Časopis Udruženja kardiologa Srbije

SRCE i krvni sudovi

Heart and Blood Vessels

Journal of the Cardiology Society of Serbia

1955 UKS CSS
UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA
www.uksrb.org

Uticaj antibradikardne pejsmejker stimulacije na razvoj srčane slabosti
The influence of antibradycardial pacemaker stimulation to heart failure development

Patogenetski mehanizmi indukcije ubrzane ateroskleroze kod pušača

Najnovije preoporuke u lečenju aortne stenoze: (T)AVR u fokusu
Current recommendations in the treatment of aortic stenosis: (T)AVR in focus

Diagnostički značaj neinvazivne procene koronarne rezerve protoka transtorakalnom dopler ehokardiografijom kod nedijagnostičkih i inkonkluzivnih stres ehokardiografskih testova
The diagnostic value of coronary flow reserve by trans- thoracic Doppler echocardiography in non-diagnostic or inconclusive stress echocardiography tests

Authorship: From Credit to Accountability. Reflections From the Editors´ Network

Volumen 38 Broj 2
2019. godina

UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI
HEART AND BLOOD VESSELS

Časopis izlazi redovno od 2011. godine i predstavlja nastavak časopisa Kardiologija (www.uksrb.rs)

Volumen 38 Broj 2 2019. godina

ADRESA UREDNIŠTVA
EDITORIAL OFFICE
Udruženje kardiologa Srbije
Višegradska 26
11000 Beograd
Email: srceikrvnisudovi.urednistvo@gmail.com
www.uksrb.org

UPUTSTVO AUTORIMA

„Srce i krvni sudovi" je časopis Udruženja kardiologa Srbije koji objavljuje originalne radove, prikaze bolesnika, kardiovaskularne slike ("cardiovascular images"), pregledne i specijalne članke. Uz rukopis obavezno priložiti pismo koje su potpisali svi autori, a koje treba da sadrži:

- izjavu da rad prethodno nije publikovan i da nije istovremeno podnet za objavljivanje u nekom drugom časopisu,
- izjavu da su rukopis pročitali i odobrili svi autori.

Rukopis rada i sve priloge uz rad dostaviti elektronskim putem na adresu: sloba.d.obradovic@gmail.com, naslovljeno na: prof. dr Slobodan Obradović, glavni urednik časopisa „Srce i krvni sudovi". Prispele rukopise uređivački odbor šalje recenzentima radi stručne procene. Ukoliko recenzenti predlože izmene i dopune, tada se recenzirani rukopis dostavlja autorima s molbom da tražene izmene unesu u tekst ili pak u protivnom da argumentovano izraze svoje neslaganje sa datim primedbama recenzenta. Konačnu odluku o prihvatanju rada za štampu donosi glavni i odgovorni urednik zajedno sa uređivačkim odborom.
Za objavljene radove se ne isplaćuje honorar, a autorska prava se prenose na izdavača.
Časopis se štampa na srpskom jeziku, sa kratkim sadržajem prevedenim na engleski jezik. Inostrani autori mogu svoje članke, u celini, poslati na engleskom jeziku.
Molimo saradnike da svoje radove za časopis „Srce i krvni sudovi" pišu jasno, koncizno, racionalno, gramatički ispravno i u skladu sa sledećim uputstvima.

UPUTSTVA ZA PISANJE RADA

Tekst rada kucati u programu za obradu teksta Word, latinicom, fontom Times New Roman i veličinom slova 12 tačaka (12pt). Sve margine podesiti na 25 mm, veličinu strane na format A4, sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm. Ukoliko se u tekstu koriste specijalni znaci (simboli), koristiti font Symbol. Stranice numerisati redom u okviru donje margine desno, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u običnim zaokruženim zagradama, i to onim redosledom kojim se pojavljuju u tekstu. Rukopis rada dostaviti urađen po sledećem redosledu:

- naslovna strana,
- sažetak na srpskom jeziku,
- sažetak na engleskom jeziku, sa naslovom i institucijom odakle dolazi rad takođe na engleskom jeziku,
- tekst rada,
- tabele,
- opisi slika,
- posebno slike (grafikoni) ili fotografije.

Naslovna strana. Na posebnoj, prvoj stranici treba navesti sledeće:

- naslov rada bez skraćenica
- puna imena i prezimena autora (bez titula)
- kratak naslov rada
- zvaničan naziv i mesto ustanova u kojima autori rade: ukoliko su u radu autori iz različitih institucija, indeksirati autore iz raličitih institucija arapskim brojevima
- na dnu stranice navesti kontakt osobu, odnosno ime i prezime, adresu, broj telefona, faksa i e-mail adresu radi korespodencije

Kratak sadržaj na srpskom i engleskom jeziku. Na sledećoj strani priložiti kratak sažetak rada obima do 250 reči. Za originalne radove kratak sadržaj rada treba da sadrži: uvod, metod, rezultati i zaključak.
Prikazi bolesnika, pregledni i specijalni članci treba da imaju nestrukturisan sažetak obima do 150 reči.
Na kraju sažetka dostaviti i 2-4 ključne reči.
Svaki sažetak, sa naslovom i institucijom, mora biti preveden na engleski jezik.

Tekst rada. Tekst treba da sadrži sledeća poglavlja: uvod, metodi, rezultati, diskusija, zaključak, literatura. Svi podnaslovi se pišu malim slovima i boldovano. U radu koristiti kratke i jasne rečenice. Za nazive lekova koristiti isključivo njihova internacionalna nezaštićena imena. U radu se mogu koristiti određene skraćenice, ali samo kada je to neophodno. Za svaku skraćenicu koja se prvi put javlja u tekstu treba navesti i pun naziv. Sve rezultate navoditi u metričkom sistemu prema Međunarodnom sistemu jedinica (SI).
Originali rad ne treba da prelaze 4000 reči.
Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura. Prikaz bolesnika ne treba da prelazi 1500 reči.
Kardiovaskularne slike (cardiovascular images) ne treba da budu struktuirane i ne treba da prelaze 500 reči.
Pregledni i specijalni članci ne moraju da budu struktuirani po prethodnom modelu. Pregledni i specijalni članci ne treba da prelazi 5000 reči.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, a broj citiranih originalnih radova mora da bude najmanje 80%. Izbegavati korišćenje apstrakta kao reference. Reference članaka koji su prihvaćeni za štampu označiti kao ,,u štampi" (in press) i priložiti dokaz o prihvatanju rada. Reference se citiraju prema Vankuverskim pravilima, koja su zasnovana na formatima koja koriste National Library of Medicine i Index Medicus. Naslove časopisa takođe treba skraćivati prema načinu koji koristi Index Medicus (ne stavljati tačke posle skraćenice).
Ukoliko rad koji se navodi ima više od 6 autora, onda navoditi tako što se posle trećeg autora staviti: et al. Stranice se citiraju tako što se navode početna i krajnja stranica (npr. 134-138).
Primer za navođenje reference iz časopisa: Leal J, Ramon Luengo-Fermnandes R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006;27:1610-1619.
Primer za navođenje reference iz knjige: Nichols A, Rourke MH. Aging and hypertension. U knjizi: Hypertension. Urednici: Nichols A, Rourke MH. Lea and Febiger; London/Melbourne, 1990:257-299.

Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu. Tabele raditi u programu Word, koristiti font Times New Roman, veličinu slova 12 pt, sa jednostrukim proredom i bez uvlačenja. Tabela mora da ima naslov i ukoliko se u tabeli koriste skraćenice, iste treba objasniti u legendi ispod tabele. Svaku tabelu dati na posebnom listu papira.

Slike (grafikoni) se označavaju arapskim brojevima po redosledu navođenja u tekstu. Na posebnom listu dati naslov sa opisom slika (grafikona) i ukoliko se koriste skraćenice, iste treba objasniti u nastavku. Svaki grafikon treba dati na posebnom listu papira. Slike (grafikone) dati u formatu ppt, ai ili eps.
Fotografije se označavaju arapskim brojevima po redosledu navođenja u tekstu. Primaju se isključivo originalne fotografije (crno-bele ili u boji) na sjajnom, glatkom (a ne mat) papiru. Na poleđini svake fotografije treba napisati redni broj. Fotografije moraju da budu u tif, eps ili ai formatu, najmanje rezolucije 300dpi.

Napomena. Rad koji ne ispunjava sve gore navedene tehničke uslove neće biti poslat na recenziju i biće vraćen autorima da ga dopune i isprave.
Glavni urednik i uređivački odbor zadržavaju pravo da radove, za koje smatraju da ne zadovoljavaju osnovne kvalitete i interesovanja publikovanja u časopisu, ne pošalju recenzentima i vrate autorima.

INSTRUCTIONS FOR AUTHORS

Heart and Blood Vessels is the official journal of the Serbian Cardiology Society and publishes Original articles, Case reports, Cardiovascular images, Review articles and Special articles. It is mandatory to enclose, along with the manuscript, a letter to the Editor-in-chief stating that the manuscript:

- has not been previously published or is currently submitted for review to another journal
- was read and approved by all authors

The manuscript with all appendices should be addressed to:
Prof. Slobodan Obradovic, MD, PhD
Editor-in-Chief, Heart and Blood Vessels
and mailed to sloba.d.obradovic@gmail.com

The Editorial Board will send it to reviewers for evaluation. Reviewers' comments will be forwarded to the author to either correct the original manuscript in accord with the suggestions or to express their opinion with adequate arguments in a letter to the Editor-in-chief explaining why they refrained from doing as reviewers deemed appropriate. The final decision will be made by the Editor-in-Chief together with the Editorial Board whether to accept the manuscript for publishing or not. For published manuscripts authors don't get fees, while copyright is transferred to the publisher. The journal is published in Serbian with summaries in English. Foreign authors can submit their manuscripts entirely in English.
We kindly request authors to keep their manuscripts for Heart and Blood Vessels clear, concise, rational, grammatically correct and in accord with the following instructions.

GENERAL INSTRUCTIONS

Manuscript text should be prepared using a Word processing package, in Times New Roman font size 12. All margins set at 25mm of an A4 page, with no alignment and 10mm tab at the beginning of each paragraph. In case special signs are used, please use Symbol font. Keep page numbering in the footer, starting from the Title page. References should be marked by order of appearance in the text in Arabic numerals in round brackets. The manuscript should be submitted in the following order:

- Title Page,
- Abstract,
- Body of the text,
- Tables, Figures' descriptions,
- Figures or photographs.

Title page. A separate, first page should encompass the following:

- the title
- the name(s) of authors,
- the institution(s) and location of all authors (Please, index in Arabic numerals the different Institutions by order of appearance),
- short title,
- at the bottom of the page cite the corresponding author with his contact address, phone, fax number and email address.

Abstract. Next page should contain a 250 words abstract. Original papers should encompass: Introduction, Methods, Results and Conclusion. Structured form of abstracts is not mandatory for case reports, review and special articles, but should not exceed 150 words.

The text should encompass: Introduction, Methods, Results, Discussion, Conclusions, and References. Subtitles should be typed in regular font and bold. Short and simple sentences are advised. For medication, it is recommended not to use trade names, but their generic names. Abbreviations can be used in the text, but only when necessary and properly introduced. All results should be cited in standard SI units.
An original paper should be up to 4000 words.
A Case Report consists of an Introduction, Case presentation, Discussion and References. A Case Report should be up to 1500 words. Cardiovascular Images shouldn't be structured and should be up to 500 words.
Review and Special Articles don't have to be structured and shouldn't exceed 5000 words.

References. References should be marked in order of appearance in Arabic numerals. The number of quoted references shouldn't exceed 50 out of which 80% should be original articles. It is advised to avoid abstracts as references. When quoting papers that are accepted for publishing, however, not yet published, mark them as in press and enclose a printed proof of the manuscripts' acceptance. References are quoted according to Vancouver style based on the formats used by National Library of Medicine and Index Medicus. Journals' titles should be shortened in accord with Index Medicus (no full stops after the abbreviation). If the paper quoted has over 6 authors, after the third one, et al. should be used Pages are quoted as first and last (i.e. 134-136).
Article citation example: Leal J, Ramon Luengo-Fermnandes R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006;27:1610-1619.
Book citation example: Nichols A, Rourke MH. Aging and hypertension. In: Hypertension. Editors: Nichols A, Rourke MH. Lea and Febiger;London/Melbourne, 1990:257-299.

Tables are marked in order of appearance in Arabic numerals. Tables should be prepared using a Word processing package, Times New Roman font size 12, single spaced with no indent. Each Table should have a title. If abbreviations are used in the Table, they should be defined in the explanatory footnote below. Each table should be presented on a separate page.
Figures are marked in order of appearance in Arabic numerals. Please, provide on seprate page Figure legends. Each Figure should be prepared on a separate page using following format: ppt, ai or eps.
Photographs are marked in order of appearance in Arabic numerals. Only original photographs are accepted (black and white or color) on glossy paper. The back of each photograph should have the number and an arrow marking the top. The photograps should be prepared in following format: tip, eps, or ai, with minimal resolution of 300dpi.

Note. A paper not fully compliant with all aforementioned rules and regulations, will not be forwarded to reviewers, but returned to authors for correction. The Editor-in-Chief and the Editorial Board can reject any manuscript they deem not in the scope of the journal or not acceptable in terms of baseline quality of publishing material, even prior seeking reviewers' opinion.

CIP - Katalogizacija u publikaciji
Narodna biblioteka Srbije, Beograd

Srce i krvni sudovi: Časopis Udruženja kardiologa Srbije
Heart and blood vessels: Journal of Cardiology society of Serbia
Editor in-chief Slobodan Obradović, Godina 8,
Volumen 38, Broj 2
Beograd, Višegradska 26: Udruženje kardiologa Srbije
2018-Beograd: Newassist doo
Tromesečno-Broj 1 izašao 2011. god.

ISSN 182-4835=Srce i krvni sudovi
COBISS.SR-ID 174253580

1955 UKS CSS
UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI
HEART AND BLOOD VESSELS

Volumen 38 Broj 2 2019. godina

Sadržaj / *Content*

Uticaj antibradikardne pejsmejker stimulacije na razvoj srčane slabosti **75**
The influence of antibradycardial pacemaker stimulation to heart failure development
Vladimir Mitov, Aleksandar Jolić, Dragana Adamović, Milan Nikolić, Marko Dimitrijević, Zoran Perišić, Tomislav Kostić, Milan A Nedeljković

Patogenetski mehanizmi indukcije ubrzane ateroskleroze kod pušača **80**
Jakša Dubljanin, Čedomir Uštević, Nikola Gošnjić, Nemanja Pejić, Ivan Ranković, Ljubica Jovanović, Žaklina Leković, Ivana Veljić, Nebojša Antonijevi, Vladimir Kanjuh

Najnovije preoporuke u lečenju aortne stenoze: (T)AVR u fokusu **91**
Current recommendations in the treatment of aortic stenosis: (T)AVR in focus
Milena Pandrc, Mirjana Stanić, Vanja Kostovski, Danijela Vraneš, Snježana Vukotić, Andjelka Ristić, Nemanja Djenić

Diagnostički značaj neinvazivne procene koronarne rezerve protoka transtorakalnom dopler ehokardiografijom kod nedijagnostičkih i inkonkluzivnih stres ehokardiografskih testova **95**
The diagnostic value of coronary flow reserve by trans- thoracic Doppler echocardiography in non-diagnostic or inconclusive stress echocardiography tests
Marija Kotevska, Srđan Dedić, Nikola Bosković, Vojislav Giga, Milorad Tešić, Srđan Aleksandrić, Milan Dobrić, Branko Beleslin, Ana Djordjevic Dikić

Authorship: From Credit to Accountability. Reflections From the Editors´ Network **101**

Srce i krvni sudovi 2019; 38(2): 75-79

Pregledni rad

Uticaj antibradikardne pejsmejker stimulacije na razvoj srčane slabosti

Vladimir Mitov[1], Aleksandar Jolić[1], Dragana Adamović[1], Milan Nikolić[1], Marko Dimitrijević[1], Zoran Perišić[2], Tomislav Kostić[2], Milan A Nedeljković[3]

[1]Odeljenje kardiologije, Medicinski centar Zaječar, [2]Odeljenje invazivne dijagnostike, Univerzitetska bolnica Niš, [3]Klinika za kardiologiju, Klinički centar Srbije; Medicinski fakultet, Univerzitet u Beogradu

Sažetak Bolesti sprovodnog sistema srca koje se karaterišu usporenom srčanom frekvencom, neophodno je lečiti arteficijalnom pejsmejker stimulacijom iz desne komore i iz desne pretkomore. Međutim, postavlja se pitanje da li arteficijalnom stimulacijom iz vrha desne komore ili iz izlaznog trakta desne komore možemo nepovoljno uticati na miokardnu funkciju, posebno na funkciju leve komore. Procenjujući nepovoljni uticaj permanentne antibradikardne stimulacije na funkciju leve komore, analizirani su širina QRS kompleksa i položaj komorske elektrode u pejsmejker stimulaciji. Pejsmejker stimulacija predstavlja terapijsku neminovnost kod bolesti i stanja koja se karakterišu nedovoljnom srčanom frekvencom i hronotropnom inkopetencijom. Pejsmejker stimulacija iz vrha desne komore daje šire QRS komplekse, intra ventrikularnu, interventrikularnu asinhroniju i veći rizik od razvoja srčane slabosti. Implantacija elektrode u izlazni trakt desne komore predstavlja jednostavno i dobro ili barem ne gore terapijsko rešenje u prevenciji razvoja srčane slabosti, posebno kod pacijenata sa sniženom sistolnom funkcijom leve komore.

Ključne reči RVA, RVOT, pejsmejker stimulacija, srčana slabost

Uvod

Bolesti sprovodnog sistema srca koje se karaterišu usporenom srčanom frekvencom, neophodno je lečiti arteficijalnom pejsmejker stimulacijom iz desne komore (VVIR pejsmejker mod) i iz desne pretkomore (DDDR mod). Danas se u svetu prosečno implantira 1000 pejsmejkera na milion stanovnika, u Srbiji oko 400 na milion stanovnika, ili preko 3000 implantacija godišnje[1,2,3]. Međutim, postavlja se pitanje da li arteficijalnom stimulacijom iz vrha desne komore (Right Ventricular Apex-RVA) ili iz izlaznog trakta desne komore (Right Ventricular Outflow Tract-RVOT) možemo nepovoljno uticati na miokardnu funkciju, posebno na funkciju leve komore.

Pejsmejker stimulaija iz vrha desne komore

Prve elektrode pejsmejkera su postavljane epikardnom fiksacijom i podrazumevale su torakotomiju. Novi pristup, endovenskim plasiranjem elektrode i endokardnom stimulacijom miokarda, prvi je uveo Furman 1959. godine[4]. Od tada, endokardna stimulacija miokarda, komorskom elektrodom iz vrha desne komore postala je standardno mesto stimulacije, zbog jednostavnosti pri implantaciji, lake anatomske orijentacije na rendgenskopiji i stabilnog položaja elektrode. Ektopično stvoren talas deporalizacije, širi se sa mesta stimulacije (kontakt elektrode sa miokardom) kroz miokard, van sprovodnog sistema srca, pa se na EKG-u prezentuje u vidu proširenih QRS kompleksa, morfologije bloka leve grane (BLG), koji su najmanje dvostruko širi od normalno sprovedenog impulsa[5]. Uočeno je da su prošireni QRS kompleksi udruženi sa simptomima i znakovima srčane slabosti.

Pejsmejker stimulacija iz izlaznog trakta desne komore

RVOT predstavlja trapezoidni prostor između trikuspidalne i plućne valvule, ograničen slobodnim zidom desne komore, napred, a gornjim delom interventrikularnog septuma, pozadi[6]. Na rendgenskopiji razlikuju se 4 segmenta izlaznog trakta desne komore: visoki (infundibularni) i niski septum, visoki (infundibularni) i niski deo slobodnog zida. U letaraturi se često pod RVOT-om podrazumeva pravi izlazni trakt sa opisanim delovima, ali i srednje partije septuma, a nekada i regija oko vrha. Upravo ova konfuznost dovela je do novog termina, pejsmejker stimulacija van vrha desne komore[7].

