Pretilost i fibrilacija atrija

Obesity and atrial fibrillation

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SAŽETAK: Pretilost se kao zdravstveni poremećaj povezuje s brojnim kroničnim bolestima. Rezultati većine istraživanja pokazuju pozitivnu povezanost patofizioloških procesa u osoba prekomjerne tjelesne mase s nastankom fibrilacije atrija (FA), njezinih komplikacija te uspješnosti liječenja. Povećano volumno opterećenje srca pri pretilosti te prekomjerno nakupljanje epikardijalnoga masnoga tkiva smatraju se glavnim uzrocima za nastanak FA-a. Osim toga, neka druga stanja poput opstruktivne apneje u spavanju mogu utjecati na ishode liječenja i učestalost pojavnosti FA-a. Ipak, postoje istraživanja koja daju oprečne rezultate. Rezultati istraživanja provedenog na Klinici za bolesti srca i krvnih žila Kliničkog bolničkog centra Zagreb pokazali su da strukturni plan gubitka tjelesne mase smanjuje kardiometabolički rizik, a samim time i inzulinsku rezistenciju, te upalne procese u tijelu za koje se vjeruje da su bitan čimbenik nastanka FA-a. Vjerujemo kako bi se promjenom životnih navika, prije svega povećanjem tjelesne aktivnosti i smanjenjem sjedilačkog načina života, u bolesnika s povišenom tjelesnom masom moglo postići i smanjenje incidencije FA-a.

SUMMARY: As a health disorder, obesity is associated with many chronic diseases. Most study results indicate a positive association between pathophysiological processes in persons with excess body weight and the development of atrial fibrillation (AF), AF complications, and treatment success. Increased cardiac volume load in obesity and excess accumulation of epicardial adipose tissue are considered to be the main reasons for the development of AF. Additionally, some other conditions such as obstructive sleep apnea can influence treatment results and AF incidence. However, some studies have reported contradicting results. The results of this study performed at the Clinic for Cardiovascular Diseases at the Zagreb University Hospital Centre showed that a structured plan of body weight loss reduced cardiometabolic risk and thus also insulin resistance as well as inflammatory processes in the body that are considered to be an important factor for the development of AF. We believe that changing lifestyle habits, primarily through increased physical activity and reducing the sedentary lifestyle, could achieve a reduction of AF incidence in patients with increased body mass.

KLJUČNE RIJEČI: pretilost, fibrilacija atrija, aritmije.

KEYWORDS: obesity, atrial fibrillation, arrhythmias.

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Uvod

Pretilost u modernome svijetu, kao glavni preventabilni čimbenik rizika od nastanka kroničnih nezaraznih bolesti i smrti, sve je veći javnozdravstveni problem. Prevalencija pretilosti od 1975. do 2016. godine gotovo se utrostručila. U Hrvatskoj 57,4 % osoba starijih od 18 godina ima indeks tjelesne mase (ITM) viši od 25 kg/m^2, od čega 38,7 % ima prekomjernu tjelesnu masu, a 18,7 % pretilost. Stratifikacijom prema spolu, pretilost ima 20,8 % muškaraca te 16,8 % žena.[1] Istraživanja pokazuju da porast srednje vrijednosti ITM-a od 1,31 kg/m^2 u žena te 1,41 kg/m^2 u muškaraca skraćuje očekivano trajanje života za jednu godinu.[2]

Introduction

As the main preventable risk factor for the development of chronic non-infectious diseases and death, obesity is a growing public health issue in the modern world. The prevalence of obesity has nearly doubled between 1975 and 2016. In Croatia, 57.4% persons older than 18 have a body-mass index (BMI) higher than 25 kg/m^2, of which 38.7% are overweight and 18.7% obese. When stratified according to sex, obesity is present in 20.8% men and 16.8% women.[1] Studies have shown that increase in mean BMI from 1.31 kg/m^2 in women and 1.41 kg/m^2 in men reduces the expected lifespan by one year.[2]

Povezanost i utjecaj pretilosti na nastanak fibrilacije atrija (FA) postala je jasnija nakon objave metaanalitičkog istraživanja prema kojemu svaki jedinični porast ITM-a povećava rizik od FA za 3,5 – 5,3 %.[3] Pretilost (definirana ITM >30 kg/m^2) zajedno s arterijskom hipertenzijom (definirana povišenim vrijednostima arterijskoga tlaka >139/89 mmHg), prekomjernom konzumacijom alkohola, dijabetesom, pušenjem te hiperlipidemijom uzrokuje pogoršanje dijastoličke funkcije srca te potiče upalu i odlaganje masnoga tkiva u području perikarda.[4,5]

