatak o krvarenju). Svaki navedeni parametar pridonosi ukupnome broju (0 – 9) koji upućuje na rizik od velikoga krvarenja unutar godine dana¹⁸. Krvarenje uz liječenje oralnim antikoagulantnim lijekovima zbog FA pojavljuje se češće u starije populacije (češće žene) i onih s kroničnim bolestima. Krvarenje je češće u osoba s kroničnom bubrežnom bolesti, kao i zbog interakcija lijekova (tvari koje induciraju P-gp sistem u jetri, npr. rifampicin i gospina trava), ili ga inhibiraju (statini, antiaritmici, antifungici, antivirusni lijekovi)¹⁹.

Mnoga su istraživanja pokazala razliku u upotrebi antikoagulantnih lijekova između žena i muškaraca²⁰. Razlika se prati i kroz populacije i kroz različite dobne skupine. Ako se gleda dugogodišnje praćenje (2 – 5,3 godine) muškarci s FA-om imaju viši rizik od smrti negoli žene. Prema rezultatima istraživanja, ključne su razlike u liječenju žena: u povećanom protrombotskom stanju u žena, različitom cerebralnom protoku krvi, genskoj predispoziciji, pa i sociokulturnim uzrocima (kasnije traženje medicinske pomoći, primjena varfarina). U liječenju FA-a u žena primijećeno je da su one češće podvrgnute kontroli frekvencije, a rjeđe kontroli ritma²¹.

Što se tiče kateterske ablacije FA-a, žene podvrgnute tom postupku bile su više životne dobi, dok su ishodi i komplikacije bili podjednaki kao u skupini muškaraca. Što se tiče razlika u sklonosti krvarenju, provedene su *post hoc* analize u svim većim istraživanjima novih antikoagulantnih lijekova i u njima nisu nađene znatne spolne razlike glede većih krvarenja. Analize ARISTOTLE i ROCKET AF pokazale su da je rizik od krvarenja manji u žena nego u muškaraca.

Zaključak

Klinička slika KBS-a može se očitovati drukčije u žena mlađih od 65 godina u usporedbi sa starijim ženama i muškarcima: češće se nalaze atipične tegobe, znojenje, umor, kratkoća daha, dispneja i atipični bol. Stoga sustavni pristup zbrinjavanju STEMI-ja pridonosi smanjenju razlika u zbrinjavanju i ishodu među spolovima.

U usporedbi s drugim područjima moderne kardiologije ima još uvijek nedoumica u svakodnevnom radu vezanih uz razlike između spolova u zbrinjavanju FA-a. Upravo bi različitosti (posebice u mlađoj dobi zbog hormonske različitosti) mogle pridonijeti terapijskoj opciji (kontrola ritma, a ne samo frekvencije) i prognozi (primarno prevencija moždanog udara).

fraction (HFpEF). Female sex is an independent risk factor for stroke caused by AF and for systemic thromboembolism. It was included in the CHA₂DS₂-VASc scoring system (congestive heart failure/systolic dysfunction/hypertension/age>65, diabetes, stroke/TIA/thromboembolism, vascular disease, female sex). All of the parameters contribute to the final score (0-9) that indicates the risk level for stroke¹⁷. Female sex has also been included in the risk assessment in the HAS-BLED scoring system (hypertension, functional disorder of the liver or kidneys, history of stroke, and history of bleeding). Each of the parameters contributes to the final score (0-9) that indicates the risk of major bleeding within a year¹⁸. Bleeding from anticoagulation medication for AF is more common in the older population (and in women) as well as in patients with chronic diseases. It is also more common in persons with chronic renal disease and due to medication interactions (substances that induce the P-gp system in the liver (for instance rifampicin and St John's wort) or inhibit it (statins, antiarrhythmics, antifungal and antiviral medication)¹⁹.

Many studies have found a difference in the use of anticoagulation medication between men and women²⁰. Differences has also been found among populations and different age groups. In long-term follow-up (2-5.3 years), men with AF had a higher risk of death compared with women. According to study results, the differences in the treatment of women are crucial: in the elevated prothrombine state in women, different cerebral blood flow, genetic predisposition, and socio-cultural causes (later seeking of medical aid, application of warfarin). In the treatment of AF in women, it has been noted that they are more often subjected to frequency control and more rarely to rhythm control²¹.

As far as catheter ablation for AF is concerned, women who underwent it were of a more advanced age, whereas the outcomes and complications were similar as in the male group. Regarding differences in bleeding propensity, *post hoc* analyses performed in all larger studies of new anticoagulation medication did not find significant differences in major bleeding between the sexes. The ARISTOTLE and ROCKET AF analyses demonstrated that the risk of bleeding is lower in women than in men.

Conclusion

The clinical picture of CAD can present differently in women younger than 65 in comparison with men and older women: atypical symptoms are more common, as well as sweating, fatigue, shortness of breath, dyspnea, and atypical pain. Therefore, a systemic approach to STEMI management contributes to a reduction in the differences in management and outcomes among the sexes.

In comparison with other fields in modern cardiology, there are still unclarified questions regarding everyday practice related to the differences among the sexes and AF management. It is these differences that could (especially at a young age due to hormonal differences) contribute to treatment options (controlling rhythm, not just frequency) and prognosis (primarily stroke prevention).

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