Uticaj pejsmejker stimulacije iz vrha desne komore na abnormalnu kontraktilnost leve komore

Dovodi do poremećaja kontraktilnosti unutar leve komore, posebno između septuma i lateralnog zida[8,9]. Mišićna vlakna septuma se još u fazi izovolumetrijske kontrakcije

Corresponding author: Vladimir Mitov, e-mail: drvladimirnitov@gamil.com

prevremeno kontrahuju i brzo skrate, do 10% svoje dužine, dok su mišićna vlakana ostalih zidova komore, još uvek relaksirana. Ovo rapidno, prevremeno skraćivanje mišićnih vlakana septuma praćeno je i dodatnim, sistolnim rastezanjem lateralnog zida. Rastezanje mišićnih vlakana lateralnog zida leve komore, do 15% u ranoj fazi sistole, dovodi do zakasnele kontrakcije ovog dela miokarda, za razliku od prevremeno kontrahovanog septuma. Ova diskordiniranost u kontrakciji između rano aktiviranog septuma i kasno aktiviranog lateralnog zida, vodi do nižeg minutnog volumena i smanjenja efikasnosti miokarda kao pumpe. Ehokardiografskim pregledom abnormalna kontrakcija u pejsmejker stimulaciji iz vrha desne komore, registruje se kao paradoksalni pokret septuma. U stvari, taj pokret septuma nije pravi paradoksalni pokret, već je posledica dejstva različitih sila. Pokret septuma izazvan je asinhronijom između desne i leve komore i presisitolnim skraćenjem mišićnih vlakana septuma[6].

Uticaj pejsmejker stimulacije iz vrha desne komore na električni i strukturni remodeling leve komore

Asinhrona električna aktivnost dovodi do akutnih mehaničkih promena, a potom do hroničnih funkcionalnih i strukturnih promena miokarda. Adaptacija miokarda na komorsku stimulaciju je „memorijski efekat miokarda“. Costard-Jackle i Franz[10] demonstrirali su da dolazi do promena u reporalizaciji koje se razlikuju u udaljenim regionima i regionima oko mesta pejsmejker stimulacije. Repolarizacione anomalije koje su u vezi sa kratkotrajnim memorijskim efektom imaju i mehaničke posledice. Neposredno nakon prekida komorske pejsmejker stimulacije, dolazi do poremećaja relaksacije, i pogoršanja sistolne funkcije, koja može trajati od narednih 2h, do nedelju dana. Nakon 3 nedelja pejsmejker stimulacije dugotrajni memorijski efekat miokarda izaziva strukturne promene miokarda. Nakon zaustavljanja komorske pejsmejker stimulacije koja je trajala nedelju dana, potrebno je $1^{1/2}$ dan da se ejekciona frakcija vrati na vrednosti pre stimulacije[6]. Komorska pejsmejker stimulacija koja je trajanja preko mesec dana, pored memorijskog efekta, daje i strukturne promene, kao što su dilatacija komore i asimetrična hipertorfija. Kao dodatni uzrok redukcije pumpne funkcije za vreme asinhrone aktivacije je i mitralna insuficijencija. Mitralna insuficijencija za vreme pejsmejker stimulacije iz vrha desne komore posledica je asinhronije papilarnog mišića. Mitralna insuficijencija direktno smanjuje pumpnu funkciju leve komore redukcijom volumena i indirektno, redukcijom šupljine leve komore, koja je posledica hipertofije[11].

Diskusija

Uticaj pejsmejker stimulacije na funkciju leve komore

Procenjujući mogući nepovoljni uticaj permanentne antibradikardne stimulacije na funkciju leve komore, analizirani su širina QRS kompleksa i položaj komorske elektrode u pejsmejker stimulaciji.

Širina QRS kompleksa u pejsmejker stimulaciji

U PREDICT-HF studiji 3 godine je praćen uticaj širine QRS kompleksa na pojavu srčane slabosti, kod pacijenata sa pejsmejker stimulacijom iz vrha desne komore, bez predhodne srčane slabosti i sa normalnom širinom QRS pre implantacije pejsmejkera. Našli su da u grupi sa QRS do 160 ms u pejsmejker stimulaciji, 9,4% pacijenata je imalo srčanu slabost, u grupi sa QRS 160-190 ms povećava se broj pacijenata sa srčanom insuficijencijom na 27,8%, dok je u grupi sa QRS >190 ms bilo 56,8% pacijenata sa srčanom insuficijencijom. Autori ove studije nalaze da je širina QRS preko 165 ms u pejsmejker stimulaciji, granica iznad koje se povećava rizik za razvoj srčane slabosti[12]. I u drugim preglednim i originalnim radovima, koji su analizirali razliku u pejsmejker stimulaciji iz vrha desne komore i sa alternativnih pozicija, zaključuju da je vodeći razlog nastanka srčane slabosti produženje trajanja QRS kompleksa, i predlažu korišćenje alternativnih mesta iz izlaznog trakta desne komore, ili implantaciju CRT radi prevencije srčane slabosti[13,14,15-19].
Zajedničko kod svih autora je da izmerena širina QRS kompleksa u RVOT pejsmejker stimulaciji (u bilo kom delu) uvek je manja u odnosu na stimulaciju iz RVA[20].

Bolji RVOT vs RVA

Permanentna pejsmejker stimulacija iz vrha desne komore je bila snažan prediktor za smanjenje sistolne funkcije leve komore[21-22], kao i za pojavu srčane insuficijencije[23,24,25,26]. U preglednim člancima gde su zbirno analizirani objavljeni rezultati pojedinačnih studija, na ukupno 3000 pacijenata, svi autori su našli prednost RVOT u odnosu na RVA pejsmejker stimulaciju. Rezultati ovih studija, potvrđuju važnost mesta pejsmejker stimulacije, u desnoj komori, na dugoročno očuvanje funkcije leve komore i od pomoći su da se razjasni koje je optimalno mesto stimulacije iz desne komore. Weizong i saradnici analizirali su podatke iz 20 randomizovanih studija, na 1114 pacijenata. Zaključili su da RVOT pacijenti imaju bolji efekat na funkciju leve komore, u smislu manje interventrikularne asinhronije, poboljšanja vrednosti EF i smanjenja endsistolnog volumena leve komore[24]. Do istih saznanja o uticaju RVOT na funkciju leve komore došli su i drugi autori[27,28,29].
Ako se pejsmejker implantira pacijentima sa normalnom funkcijom leve komore, bez srčane slabosti, povoljniji je uticaj na funkciju leve komore, kod stimulacije iz izlaznog trakta desne komore, u odnosu na stimulaciju iz vrha desne komore[30,31-33]. QRS kompleksi biće užeg trajanja, izazvaće manju disinhroniju leve komore, imaće povoljniji efekat na očuvanje ejekcione frakcije[18,34-39].
Ventrikularnu disinhronizaciju izazvanu stimulacijom iz vrha desne komore, lošije podnose pacijenti sa već postojećom srčanom insuficijencijom, pre implantacije. Treba smanjivati vreme komorske pejsmejker stimulacije iz vrha desne komore, kod pacijenata sa lošom funkcijom leve komore i verifikovanom mehaničkom asinhronijom leve komore[40]. Modi i saradnici smatraju da pacijentima sa srednje teškom i teškom disfunkcijom i

indikacijom za antibradikardni pejsmejker, a u odsustvu indikacija za CRT, treba implantirati komorsku elektrodu u RVOT[41]. Dosadašnje 20-godišnje iskustvo na osnovu rezultata randomizovanih multicentričnih studija pokazuje jasnu korist od pejsmjker stimulacije sa alternativnih mesta, kod pacijenata sa sniženom EF, dok je bez koristi kod pacijenata sa očuvanom EF leve komore[42-44].

Nema razlike RVOT vs RVA

Kod pacijenata koji su na početku studije imali očuvanu EF nije bilo razlike između stimulacije iz septuma ili vrha desne komore[17,45]. Gong sa saradnicima, nakon 12-mesečnog praćenja 96 pacijenata, sa normalnom funkcijom leve komore, ehokardiografski nije našao razliku u funkciji leve komore, kod pejsmejker stimulacije iz izlaznog trakta i vrha desne komore[46]. Još uvek nemamo jasno dokazanu kliničku korist od alternativnih mesta stimulacije iz desne komore. Svakako RVOT u odnosu na RVA sigurno nije gori, i neki autori zastupaju ideju da se svim pacijentima pozicionira elektroda u RVOT, to su obično nove generacije pejsmejker implantera[47-48].
U ROVA studiji, kod 103 pacijenata sa srčanom insuficijencijom NYHA II i III, EF manjom od 40% i permenentnom atrijalnom fibrilacijom, nije nađena razlika u kvalitetu života ili kliničkim komplikacijama[49]. Iznenađujuće je da razlike u pejsmejker stimulaciji iz vrha ili septuma desne komore na sistolnu funkciju leve komore, nije bilo ni kod pacijenata sa CRT[50-53]. U REVERSE studiji kod pacijenata sa CRT, položaj eletktrode u desnoj komori nije bio od značaja, na praćene ehokardiografske parametere, funkcionalni status, ili broj komplikacija[54]. U PACE studiji[55] i drugi autori, daju prednost pejsmejker stimulaciji iz leve komore, u odnosu na bilo koji deo desne komore, kod odraslih[6,56-58], kao i kod dece[59-60].
Ukupno je bilo 25 studija sa pacijentima sa antibradikardnim pejsmejkerom i očuvanomsistolnom funkcijom leve komore i 11 studija kod pacijenata sa sniženom EF i antibradikardnim pejsmejkerom ili CRT-om. Zbirno gledano, u 16 (44%) radova nije bilo razlike između RVOT i RVA, a u 20 (56%) radova nađena je prednost RVOT stimulacije[20].

Zaključci

Pejsmejker stimulacija predstavlja terapijsku neminovnost kod bolesti i stanja koja se karakterišu nedovoljnom srčanom frekvencom i hronotropnom inkopetencijom. Pejsmejker stimulacija iz vrha desne komore daje šire QRS komplekse, intra ventrikularnu, interventrikularnu asinhroniju i veći rizik od razvoja srčane slabosti. Implantacija elektrode u izlazni trakt desne komore predstavlja jednostavno i dobro ili barem ne gore terapijsko rešenje u prevenciji razvoja srčane slabosti, posebno kod pacijenata sa sniženom sistolnom funkcijom leve komore.

Literatura

1. Mitov V. Implantacija pejsmejkera u pejsmejker kabinetu u Zajeèaru u 2008. god. Timočki medicinski glasnik. 2009;34:4.
2. Milašinović G, Perišić Z, Kovačević D, et all. Registar bolesnika sa implantiranim pejsmejkerima u Srbiji. Srce i krvni sudovi. 2009;1:29.
3. Milašinović G, Perišić Z, Kovačević D, et all. Dvanaestogodišnji trend implantacija antibradikardnih pejsmejkera u Srbiji. Srce i krvni sudovi. 2009;1:28.
4. Furman S, Schwedel JB. An intracardiac pacemaker for Stokes-Adams seizures. N Engl J Med. 1959;261:943-8.
5. Vassalo JA, Cassidy DM, Miller JM, et al. Left ventricular endocardial activation during right ventricular pacing: effect of underlying heart disease. J Am Coll Cardiol. 1986;7:1228-33.
6. Prinzen FW, Strik M, Regoli F, Auricchio A. Basic physiology and hemodynamics of cardiac pacing. U knjizi Ellenbogen KA ed. Clinical Cadiac Pacing, Defibrillation, and Resynhronization Therapy. Philadelphia. Elsevier Saunders. Fourth edition., 2011:203-233.
7. Lieberman R, Grenz D, Mond HG, et al. Selective site pacing: Defining and reaching the selective site. PACE. 2004;27:883-6.
8. Prinzen FW, Vernooy K, DeBoeck BWL, Delhaas T. Mechano-energetics of the asynchronous and resynchronizedheart. Heart Fail Rev. 2011;16:215-24.
9. Strik M, Regoli F, Auricchio A, Prinzen F. Electrical and Mechanical Ventricular Activation During Left Bundle Branch Bloc and Resynchronization. J of Cardiovasc Trans Res. 2012;5:117-26.
10. Costard-Jäckle A, Franz MR. Slow and long-lasting modulation of myocardial repolarization produced by ectopic activation in isolated rabbit hearts: evidence for cardiac „memory". Circulation. 1989;80:1412-20.
11. Manolis AS. The Deleterious Consequences of Right Ventricular Apical Pacing: Time to Seek Alternative Site Pacing. Pacing Clin Electrophysiol. 2006;29(3):298-315
12. Stambler BS, Reynolds DW. Hemodynamics of cardiac pacing and pacing mode selection. In: Ellenbogen KA ed. Cardiac Pacing and ICDs. 2008; Blackwell Publishing Ltd. 2008:116-174.
13. Chen S, Yin Y, Lan X, et al. Paced QRS duration as a predictor for clinical heart failure events during right ventricular apical pacing in patients with idiopatic complete atrioventricular block: results fom an observational cohort study (PREDICT-HF). Eur J of Heart Failure.2013;15:352-9.
14. Tse HF, Yu C, Wong KK, t al. Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. J Am Coll Cardiol. 2002;40:1451-8.
15. Mazza A, Bendini MG, Leggio M, et all. Incidence and predictors of heart failure hospitalization and death in permanent pacemaker patients: a single-centre experience over medium-term follow-up. Europace. 2013;doi:10,1093/europace/eut041. First published online: Feb 26,2013.
16. Manolis AS. The Deleterious Consequences of Right Ventricular Apical Pacing: Time to Seek Alternative Site Pacing. Pacing Clin Electrophysiol. 2006;3:298-315.
17. Manolis AS, Sakellariou D, Andrikopoulos GK. Alternative site pacing in patients at risk for heart failure. Angiology. 2008;2:97s-102s.
18. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. J Am Coll Cardiol. 2009;9:764-76.
19. Varma N. Alternative site pacing: accessing normal precordial activation: is it possible? Journal of Electrocardiography. 2012; 45:660-2.
20. Mitov V. Uticaj položaja pejsmejker elektrode na funkciju leve komore kod pacijenata sa permanentnom antibradikardnom pejsmejker stimulacijom. Doktorska disertacija. Medicinski fakultet u Nišu 2013; 1-102.
21. Pastore G, Noventa F, Piovesana P, et al. Left ventricular dyssynchrony resulting from right ventricular apical pacing: relevance of baseline assessment. Pacing Clin Electrophysiol. 2008;31:1456-62.
22. Abreu CD, Nunes M, BM, et al. Ventricular dyssynchrony and increased BNP levels in right ventricular apical pacing. Arq Bras Cardiol 2011;97:156-62.
23. Sharif D, SN, Radzievsky N, et all. Palpography detects mechanical dyssynchrony and worsens with right ventricular pacing and reduced left ventricular ejection fraction. Pacing Clin Electrophysiol. 2011;34:875-83.
24. Weizong W, Zhongsu W, Yujiao Z, et al. Effects of Right Ventricular Nonapical Pacing on Cardiac Function: A Meta-analysis of Randomized Controlled Trials. Pacing and Clinical Electrophysiology 2013;Article published online:25 feb 2013.doi:10,1111/pace,12112.

25. Barold SS, Stroobandt RX, Sinnaeve AF. Cardiac Pacemacers and Resynchronisation. Step by step. Wiley BlackWell. Second edition. 2010.
26. Zhang XH, Chen H, Siu CW, et al. New-onset heart failure after permanent right ventricular apical pacing in patients with acquired high-grade atrioventricular block and normal left ventricular function. J Cardiovasc Electrophysiol. 2008;2:136-41.
27. Vanagt WY, Prinzen FW, Delhaas T, et al. Physiology of cardiac pacing in children: the importance of the ventricular pacing site. Pacing Clin Electrophysiol. 2008;31:24-7.
28. De Cock CC, Giudici MC, Twisk J. Comparison of the haemodinamic effects of right ventricular outflow tract pacing with right ventricular apex pacing: a quantitative review. Europace. 2003;5:275-8.
29. Shimony A, Eisenberg MJ, Filion KB, Amit G. Beneficial effects of right ventricular non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials. Europace. 2012;14:81-91.
30. Tse HF, Wong KK, Siu CW, et al. Upgrading pacemaker patients with right ventricular apical pacing to right ventricular septal pacing improves left ventricular performance and functional capacity. J Cardiovasc Electrophysiol. 2009;20:901-5.
31. Wang F, Shi H, Sun Y, t al . Right ventricular outflow pacing induces less regional wall motion abnormalities in the left ventricle compared with apical pacing. Europace. 2012;14:351-7.
32. Takemoto Y, Hasebe H, Osaka. Right ventricular septal pacing preserves long term left ventricular function via minimizing pacing induced left ventricular dyssynchrony in patients with normal baseline QRS duration. Circ J. 2009;10:1829-35.
33. Sanaa I, Franceschi F, Prevot S, et al. Right ventricular apex pacing: is it obsolete? Arch Cardiovasc Dis. 2009;2:135-41.
34. Flevari P, Leftheriotis D, Fountoulaki K, et al. Long-term nonutflow septal versus apical right ventricular pacing: relation to left ventricular dyssynchrony. Pacing Clin Electrophysiol. 2009;3:354-62.
35. Fang F, Chan JYS, Kwok GW, et al. Prevalence and determinants of left ventricular systolic dyssynchrony in patinents with normal ejection fraction recived right ventricular apical pacing: a real-time three-dimensional echocardiographic study. In: 11 ed, 2010:109-18.
36. Kachboura S, Ben Hallima A, Fersi I, et al. Assessment of heart failure and left ventricular systolic dysfunction after cardiac pacing in patients with preserved left ventricular systolic function. Ann Cardiol Angeiol. 2008;1:29-36.
37. Inoue K, Okayama H, Nishimura K, et al. Right ventricular septal pacing preserves global left ventricular longitudinal function in comparison with apical pacing. Circulation. 2011;7:1609-15.
38. Lewicka-Nowak E, Dabrowska-Kugacka A, Tybura S, et al. Right ventricular apex versus right ventricular outflow tract pacing: prospective, randomised, long term clinical and echocardiographic evaluation. Kardiol Pol. 2006;10:1082-91.
39. Cano OJ, Osca MJ, Sancho-Tello JM. Comparison of effectiveness of right ventricular septal pacing versus right ventricular apical pacing. The American Journal of Cardiology. 2010;10:1426-32.
40. Stambler BS, Ellenbogen KA. Pacing for Atrioventricular Conduction System Disease. In: Ellenbogen KA KGLCWBL, ed. Clinical Cadiac Pacing, Defibrillation, and Resynhronization Therapy. Philadelphia.:ElsevierSaunders. Fourth edition., 2011:323-360.
41. Modi S, Krahn A, Yee R. Current concepts in pacing 2010-2011: the right and wrong way to pace. Curr Treat Options Cardiovasc Med. 2011;13:370-84.
42. Tse HF, Wong KK, Siu CW, et al. Impacts of ventricular rate regularization pacing at right ventricular apical vs. Septal sites on left ventricular function and exercise capacity in patients with permanent atrial fibrilation. Europace. 2009;5:594-600.
43. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESCGuidelines on cardiac pacing and cardiacresynchronization therapy. TheTask Force on cardiac pacing and resynchronization therapy of theEuropean Society of Cardiology (ESC). Developed in collaborationwith the European Heart Rhythm Association (EHRA). European Heart Journal 2013;doi:10,1093/euroheartj/eht150:1-49.
44. Victor F, Mabo P, ansour H, et al. A randomized comparison of permanent septal versus apical right ventricular pacing: short term results. J Cardiovasc Electrophysiol. 2006;17:238-42.
45. Andrzej R, Piotr R, Tomasz S, et all. Comparison of the acute hemodynamic effect of right ventricular apex, outflow tract, and dual-site right ventricular pacing. Ann Noninvasive Electrocardiol. 2010;15:353-9.
46. Gong X, Su Y, Pan W, et al. Is right ventricular outflow tract pacing superior to right apex pacing in patients with normal cardaiac function? Clinical Cardiology 2009;12:695-9.
47. Mitov V, Jolić A. Analiza parametara implantacije ventrikularne elektrode u izlazni trakt desne komore vs. u vrh desne komore. Srce i krvni sudovi. 2011;1:86.
48. Mitov V, Jolić A, Aleksić Ž, et all. The efect of pacemaker lead positioning on left ventricle function and patient functional capacity. Eur J Heart Fail. 2012;11:57.
49. Stambler BS, Ellenborgen K, Zhang X, et al. Right ventricular outflow versus apical pacing in pacemacer patients with congenstive heart failure and atrial fibrillation. J Cardiovasc Electrophysiol. 2003;14:1180-6.
50. Khan FZ, Salahshouri P, Duehmke R, et al. The Impact of the Right Ventricular Lead Position on Response to Cardiac Resynchronization Therapy. Pacing Clin Elektrophysiol. 2011;34:467-74.
51. Kristiansen HM, Vollan G, Hovstadt T, et all. A randomized study of haemodynamic effects and left ventricular dyssynchrony in right ventricular apical vs. high posterior septal pacing in cardiac resynchronization therapy. Eur J Heart Fail. 2012;14:506-16.
52. Stockinger J, Staier K, Schiebeling-Romer J, Keyl C. Acute Hemodynamic Effects of Right and Left Ventricular Lead Positions during the Implantation of Cardiac Resynchronization Therapy Defibrillators. Pace. 2011;34:1537-43.
53. Delnoy PM, Ottervanger JP, Oude H, et al. Pressure-volume loop analysis during implantation of biventricular pacemaker/cardiac resynchronization therapy device to optimize right and left ventricular pacing sites. European Heart Journal. 2009;30:797-804.
54. Thebault C, Donal E, Meunier C, et al. Sites of left and right ventricular lead implantation therapy observations from the REVERSE trial. Eur Heart J. 2012;33:2662-71.
55. Chan JYS, Fang F, Zhang Q. Biventricular pacing is superior to right ventricular pacing in bradycardia patients with preserved systolic function: 2-year results of the PACE trial. European Heart Journal. 2011;32:2533-40.
56. Bildirici U, Vural A, Agacdiken A, et al. Comparison of the effects of left vs. right ventricular pacing on left ventricular remodeling. Europace. 2008;10:1387-91.
57. Stockburger M, Gómez-Doblas JJ, Lamas G, et al. Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: results from a multicentre international randomized trial (PREVENT-HF). Eur J Heart Fail. 2011;13:633-41.
58. den Besten T, Sedney MI, Frederiks J. Left ventricular dysfunction due to right ventricular stimulation: is biventricular upgrade really necessary? Neth Heart J. 2010;18:604-5.
59. Gebauer RA, Tomek V, Kubus P, et al. Differential effects of the site of permanent epicardial pacing on left ventricular synchrony and function in the young: implications for lead placement. Europace. 2009;11:1654-9.
60. Vanagt WY, Prinzen FW, Delhaas T. Reversal of pacing-induced heart failure by left ventricular apical pacing. N Engl J Med. 2007;357:2637-8.