Utjecaj pretilosti na FA može se promatrati preko nekoliko varijabli.

a) Volumen krvi. U pretilih osoba povećani volumen krvi opterećuje srce te dovodi do hipertrofije i u konačnici do dilatacije. Povećanje lijevog atrija (LA), kao posljedice volumnog preopterećenja, dobro je poznat etiološki čimbenik u nastanku FA-a.[6] Mnoga su istraživanja pokazala da je pretilost neovisni prediktor nastanka ventrikulske dijastoličke disfunkcije koja je također rizični faktor za nastanak FA-a.[7] Abed *i sur.* u svojemu su randomiziranom *case-control* istraživanju[8] dokazali da se u ispitanika koji su bili podvrgnuti strogo kontroliranoj tjelesnoj aktivnosti i kontroli prehrane smanjila tjelesna težina, a time se poboljšala i dijastolička funkcije srca i smanjili simptomi FA. Transtorakalnom ehokardiografijom uočilo se i poboljšanje strukture srca, smanjenje volumena LA te debljine septuma i stražnje stijenke miokarda. U kontrolnoj skupini ispitanici su bili usmeno savjetovani o promjeni prehrane i tjelesnoj aktivnosti, no njihovi rezultati nisu bili značajni.

b) Perikardijalno masno tkivo. Framinghamsko istraživanje zajedno s još jednim kohortnim istraživanjem („*Third Generation Cohorts*"), u kojemu je sudjelovalo 2317 ispitanika, dokazalo je povezanost prevalencije FA-a s volumenom masnoga tkiva u perikardu izmjerenim CT-om.[9] Spomenuto istraživanje upućuje na važnost smještaja masnoga tkiva, dok je njegova ukupna količina u tijelu manje bitna. Prema tome, perikardijalno masno tkivo jače je povezano s prevalencijom FA-a nego masno tkivo prsnoga koša i abdomena. Epikardijalno masno tkivo u izravnom je kontaktu s miokardom s kojim dijeli mikrocirkulaciju te je metabolički aktivno.[10] Godine 2010. objavljeno je istraživanje Chekakiea *i sur.*[11] koje pokazuje da svaki porast volumena masnoga tkiva perikarda od 10 mL za 13 % povećava šansu za nastanak FA-a. Wong *i sur.* također dokazuju isto, uz zaključak da se porastom količine perikardijalnoga masnoga tkiva povećavaju i šanse za rekurentnu FA nakon kateterske ablacije.[12] Iako je istraživan utjecaj masnoga tkiva cijelog perikarda, smatra se da bi periatrijalno masno tkivo moglo biti važniji prediktor u nastanku FA-a.[13] Upravo je to u svojem istraživanju potvrdio Gierd uočivši jaču povezanost faktora upale i debljine periatrijalnoga masnoga tkiva.[14]

c) Sindrom opstruktivne apneje u spavanju. Mehanizam povezanosti FA-a i opstruktivne apneje u spavanju još uvijek nije razjašnjen, no postavljene su dvije moguće teorije koje bi mogle razriješiti ovu pojavu. Prva govori o rastezanju atrija i pulmonalnih vena zbog apneje, što uzrokuje drastične promjene transmuralnoga tlaka i posljedičnu dilataciju atrija.[15] Druga povezuje nastanak FA-a s aktivacijom vagusa zbog negativnoga trahealnog tlaka u apneji.[16] Težina apneje u spavanju može biti uzrok rezistencije FA-a na antiaritmičku terapiju.[17]

Pojava FA-a uočena je pri upalnim stanjima kao što su perikarditis i miokarditis i nakon njih te pri stanjima nakon razli-

The association and influence between obesity and the development of atrial fibrillation (AF) has become clearer after the publication of a metanalysis according to which every round-number increase in BMI increased the risk of AF by 3.5-5.3%.[3] Obesity (defined as BMI >30 kg/m^2) together with arterial hypertension (defined as increased arterial pressure values >139/89 mmHg), excessive consumption of alcohol, diabetes, smoking, and hyperlipidemia causes deterioration of the diastolic function of the heart and leads to inflammation and fatty tissue deposits in the pericardium.[4,5]

The influence of obesity on AF can be evaluated through several other variables:

a) Blood volume. Increased blood volume in obese persons creates a load on the heart and leads to hypertrophy and ultimately to dilatation. Left atrial (LA) enlargement as a consequence of volume overload is a well-known etiological factor for the development of AF.[6] Many studies have shown that obesity is an independent predictor for the development of ventricular diastolic disfunction, which is also a risk factor for the development of AF.[7] Abed *et al.* performed a randomized case-control study[8] demonstrating that participants who underwent strictly controlled physical activity and diet control experienced a reduction in body weight and improvement in diastolic heart function and reduced AF symptoms. Transthoracic echocardiography also showed improved heart structure, a reduction in LA volume and septum and inner myocardial wall thickness. Participants in the control group were orally advised on changes to diet and physical activity, but their results were not significant.

b) Pericardial fatty tissue. The Framingham Heart Study together with another cohort study (*Third Generation Cohorts*) that included 2317 participants demonstrated an association between AF prevalence with pericardial fatty tissue volume as measured by CT.[9] This study indicates the important of the localization of fatty tissue, whereas its total volume in the body is less important. Pericardial fatty tissue is thus more strongly associated with AF prevalence than fatty tissue in the chest or abdomen. Epicardial fatty tissue is in direct contact with the myocardium, with which is shares microcirculation, and is metabolically active.[10] A study published in 2010 by Chekakiea *et al.*[11] showed that every increase in pericardial fatty tissue of 10 mL increases the chance of AF development by 13%. Wong *et al.* also presented the same results, with the conclusion that increase in pericardial fatty tissue also increases the chances of recurrent AF after catheter ablation.[12] Although the influence of the fatty tissue in the pericardium as a whole was studied, it is believed that periatrial fatty tissue might be a more important predictor for the development of AF.[13] This was confirmed in a study by Gierd, which noted a stronger correlation of inflammatory factors and pericardial fatty tissue thickness.[14]

c) Obstructive sleep apnea syndrome. The mechanism of the association between AF and obstructive sleep apnea has still not been elucidated, but two possible theories have been established that could explain this phenomenon. The first focuses on distension of the atrium and pulmonary arteries due to apnea, which causes drastic changes in transmural pressure and consequent atrial dilatation.[15] The second theory connects the development of AF with vagus nerve activation due to negative tracheal pressure in apnea.[16] Sleep apnea severity can be the cause of AF resistance to antiarrhythmic therapy.[17]

Development of AF has been observed in inflammatory states such as pericarditis and myocarditis as well as after

čitih kardiokirurških operacija.[18] Tako je i pretilost kao upalno stanje mogući „okidač" nastanka FA-a. Mnoga su istraživana usmjerena na dokazivanje povezanosti adiponektina i leptina s nastankom FA-a pa je tako na životinjskim modelima uočeno da leptin ima ulogu u ožiljkavanju atrija i posljedičnom nastanku FA-a.[19] Adiponektin je prije smatran zaštitnim faktorom u upali potaknutoj pretjeranim odlaganjem masnoga tkiva. No današnja istraživanja pokazuju da pokatkad i povećane razine adiponektina imaju zaštitnu ulogu.[20]

Iako mnoga istraživanja ispituju utjecaj tjelesne mase na prognozu FA-a, rezultati i dalje ostaju kontroverzni, pa je stoga važno svako istraživanje koje može pridonijeti boljem razumijevanju ovoga sve prisutnijeg problema današnjega životnog stila.

Bolesnici i metode

Istraživanje je provedeno u sklopu Dnevne bolnice Zavoda za endokrinologiju Kliničkog bolničkog centra (KBC) Zagreb između 2013. i 2016. godine kako bismo istražili utjecaj gubitka tjelesne težine na kardiovaskularne čimbenike rizika te na strukturno i funkcionalno remodeliranje srca. Uključeno je 85 pretilih ispitanika (56 žena i 29 muškaraca) prosječne dobi 58 godina (raspona od 36 do 71 godine). Kontrolna je skupina sadržavala 40 bolesnika podjednake dobi i spola koji su samo primili savjete za mršavljenje, ali nisu redovito nadzirani, dok je ukupno 45 bolesnika bilo podvrgnuto intenzivnom programu redukcije tjelesne težine poznatijemu kao „Ambulantni petodnevni program mršavljenja" u sklopu Dnevne bolnice KBC-a Zagreb. Razlike između spolova nisu bile uspoređivane.

Pojam „Ambulantni petodnevni program" obuhvaćao je profesionalnu strukturiranu i vođenu promjenu životnoga stila, promjenu prehrane, pojačane tjelesne aktivnosti i regulacije kvalitete i trajanja sna. Svi su bolesnici praćeni ambulantno preko poliklinike tijekom 12 mjeseci, u tromjesečnim intervalima, te im je predloženo unaprjeđenje životnoga stila (npr. smanjenje obroka, dijeta redukcijska u kcal) i spoznaja prehrambenih navika (hrana s niskim glikemijskim indeksom, adekvatna hidratacija 1600 mL vode, pojačana tjelesna aktivnost uz individualno savjetovanje i češće od 3 mjeseca te mogućnost ranije telefonske konzultacije). Na početku i tijekom praćenja, kao i na kraju razdoblja od 12 mjeseci provedeni su analiza kardiovaskularnih čimbenika rizika, ehokardiografija, ergometrija, 24-satno snimanje EKG-a (holter EKG) i 24-satno kontinuirano mjerenje arterijskog tlaka (KMAT). U svih je bolesnika na početku i nakon praćenja u krvi određena razina CRP-a, razina glikemije i inzulina te je izračunan HOMA indeks (određivanje inzulinske rezistencije; serumski inzulin natašte (μU/mL) × glukoza u plazmi natašte (mmol/L) / 22,5).[21]