Abstract

The influence of antibradycardial pacemaker stimulation to heart failure development

Vladimir Mitov[1], Aleksandar Jolić[1], Dragana Adamović[1], Milan Nikolić[1], Marko Dimitrijević[1], Zoran Perišić[2], Tomislav Kostić[2], Milan A Nedeljković[3]

[1]Department of Cardiology, Medical center Zaječar

[2]Department of invasive diagnostic, University Hospital Niš

[3]Clinic of Cardiology, Clinical centre of Serbia; Medical faculty, Universisity of Belgrade

Conduction tissue diseases of the heart, which are characterized by slowing of the heart rate are treated by pacemaker stimulation from right atrium and right ventricle. However, there is a rising question whether this kind of stimulation, either from the apex of the right ventricle outflow tract can have a deleterious effect on left ventricle function. Analyzing this effect of permanent pacemaker stimulation on left ventricle function we measured QRS duration according to ventricle lead position in right ventricle. This stimulation is without alternative in all the conduction tissue diseases which are characterized by chronotropic incompetence and bradycardia. The stimulation from right ventricle apex gives arise to inter and intraventricular dissinchrony and thus creates greater risk of heart failure developmen. Right ventricle outflow tract position of the pace maker electrode represents simple and if not better, than at least not worse solution in heart failure prevention due to pacemaker stimulation, especially in patients with already reduced ejection fraction.

Key words: RVA, RVOT, pacemaker stimulation, heart failure

Srce i krvni sudovi 2019; 38(2): 80-90

Pregledni rad

Patogenetski mehanizmi indukcije ubrzane ateroskleroze kod pušača

Jakša Dubljanin[1], Čedomir Uštević[2], Nikola Gošnjić[3], Nemanja Pejić[4], Ivan Ranković[5], Ljubica Jovanović[6,7], Žaklina Leković[6], Ivana Veljić[6], Nebojša Antonijevi[6,7], Vladimir Kanjuh[8]

[1]Služba za kardiologiju Kliničko bolnički centar Zemun, [2]Specijalna bolnica "Termal", Vrdnik, , [3]Klinika za gastroenterohepatologiju, Klinički centar Srbije, [4]Klinika za urgentnu hirurgiju, Urgentni Centar KCS, [5]Katedra za farmakokinetiku i kliničku farmaciju, Farmaceutski fakultet Univerziteta u Beogradu, [6]Klinika za Kardiologiju, Klinički centar Srbije, [7]Medicinski fakultet Univerziteta u Beogradu, [8]Odbor za kardiovaskularnu patologiju SANU

Sažetak

U opštoj i stručnoj javnosti postoji nedovoljna svest o o ulozi pušenja u ubrzanju ateroskleroze, nastanku infarkta miokarda, sekundarnih kardiovaskularnih komplikacija, cerebrovaskularnih oboljenja, bolesti perifernih arterija i drugih entiteta u čijoj patogenezi aterotromboza ima važnu ulogu. Brojni su dokazi o uticaju pušenja na vazomotornu disfunkciju, inflamaciju, povišenu trombogenost i modifikaciju lipidnog profila. Pušenje dovodi do smanjenja vazodilatacije, smanjujući raspoloživost azot monoksida (NO). Slobodni radikali iz duvanskog dima utiču na oksidativnu modifikaciju LDL, ključnih molekula za započinjanje inflamatorne reakcije, kao i na nukleusni faktor κB (NF-kB), koji je ključan faktor za transkripciju inflamatornih citokina. Nikotin utiče na ekspresiju gena odgovornih za disfunkciju endotela (e-NOS, ACE, VCAM-1, tPA, PAI-1 i vWF), dovodi do proliferacije glatkih mišićnih ćelija, fibroblasta i povećava mitogeni efekat angiotenzina II. Broj leukocita u perifernoj krvi pušača veći je za 20-25%, povišeni su markeri zapaljenja - CRP, IL-6, TNF-α, VCAM-1, ICAM-1 i E-selektin. Monociti pušača imaju povećanu ekspresiju integrina CD11b/CD18 koji povećavaju adheziju monocita i dovode do dvostruko veće migracije monocita kroz endotel. Pušenje dovodi do povećanja aktivacije, agregacije i adhezije trombocita, do promena protrombotičkih (povećanja fibrinogena i tkivnog faktora TF), antitrombotičkih (smanjenja inhibitora puta tkivnog faktora TFPI-1) i fibrinolitičkih faktora (smanjenja tkivnog aktivatora plazminogena (tPA) i promene odnosa tPA i inhibitora aktivatora plazminogena PAI- 1). Pušenje povećava ukupni holesterol, trigliceride, LDL, snižava HDL i ubrzava penetraciju oksidovanog LDL u zid krvnog suda. Za stepen ubrzanog razvoja ateroskleroze kod pušača bitna je i genetska predispozicija. Razumevanje i sagledavanje patofizioloških mehanizama uticaja pušenja na aterosklerozu bitno je radi prepoznavanja pušenja kao važnog faktora rizika za nastanak kardiovaskularnih bolesti i isticanje značaja borbe protiv pušenja na svim nivoima u opštoj i stručnoj populaciji.

Ključne reči pušenje, rana ateroskleroza, kardiovaskularne bolesti, tromboza, faktori rizika

Veliki broj radova razmatra uticaj pušenja na nastanak plućnih bolesti, hronične opstruktivne bolesti pluća, karcinoma pluća i tumora drugih organa. Smatramo da obim problema koji pušenje ima na razvoj procesa ateroskleroze i aterotromboze, kao i posledičnih poremećaja koji ih prate na pojedinca i društvo u celini nije dovoljno prepoznat i shvaćen. Aterotromboza predstavlja glavni uzrok mortaliteta i prerane invalidnosti u razvijenim zemljama[1]. Ateroskleroza čini osnovu oko 80% kardiovaskularnih oboljenja i ima veliki zdravstveno-socijalni značaj.[2]

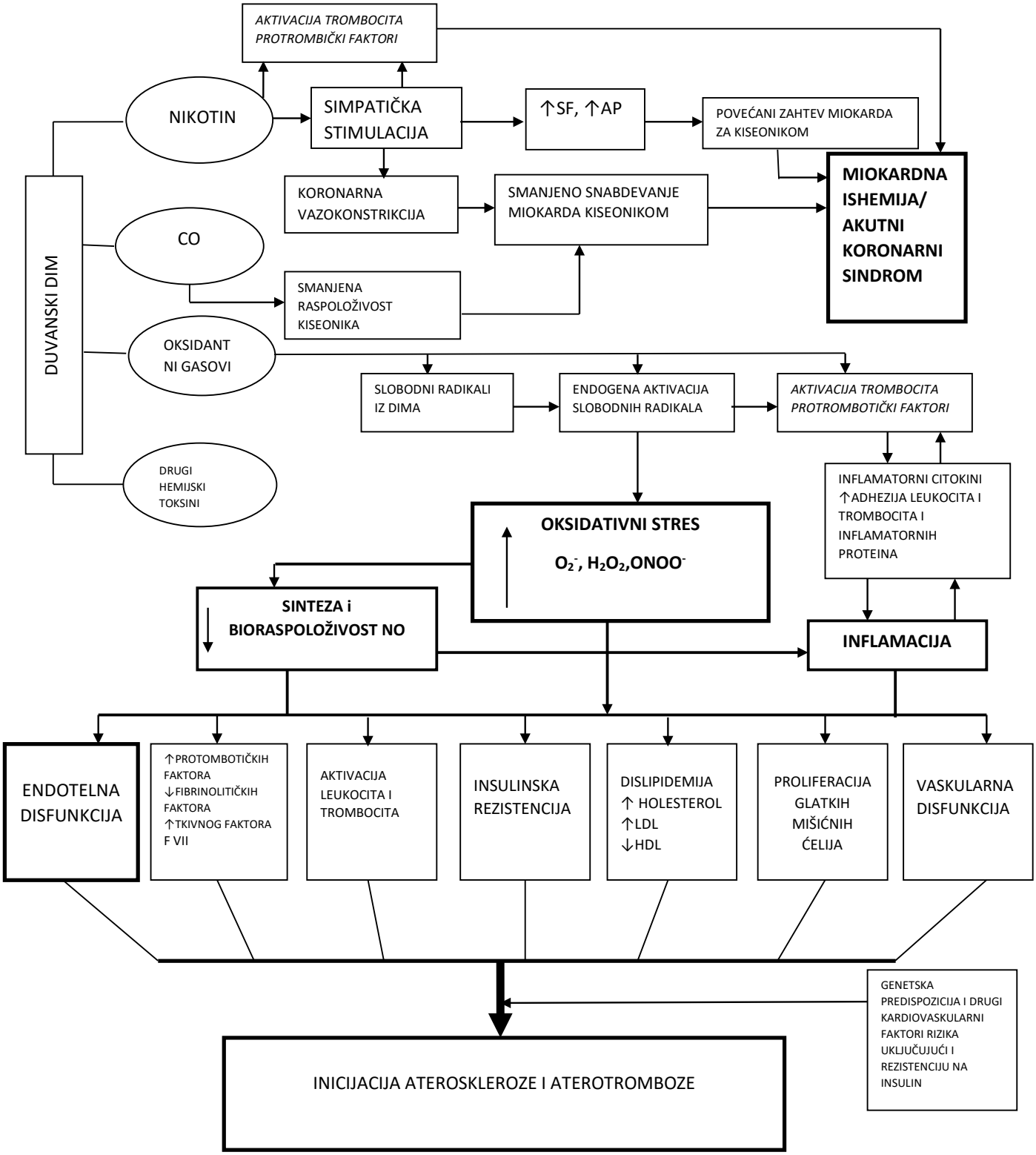
Ateroskleroza kao najčešće oboljenje arterija počinje disfunkcijom endotela, odnosno predstavlja strukturnu promenu koja primarno zahvata intimu arterija, a kasnije dovodi do fokalnog nagomilavanja lipida, kalcijuma, veziva (kolagena, elastina, mukoolisaharida), drugog detritusa i određenih krvih ćelija i izmenjenih glatkih mišićnih ćelija, promena u drugim delovima arterija, mediji i adventiciji, remodelovanja arterije, atrofije medije iza aterosklerotične ploče, suženja i tromboze lumena, periadventicijalnih infiltrata sastavljenih od limfocita i plazmocita. Aterosklerotični plak u većem delu života može ostati asimptomatski, ali je sklon pucanju, izlivanju lipidnog sadržaja u lumen krvnog suda, posle čega dolazi do lokalne aktivacije i agregacije trombocita i stvaranja tromba, odnosno aterotromboze sa stenozom, lokalnom okluzijom ili distalnom embolizaciom. Pored najpoznatijih kliničkih manifestacija aterotromboze kao što su koronarna bolest (angina pektoris, infarkt miokarda, aritmije), cerebralna ishemija (reverzibilni ishemijski atak i cerebrovaskularni insult), periferna arterijska bolest sa posledičnim gangrenama ekstremiteta, atero-

Autor za korespondenciju: Čedomir Uštević, Braće Jugovića 8/12, Aranđelovac, cedomir91.ustevic@gmail.com, telefon 069/4689-408

Tabela 1. Najznačajniji sastojci duvanskog dima u gasnoj kapljičnoj fazi[5]

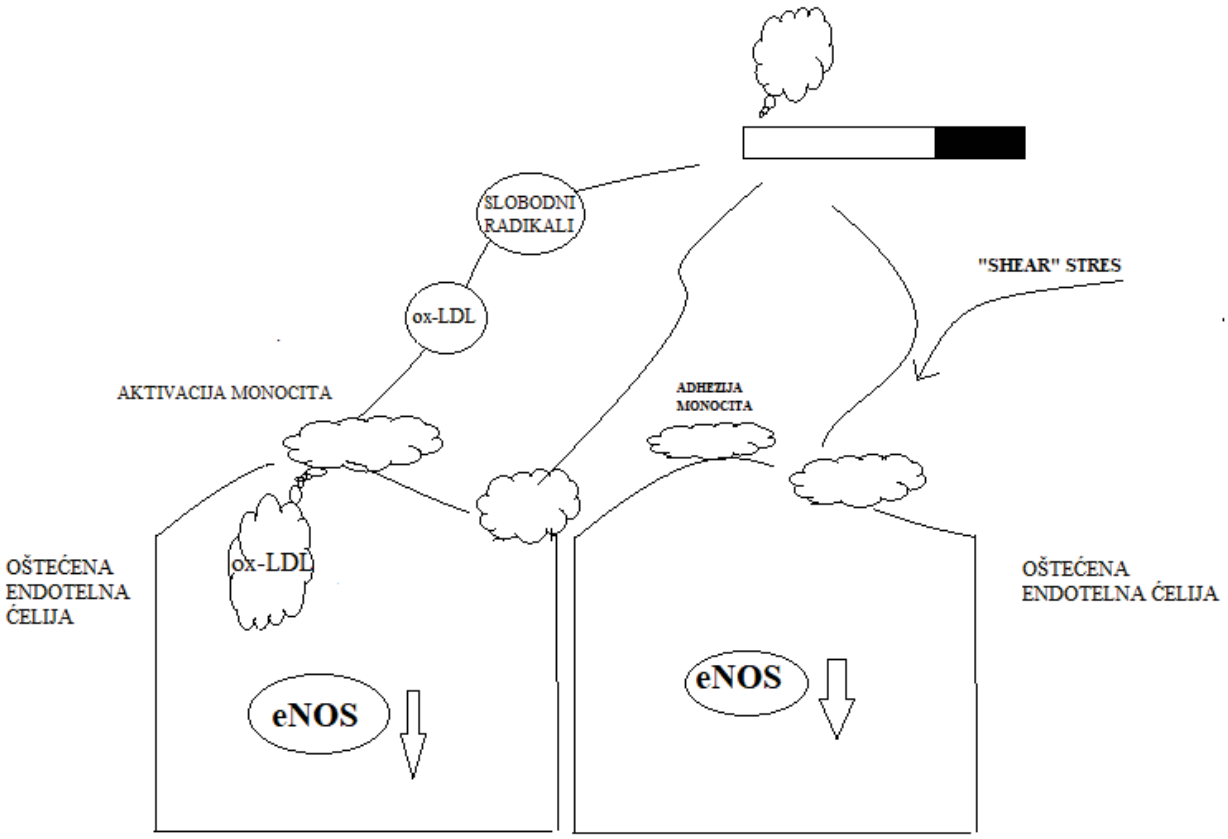
Faze	Sastojci
Gasna	Gasovi (NH_3, CO, CO_2, HCN), etanol, formaldehid, akrolein, krotonaldehid, benzenska para, aceton, vinilhlorid, nezasićeni ugljovodonici (butadien, izopren), slobodni radikali (NO, NO_2, NO_3^-, nitrozo karbonradikali)
Kapljična	Nikotin, metali (Cd, Ni, Pb, Fe, Cr, As, Be, Ra-222, Po-210), fenoli, aromatični ugljovodonici (benzpiren, benzantracen), 4-amino-bifenil, stabilniji slobodni radikali (hinon/hidrohinon kompleks – Q/QH2)