Isključeni su bili bolesnici s kroničnom bubrežnom bolesti, šećernom bolesti tipa 2, šećernom bolesti tipa 1, infekcijom ili bilo kojim akutnim stanjima.

Bolesnici su imali potpisani informirani pristanak, a istraživanje je provedeno u skladu s etičkim načelima.

Svi su rezultati analizirani t-testom za male parne uzorke koji su bili sami sebi kontrola.

Rezultati

Rezultati istraživanja pokazali su statistički značajno poboljšanje volumena lijevog i desnog atrija, smanjenu masu ventrikula, smanjenje sistoličkoga tlaka i poboljšane rezultate er-

these states as a consequence of various cardiosurgical procedures.[18] Obesity is, as an inflammatory state, also a possible trigger for AF development. Many studies have focused on establishing the association between adiponectin and leptin and development of AF, and animal models have shown that leptin has a role in the scarring of the atrium and consequent development of AF.[19] Adiponectin was considered a protective factor in inflammation caused by excess fatty tissue deposits. However, current studies show that increased levels of adiponectin sometimes have a protective role.[20]

Although many studies have examined the influence of body mass on AF prognosis, the results are still controversial, so every study is important in order to contribute to better understanding of this increasingly common issue in the modern lifestyle.

Patients and Methods

This study was conducted in the Day Hospital of the Endocrinology Department at the Zagreb University Hospital Centre (UHC) between 2013 and 2016 to examine the effect of weight loss on cardiovascular risk factors and structural and functional remodeling of the heart. We included 85 obese participants (56 women and 29 men) with an average age of 58 (range 36-71). The control group comprised 40 patients of similar age and sex who only received advice for losing weight but were not regularly monitored, while 45 patients underwent an intensive program for losing body weight known as the Clinical Five-day Weight Loss Program at the Zagreb UHC Day Hospital. Differences between sexes were not compared.

The Clinical Five-day Weight Loss Program comprised professionally structured and guided lifestyle changes, changes in diet, increase in physical activity, and regulation of sleep duration and quality. All patients were clinically monitored through the polyclinic over a period of 12 months in three-month intervals, and received recommendations to improve their lifestyle (e.g. reduction in meals, dietary reduction in kcal) and to increase awareness of dietary habits (food with a lower glycemic index, adequate hydration with 1600 mL of water, increased physical activity with individual advisement more frequent than every 3 months, and the option for early phone consultations). At the start and during the monitoring, as well as at the end of the 12-month period, we performed an analysis of cardiovascular risk factors, echocardiography, ergometry, 24-hour Holter monitoring, and 24-hour continuous arterial pressure monitoring (CAPM). CRP levels, insulin and glycemia levels, and the HOMA index (determining insulin resistance; fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L) / 22.5) were measured in all patients at the start of the study and after monitoring.[21]

We excluded patients with chronic kidney disease, diabetes type 2, diabetes type 1, infection, or any acute condition.

Patients signed a written informed consent form, and the study was conducted in adherence with ethical principles.

All results were analysed with the t-test for small binary samples who served as their own controls.

Results

The results of the study showed a statistically significant improvement of left and right atrial volume, a reduction in ventricular mass, reduction in systolic pressure, and improved

gometrije. Inzulinska rezistencija, mjerena HOMA indeksom, također se smanjila uz znatan pad CRP-a.

Rezultati holtera EKG-a pokazali su znatno smanjenje epizoda FA-a i supraventrikulskih ekstrasistola (SVES). Ejekcijska frakcija nešto se manje značajnije promijenila nakon 12 mjeseci mršavljenja. Broj SVES-a u vođenoj grupi smanjio se gotovo tri puta u odnosu prema početnim vrijednostima, dok u kontrolnoj grupi nije bilo značajnijih promjena. Prosječan broj paroksizama FA (duljih od 30 sekundi) evidentiranih u holteru bio je do 3 puta manji u usporedbi s početnim vrijednostima, dok je i u kontrolnoj grupi zabilježeno statistički značajno manje paroksizama. Svi objašnjeni rezultati prikazani su u **tablici 1**.

ergometry results. Insulin resistance measured with the HOMA index was also significantly reduced, with a significant drop in CRP.