tromboza kao završni stadijum ateroskleroze dovodi do mezenterijalne i drugih visceralnih ishemija, seksualne disfunkcije, formiranja aneurizmi aorte i drugih arterija.[3]
Za razumevanje ovakvog efekta pušenja, najpre se mora razumeti sastav cigareta i procesa njihovog sagorevanja. Cigareta se sastoji od osušenih listova duvana, cigaret papira, raznih aditiva i drugih organskih jedinjenja. Prilikom pušenja, dolazi do njihove pirolize i nastanka duvanskog dima koji predstavlja aerosol i sačinjen je iz kapljične faze ili katrana i gasne faze. Kapljična faza je dispergovana u gasnoj fazi. Kapljičnu fazu čine susptance koje imaju veći promer od 0,1μm i 99,9% ovih supstanci se zadržava u Kembridžovom filteru od staklenih vlakana (*eng. Cambridge glass-fiber filter*) čineći totalni aerosolni ostatak (eng. *tar – total aerosol residue*). Gasnu fazu čine supstance koje su manje od 0,1μm[4]. Najznačajniji sastojci gasne i kapljične faze duvanskog dima mogu se videti u Tabeli 1.
U zavisnosti od temperature sagorevanja razlikuje se još i primarni i sekundarni duvanski dim. Primarni nastaje na višoj temperaturi sagorevanja (oko 900°C) i to je dim koji prolazi kroz cigaretu i koji pušači direktno uvlače u usta. Sekundarni duvanski dim nastaje na nižoj temperaturi sagorevanja (oko 500-600°C) i to je dim koji nastaje prilikom spontanog sagorevanja cigarete. Sekundarni duvanski dim ima više štetnih materija koje nastaju nepotpunom oksidacijom organskih jedinjenja iz cigareta na nižim temperaturama sagorevanja5. Duvanski dim u prostorijama čini oko 85% sekundarnog i oko 15% primarnog dima kog pušači izdahnu i ovaj dim udišu pasivni pušači.[6]
U duvanskom dimu je izolovano preko 5000 hemijskih jedinjenja [7]. Po biološkom dejstvu ova jedinjenja mogu biti iritansi, inhibitori enzima, neurotoksični agensi, farmakološki aktivne supstance, mutageni i kancerogeni[5]. Više stotina jedinjenja je dokazano toksično, a preko 70 kancerogeno.
I pored činjenice da obrazlažemo problem dejstva pušenja na aterotrombozu smatramo da je celishodno spomenuti brojne materije iz duvanskog dima kao što su su formaldehid, benzen, 4-aminobifenil, arsen, radioaktivni radon 222 i njegov raspadni produkt radioaktivni polonijum 210, vinil hlorid, etilen oksid, nitrozoamini, slobodni radikali itd. Ove materije dovode do direktnog oštećenja DNK favorizujući kancerogenezu.
Neke materije kao npr. nikotin nisu direktno kancerogene, ali pospešuju rast tumora stimulišući angiogenezu[5].
Pušenje se dovodi u vezu sa najmanje 14 različitih vrsta malignih tumora: usta, nosa, ždrela, dušnika, ezofagusa, pluća, jetre, pankreasa, želudca, bubrega, debelog creva, jajnika, mokraćne bešike, cerviksa i leukemije, od kojih su maligni tumori pluća na prvom mestu. [8,9]
Sastojci duvanskog dima dospevaju u organizam i cirkulaciju najviše preko respiratornog sistema. Manji deo se resorbuje preko bukalne sluzokože, rastvara se u pljuvačci i guta, a deo (naročito kapljična faza) se rastvara i deponuje u tečnosti koja oblaže mukozu respiratornog trakta.[5]
Sastojci duvanskog dima od najvećeg značaja za nastanak i razvoj ateroskleroze su slobodni radikali, aromatična jedinjenja, gasovi ugljen monoksid (CO) i cijanovodonik (HCN) kao i nikotin u nešto manjoj meri.[11-15]
Slobodni radikali. U kapljičnoj fazi se nalaze stabilniji slobodni radikali sa poluživotom od nekoliko sati do nekoliko meseci. Ima ih preko 10^{17} u gramu i najznačajniji su kompleksi hinon-semihinon-hidrohinon (QH/QH$^{\bullet}$/QH2). Oni u toku celog svog života proizvode superokside. U gasnoj fazi se nalaze azotni i kiseonični slobodni radikali. Oni su reaktivniji, sa poluživotom od nekoliko sekundi, i ima ih preko 10^{15} u dahu. Azot monoksid iz duvanskog dima reaguje sa kiseonikom iz vazduha formirajući azot dioksid koji je reaktivniji i stupa u reakciju sa izoprenom i butadienom iz duvanskog dima formirajući toksične nitrozokarbon radikale. Azot monoksid reaguje i sa superoksidima formirajući toksične peroksinitrite. Peroksinitriti i nitrozokarbon radikali imaju najveći oksidacioni potencijal. Slobodni radikali iz duvanskog dima su najodgovorniji za oksidativni stres.[16-18]
Aromatična jedinjenja. Od aromatičnih jedinjenja najveći značaj za patogenezu ateroskleroze imaju policiklični aromatični ugljovodonici i aromatični amini. Policiklični aromatični ugljovodonici ispoljavaju direktno toksično dejstvo na ćelije endotela, izazivaju zapaljenje i ubrzavaju aterosklerozu. Oni takođe smanjuju i broj endotelnih progenitorskih ćelija. Iako se poznaje mehanizam njihove kancerogeneze, tačan mehanizam oštećenja endotelnih ćelija se još uvek ne zna, ali se pretpostavlja da oni učestvuju direktno, kao i produkti njihovog metabolizma u oštećenju DNK, kao i inaktivaciji ključnih enzima za funkcionisanje ćelija. Aromatični amini inhibiraju sintezu tetrahidrobiopterina (THB) i prostaciklina PGI_2. Tetrahidrobiopterin je glavni kofaktor endotelne NO sintetaze (eNOS) i neophodan je za normalnu produkciju azot monoksida. U odsustvu ovog kofaktora, endotelne NO sintetaze, se ne sintetiše azot monoksid, već sintetiše superokside i perokside. Inhibicija sinteze prostaciklina PGI_2 (aromatični 2-naftilamin) dovodi do povećane sinteze tromboksana A_2 u metabolizmu arahidonske kiseline što ima protrombogeni efekat.[19-23]
Gasovi ugljen monoksid i cijanovodonik ne deluju direktno na aterosklerozu, već indirektno. Ugljen monoksid (CO) može ispoljiti svoje potencijalno štetno dejstvo na srce i krvne sudove na dva načina, bilo izazivanjem akutnih kratkotrajnih efekata, preko formiranja karboksihemoglobina, kompeticijom vezivanja kiseonika za hemoglobin i blokiranjem transporta kiseonika do perifernih tkiva ili doprinoseći razvoju kardiovaskularnih



Shema 1. Shematski prikaz patogeneze ateroskleroze i aterotromboze pušača. Preuzeto i modifikovano od: Ambrose and Barua, 2004 i Salahuddin, 2012[10]

Centralno mesto zauzima oksidativni stres, zatim inflamacija i smanjenje sinteze i bioraspoloživosti azot monoksida NO. Nastaje vazomotorna disfunkcija, povećana trombogenost, modifikacija lipidnog profila, oksidacija LDL molekula, širenje i održavanje zapaljenja što dovodi do inicijacije i progresije ateroskleroze i aterotromboze. Skraćenice: SF – srčana frekvenca, AP – arterijski pritisak, NO – azot monoksid, CO – uglen monoksid, O_2^-, H_2O_2, $ONOO^-$ - kiseonički radikali kao produkti oksidativnog stresa.



Slika 1. Shematski prikaz zapaljenja uzrokovanog puše njem i razvoja ateroksleroze

Modifikovano prema: Powell JT.Vasc Med. 1998;3(1):21-8. Review.[26]
oxLDL – oksidirani lipoproteini male gustine, eNOS – endogeni azot monoksid

bolesti kao što je ateroskleroza i aterotromboza. Kod pušača od 2 - 10% hemoglobina može biti zamenjeno karboksihemoglobinom. In vitro studije su pokazale da je nakon kratkotrajnog izlaganja ugljen monoksidu (meren šesnaest sati nakon izlaganja) dokazan aterogeni uticaj na makrofage, stvaranjem arterijske makrofagne ćelijske formacije, penaste ćelije, kao znaka rane ateroskleroze.[24]

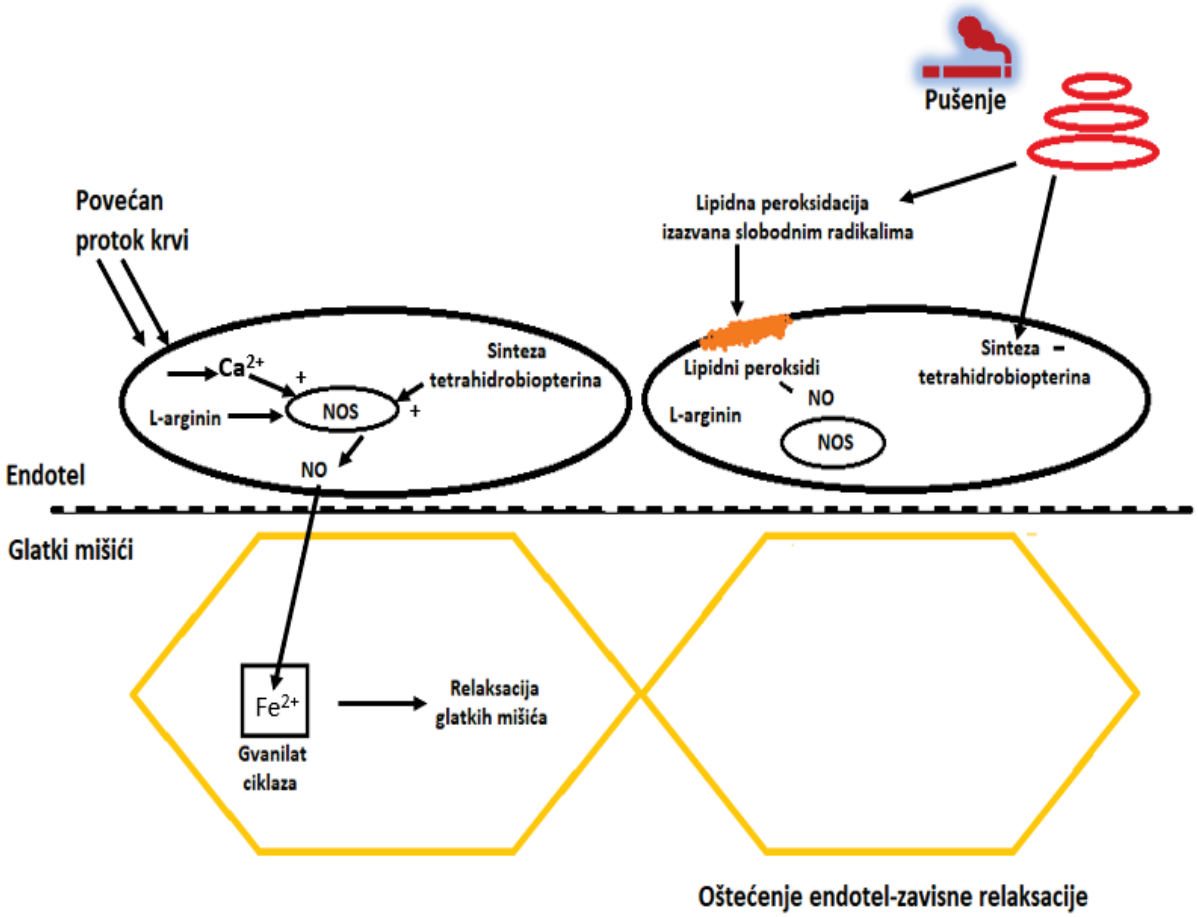
Cijanovodonik (HCN) se vezuje za gvožđe citohrom oksidazu blokirajući ćelijsku respiraciju na nivou mitohondrija. Nastaje hipoksija koja favorizuje stvaranje endogenih slobodnih radikala koji učestvuju u oksidativnom stresu. Hipoksija kod pušača dovodi i do reaktivne eritrocitoze koja povećava viskoznost krvi što deluje protrombogeno, mada viskoznost krvi ima veći značaj u patogenezi tromboze dubokih vena.[13,23,22]

Nikotin ne utiče direktno na inicijaciju ateroskleroze, ali utiče na rast aterosklerotskog plaka stimulišući proliferaciju vaskularnih mišićnih ćelija i fibroblasta. Nikotin povećava mitogeni efekat angiotenzina II i povećava ekspresiju gena koji kodiraju proteine odgovorne za angiogenezu čime takođe utiče na rast aterosklerotskog plaka. Ispitivanja na endotelnim ćelijama humanih koronarnih arterija su pokazala da nikotin povećava transkripciju gena koji kodiraju proteine odgovorne za vaskularni tonus i trombogenost (e-NOS, ACE, tPA, PAI-1, vWF i VCAM-1), ali se još uvek ne zna koliki značaj ovaj mehanizam ima u patogenezi ateroskleroze. Nikotin preko svojih perifernih receptora u autonomnim ganglijama i srži nadbubrega povećava tonus simpatikusa i povećava nivo cirkulišućih kateholamina, čime deluje indirektno na aterosklerozu, jer kateholamini povećavaju lipolizu i dovode do modifikacije lipidnog profila. Nikotin preko svojih centralnih receptora u mezolimbičkom dopaminergičkom sistemu i nukleusu akumbensu utiče na lučenje dopamina i endorfina što je osnov za stvaranje zavisnosti[14,15].

U oksidativnom stresu učestvuju i endogeni slobodni radikali koji nastaju zbog hipoksije i zapaljenja. To su visoko reaktivni kiseonični slobodni radikali – superoksidi, vodonik peroksid i hidroksilni radikali. Hipoksija tkiva zbog smanjenog dopremanja kiseonika i inhibicije ćelijske respiracije dovodi do nepotpune redukcije kiseonika u elektronskom transportnom lancu mitohondrija. Aktiviraju se i Ca^{2+}-zavisne oksidaze (ksantin oksidaza i NADPH oksidaza), a zapaljenje koje nastaje kao reakcija na oštećenja izazvana slobodnim radikalima iz duvanskog dima i aromatičnim jedinjenjima dovodi do aktivacije mijeloperoksidaze u leukocitima. Takođe, usled smanjenja sinteze THB (tetrahidrobinola), ne proizvodi azot monoksid, već superokside i perokside. Sve ovo dovodi do povećanog stvaranja slobodnih radikala. Kod pušača je smanjena aktivnost superoksid dizmutaze i katalaze, dok je aktivnost glutation peroksidaze pojačana.

Oksidativni stres

U oksidativnom stresu učestvuju slobodni radikali iz duvanskog dima, kao i endogeni slobodni radikali. Slobodni radikali su visoko reaktivni molekuli koji sadrže jedan nes-



Slika 2. Shematski prikaz vazomotorne disfunkcije i izostanka endotel-zavisne relaksacije na povećan protok krvi kod oštećenog endotela (desno) i normalne reakcije endotela na povećan protok krvi (levo)

Modifikovano prema: Powell JT.Vasc Med. 1998;3(1):21-8. Review[26], NO – azot monoksid; NOS – azot monoksid sintetaza

paren elektron. Kada dođu u kontakt sa drugim molekulima, preuzimaju elektron od njih, čime pretvaraju molekule u nove slobodne radikale, tako da nastaje lančana reakcija. Najznačajnija lančana reakcija je lipidna peroksidacija koja oštećuje ćelijsku membranu ćelija. Slobodni radikali dovode i do oksidacije lipoproteina male gustine (LDL) stvarajući oksidovani LDL (ox-LDL). Oni smanjuju i aktivnost paraoksonaze 1 lipoproteina velike gustine (HDL) – glavnog enzima koji razlaže hidroperokside lipida LDL i štiti LDL od oksidacije. Slobodni radikali kao i ox-LDL povećavaju aktivnost NF–κB, koji dovodi do povećane transkripcije gena proinflamatornih citokina (IL-6, TNF-α), dovodeći do zapaljenja. Slobodni radikali utiču i na smanjenje endogenog azot monoksida.[25]

Inflamacija

Proinflamatorni citokini dovode do povećane ekspresije ćelijskih adhezionih molekula (VCAM-1, ICAM-1, E-selektin) na površini endotela. Aktiviraju i monocite te dolazi do povećane ekspresije integrina CD11b/CD18 na površini monocita. Povećana ekspresija ćelijskih adhezionih molekula i integrina dovode do adhezije monocita za endotelne ćelije. Monociti migriraju unutar zida krvnog suda, transformišu se u makrofage, fagocituju ox-LDL i pretvaraju se u penaste ćelije. ox-LDL značajno povećava ekspresiju tzv. *scavanger* receptora na površini makrofaga. Pušači imaju značajno povišene vrednosti C-reaktivnog proteina (CRP), broj leukocita u perifernoj krvi pušača je veći za 20-25% u odnosu na nepušače i kod pušača je povećana transendotelna migracija monocita.[11]

Smanjenje bioraspoloživosti i produkcije NO

Endogeni azot monoksid reaguje sa superoksidima formirajući peroksinitrite i reaguje sa lipidnim peroksidima pokušavajući da zaustavi lančanu reakciju lipidne peroksidacije. Ove reakcije dovode do smanjivanja koncentracije raspoloživog azot monoksida. Zbog nedostatka THB, eNOS ne proizvodi azot monoksid čime se dodatno smanjuje njegova raspoloživost. NO ima značajnu ulogu u izazivanju relaksacije endotela krvnog suda, tako što difunduje unutar glatkih mišićnih ćelija, vezuje se za gvožđe guanilat ciklazu, aktivira je i povećava stvaranje cikličnog guanozin monofosfata cGMP, što dovodi do relaksacije glatkih mišićnih ćelija. Sličnim mehanizmom NO sprečava aktivaciju trombocita. Kao rezultat manjka NO nastaje vazomotorna disfunkcija, prvi znak oštećenja endotela koji se može detektovati, i ima protrombogeni i proinflamatorni efekat. Postoje studije koje pokazuju da manjak NO dovodi do hiperinsulinemije i povećane rezistencije na insulin, što takođe ima značaja u patogenezi ateroskleroze.[23]
Azot monoksid iz duvanskog dima reaguje sa nikotinom formirajući nitrozonornikotin, sa superoksidima formira

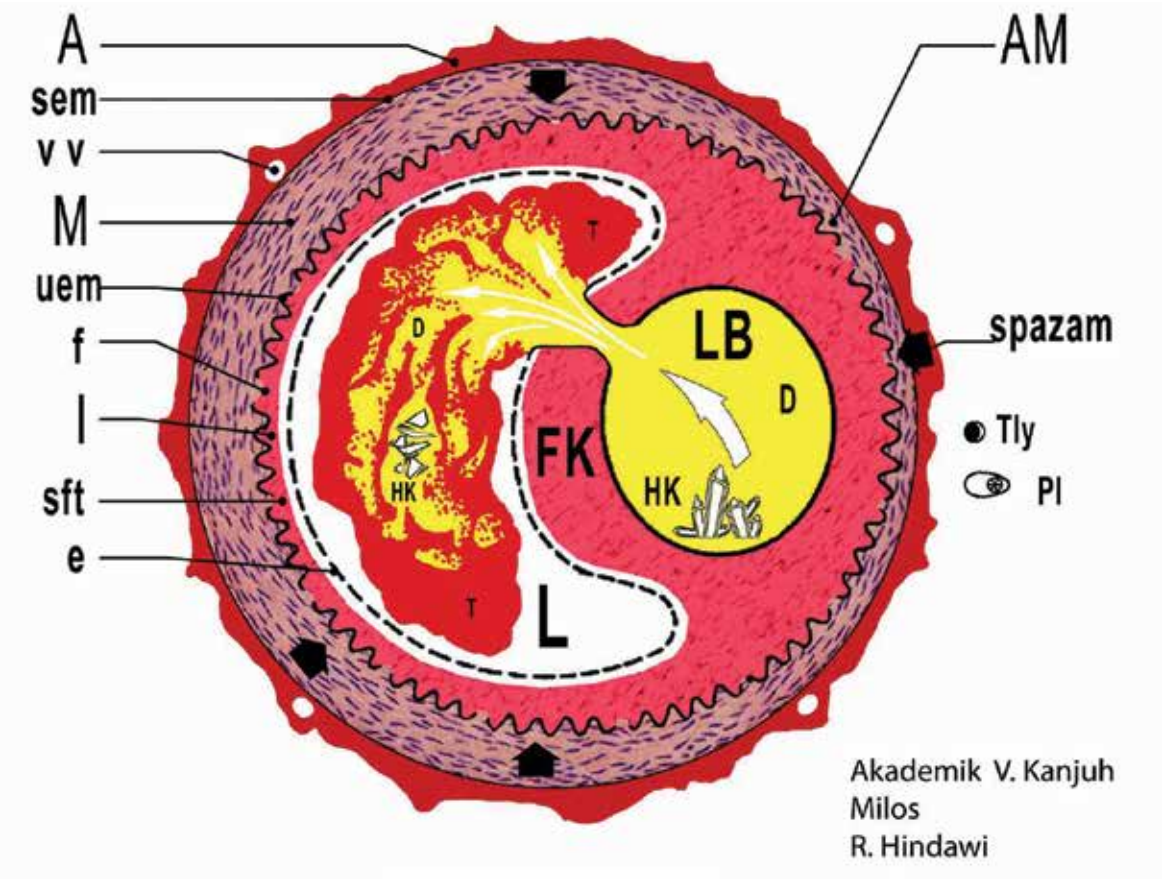
peroksinitrite i sa drugim jedinjenjima duvanskog dima formira potencijalno kancerogene materije. Deo koji dospe u cirkulaciju vezuje se za hemoglobin i druge proteine plazme. Nitrozoalbumini koji nastaju na ovaj način bi mogli poslužiti kao NO donori, međutim njihova koncentracija u krvi pušača je previše niska da bi imali bilo kakav koristan efekat.[23]

Trombogeneza

Smanjenje raspoloživog azot monoksida, smanjenje sinteze prostaciklina PGI_2 i povećana sinteza tromboksana A_2 dovodi do aktivacije trombocita i njihove pojačane agregacije i adhezije. Oštećenje endotelnih ćelija (deskvamacija, erozija, fisura) dovodi do denudacije endotela i otkrivanja subendotelnog matriksa, naročito kolagena i tkivnog faktora koji deluju protrombogeno. Kod pušača je povišen nivo fibrinogena, faktora VII i cirkulišućeg tkivnog faktora, dok su antitrombotički faktori sniženi (inhibitor puta tkivnog faktora – TFPI–1), kao i fibrinolitički faktori (smanjenje tkivnog aktivatora plazminogena i promena odnosa između tkivnog plazminogen aktivatora tPA i plazminogen aktivator inhibitora 1 PAI–1)[13,27]. Ruptura aterosklerotskog plaka može nastati usled skoka pritiska zbog pojačane aktivnosti simpatikusa ili zbog povećane viskoznosti krvi, čime lipidni bazen koji je jako trombogen dolazi u kontakt sa cirkulišućom krvi, zbog čega može nastati akutni koronarni događaj. Povećana viskoznost krvi usled reaktivne eritrocitoze zbog hronične hipoksije pušača pogoduje nastanku tromba, ali kao što je napomenuto, veći značaj ima za patogenezu tromboze dubokih vena.[27]

Modifikacija lipidnog profila

Pušenje utiče na nastanak proaterogenog lipidnog profila. Kod pušača su u odnosu na nepušače povišeni nivoi ukupnog holesterola, LDL i trigliceridi, dok su vrednosti HDL-a snižene. Tačni mehanizmi kojim pušenje dovodi do promena u lipidnom profilu nisu u potpunosti rasvetljeni. Kod pušača je pojačana lipoliza zbog povećane koncentracije cirkulišućih kateholamina, pušači imaju hiperinsulinemiju i povećanu rezistenciju na insulin usled smanjivanja koncentracije azot monoksida i imaju smanjen nivo estrogena, naročito žene, zbog povećane hidroksilacije i inaktivacije estradiola, zbog povećanog cirkulišućeg SHBG (*sex hormone binding* globulina), koji vezuje cirkulišući estradiol kao i zbog direktnog toksičnog efekta na folikule. Na modifikaciju lipidnog profila pušača može uticati i ishrana. Studije su pokazale da



Slika 3. Kanjuh V. et al. Posledipl. udžb. Kardiologija. 2011; str.293, Bgd. [29]

Ruptura fibrozne kape, tj. neointime (FK) aterosklerotične ploče sa sledujućom sekundarnom opstruktivnom trombozom (T), koja dovodi do akutnog infarkta miokarda ili iznenadne ishemijske srčane smrti. Spazam (crne strelice) koronarne arterije (čest kod pušača!) komprimuje lipidni bazen (LB), koji sadrži više ateromatoznog kašastog detritusa (D) nego holesterolskih kristala (HK) i zbog toga je stišljiviji. Dolazi do "vulkanske erupcije" LB kroz rupturu FK i veoma trombogeni sadržaj se izručuje u lumen (L) arterije, tj. u cirkulišuću krv. Odmah nastaje opstruktivna tromboza (u stvorenom trombu vide se izbačeni HK i D, koji eventualno embolizuju distalni deo koronarne arterije. A - adventicija sa vasa vasorum (v v). sem i uem - spoljašnja i unutrašnja elastična membrana. M - mišićna medija, koja je atrofična iza aterosklerotične ploče. f - fenestra (prozor) na uem. I – intima sa subendotelnim fibroznim tkivom (sft) i endotelom (e). Periadventicijalno, uz aterosklerotičnu ploču, zapaljenski infiltrati od imunih ćelija: T-linfocita (Tly) i plazmocita (Pl).

pušači jedu ređe, da unose više šećera i životinjskih masti, kao i da unose manje polinezasićenih masti i antioksidanasa u odnosu na nepušače. Polimorfizmi gena apolipoproteina i transfer proteina holesterolskih estara mogu uticati na pojavu proaterogenog lipidnog profila kod pušača. Pušači imaju i znatno veće vrednosti homocisteina u odnosu na nepušače.[28]
Značajan nepovoljni efekat koji pušenje ostvaruje na lipide jeste smanjenje nivoa atero – protektivnog HDL-a. Međutim, pored smanjenja nivoa HDL-a, cigarete deluju i na smanjenje njegove funkcije, čak i bez uticaja na samu koncentraciju. Ovakvi efekti su dokazani u zdravih pušača kod kojih je nakon obustave pušenja uočena poboljšana funkcionalnost HDL-a kroz smanjenje inflamacije kapaciteta fluksa holesterola bez promene koncentracije HDL-a.[28]

Pušenje i rezistencija na insulin

Pušači u poređenju sa nepušačima imaju veći nivo HbA1C, zahtevaju veće doze insulina i imaju veći rizik ka razvoju mikrovaskularnih i makrovaskularnih komplikacija dijabetesa[30]. Izloženost eksperementalnih životinja tercijarnom obliku duvanskog dima, dovelo je do porasta nivoa glukoze u krvi, koja se može klasifikovati kao predijabetes, takav oblik hiperglikemije je bio teže regulisan na primenu insulina u odnosu na kontrolnu grupu[31,32]. Povišene vrednosti triglicerida, ukupnog holesterola i LDL, smanjene vrednosti HDL i poremećaj u metabolizmu insulina predstavljeni su „metaboličkim sindromom", stanje koje povećava rizik od nastanka šloga, akutnog koronarnog sindroma i tip 2 dijabetesa[33,34]. Pojedine studije pokazale su nedostatak insulinskih receptora, fosfoinozitid 3-kinaze i AKT (poznatijeg kao protein kinaza B), kao i svi važni molekuli u insulinskoj signalizaciji koji unose glukozu u ćelije[32]. Inhibicija ovih signalnih puteva će uzrokovati da GLUT 4 transporter ostane u citosolu ćelije, umesto da bude transportovan na površini membrane i dozvoli ulazak glukoze u ćelije. Ovo će rezultirati povećanjem vrednosti glukoze u krvi (hiperglikemijom). Efekat insulinske rezistencije, uzrokovanog tercijarnim oblikom pušenja, determinisan je oksidativnim stresom, koji prouzrokuje oštećenja na proteinima, lipidima i molekulu DNK.[35]

Akutna i hronična dejstva nikotina i intoksikacija nikotinom

Nikotin kao najpoznatiji sastojak duvana je alkaloid, koji se nalazi u listovima biljke i u prirodi služi kao njena odbrana od insekata, pa se ranije često koristio kao insekticid. Nikotin pored brojnih efekata na centralni nervni sistem (osećaj relaksacije, ugodnosti, povećanje pažnje, budnosti, koncentracije, smanjenje apetita, ubrzanje metabolizma, povećanje libida, smanjenje osećaja straha, povećanje osetljivosti u moždanom centru za nagrađivanje), dovodi do povećanog lučenja adrenalina (epinefrina) i drugih kateholamina i aktivacije simpatičkog nervnog sistema. Nikotin uzrokuje akutne i hronične efekte. Akutni efekti unosa nikotina u manjim dozama su posledica njegovog simpatomimetičkog dejstva, povećane srčane frekvence, vazokonstrikcije, povećanja arterijskog pritiska i kontraktilnosti srca.
Trovanje nikotinom se može javiti posle prve cigarete, prekomernog pušenja, ili posle akcidentalnog unošenja nikotina primenjenog zadesno kod dece u vidu žvakaćih guma ili transdermalnih flastera i kod odraslih kada se dođe u kontakt sa nikotinom bogatim insekticidom uz napomenu da se preko kože i mukoze odlično resorbuje. Nikotin u prvoj fazi deluje na ganglijske nervne ćelije depolarizacijom i stimulaciom neurona, a u drugoj fazi deluje depresivno i na kraju uzrokuje blok ganglija. Zbog stimulacije parasimpatičkih ganglija i nikotinskih receptora na neuromišićnoj spojnici može doći do bradikardije, mučnine, povraćanja, povećanog lućenja pljuvačke, pojačanja peristaltike, učestalih stolica, dijareja, nesvestice, kao i fascikulacije skeletnih mišića. Intoksikacija nikotnom najčešće izaziva vrtoglavicu, bledilo, obilno znojenje odnosno dijaforezu, nekada nastaju bol u trbuhu praćen prolivom, pojačano lučenje pljuvačke i suza. Kod teških trovanja nikotinom javljaju se zbunjenost, agitacija, letargija i konvulzije, a umesto početne tahikardije i hipertenzije može nastati bradikardija i hipotenzija, dok na kraju dolazi do paralize skeletnih mišića, slabosti respiratorne muskulature, depresije disanja, respiratorne insuficijencije i kome.[36]
Dugotrajni efekti nikotina su takođe posredovani vazokonstrikcijom malih krvnih sudova (hladne ruke i noge, dok na velikim krvnim sudovima dolazi do propadanja vasa vasorum koji ishranjuju velike krvne sudove) i ubrzanja ateroskleroze. Od značaja je i indirektni uticaj nikotina na poremećaj metabolizma glukoze, nastanak hiperglikemije i indukcije aterotromboze preko tog poznatog mehanizma. Nakon dugotrajnog korišćenja nikotina, dolazi do strukturnih i funkcionalnih promena vaskularnih glatkih mišića i endotelnih ćelija koje kao krajnji efekat imaju endotelnu proliferaciju i progresiju aterosklerotskog plaka. Posledično, nastaju miointimalna zadebljanja, aterogene i ishemične promene.[36,37]
Hipersekrecija hlorovodonične kiseline uzrokovana pušenjem je samo jedan od mehanizama kojim pušenje toksično deluje na gastroduodenalnu mukozu, i na taj način doprinosi pojačanom toksičnom dejstvu acetilsalicilne kiseline, drugih antitrombotskih agenasa i nesteroidnih antiinflamatornih lekova na mukozu gornjeg gastrointestinalnog trakta, naročito kod onih sa peptičkim ulkusom u anamnezi. Mnogobrojne epidemiološke studije su utvrdile vezu između pušenja i pojave gastritisa odnosno ulkusne bolesti želuca (takozvane ulkusne gastrogeneze). Mehanizmi nikotinom uzrokovanih ulkusa su različiti i obuhvataju povećanu produkciju leukotrijena (histaminoliberacija), migraciju neutrofila u želudačnu mukozu, poremećaj ravnoteže prostaglandina, disproliferaciju epitela želudačne sluznice kao i pojavu neovaskularizacije. Svi nabrojani fenomeni su uključeni u proces zapaljenja, pa sveobuhvatno gledano, pušenje i indukcija zapaljenja utiču na sistemske i lokalne efekte, koji su značajni faktori nastanka ulkusne gastrogeneze i na taj način agraviraju nastanak neželjenih dejstava antitrombotskih lekova, koji imaju važnu ulogu u lečenju bolesti indukovanih aterotrombozom.[38-40]

Epidemiološki podaci

Epidemiološke studije konstantno ukazuju na štetnost pušenja i povećan rizik od ateroskleroze i drugih kardiovaskularnih bolesti. Procenjuje se da pušači u odnosu na nepušače žive kraće za oko jednu deceniju. Pušenje povećava rizik od koronarne bolesti i šloga za 2 do 4 puta, dok prestanak pušenja smanjuje rizik od koronarne bolesti za 1/3, smanjuje rizik od kardiovaskularnog mortaliteta za 36% i ukupnog mortaliteta za 46%. Pušači koji su preživeli akutni infarkt miokarda, ako prestanu da puše, smanjuju rizik od ponovnog infarkta i smrtnog ishoda u narednih 2-10 godina za 50%. Ono što još više zabrinjava je da pasivni pušači u okruženju aktivnih pušača imaju povećan rizik od kardiovaskularnih bolesti za 25-30%. Pušenje u prisustvu nepušača je jedan vid nasilja. Prospektivna studija u Danskoj je pokazala da smanjenje pušenja neznatno smanjuje rizik od kardiovaskularnih bolesti, dok najveći uticaj na smanjenje rizika ima potpuni prestanak pušenja.[41] Ako se pušenje prekine pre 40. godine života, rizik se redukuje za oko 90%.[42]

Nastavak pušenja u bolesnika kojima je rađena operacija koronaro-arterijskog premošćavanja (*CABG*) kompletno poništava korist od prethodno urađene operacije, povećava broj ishemija na perfuzionoj scintigrafiji i utiče na porast mortaliteta.[43]

Pušenje cigareta povećava rizik od moždanog udara za dva do tri puta. Najjača povezanost između pušenja i moždanog udara je uočena kod pušača ženskog pola koje uzimaju oralne kontraceptive. Šta više, rizik od moždanog udara raste sa porastom broja popušenih cigareta (*odds ratio* – OR se povećava sa 2,2 u pušača koji konzumiraju 1-10 cigareta na dan na 2,5; u pušača koji konzumiraju 11-20 cigareta na dan; dok se OR sa 4,3 u pušača koji konzumiraju 21-39 cigareta na dan povećava na 9.1 u pušača koji konzumiraju ≥ 40 cigareta na dan). Rizik se može smanjiti sa prestankom pušenja, uz napomenu da najveću korist od prestanka pušenja imaju oni koji pušenje ostave pre tridesete godine života, jer tada mogu potencijalno očekivati da će im životni vek biti sličan nepušačima. Istraživanja su pokazala da sekundarno (pasivno) pušenje povećava rizik od moždanog udara za 25-52% zavisno od stepena izloženosti.[44]

Pušenje je najvažniji pojedinačni faktor rizika za nastanak periferne arterijske bolesti.[45] Nastavljanje pušenja kod bolesnika sa perifernom arterijskom bolesti dovodi do progresije bolesti, tri puta češće okluzije femoralno-arterijskih graftova, restenoze posle endovaskularnih revaskularizacija, većeg morbiditeta od infarkta miokarda i ukupnog mortaliteta.[46]

I pored činjenice da aterotromboza ne zahvata vene (izuzetak je venski graft vene safene u aortokoronarnoj hirurgiji), treba naglasiti da je pušenje faktor koji doprinosi nastanku venskog tromboembolizma (VTE), uz napomenu da je kod pušača u odnosu na nepušače viši rizik nastanka provociranog VTE (*hazard ratio 1,75; 95% CI 1,14-2,69*) i totalnog VTE (*hazard ratio 1,46, CI 1,04-2,05*).[47]

Pušački paradoks

Neke studije reperfuzije (GUSTO-I studija) su pokazale da su pušači koji su preživeli infarkt miokarda imali bolje kratkoročno preživljavanje u odnosu na nepušače. Detaljnija analiza ovih podataka je pokazala da su pušači u proseku 11 godina ranije dobijali infarkt u odnosu na nepušače. Razlika u godinama bi mogla da utiče na bolje preživljavanje pušača. Neke studije koje su pokazale pušački paradoks, nisu mogle da ga objasne razlikom u godinama, tako da je moguće da pušači imaju bolje razvijene kolaterale u miokardu u odnosu na nepušače. U svakom slučaju termin je najbolje ne pominjati i ne objašnjavati pred pacijentima, jer deluje zbunjujuće i može ih demotivisati da prestanu sa pušenjem. Čak i da se dokaže da pušenje ima nekakav koristan efekat, broj štetnih efekata bi i dalje daleko nadmašio potencijalni broj korisnih efekata da bi postojalo bilo kakvo medicinsko opravdanje za nastavak sa pušenjem.[48]

Bezdimni duvan (*smokeless tobacco*):

Duvanski proizvodi bez dima sastoje se od duvana ili duvanske mešavine koja se žvaće ili šmrče (ili sisa)[49]. Duvanski proizvodi bez dima proizvode veću količinu nikotina nego klasični duvan za pušenje[50]. Efekti koji se viđaju kod upotrebe duvanskih proizvoda, slični su onima koje izaziva pušenje cigareta, uključujući koronarnu vazokonstrikciju, povećanje broja otkucaja i *cardiac output*[51]. Postoje kontraverzni dokazi iz više studija (*INTERHEART* studija) koji ukazuju na povećanu kardiovaskularnu smrtnost ili učestaliju frekvenciju infarkta miokarda, veći rizik od nefatalnog infarkta miokarda među žvakačima duvana, odnosno duvanskim proizvodima bez dima.[52]

Sekundarni dim (duvanski dim iz okoline, pasivno pušenje) može biti definisan kao dim koji nastaje izgaranjem duvanskog proizvoda, koji udišu nepušači i pušači.[53] Udisanje sekundarnog dima naziva se nevoljnim ili pasivnim pušenjem. Smatra se da prouzrokuje sličan rizik po zdravlje isto kao i direktno pušenje. Smatra se da se u Sjedinjenim Američkim Državama registruje približno 40 000 smrtnih slučajeva godišnje koji nastaju zbog bolesti srca koje su indukovane sekundarnim duvanskim dimom.[54] Eksponiranost sekundarnom duvanskom dimu, kao i direktno pušenje, pored spomentnih kardiovaskularnih komplikacija, akutnih koronarnih događaja, šloga, nagle srčane smrti utiče i na kancerogenezu.[54,55] Pored toga sekundarni duvanski dim povećava rizik od iznenadne smrti odojčeta, akutne respiratorne infekcije, dovodi do problema sa ušima i nastanka težih oblika opstruktivne bolesti pluća.[56]

Tercijarni duvanski dim je nevidljiva duvanska „prašina“ (ili hemikalije), koja se taloži u okruženju i ostaje tamo i nakon gašenja cigarete. Znamo da su deca u većem riziku izloženija tercijarnom dimu, jer im je izmeren viši nivo kotinina (nusproizvoda nikotina) u mokraći i krvi. Tercijarni dim sadrži više od 250 hemikalija među kojima su cijanovodonik, butan, toluen, arsen, olovo, ugljen-monoksid i polonijum 210 koji ima najveći kancerogeni potencijal.[57] Ove štetne hemikalije se mogu naći u kosi, na odeći, pro-

stirkima, zavesama, igračkama, kaputu, svakoj površini u domu ili automobilu. Kućni ljubimci su takođe u opasnosti jer toksini ostaju na krznu ili repu. Duvanska kućna prašina sadrži značajno veći nivo toksičnih materija uključujući, nikotin, PAHs i TSNAs. U kući pušača izmerene su veće koncentracije nikotina po gramu prašine.[58,59] Uzorak vazduha u kazinu koji je testiran nakon zabrane pušenja, pokazao je da je koncentracija nikotina mesecima nakon prestanka pušenja još uvek merljiva, demonstrirajući nam pri tome značaj tercijarnog pušenja.60]. Analiza prašine u automobilima u kojima se pušilo pokazuje visok nivo kontaminacije sa nikotinom i prisustvo drugih toksičnih produkata tercijarnog pušenja. Mat i saradnici su pokazali da nepušači koji žive u kućama u kojima su prethodno živeli pušači, imaju viši nivo nikotina, otkrivenog na njihovim prstima i viši nivo kotinina (metabolit nikotina) otkrivenog u urinu, u odnosu na nepušače koji su živeli u kućama u kojima su prethodno živeli nepušači. Ovaj fenomen je zapažen čak pored činjenice da su kuće pušača bile očišćene pre analize, i registovan je i do 2 meseca od kako su se pušači odselili.[59]

Vulnerabilne populacije

Deca, posebno odojčad i mala deca, su posebno vulnerabilna populacija stanovništva najosetljivija na tercijarni vid pušenja,[58,60-67] jer su izložena produktima tercijarnog pušenja u kućnoj prašini i različitim površinama na više načina: oralno, preko disanja, kao i transdermalno čak i preko odeće i kože roditelja.[68] Deca udišu više vazduha, nego odrasli, u odnosu na procenat njihove mase. Deca, takođe, imaju veći odnos površine tela i mase, nego odrasli.