Holter ECG showed a significant reduction in AF episodes and supraventricular extrasystoles (SVES). Ejection fraction changed somewhat less significantly after 12 months of weight loss. The number of SVES in the guided group was almost three times lower in comparison with the baseline values, whereas there were no significant changes in the control group. The average number of AF paroxysms (longer than 30 seconds) evidenced in Holter ECG was 3 times lower compared with baseline values, but there were also statistically significantly less paroxysms in the control group as well. All the above results are shown in **Table 1**.

TABLE 1. Results of weight loss and its impact on cardiometabolic profile.

	Start		After 12 months		p value
	Control group (n=40)	Guided group (n=45)	Control group	Guided group	
Weight (kg)	100±11	100±12	97±15	88±12	<0.01
BMI (kg/m^2)	36±8	36.8±9	35.5±8	32.7±4	<0.01
Left atrium volume (mL)	109±25	105±19	110.7±21	96.6±9	<0.01
Right atrium volume (mL)	97±19	99±9	96±17	85±13	<0.01
Ventricular mass (g)	138±38	139±26	136±34	121±20	<0.01
Systolic pressure (mmHg)	147±21	149±16	138±17	132±12	<0.01
Ejection fraction (%)	61.5±2.8	60±3.4	61.8±2.3	63±3.1	<0.05
MET	7.3±1.3	7.1±1.4	7.0±1.0	8.4±1.0	<0.01
HOMA	8.5±4	12±5	7±3	9±2	NS
CRP	2.8±0.9	3.0±1.9	2.2±1.1	1.3±0.9	<0.01
PAC number	349±89	407.5±77	330.5±60	162.5±48	<0.01
Number of AF paroxysms	64±12	75±18	41±8	25±7	<0.01

BMI = body mass index, MET = equivalent 3.5mL/min/kg of body mass, CRP = C-reactive protein, PAC = premature atrial contractions, AF = atrial fibrillation with duration longer than 30 seconds, NS = not significant.

Rasprava

Tijekom 2010. godine u svijetu je 12,6 milijuna žena i 20,9 milijuna muškaraca bolovalo od FA-a.[22] Procjenjuje 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. Kako populacija stari, prevalencija i troškovi vezani za zbrinjavanje FA-a neprekidno se povećavaju pa je stoga istraživanje koje može pridonijeti spoznaji o preventibilnim mjerama ovoga problema više nego potrebno.

Rizični čimbenici za FA danas su najčešće povećani ITM, porast životne dobi i arterijska hipertenzija. U osnovi je proces razvoja ateroskleroze koji je pospješen povišenom razinom adipocitokina leptina, interleukina (IL)-6 te (MCP-1) koje luče adipociti te tumor nekroza faktora (TNFα) i MCP-1 izlučenih iz upalom potaknutih makrofaga, sa skladištenjem lipida u masnome tkivu, a potom u mišićima, jetri, epikardu i ostalim organima.[23] Takvo nakupljanje pospješuje inhibiciju signal-

Discussion

In 2010, 12.6 million women and 20.9 million men were suffering from AF across the world.[22] It is estimated that by 2030 the EU will have 14 to 17 million patients with AF, i.e. that 120 000 to 250 000 new patients are diagnosed every year. As the population ages, prevalence and costs associated with AF are constantly increasing, and research that can contribute to insights into preventive measures for this issue is more than necessary.

Today, risk factors for AF are usually increased BMI, advanced age, and arterial hypertension. The underlying cause is a process of atherosclerosis progression that is exacerbated by elevated levels of adipocytes, leptin, interleukin (IL)-6, and MCP-1 that are secreted by adipocytes as well as tumor necrosis factor (TNFα) and MCP-1 secreted from inflammation-stimulated macrophages, with lipid deposition in fatty tissue, followed by muscles, liver, epicardium, and other organs.[23] Such accumula-

nog puta inzulina fosforilacijom supstrata inzulinskog receptora na mjestu serina (potaknutu povišenom razinom TNFα) umjesto tirozina.[23] Masno je tkivo dodatan izvor angiotenzinogena koji se inače proizvodi u jetri, a usto adipociti na svojoj membrani posjeduju receptor za angiotenzin (AR-1), što povisuje sustavan arterijski tlak.[24] Vezanjem IL-6 za hepatocite povećano je lučenje C-reaktivnog proteina (CRP), čija se uloga u aterogenezi razmatra u svjetlu mogućeg uzroka infarkta miokarda, moždanog udara te periferne arterijske bolesti.[25]

Pronađeno smanjenje razina CRP-a u plazmi ispitanika povezano sa smanjenjem broja paroksizama FA-a i volumena LA-a ide u prilog teorijama o utjecaju CRP-a na nastanak i liječenje FA-a.