Drugu, posebno na toksične efekte primarnog, sekundarnog i tercijarnog pušenja, vulnerabilnu populaciju, predstavljaju trudnice, posebno u smislu nastanka ishemije i infarkta placente (Asmussen (1977;1978). Elektronsko ispitivanje mikroskopom placente žena porođenih u periodu termina ukazalo je na niz histopatoloških promena: proširenu bazalnu membranu placentarnih resica, povećanje kolagena, promene u intimi kapilara i arteriola placentalnih resica sa jako izraženim edemom endotela, vazokonstrikciju, redukciju prokrvljenosti.[69]

Produkti tercijarnog pušenja inhibiraju mehanizme regeneracije i reparacije ćelija i prouzrokuju oštećenje DNK i mitohondrija. Toksikološke studije na eksperimentalnim životinjama pokazale su brojne štetne efekte tercijarnog pušenja na organe i ćelije, uključujući slabije zarastanje rana, oštećenje pluća i jetre, metaboličke efekte, kao što su povećanje nivoa triglicerida, ukupnog holesterola, LDL, smanjivanje nivoa HDL, poremećaj metabolizma insulina, trajnu promenu u sastavu imunog odgovora periferne krvi. Životinje izložene tercijarnom pušenju pokazale su poremećaje ponašanja, po tipu hiperaktivnosti.[69]

Genetski faktori i pušenje

Pojedine studije pokazale su da geni utiču na metabolizam nikotina i specifičnih hemijskih supstanci proizvedenih tokom sagorevanja, i mogu pojačati (ili smanjiti) patofiziološke mehanizme povezane sa aterogenim efektom pušenja, uključujući oksidativni stres, inflamatorni proces i prokoagulantni potencijal.[70] Kod teških pušača pokazana je interakcija između duvanskog dima i glutation-S-transferaze teta (GSTT-1), koja dovodi do prekliničke ateroskleroze povezane sa povećanjem debljine intime i medije.[71] Pokazano je da polimorfizam A640G U CYBA genu može uticati na individualnu predispoziciju za kardiovaskularne bolesti kroz interakcije sa pušenjem i hiperholesterolemijom.[72,73] Takođe, pokazano je da polimorfizmi u genima za eNOS i citihrom P450 (CYP1A1), utiču na pojavu ateroskleroze kod pušača.[74,75]

Kod pušača sa značajnim stenozama većeg stepena povećana je učestalost homozigotnih nosilaca za 4a alel (eNOS4a/4a), u poređenju sa ispitanicima onim sa manjim stenozama ili bez njih.[76]

Zaključak

Mehanizmi kojim pušenje i komponente duvanskog dima dovode do inicijacije i progresije ateroskleroze su brojni. Pušenje indukuje disfunkciju endotela ometajući biosintezu NO, smanjuje sintezu zaštitnog prostaglandina PGI_2 (prostaciklina) u endotelu, povećava dejstvo štetnog tromboksana A_2, povećava oksidaciju štetnog LDL holesterola i njegovo prodiranje u zid krvnog suda, smanjuje nivo i funkciju korisnog HDL holesterola, povećava nivoe fibrinogena, CRP, ICAM-1 (*intracellular adhesion molecule-1*), i homocisteina, povećava adheziju monocita za endotel, povećava agregabilnost trombocita, čineći trombocite pušača osetljivijim na agregacijske stimulanse, stimuliše simpatičko adrenergički sistem, inhibira proces fibrinolize, kao i uticaj antitrombotičkih faktora, može doprineti nastanku spazma koronarnih krvnih sudova.[77,78] Pored vazomotorne disfunkcije, inflamacije, povećanja trombogenosti, smanjenja bioraspoloživosti NO, modifikacije lipidnog profila, oksidativni stres ima jednu od najvažnijijih uloga u akceleraciji aterotromboznih procesa. Ne postoji linearno dozna zavisnost između broja popušenih cigareta i štetnih efekata na kardiovaskularni sistem, što implikuje da se zaštitni mehanizmi brzo zasite. Treba istaći da smanjenje pušenja neznatno smanjuje rizik od kardiovaskularnih bolesti, dok potpuni prestanak pušenja značajno smanjuje rizik. S obzirom na činjenicu da jedno od centralnh mesta u patogenezi ateroskleroze pušača pripada oksidativnom stresu i ulozi slobodnih radikala, treba istaći da nema ubedljivih dokaza da upotreba antioksidanasa (vitamin C, vitamin E, β karoten, koenzim Q10) može da smanji štetni efekat ne samo slobodnih radikala, već i drugih multiplih mehanizama toksičnog dejstva duvanskih produkata. Pušenje i komponente duvanskog dima na globalnom nivou, predstavljaju jedan od glavnih faktora koji dovodi do indukcije aterotromboze i kardiovaskularnih komplikacija kao što su infarkt miokarda i naprasna srčana smrt, ali i do ostalih potencijalno fatalnih posledica u prvom redu cerebrovaskularnih i oboljenja perifernih krvnih sudova.

Opšta i profesionalna javnost nije u punoj meri upoznata sa svim mehanizmima kojima pušenje dovodi do početka i razvoja aterotromboze. Treba naglasiti da je ne-

ophodna sveobuhvatna kampanja protiv pušenja, orijentisana ka navikama pojedinaca, poštovanju određenih socijalnih obaveza, brizi i za tuđe živote imajući u vidu opasnost od sekundarnog i tercijarnog pušenja, uz uključivanje farmakoloških mera u borbi protiv nikotinske zavisnosti, odnosno zavisnosti od pušenja, uz opsežne mere svih službi koje se bave javnim zdravljem na svest celokupne društvene zajednice. Veoma je važno istaći značaj borbe protiv pušenja na svim nivoima zdravstvene zaštite radi sprečavanja najtežih aterotrombotskih komplikacija.

Literatura

1. Libby P, et al. The vascular biology of atherosclerosis, Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 11th Edition, Elsevier, 2018:44:859-75.
2. Kanjuh V, Ostojić M, Bojić M, et al. Ateroskleroza na pragu III milenijuma (Morfološko-klinička korelacija aterosklerotičnih lezija i relevantnih kliničkih sindroma) U: Nedeljković SI, Kanjuh VI, Vukotić MR, Kardiologija, Izdavač „Beograd'', 2000, 2(18.38): 2393–423.
3. Kanjuh V, Tatić V, Rafajlovski S, et al. Degenerativno-zapaljenska oboljenja arterija i arteriola-arterioskleroza i arterioloskleroza. U: Ostojić M, Kanjuh V, Beleslin B, Kardiologija, Zavod za udžbenike „Beograd", 2011:274-83.
4. Pryor WA, Stone K. Oxidants in cigarette smoke radicals, hydrogen peroxide, peroxynitrate, and peroxynitritea. Ann New York Acad Sci 686.1 (1993):12-27.
5. Jokanovic M. Otrovi. U: Jokanovic M, Toksikologija, Elit-Medica, 2010: 298-323.
6. Taylor AE, Johnson DC, Kazemi H. nvironmental tobacco smoke and cardiovascular disease. A position paper from the Council on Cardiopulmonary and Critical Care, American Heart Association. Circulation 1992; 86):699-702.
7. Reinskje T, et al. Hazardous compounds in tobacco smoke. Int J Environment Res Publ Health 2011;8(2): 613-28.
8. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum. 2004: 83:1-1438.
9. Samet JM. Tobacco smoking: the leading cause of preventable disease worldwide. Thor Surg Clin 2013;23 (2):103-12.
10. Salahuddin K, et al. Tobaco and CVD. Global Heart 2012;7 (2).
11. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 20004; 43 (10):1731-7.
12. Curfs A, Daniëlle MJ, et al. Polycyclic aromatic hydrocarbons induce an inflammatory atherosclerotic plaque phenotype irrespective of their DNA binding properties. FASEB journal 2005; 19(10):1290-2.
13. Cooper CE, Brown GC. The inhibition of mitochondrial cytochrome oxidase by the gases carbon monoxide, nitric oxide, hydrogen cyanide and hydrogen sulfide: chemical mechanism and physiological significance. J Bioenerg Biomembran 2008;40(5): 533-9.
14. Zhang S, Day I, Ye S. Nicotine induced changes in gene expression by human coronary artery endothelial cells. Atherosclerosis 2001;154 (2):277-83.
15. Li JM, et al. Nicotine enhances angiotensin II-induced mitogenic response in vascular smooth muscle cells and fibroblasts. Arterioscl Thromb Vasc Biol 2004;24 (1):80-4.
16. Pryor W., et al. The radicals in cigarette tar: their nature and suggested physiological implications. Science 1983; 220(4595): 425-7.
17. Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco smoke: Involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. Int J Environment Res Publ Health 2009;6(2):445-62.
18. Church DF, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. Environment Health Perspectives 1985;64:111.
19. Penn A, Snyder C. Arteriosclerotic plaque development is 'promoted' by polynuclear aromatic hydrocarbons. Carcinogenesis 1988; 9(12):2185-9.
20. Van Grevenynghe J, et al. Human endothelial progenitors constitute targets for environmental atherogenic polycyclic aromatic hydrocarbons. Biochem Biophysic Res Comm 2006;341(3): 763-9.
21. Higman DJ, et al. Smoking impairs the activity of endothelial nitric oxide synthase in saphenous vein. Arterioscl Thromb Vasc Biol 1996;16(4):546-52.
22. Jeremy JY, Mikhailidis DP, Dandona P. Cigarette smoke extracts inhibit prostacyclin synthesis by the rat urinary bladder. Brit J Cancer 1985;51(6):837.
23. Powell JT. Vascular damage from smoking: disease mechanisms at the arterial wall. Vasc Med 1998;3(1):21-8.
24. Petrick, L, Rosenblat M, Aviram M. In vitro effects of exogenous carbon monoxide on oxidative stress and lipid metabolism in macrophages. Toxicol Industrial Health 2004;32(7):1318-23.
25. Doll R, et al. Mortality from cancer in relation to smoking: 50 years observations on British doctors. Brit J Cancer 2005;92(3):426-9.
26. Powell JT. Review.Vasc Med 1998;3(1):21-8.
27. Al Qahtany FS, Algahtani FH, Alshebly MM, et al. Association between cigarette & shisha smoking and the severity of polycythemia: A cross sectional study. Saudi J Biol Sci 2020;27(1):460-4.
28. Chen HY, Li SC, Chen LF, Wang W, et al. The effects of cigarette smoking and smoking cessation on high-density lipoprotein functions: implications for coronary artery disease. Ann Clin Biochem 2019 01;56(1):100-11.
29. Kanjuh V, Lastić Maletić S, Gojković Bukarica Lj, et al. Korelacija koronarnih histopatoloških aterotrombotičnih lezija sa kliničkim sindromima koronarne bolesti. U: Ostojić M, Kanjuh V, Beleslin B, Kardiologija, Zavod za uđbenike „Beograd", 2011: 293.
30. Facchini FS, Hollenbeck CB, Jeppe-Sen J, et al. Insulin resistance and cigarette smoking. Lancet 1992; 339:1128–30.
31. Martins-Green M, Adhami N, Frankos M, et al. Cigarette smoke toxins deposited on surfaces: implications for human health. PLoS One. 2014;9:e86391.
32. Adhami N, Starck SR, Flores C, Martins Green M. A health threat to bystanders living in the homes of smokers: how smoke toxins deposited on surfaces can cause insulin resistance. PLoS One. 2016;11:e0149510.
33. Venn A, Britton J. Exposure to secondhand smoke and biomarkers of cardiovascular disease risk in never-smoking adults. Circulation 2007;115:990–5.
34. Zhang YJ, Iqbal J, van Klaveren D, et al. Smoking is associated with adverse clinical outcomes in patients undergoing revascularization with PCI or CABG: the SYNTAX trial at 5-year follow-up. J Am Coll Cardiol 2015;65(11):1107-15.
35. Adhami N, Starck SR, Flores C, et al. A health threat to bystanders living in the homes of smokers: how smoke toxins deposited on surfaces can cause insulin resistance. PLoS One. 2016;11:e0149510
36. Kent RO, Ilene BA, et al. Nicotine, poesining & drug overedose, McGraw-Hill Education, 2018:277–279.
37. Mishra A, et al. Harmful effects of nicotine. Indian journal of medical and paediatric oncology J Indian Soc Med & Paediatric Oncology 2015;36.1:24.
38. Sipponen P, Maaroos HI. Chronic gastritis. Scand J Gastroenterol 2015;50(6):657-67.
39. Genta RM, Lash RH. Editorial: No bugs bugging you? Emerging insights into Helicobacter-negative gastritis. Am J Gastroenterol 2013;108(1):72–74.
40. Maguilnik I, Neumann WL, Sonnenberg A et al. Reactive gastropathy is associated with inflammatory conditions throughout the gastrointestinal tract. Aliment Pharmacol Ther 2012;36:736–43.
41. Zhang YJ, Iqbal J, van Klaveren D, et al. Smoking is associated with adverse clinical outcomes in patients undergoing revascularization with PCI or CABG: the SYNTAX trial at 5-year follow-up. J Am Coll Cardiol. 2015;65(11):1107-15.
42. Kulik A, Ruel M, Jneid; H, et al; on behalf of the American Heart Association Council on Cardiovascular Surgery and Anesthesia. Secondary prevention after coronary artery bypass graft surgery. A Scientific Statement From the American Heart Association. Circulation 2015;131:927-64.

43. Lindsay GM, Tolmie EP, Martin WM, et al. Smoking after coronary artery bypass: high three-year mortality. Thorac Cardiovasc Surg 2009;57(3):135-40.
44. Kuklina EV, et al. Epidemiology and prevention of stroke: a worldwide perspective. Expert Rev Neurother 2012;12(2):199-208.
45. Willigendael EM, Teijink JA, Bartelink ML, et all. Influence of smoking on incidence and prevalence of peripheral arterial disease. Journal of vascular surgery. 2004 Dec 1;40(6):1158-65.
46. Willigendael EM, Teijink JAW, Bartelink ML, et al. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. J Vasc Surg 2005;42:67-74
47. Enga KF, Braekkan SK, Hansen-Krone IJ, et al. Cigarette smoking and the risk of venous thromboembolism: the Tromsø Study. J Thromb Haemost. 2012
48. Zubairi Y, Hafidz I, Ahmad WA, et al. The bizzare phenomenon of smokers' paradox in the immediate outcome post acute myocardial infarction: an insight into the Malaysian National Cardiovascular Database-Acute Coronary Syndrome (NCVD-ACS) registry year 2006-2013. Springerplus 2016;5:534.
49. National Cancer Institute. Smokeless tobacco or health: an international perspective. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 1992.
50. Gupta R, Gurm H, Bartholomew JR. Smokeless tobacco and cardiovascular risk. Arch Intern Med 2004;164:1845–9.
51. Ramakrishnan S, Thangjam R, Roy A, et al. Acute effects of tobacco chewing on the systemic, pulmonary and coronary circulation. Am J Cardiovasc Drugs 2011;11:109–14.
52. Teo KK, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case–control study. Lancet 2006;368:647–58.
53. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control (CDC). The Health Consequences of Involuntary Smoking: A Report of the Surgeon General. Washington DC: Government Printing Office (GPO): 1986
54. Steenland K, Thun M, Lally C, Heath Jr C. Environmental tobacco smoke and coronary heart disease in the American Cancer Society CPS-II cohort. Circulation 1996;94:622.
55. National Cancer Institute (NCI). Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency. Smoking and Tobacco Control Monograph 10. Bethesda, MD: NCI. 1999
56. Neuberger, Manfred. Effects of involuntary smoking and vaping on the cardiovascular system. 2019.
57. S. Department of Health and Human Services (HHS). The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health: 2006
58. Winickoff JP et al. Beliefs about the health effects of „thirdhand" smoke and home smoking bans. Pediatrics 2009;123(1):e74-e79.
59. Matt GE, Quintana PJ, Zakarian JM, et al. When smokers move out and non-smokers move in: residential thirdhand smoke pollution and exposure. Tob Control 2011;20:e1.
60. Matt GE, et al. When smokers quit: exposure to nicotine and carcinogens persists from thirdhand smoke pollution. Tobacco control 2017;26(5):548-56.
61. Quintana PJE, Matt GE, Hoh E, et al. Thirdhand tobacco smoke pollutants in a casino measured before and after smoke-free status. International Society of Exposure Science (ISES) Conference; Henderson, NV. October, 2015; Herndon, VA, USA: International Society of Exposure Science ISES Secretariat; 2015.
62. Matt GE, Quintana PJ, Destaillats H, et al. Thirdhand tobacco smoke: emerging evidence and arguments for a multidisciplinary research agenda. Environ Health Perspect 2011;119: 1218–26.
63. Sleiman M, Gundel LA, Pankow JF, et al. Formation of carcinogens indoors by surface-mediated reactions of nicotine with nitrous acid, leading to potential thirdhand smoke hazards. Proc Natl Acad Sci U S A. 2010;107:6576–81.
64. Matt GE, Quintana PJE, Hovell MF, et al. Households contaminated by environmental tobacco smoke: sources of infant exposures. Tobacco Control 2004;13:29–37.
65. Matt GE, Quintana PJ, Hovell MF, et al. Residual tobacco smoke pollution in used cars for sale: air, dust, and surfaces. Nicotine Tob Res 2008;10:1467–75.
66. Sleiman M, Destaillats H, Smith JD, et al. Secondary organic aerosol formation from ozone-initiated reactions with nicotine and secondhand tobacco smoke. Atmos Environ 2010;44:4191–8.
67. Drehmer JE, Ossip DJ, Rigotti NA, et al. Pediatrician interventions and thirdhand smoke beliefs of parents. Am J Prev Med 2012;43: 533–6.
68. WHO Children's Health and the Environment. available at http://www.who.int/ceh/capacity/Children_are_not_little_adults.pdf (July 2008).
69. Jacob III P, et al. Thirdhand smoke: new evidence, challenges, and future directions. Chem Res Toxicol 2017;30(1):270-94.
70. Winkelmann BR, von Holt K, Unver-dorben M. Smoking and atheroscle-rotic cardiovascular disease: part IV: genetic markers associated with smoking. Biomark Med 2010;4:321–33.
71. Olshan AF, Li R, Pankow JS, et al. Risk of atherosclerosis: interaction of smoking and glutathione S-transferasa genes. Epidemiology 2003;14:321–7.
72. Niemiec P, Nowak T, Balcerzyk A, et al. The CYBA gene A640G polymorphism influences pre-dispositions to coronary artery disease through interactions with cigarette smoking and hypercholesterolemia. Biomarkers 2011;16:405–12.
73. Macias-Reyes A, et al. Insight into the role of CYBA A640G and C242T gene variants and coronary heart disease risk. A case-control study." Free radical Res 2008;42(1): 82-92.
74. Wang XL, et al. Effect of CYP1A1 MspI polymorphism on cigarette smoking related coronary artery disease and diabetes. Atherosclerosis 2002;162(2):391-7.
75. Wang XL, et al. Genotype dependent and cigarette specific effects on endothelial nitric oxide synthase gene expression and enzyme activity. FEBS letters 2000;471(1):45-50.
76. Wang XL, et al. Genetic contribution of the endothelial constitutive nitric oxide synthase gene to plasma nitric oxide levels. Arterioscl Tromb Vasc Biolo 1997;17(11):3147-53.
77. Antonijević N, Kanjuh V. Ateroskleroza i tromoboza. U: Ostojić M, Kanjuh V, Beleslin B, Kardiologija, Zavod za udžbenike „Beograd", 2011: 300-331.
78. Mongirdiene A, Viezheliene D, Kurshvetene L. Effect of nicotine and tar present in cigarette smoke on the process of atherogenesis. Kardiologiia, 2012;52(9):87-93.

Srce i krvni sudovi 2019; 38(2): 91-94

Review article

Current recommendations in the treatment of aortic stenosis: (T)AVR in focus

Milena Pandrc[1], Mirjana Stanić[1], Vanja Kostovski[2], Danijela Vraneš[1], Snježana Vukotić[1], Andjelka Ristić[1], Nemanja Djenić[1]

[1]Department of Urgent Internal Medicine, Military Medical Academy, Belgrade, Serbia; [2]Clinic for Thoracic Surgery, Military Medical Academy, Belgrade, Serbia.

Summary According to US data, one-third of all patients with aortic stenosis have severe aortic stenosis, as well as numerous comorbidities and comedication, and transcatheter intervention is the recommended treatment modality in cases where there is a primary indication for aortic valve replacement, as an equally effective and much safer technique compared to standard surgery.

Key words aortic stenosis, heart failure, transcatheter aortic valve replacement

Aortic stenosis (AS) and modalities of treatment

The prevalence of significant aortic stenosis (moderate or severe) is known to increase with age. Two large epidemiological studies involving nearly 29,000 participants point out that the prevalence of AS ranges from a negligible 0.02% to 0.1% in persons between 18 and 44 years of age to a significant 4.6% in patients older than 75 years[1-2].

The only effective treatment modality for severe AS is valve replacement (AVR)[3]. Although they alleviate symptoms in the short term, optimal drug therapy and balloon valvuloplasty alone do not affect the prognosis and further evolution of AS[3]. According to data from the USA, one third of all patients with aortic stenosis have severe aortic stenosis, as well as numerous comorbidities and comedication[1]. Current AHA / ACC recommendations emphasize the place of TAVR as the primary modality of definitive treatment of AS or as an alternative technique to SAVR in patients in whom classical surgery is contraindicated, or operative risk is elevated (high or intermediate)[3-5]. In some developed countries, TAVR is becoming the standard (USA) and dominant (Germany) modality of definitive aortic valve management[6-7]. In high-risk patients with severe aortic stenosis and left ventricular dysfunction, comparable mortality and recovery of LV function have been reported between the two techniques, with TAVR proving to be a practical alternative for patients with severe AS and LV dysfunction who are at increased operative risk for classical surgery[5].

The most significant predictors of unfavorable TAVR outcome are poor functional capacity (estimated by a 6-minute walk test) and low mean transaortic systolic pressure gradient. The remaining significant negative predictors include lung diseases that require oxygen therapy, kidney damage, as well as ischemic brain disease with pre-existing cognitive dysfunction[8].

Assessment of the severity of aortic stenosis and recommended diagnostic-therapeutic modalities

The assessment of the severity of aortic stenosis includes the following parameters: aortic valve morphology (calcified / non calcified), mean transaortic systolic pressure gradient (low / high gradient AS), aortic valve area (AVA; severe / moderate), flow (flow; low / normal SVI). AVA is a sensitive but insufficiently specific parameter that is under subjective influences, so, according to the current recommendations, in assessing the severity of AS, besides anatomy, valvular hemodynamics (systolic pressure gradient over the aortic orifice (ΔP), maximum velocity of the jet passing through the stenotic orifice) and hemodynamic consequences (left ventricular ejection fraction, indexed systolic volume) are included (Table 1)[4]. Based on all previous said, aortic stenosis staging has been proposed (Table 1)[3,9-10].

There are four stages of AS: risk of AS, progressive AS (mild and moderate), asymptomatic and symptomatic AS[3-4,9-10]. Surgical (SAVR) or transcatheter aortic valve replacement (TAVR) is indicated primarily for stage D AS with some exceptions for stage C[4,9-10].

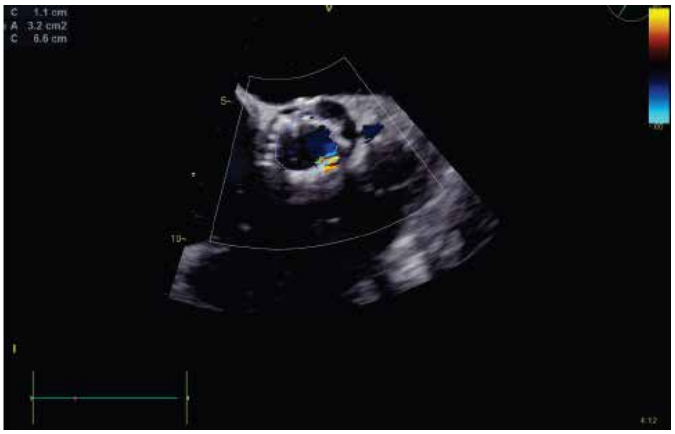
Aortic valve replacement (AVR) for moderate AS should be considered at the same time with cardiac surgery due to other indications (class IIA). There is no current indication for primary intervention in the treatment of moderate AS[4-5,10-12]. A study (TAVR UNLOAD) testing the premise that transcatheter aortic valve replacement (TAVR) and

Corresponding author: Milena S. Pandrc, MD, PhD; Department of Urgent Internal Medicine, Military Medical Academy, Crnotravska 17, 11000 Belgrade, Serbia; phone number: +381-64-291-6310; E-mail: pandrcmilena@yahoo.com .

Table 1 Aortic stenosis staging (adopted from *Kanwar A, Thaden JJ, Nkomo VT. Management of Patients with Aortic Valve Stenosis. Mayo Clin Proc. 2018;93(4):488-508.*)

Stage	Definition and symptoms	Valve anatomy, valve hemodynamic and hemodynamic consequences	AVR
A	At risk of AS None symptoms	Bicuspid AV, another congenital valve anomaly, aortic valve sclerosis, aortic Vmax < 2m/s	Not recommended
B	Progessive AS None symptoms	Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or rheumatic valve changes wuth commissural fusion; **- mild** aortic Vmax 2-2,9 m/s or mean ΔP< 20 mmHg **- moderate** aortic Vmax 3-3,9 m/s or mean ΔP 20-39 mmHg LV diastolic dysfunction Normal LVEF	B2 stage (TAVR UNLOAD)
C1	Asymptomatic severe AS None symptoms	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening aortic Vmax ≥4m/s or mean ΔP≥40 mmHg AVA typically ≤ 1 cm² (AVAi ≤ 0.6 cm²/m²) **Very severe** aortic Vmax ≥5 m/s or mean ΔP≥60 mmHg LV diastolic dysfunction Mild LV hypertrophy Normal LVEF -Exertional testing for confirming symptom status	AVR should be considered in symptomatic very severe aortic stenosis
C2	Asymptomatic severe AS with left ventricular dysfunction None symptoms	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening aortic Vmax ≥4m/s or mean ΔP≥40 mmHg AVA typically ≤ 1 cm² (AVAi ≤ 0.6 cm²/m²) LVEF <50%	AVR is recommended for LVEF preservation
D1	Symptomatic severe high-gradient AS Exertional dyspnea or decreased exercise tolerance Exertional angina Exertional presyncope or syncope	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening aortic Vmax ≥4m/s or mean ΔP≥40 mmHg AVA typically ≤ 1 cm² (AVAi ≤ 0.6 cm²/m²) but may be larger with mixed AS/AR LV diastolic dysfunction Mild LV hypertrophy Pulmonary hypertension may be present	Recommended
D2	Symptomatic severe AS(*low- flow/low- gradient*) with reduced LVEF Heart failure, angina, presyncope and syncope	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening AVA ≤ 1 cm² with resting aortic v max <4m/s or mean ΔP<40 mmHg Dobutamine stress echocardiography: AVA ≤ 1 cm² with v max ≥4m/s with any flow rate LV diastolic dysfunction Mild LV hypertrophy LVEF <50%	AVR should be considered in severe aortic stenosis (LVEF recovery even in patients with no coronary flow reserve)
D3	Symptomatic severe *low-gradient* AS with normal LVEF or paradoxical *low-flow* severe AS Heart failure, angina, presyncope and syncope	Severe lefleat calcification or congenital stenosis with severely reduced leaflet opening AVA ≤ 1 cm² with resting aortic v max <4m/s or mean ΔP<40 mmHg AVAi ≤0.6 cm²/m² SVi <35ml/m² Measured when patient is normotensive (systolic BP < 140mmHg) Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling , LVEF ≥50%	AVR should be considered in symptomatic patients with severe AS and no other reasons for symptoms

AS- aortic stenosis, AR-aortic regurgitation, AVA -aortic valve area, AVAi - aortic valve area indexed to body surface area, BP -blood pressure, HF- heart failure, LV – left ventricular, LVEF – left ventricular ejection fraction, mean ΔP- mean systolic pressure gradient over the aortic orifice
aortic v max -maximum velocity of the jet passing through the stenotic orifice



Figures 1a, 1b, 1c. Valve implantation during TAVI: positioning, partial opening and complete expansion of the valve (Nemanja Djenić, Zorica Mladenović)

optimization of heart failure therapy improves clinical outcomes compared to optimal heart failure therapy per se in patients with heart failure with reduced EF (HFrEF) and proven moderate AS is underway[12]. The previously cited study is based on the fact that the afterload reduction is the basis for the modern treatment of heart failure. Moderate AS increases afterload, and can be effectively treated by TAVR, and if study results support the implementation of TAVR in the treatment of this category of patients with AS, it may significantly facilitate the therapeutic decision considering optimal valve replacement time in patients with moderate AS.

Stage C1 implies asymptomatic severe aortic stenosis with preserved EF, and an exercise stress test is indicated in these patients as a part of the evaluation of physical exertion tolerance (Table 1). AVR is recommended in patients who have developed symptoms or blood pressure decline during a stress test (Table 1)[4-5,10-12]. Having in mind all previous said facts, the design of the EARLY TAVR study (Evaluation of transcatheter aortic valve replacement compared to surveillance for patients with asymptomatic severe aortic stenosis) seems to be promised, expecting to define the role of TAVR in the treatment of patients with asymptomatic severe aortic stenosis[13]. A mechanism that explains the improvement of coronary flow reserve in patients immediately after TAVR procedures include a prompt decline in microvascular resistance and a concomitant increase in microvascular flow, leading to an increase in coronary vasodilator reserve and from the standpoint of cardiac function physiology justifying the implementation of the technique in standard treatment[14].

Stage C2 includes asymptomatic AS with LK dysfunction (Table 1). Due to LV dysfunction, the exertional testing is contraindicated[4]. AVR is recommended (class I)[4]. The HAVEC group points out asymptomatic patients with "paradoxical" LF-LG AS (stage C3?) in whom AVR should be considered if high risk of progression to symptomatic AS has been assessed based on complementary imaging methods (class IIa)[6]. Here, the importance of strain analysis as an additional diagnostic tool in the assessment of subclinical LV dysfunction should be especially emphasized[16]. Namely, deformation indices such as myocardial strains (global, longitudinal, circumferential, radial) of the left ventricle are considered to be more sensitive markers of myocardial dysfunction than the ejection fraction. This stems from the fact that the myocardial strain is a measure of the deformation of primarily subendocardial myocardial fibers, which are the first to react to ischemia and other adverse stimuli, with preserved EF.

Using strain echocardiography, LV systolic dysfunction can be early detected in patients with AS who have normal EF. In this way, reliable data for the clinical early diagnosis and treatment of LV dysfunction, as well as for monitoring the therapeutic effect of therapy are obtained[16]. Taking into account that preserved global longitudinal strain (GLS) is indicative of myocardial reserve and preserved myocardial tissue plasticity, it is not surprising that there is a clear link between increased basal strain values and increased risk of progression to symptomatic AS that implies AVR. Besides strains, the risk assessment includes the calcium score on cardiac MSCT and assessment of myocardial fibrosis extensiveness by CMR[15].

Stage D1 is a morpho-functionally symptomatic severe AS with high mean transaortic systolic pressure gradient

(ΔP) and preserved systolic LV function (Table 1). AVR is recommended (class I recommendation)[4]. Stage D2 occurs in patients with AS, often associated with coronary artery disease. Ischemic cardiomyopathy is the cause of decreased LVEF in these patients[4]. AVR should be considered in severe aortic stenosis because LVEF recovery has been observed even in patients without coronary flow reserve (IIa)[18].

In stage D1, a low-dose dobutamine stress echocardiography is recommended to assess AS severity and coronary reserve[4,17,18]. If the coronary reserve is reduced (during a low-dose dobutamine test an increase in LVEF less than 5% or an increase in SVi less than 20%), TAVR has an advantage over standard intervention, with the proviso that, according to the guidelines of European associations of cardiologists and cardiac surgeons, LVEF <20% is relative contraindication for TAVI (Figures 1a, b, c)[4,7,17,18].

Stage D3 is a symptomatic *low flow-low gradient* severe AS. The most common cause is hypertrophic LV, where indexed stroke volume is reduced despite preserved EF. At this stage, aortic valve replacement should be considered (IIa)[4]. Stage D4 includes patients with symptomatic severe AS with normal flow and low mean transaortic systolic pressure gradient. As part of the morphological evaluation of the degree of stenosis, it is indicated to complete the examination with a calcium score[4,15,18]. If severe AS is very likely (calcium score in men ≥3000 and in women ≥1600), AVR should be considered (IIa)[18].

References

1. Thaden J, Nkomo VT, Enriquez-Sarano M. The global burden of aortic stenosis. Prog Cardiovasc Dis 2014;56(6):565-71.
2. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. Lancet 2006;368(9540): 1005-11.
3. Kanwar A, Thaden JJ, Nkomo VT. Management of patients with aortic valve stenosis. Mayo Clin Proc 2018;93(4):488-508.
4. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159–e1195.
5. Elmariah S, Palacios IF, McAndrew T, et al.; PARTNER Investigators. Outcomes of transcatheter and surgical aortic valve replacement in high-risk patients with aortic stenosis and left ventricular dysfunction: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (cohort A). Circ Cardiovasc Interv 2013;6(6):604-14.
6. Reinöhl J, Kaier K, Reinecke H, et al. Effect of availability of transcatheter aortic-valve replacement on clinical practice. N Engl J Med 2015;373(25):2438-47.
7. Grover FL, Vemulapalli S, Carroll JD, et al.; STS/ACC TVT Registry. 2016 Annual Report of The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. J Am Coll Cardiol 2017;69(10):1215-30.
8. Arnold SV, Reynolds MR, Lei Y, et al.; PARTNER Investigators. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. Circulation 2014;129(25):2682-90.
9. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: A Focused Update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30(4):372-92.
10. Baumgartner H. Aortic stenosis: medical and surgical management. Heart 2005;91(11):1483-8.
11. Zakkar M, Bryan AJ, Angelini GD. Aortic stenosis: diagnosis and management. BMJ 2016;355: i5425.
12. Spitzer E, Van Mieghem NM, Pibarot P, et al. Rationale and design of the transcatheter aortic valve replacement to UNload the Left ventricle in patients with ADvanced heart failure (TAVR UNLOAD) trial. Am Heart J 2016; 182:80-8.
13. McConkey HZR, Marber M, Chiribiri A, et al. Coronary microcirculation in aortic stenosis. Circ Cardiovasc Interv 2019; 12(8): e007547.
14. Wiegerinck EM, van de Hoef TP, Rolandi MC, et al. Impact of aortic valve stenosis on coronary hemodynamics and the instantaneous effect of transcatheter aortic valve implantation. Circ Cardiovasc Interv 2015;8(8): e002443.
15. Dulgheru R, Pibarot P, Sengupta PP, et al. Multimodality imaging strategies for the assessment of aortic stenosis: viewpoint of the Heart Valve Clinic International Database (HAVEC) Group. Circ Cardiovasc Imaging 2016;9(2): e004352.
16. Vollema EM, Sugimoto T, Shen M, et al. Association of left ventricular global longitudinal strain with asymptomatic severe aortic stenosis: natural course and prognostic value. JAMA Cardiol 2018;3(9):839-47.
17. Kanwar A, Thaden JJ, Nkomo VT. Management of patients with aortic valve stenosis. Mayo Clin Proc 2018;93(4):488-508.
18. Banović M, Vujisić Tešić BV, Nedeljković I. Značaj dobutaminskog stres-ehokardiografskog testa u proceni rizika kod asimptomatskog pacijenta sa tesnom aortnom stenozom i očuvanom ejekcionom frakcijom u miru – prikaz slučaja. Srce i krvni sudovi 2013; 32(2): 121-4.

Sažetak

Najnovije preoporuke u lečenju aortne stenoze: (T)AVR u fokusu

Milena Pandrc[1], Mirjana Stanić[1], Vanja Kostovski[2], Danijela Vraneš[1], Snježana Vukotić[1], Andjelka Ristić[1], Nemanja Djenić[1]

[1]Klinika za urgentnu internu medicinu, Vojnomedicinska akademija, Beograd; [2]Klinika za grudnu i kardijalnu hirurgiju, Vojnomedicinska akademija, Beograd.

Prema podacima iz SAD, trećina svih pacijenata sa aortnom stenozom imaju tesnu aortnu stenozu, kao i brojne komorbiditete i komedikaciju, te se kao preporučen modalitet lečenja u slučajevima kada postoji primarna indikacija za zamenu aortnog zalistka nameće transkateterska intervencija, kao jednako efikasna i znatno bezbednija tehnika u poredjenju sa standardnom hirurgijom.

Ključne reči: *aortna stenoza, srčana slabost, transkateterska zamena aortnog zalistka*

Srce i krvni sudovi 2019; 38(2): 95-100

Case report

The diagnostic value of coronary flow reserve by transthoracic Doppler echocardiography in non-diagnostic or inconclusive stress echocardiography tests

Marija Kotevska, Srđan Dedić, Nikola Bosković, Vojislav Giga, Milorad Tešić, Srđan Aleksandrić, Milan Dobrić, Branko Beleslin, Ana Djordjevic Dikić

Cardiology Clinic, Clinical center of Serbia, Faculty of Medicine, University of Belgrade

Abstract

Background: An inconclusive or non-diagnostic stress echocardiography test (SET) implies a need for additional tests, which often results in unnecessary invasive examinations and higher health costs.
Aim: The aim of our study was to investigate the value of non-invasive transthoracic Doppler echocardiography (TTDE) derived coronary flow reserve (CFVR) in patients with non-diagnostic and inconclusive SET.
Methods: The study group consisted of 122 patients (73 male, 49 females: mean age 63±8 years) with non-diagnostic SET (target heart rate (HR) not reached, chest pain without electrocardiographic (ECG) and echocardiographic changes; and inconclusive SET (target HR reached, chest pain without ECG and echocardiographic changes). All patients were referred for TTDE assessment of CFVR in left anterior descending artery (LAD). CFVR was calculated as the ratio of maximal hyperemic and baseline coronary flow velocity. CFVR LAD ≤ 2 was considered abnormal. All patients were scheduled for invasive coronary angiography (CA).
Results: Mean CFVR LAD was 2.4±0.44. CFVR LAD was abnormal in 22 (18%) and preserved in 100 (82%) patients. Significant LAD stenosis was found in 15 (12.2%) out of 122 patients. Sensitivity of reduced CFVR LAD ≤ 2 was 88% for significant LAD stenosis, while preserved CFVR >2 had negative predictive value of 95%. Correlation analysis found significant correlation between invasive CA and CFVR LAD (r -0.356; p<0.0001).
Conclusions: Reduced CFVR LAD ≤ 2.0 has additive diagnostic value in detection of significant LAD stenosis in patients with non-diagnostic and inconclusive SET.

Key words coronary flow reserve, non-diagnostic stress ehocardiography test

Background

Stress echocardiography test (SET) is an established non-invasive method in clinical cardiology guidelines[1-5] that is routinely used for diagnosis, risk stratification and prognosis of patients with suspected or known coronary artery disease (CAD).
Diagnostic end-point for detection of myocardial ischemia during SET is an achievement of the target heart rate and/or electrocardiographic (ECG) changes and/or occurrence of the chest pain and/or echocardiographic regional wall motion abnormalities (RWMA)[2]. However, a number of patients have inconclusive or non-diagnostic results because they either do not reach target heart rate or fulfill ECG or echocardiographic diagnostic criteria for myocardial ischemia. An inconclusive or non-diagnostic exercise test results are in most cases followed by another provocation test in order to reach correct diagnosis[6].

Advancements in ultrasound technology have made noninvasive visualization of coronary arteries and assessment of coronary flow velocity reserve (CFVR) available technique in routine clinical practice[7,8]. Today, non-invasive assessment of CFVR during vasodilator SE has been endorsed by the European Society of Echocardiography for the diagnosis of microvascular angina[2], but there is a growing body of evidence that it could be used for detection of hemodynamically significant stenosis of the epicardial artery[9].
In our institution, non-invasive transthoracic Doppler echocardiography (TTDE) derived CFVR of left anterior desending (LAD) artery is often used as additional test following non-diagnostic or inconclusive SET, since it has been shown to have excellent diagnostic and prognostic value[10].
The aim of this prospective study was to investigate diagnostic value of TTDE CFVR in detecting significant stenosis in LAD in patients with known or suspected CAD and non-diagnostic and inconclusive SET results.