Girerd *i sur.* dokazuju da povećane razine CRP-a, zajedno s povećanim opsegom struka, pridonose povećanom riziku za nastanak postoperativne FA nakon ugradnje aortokoronarne premosnice.[4] Istraživanje na životinjskim modelima potkrepljuje spomenute činjenice.[26] Istraživanje Pathaka *i sur.*, osim ukupnog gubitka tjelesne težine, uzelo je u obzir i fluktuaciju gubitka tjelesne težine, tj. brzinu kojom se težina gubila između mjerenja. Ispitanici koji su izgubili >10 % tjelesne mase imali su šest puta veću šansu da ne obole od aritmija, za razliku od onih koji su izgubili <3 % tjelesne mase. S druge strane, ispitanici s fluktuacijom tjelesne mase >5 % imali su mnogo veći rizik za pojavu rekurentne FA nego oni čija je fluktuacija bila <2 %. Stoga nastanku FA-a pogoduju velika tjelesna masa, kao i velike fluktuacije u njezinu gubitku.[27]

Ovo je istraživanje pokazalo znatno smanjenje volumena srca i arterijskoga tlaka, kao i smanjenu aritmogenost i pojave epizoda supraventrikularne ekstrasistolije u skupini nadziranog, vođenog mršavljenja, što se dodatno može pripisati strukturnom i električnom remodeliranju srca uzrokovana pretilošću. Skupina bolesnika prepuštena vlastitom planu gubitka tjelesne mase imala je lošije rezultate od skupine koja je bila profesionalno vođena. Ejekcijska frakcija lijeve klijetke nije se znatnije promijenila ni u jednoj skupini, što se može objasniti kratkim vremenom praćenja.

Progresija paroksizmalne u permanentnu FA također je povezana s tjelesnom masom. Tsang *i sur.* u 3248 ispitanika s paroksizmalnom FA otkrili su da se tijekom 5 godina u njih 557 razvila permanentna FA. Nakon isključivanja drugih čimbenika rizika, kao što su dob i spol, tjelesna masa pokazala se kao neovisan faktor u nastanku permanentne FA.[28]

HOMA indeks jedan je od markera inzulinske rezistencije koji je u ovom istraživanju u usporedbi s drugim istraživanjima vrlo visok i iznosi 8,5 – 12. Primjerice, u osoba koje nemaju šećernu bolest u muškaraca iznosi 1,85 do 2,07 u žena srednje dobi od 50 godina.[29]

Ovo je istraživanje pokazalo da uz strukturni pristup promjenama životnog stila redukcijom pretilosti nastupa znatan oporavak kardiometaboličkog profila. Nakon godine dana praćenja znatno se snizila razina svih praćenih parametara, osim HOMA indeksa.

Nedostatak istraživanja jest u tome što nisu posebno razmatrani bolesnici s obzirom na prisutnost opstruktivne apneje u snu, kao i kratko vrijeme praćenja za strukturne promjene na ehokardiografskom pregledu. Također nema usporedbe muškog i ženskog spola. U nastavku istraživanja planiramo pratiti bolesnike u duljem razdoblju te pokušati ispraviti navedene nedostatke.

tion exacerbates the inhibition of the insulin signal pathway by phosphorylation of the insulin receptor substrate in place of serine (due to elevated TNFα levels) instead of tyrosine.[23] Fatty tissue is an additional source of angiotensin, which is usually produced in the liver, and adipocytes also have an angiotensin receptor (AR-1) on their membrane which increases systemic arterial pressure.[24] Binding IL-6 to hepatocytes causes increased secretion of C-reactive protein (CRP), whose role in atherogenesis is considered in the light of possible causes of myocardial infarction, stroke, and peripheral artery disease.[25]

The lowered plasma CRP levels in participants together with the reduction in the number of AF paroxysms and LA volume support theories that point to the influence of CRP on the development and treatment of AF.

Girerd *et al.* demonstrated that elevated CRP along with increased waist circumference contribute to elevated risk for the development of postoperative AF after heart bypass surgery.[4] Research on animal models corroborates these facts.[26] In addition to total weight loss, a study by Pathak *et al.* also considered the fluctuations in body weight, i.e. the speed of weight loss between measurements. Participants who lost >10% of body weight had six times higher chances of not developing arrhythmias compared with those who lost <3% of body weight. On the other hand, participants with a >5% body mass fluctuation had a much higher risk for the development of recurrent AF than those with a <2% fluctuation. Therefore, AF development is facilitated by high body mass as well as large fluctuations in body mass loss.[27]

The present study showed a significant reduction in heart volume and arterial pressure as well as a reduction in arrhythmogenicity and supraventricular extrasystole episodes in the group with supervised guided weight loss, which can also be attributed to structural and electric remodeling of the heart caused by obesity. The group of patients left to pursue their own weight loss plans had poorer results than the professionally guided group. Left ventricular ejection fraction did not change significantly in either group, which could be explained by the short follow-up period.

The progression of paroxysmal to permanent AF is also associated with body mass. Tsang *et al.* examined 3248 participants with paroxysmal AF and found that 557 participants developed permanent AF over a period of 5 years. After excluding other risk factors such as age and sex, body weight was found to be an independent predictor in the development of permanent AF.[28]

The HOMA index is one of the markers for insulin resistance, which was very high in the present study compared with other studies, at 8.5-12.0. For example, in persons without diabetes the HOMA index is 1.85 in man and 2.07 in middle-aged women of 50 years of age.[29]

This study demonstrated that a structured approach to lifestyle changes to reduce obesity leads to significant recovery in the cardiometabolic profile. After one year of follow-up, all measured parameters were significantly reduced, except for the HOMA index.

Limitations of the study include the fact that patients were not separately analysed based on the presence or absence of sleep apnea as well as the short monitoring period for structural changes on echocardiographic examination. Additionally, no comparison was made between the male and female sexes. We plan to continue the study by following the patients over a longer period of time and to attempt to correct these limitations.

Zaključak

Strukturirani i nadzirani plan gubitka tjelesne mase u godini dana smanjuje kardiometabolički rizik, a samim time i inzulinsku rezistenciju, te upalne procese u organizmu koji pridonose nastanku FA-a. Zabilježeno je znatno smanjenje volumena srca i arterijskoga tlaka, kao i smanjena učestalost FA i broja supraventrikulskih ekstrasistola. Smatramo da u pretilih bolesnika treba inzistirati na postupnoj redukciji tjelesne mase, svakako barem od 10 %, i to uz individualni pristup svakom bolesniku.

Conclusion

A structured and monitored weight loss plan reduces cardiometabolic risk within one year, and consequently also reduces insulin resistance and inflammatory processes in the body that contribute to the development of AF. We observed a significant reduction in heart volume and arterial pressure, as well as reduced frequency of AF and the number of supraventricular extrasystoles. In obese patients, we believe that gradual body mass reduction of at least 10% should be insisted upon, with the adoption of an individualized approach to every patient.

LITERATURE

1. Musić Milanović S, Bukal D. Epidemiologija debljine – javnozdravstveni problem. Medicus 2018;27(1);7-13. Available from: https://hrcak.srce.hr/file/293592
2. Musić Milanović S. Demografske, bihevioralne i socioekonomske odrednice debljine odraslih u Hrvatskoj. Doktorska disertacija, Sveučilište u Zagrebu; 2010. Available from: http://medlib.mef.hr/932/
3. Wang TJ, Parise H, Levy D, D' Agostino RB Sr, Wolf PA, Vasan RS, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA. 2004 Nov 24;292(20):2471-7. https://doi.org/10.1001/jama.292.20.2471
4. Girerd N, Pibarot P, Fournier D, Daleau P, Voisine P, O'Hara G, et al. Middle-aged men with increased waist circumference and elevated c-reactive protein level are at higher risk for postoperative atrial fibrillation following coronary artery bypass grafting surgery. Eur Heart J. 2009 May;30(10):1270-8. https://doi.org/10.1093/eurheartj/ehp091
5. Nalliah CJ, Sanders P, Kottkamp H, Kalman JM. The role of obesity in atrial fibrillation. Eur Heart J. 2016 May 21;37(20):1565-72. https://doi.org/10.1093/eurheartj/ehv486
6. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994 Feb;89(2):724-30. https://doi.org/10.1161/01.CIR.89.2.724
7. Cil H, Bulur S, Türker Y, Kaya A, Alemdar R, Karabacak A, et al; MELEN Investigators. Impact of body mass index on left ventricular diastolic dysfunction. Echocardiography. 2012 Jul;29(6):647-51. https://doi.org/10.1111/j.1540-8175.2012.01688.x
8. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013 Nov 20;310(19):2050-60. https://doi.org/10.1001/jama.2013.280521
9. Thanassoulis G, Massaro JM, O'Donnell CJ, Hoffmann U, Levy D, Ellinor PT, et al. Pericardial fat is associated with prevalent atrial fibrillation: the framingham heart study. Circ Arrhythm Electrophysiol. 2010 Aug;3(4):345-50. https://doi.org/10.1161/CIRCEP.109.912055
10. Gašparović K, Lovrić Benčić M. Epicardial fat in coronary artery disease and atrial fibrillation. Cardiol Croat. 2018;13(11-12):418. https://doi.org/10.15836/ccar2018.418
11. Al Chekakie MO, Welles CC, Metoyer R, Ibrahim A, Shapira AR, Cytron J, et al. Pericardial fat is independently associated with human atrial fibrillation. J Am Coll Cardiol. 2010 Aug 31;56(10):784-8. https://doi.org/10.1016/j.jacc.2010.03.071
12. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. J Am Coll Cardiol. 2011 Apr 26;57(17):1745-51. https://doi.org/10.1016/j.jacc.2010.11.045
13. Batal O, Schoenhagen P, Shao M, Ayyad AE, Van Wagoner DR, Halliburton SS, et al. Left atrial epicardial adiposity and atrial fibrillation. Circ Arrhythm Electrophysiol. 2010 Jun;3(3):230-6. https://doi.org/10.1161/CIRCEP.110.957241
14. Girerd N, Scridon A, Bessiere F, Chauveau S, Geloen A, Boussel L, et al. Periatrial epicardial fat is associated with markers of endothelial dysfunction in patients with atrial fibrillation. PLoS One. 2013 Oct 15;8(10):e77167. https://doi.org/10.1371/journal.pone.0077167
15. Rajagopalan N. Obstructive sleep apnea: not just a sleep disorder. J Postgrad Med. 2011 Apr-Jun;57(2):168-75. https://doi.org/10.4103/0022-3859.81866
16. Linz D, Schotten U, Neuberger HR, Böhm M, Wirth K. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. Heart Rhythm. 2011 Sep;8(9):1436-43. https://doi.org/10.1016/j.hrthm.2011.03.053
17. Monahan K, Brewster J, Wang L, Parvez B, Goyal S, Roden DM, et al. Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter. Am J Cardiol. 2012 Aug 1;110(3):369-72. https://doi.org/10.1016/j.amjcard.2012.03.037
18. Morgera T, Di Lenarda A, Dreas L, Pinamonti B, Humar F, Bussani R, et al. Electrocardiography of myocarditis revisited: clinical and prognostic significance of electrocardiographic changes. Am Heart J. 1992 Aug;124(2):455-67. https://doi.org/10.1016/0002-8703(92)90613-Z
19. Fukui A, Takahashi N, Nakada C, Masaki T, Kume O, Shinohara T, et al. Role of leptin signaling in the pathogenesis of angiotensin IImediated atrial fibrosis and fibrillation. Circ Arrhythm Electrophysiol. 2013 Apr;6(2):402-9. https://doi.org/10.1161/CIRCEP.111.000104
20. Carnevale R, Pastori D, Peruzzi M, De Falco E, Chimenti I, Biondi-Zoccai G, et al. Total adiponectin is inversely associated with platelet activation and CHA2DS2-VASc score in anticoagulated patients with atrial fibrillation. Mediators Inflamm. 2014;2014:908901. https://doi.org/10.1155/2014/908901
21. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985 Jul;28(7):412-9. https://doi.org/10.1007/BF00280883
22. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. Nat Rev Cardiol. 2016 Jun;13(6):321-32. https://doi.org/10.1038/nrcardio.2016.45
23. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol. 2009 Jun;6(6):399-409. https://doi.org/10.1038/nrcardio.2009.55
24. Pausova Z. From big fat cells to high blood pressure: a pathway to obesity-associated hypertension. Curr Opin Nephrol Hypertens. 2006 Mar;15(2):173-8. https://doi.org/10.1097/01.mnh.0000214775.42103.a5
25. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006 Dec 14;444(7121):881-7. https://doi.org/10.1038/nature05488
26. Mahajan R, Lau DH, Brooks AG, Shipp NJ, Manavis J, Wood JP, et al. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. J Am Coll Cardiol. 2015 Jul 7;66(1):1-11. https://doi.org/10.1016/j.jacc.2015.04.058
27. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). J Am Coll Cardiol. 2015 May 26;65(20):2159-69. https://doi.org/10.1016/j.jacc.2015.03.002
28. Tsang TS, Barnes ME, Miyasaka Y, Cha SS, Bailey KR, Verzosa GC, et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur Heart J. 2008 Sep;29(18):2227-33. https://doi.org/10.1093/eurheartj/ehn324
29. Gayoso-Diz P, Otero-Gonzalez A, Rodriquez-Alvatez MX, Gude F, Garcia F, De Francisco A, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. BMC Endocr Disord. 2013 Oct 16;13:47. https://doi.org/10.1186/1472-6823-13-47