Methods

Study Population

Study population included 122 patients (73 male, 49 females: mean age 63±8 years) with suspected or known coronary artery disease prospectively enrolled from January 2016 to December 2017. All patients were referred for TTDE CFVR assessment of LAD after non-diagnostic or inconclusive SET. SET was considered **non-diagnostic** when target HR (85% the age-predicted maximum HR) was not reached, with chest pain without electrocardiographic (ECG) and/or echocardiographic changes, and **inconclusive** if the target HR was reached, with chest pain, without ECG and/or echocardiographic criteria for ischemia. Exclusion criteria were contraindications to stress testing (acute myocardial infarction, unstable angina, significant valvular heart disease, and primary hypertrophic or dilated cardiomyopathy) as well as contraindications to adenosine infusion, poor image quality of LAD, and refusal to participate in the study. All patients were scheduled for invasive coronary angiography. For the analysis, patients were divided into two groups: group 1: patients with reduced CFVR LAD (≤ 2) and group 2: patients with preserved CFVR LAD (>2). The study received institutional review board approval. Informed consent was obtained from all patients included in the study.

Stress echocardiography test

All patients performed symptom-limited treadmill exercise according to the standard Bruce protocol, with continuous ECG and blood pressure monitoring. Transthoracic stress echocardiographic studies were performed using commercially available ultrasound machine (Vivid System 9, GE) equipped with a multifrequency phased-array sector scan probe using second harmonic technology. Echocardiographic images were semiquantitatively assessed using a 17-segment, four-point scale model of the left ventricle at rest and immediately after exercise. Myocardial ischemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality[3,11].

TTDE evaluation of CFVR

TTDE CFVR measurements were performed using a commercially available ultrasound machine Vivid 9 (GE Healthcare) equipped with multifrequency transducer 4MHz using second harmonic technology. Coronary flow in the mid to distal LAD artery was searched in the low parasternal long axis section under the guidance of color Doppler flow mapping. Color Doppler flow mapping velocity range was set to 16 to 24 cm/sec. A sample volume (3–5 mm wide) was positioned on the color signal of the distal part of the LAD. Flow velocity recordings were performed at rest and maximal hyperemia, which was induced by administration of intravenous adenosine (140 mg/kg over 2 min) (2). All studies were digitally stored for offline analysis. CFVR was calculated as the ratio of hyperemic to basal peak diastolic coronary flow velocity. CFVR LAD ≤2 was considered abnormal.

Coronary angiography

Coronary angiography (CA) was performed in all patients using standard techniques. Significant LAD disease was defined by quantitatively coronary angiography as ≥50% diameter stenosis narrowing of coronary arteries in the view showing the most severe stenosis.

Statistical Analysis

Quantitative variables are expressed as mean ± standard deviation or as median (interquartile range) for data not normally distributed. Differences in quantitative variables were assessed with Student's t test. The chi square test was used for categorical variables. The differences of means of CFVR between 3 independent groups were analyzed using One way analysis of variance (ANOVA). We used Spearman´s correlation coefficient to measure the relationship between CFVR and percentage of LAD stenosis. Receiver operating characteristic (ROC) curve analysis was used to calculate sensitivity in detecting significant stenosis in the LAD and to determine the optimal cut-off value for CFVR, diagnostic for LAD disease. Negative predictive value and diagnostic accurancy were calculated according to standard formulas. Statistical significance was defined as $p < 0.05$. Data were analyzed with the statistical software package SPSS 25.

Results

Main clinical characteristics of the study population are presented in Table 1.

Table 1. Clinical characteristics of the study population

Variable	N / %
Gender (men/women)	73 (59.8%) / 49 (40.2%)
Age	62.5 ± 8.4
Non-diagnostic SET / Inconclusive SET	53 (43.4%) / 69 (56.6%)
CV risk factors	
HTA	106 (86.9%)
HLP	95 (77.9%)
Smoking	65 (63.3%)
Heredity	50 (41%)
Menopause	16 (13.1%)
DM type 2	30 (24.6%)
Angina pectoris	50 (41%)
LBBB	15 (12.3%)
AF	8 (6.6%)
Known CAD	75 (61,5%)
Prior MI	44 (36.1%)
Suspected CAD	47 (38.5%)
Anti-ischemic therapy	118 (96.7%)
Beta-blockers	101 (82.8%)
CCBs	36 (29.5%)
Nitrates	38 (31.1%)

SET, stress echocardiography test; CV, cardiovascular; HTA, arterial hypertension; HLP, hyperlipidemia; DM, diabetes melitus; LBBB, left bundle brunch block; AF, atrial fibrillation; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CAB,= coronary artery bypass grafting; CCBs, calcium channel blockers

Table 2. Heart rate during stress echocardiography test and coronary flow velocity in patients with non-diagnostic and inconclusive stress echocardiography test

	Non-diagnostic SET (N=53)	Inconclusive SET (N=69)	P value
HR basal (beats/min)	64 ± 8.5	72 ± 11.7	**0.001**
HR maximal (beats/min)	118 ± 11	143 ±10	**0.001**
V max basal (cm/sec)	24.2 ± 9	24.3 ± 6	0.980
V max Adenozin (cm/sec)	57.3 ± 15	57.4 ± 16	0.976
CFVR LAD	2.4 ± 0.4	2.3 ± 0,4	0.421

SET, stress echocardiography test; HR, heart rate; CFVR LAD, coronary flow reserve of left anterior descending artery; V max, maximal velocity of coronary flow

Most of the patients were hypertensive and with hyperlipidemia, and 83% were on a chronic therapy with beta-blockers. Out of 122 patients, 75 had known CAD (previous myocardial infarction, and/or previous percutaneous coronary intervention or previous coronary artery bypass grafting), while 47 patients had suspected CAD.

Stress echocardiography test and CFVR LAD assessment

SET was non-diagnostic in 53 patients (43.4%), and inconclusive in 69 (56.6%). Table 2 presents heart rate during SET and coronary flow recordings.

Average basal and maximal HR during SE test were significantly higher in patients with inconclusive results compared with patients with non-diagnostic results. Values of coronary flow did not differ between the two groups (Table 2). No complication occurred during both tests. Measured values of CFVR LAD were in the range 1.5–4.0 (2.4 ±0.44).

Coronary angiography and CFVR findings

Angiographic findings of LAD are presented in Table 3. Distribution of angiographic severity of coronary stenosis is presented in Table 3.

Table 3. Angiographic findings on LAD

LAD stenosis severity	
• LAD stenosis **0-50%**	91 (75%)
• LAD stenosis **50-70%**	16 (13%)
• LAD stenosis **≥70%**	15 (12%)

CAD, coronary artery disease; LAD, left anterior descending artery

CFVR LAD was reduced (≤ 2) in 22 (18%), and preserved in 100 (82%) patients. All patients (n=16) with angiographically intermediate LAD stenosis had preserved CVR.

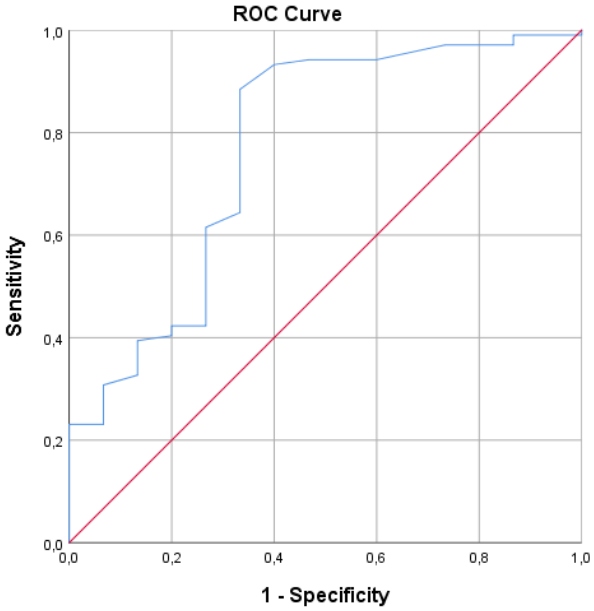


Figure 1. Sensitivity and specificity of CFVR LAD in detection of significant LAD stenosis CFVR LAD, coronary flow reserve of left anterior descending artery

In the subset of patients with LAD disease, CFVR was significantly lower in patients with stenosis ≥70% compared with those with intermediate (p =0.002) and non-significant LAD stenosis (p =0.002) (Table 4). The values of CFVR LAD were significantly lower in patients with intermediate compared with patients with non-significant stenosis. (2.38±0.35 vs 2.45±0.44; p=0.001)

According to receiver operating characteristic (ROC) analysis, a cut-off of CFVR LAD ≤ 2.02 has the best sensitivity of 88% and limited specificity of 36% in detection of significant epicardial coronary stenosis of LAD (Area 0.771 (95% CI 0.62 to 0.91) p=0.001) (Figure 1). Negative predictive value was very high (95%). Diagnostic accuracy was 85%.

Table 4. Relation of stenosis severity and CFVR

	CVFR LAD							
	N	Mean	Std. Dev.	95% CI Mean LowerBound	UpperBound	Minimum	Maximum	P value
0-50%	88	2.45	0.44	2.36	2.54	1.52	4.00	**0.001**
50-70%	16	2.38	0.35	2.19	2.57	2.05	3.00	**0.002**
≥70%	15	2.01	0.36	1.81	2.22	1.60	2.68	**0.002**

CFVR LAD= coronary flow reserve of left anterior descending artery

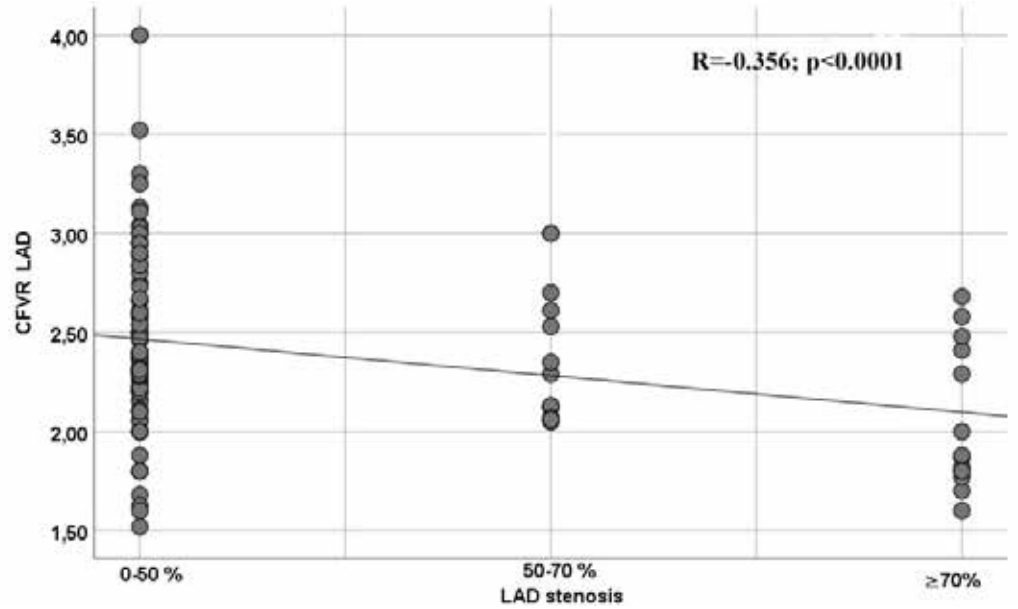


Figure 2. Correlation between invasive coronarography and TTDE CFVR LAD;

TTDE, transthoracic Doppler echocardiography; CFVR LAD, coronary flow reserve of left anterior descending artery

Correlation analysis found statistically significant correlation but with large overlap between invasive coronary angiography defined severity of stenosis and TTDE CFVR LAD (r = - 0.356; p<0.0001) shown in Figure 2.

Discussion

According to our results, reduced CFVR LAD ≤ 2 identifies patients with significant stenosis in the LAD with high sensitivity (88%) and diagnostic accuracy of 85%, while preserved CFVR >2 has high negative predictive value (95%). Moreover, we have shown that noninvasive CFVR could be used as additional test to non-diagnostic and inconclusive SET.

CFVR is an important functional parameter in pathophysiology of coronary circulation. It can be used to examine the integrity of microvascular circulation as suggested in a recent guidelines for chronic coronary syndromes[1] and to evaluate coronary stenosis[7,11]. Reduced CFVR ≤2[7,12] is not specific for epicardial coronary stenosis, because coronary flow and reserve depend on microvascular function and integrity[13]. However, in case of normal microvasculature it may indicate physiologically significant epicardial coronary stenosis[7].

A number of patients undergoing treadmill exercise stress test have non-diagnostic or inconclusive test from various reasons: low exercise capacity, beta-blocker therapy[14], atypical chest pain or failure to achieve target HR[2,5]. Failure to reach target HR is present in 15–25% of SET, and even higher among those on chronic beta-blocker therapy 30-50%[14]. In our study beta-blocker therapy was present in 83% of the patients and almost half of them, 47 (46.5 %) did not reach the target HR. Also, SET are often inconclusive in patients with left bundle brunch block (LBBB)[15], and atrial fibrillation (AF)[16].

Moreover, combine evaluation of RWMA and Doppler derived CFVR of LAD during vasodilatory SET known as „dual" imaging protocol is recommended by European guidelines for cardiovascular imaging[2]. Our results confirm usefulness of this approach in non-diagnostic/inconclusive tests.

Comparison with previous studies

Results of our study are in concordance with previous data in patients with suspected or known coronary artery disease. Matsumura et al.[11] reported similar results to our group for CFVR LAD ≤ 2 in detection of significant LAD stenosis, with sensitivity of 90%, specificity of 93%, a positive predictive value of 77%, and a negative predictive value of 97%[11]. Rigo et al.[10] reported sensitivity of stress echocardiography in detection of LAD stenosis to be 74%, while sensitivity of CFVR LAD <1.9 was 81%. When both criteria are considered, the sensitivity improves to 93%, with modest lost in specificity of 81%. When CFVR of LAD was added to wall motion abnormality analysis, the diagnostic accuracy for the detection of coronary artery disease has increased from 75% to 85%[20]. Overall, reduced CFVR LAD ≤ 2 have shown sensitivity from 85-94 % and specificity from 57-92%[20-22] in detection of significant LAD stenosis. Important findings refer also to preserved CFVR LAD > 2 that have very high negative predictive value 94-97%, allowing safe deferral from invasive procedures[11,22-24].

In our study CFVR LAD had high sensitivity (88%) in detection of significant coronary stenosis of LAD, and high negative predictive value (94%).

Study limitations

Almost all patients (96%) were studied under anti-ischemic therapy, mostly beta-blocker therapy, which may affect performance of stress test and may be responsible for non-diagnostic tests.

We only assessed CFVR in the LAD - from a practical viewpoint it is less technically demanding, and has higher feasibility than assessment of RCA or Cx. Thus, any significant coronary lesions in RCA and/or Cx myocar-

dial territories were not included in the analysis, but "dual" nature of combined CFVR and stress echocardiography imaging may compensate for absence of RCA and/or Cx coronary flow imaging. In addition and from prognostic viewpoint, LAD is stronger predictor of adverse cardiovascular events than RCA or Cx[21].

Clinical implications

Our results support aassessment of CFVR LAD into clinical non-invasive decision making before further invasive diagnostic in patients with non-diagnostic and inconclusive SET. Patients with reduced CFVR on LAD (or RCA), or both, despite absence of RWMA should be referred to invasive angiography[23]. On the other hand, preserved CFVR LAD > 2 have high negative predictive value in detection of significant coronary stenosis of LAD as previously demonstrated in many studies[11,22-24] Due to the excellent negative predictive value of preserved CFVR[23,24], unnecessary further invasive treatment and investigation may be avoided and save health care costs.

Conclusion

Our results have shown that TTDE assessment of CFVR in LAD could be used as additional test in detection of hemodynamic significant stenosis of LAD in patients with non-diagnostic and inconclusive SET. High negative predictive value of TTDE derived CFVR allows safely deferral from invasive diagnostic procedures.

References

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019 (in press).
2. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr 2008;9(4):415-37.
3. Pellikka PA, Nagueh SF, et al; American Society of Echocardiography. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 2007;20:1021-1041.
4. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.
5. Stepanovic J, et al. Stresna elektro i ehokardiografija u detekciji koronarne bolesti. Kardiologija, urednici Ostojic M, Kanjuh V, Beleslin B. Beograd 2011:97-107.
6. Marcus R, Ruff C, Burgstahler C, et al. Recent scientific evidence and technical developments in cardiovascular computed tomography. Rev Esp Cardiol 2016;69:509-514.
7. Picano E. Stress Echocardiography. Heidelberg, Germany: Springer Verlag; 2015 (6th edition).
8. Caiati C, Montaldo C, Zedda N, et al. New noninvasive method for coronary flow reserve assessment: contrast-enhanced transthoracic second harmonic echo Doppler. Circulation 1999; 99:771-778.
9. Djordjevic Dikic A, Tesic M, Boskovic N, et al. Prognostic value of preserved coronary flow velocity reserve by noninvasive transthoracic Doppler echocardiography in patients with angiographically intermediate left main stenosis. J Am Soc Echocardiogr 2019;32:74–80.
10. Rigo F, Richieri M, Pasanisi E, et al. Usefulness of coronary flow reserve over regional wall motion when added to dual-imaging dipyridamole echocardiography. Am J Cardiol 2003;91:269-273.
11. Matsumura Y, Hozumi T, Watanabe H, et al. Cut-off value of coronary flow velocity reserve by transthoracic Doppler echocardiography for diagnosis of significant left anterior descending artery stenosis in patients with coronary risk factors. Am J Cardiol 2003;92:1389–1393.
12. Tuccillo B, Accadia M, Rumolo S, et al. Factors predicting coronary flow reserve impairment in patients evaluated for chest pain: An ultrasound study. J Cardiovasc Med (Hagerstown). 2008;9:251-255.
13. Picano E, Pellikka PA. Stress echo applications beyond coronary artery disease. Eur Heart J 2014;35:1033–1340.
14. Fong MW, Teeters JC. Stress echocardiography testing: is submaximal good enough? Cardiol J 2008;15:207-208.
15. Geleijnse ML, Vigna C, Kasprzak JD, et al. Usefulness and limitations of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in patients with left bundle branch block. A multicentre study. Eur Heart J 2000;21:1666-1673.
16. Kochiadakis GE, Kallergis EM. Impact of atrial fibrillation on coronary blood flow: A systematic review. J Atr Fibrillation 2012; 5:458.
17. Flores-Blanco PJ, Cambronero F, García-Navarro M, et al. Inconclusive exercise stress echocardiography in patients with chest pain: Prevalence and clinical determinants. Rev Esp Cardiol (Engl Ed). 2018 May;71406-408.
18. Makani H, Bangalore S, Halpern D, et al. Cardiac outcomes with-submaximal normal stress echocardiography: a meta-analysis. J Am Coll Cardiol 2012;60:1393-1401.
19. Picano E, Ciampi Q, Citro R, et al. Stress echo 2020: The international Stress Echo study in ischemic and non-ischemic heart disease. Cardiovasc Ultrasound 2017;15:3.
20. Kasprzak JD, Wejner-Mik P, Nouri A, et al. Transthoracic measurement of left coronary artery flow reserve improves the diagnostic value of routine dipyridamole-atropine stress echocardiogram. Arch Med Sci 2013;9:802–807.
21. Cortigiani L, Rigo F, Sicari R, Gherardi S, Bovenzi F, Picano E. Prognostic correlates of combined coronary flow reserve assessment on left anterior descending and right coronary artery in patients with negative stress echocardiography by wall motion criteria. Heart 2009;95:1423-1428.
22. Florenciano Sánchez R, de la Morena Valenzuela Gd G, Soria Arcos F, et al. Detection of angiographic lesions in the left anterior descending coronary artery by transthoracic Doppler echocardiography: usefulness of non-invasive assessment of coronary flow reserve. Rev Esp Cardiol 2003;56:561-568.
23. Cortigiani L, Rigo F, Gherardi S, et al. Additional prognostic value of coronary flow reserve in diabetic and nondiabetic patients with negative dipyridamole stress echocardiography by wall motion criteria. J Am Coll Cardiol 2007;50:1354-1361.
24. Ferrari M, Schnell B, Werner GS, Figulla HR. Safety of deferring angioplasty in patients with normal coronary flow velocity reserve. J Am Coll Cardiol 1999;33:82-87.

Sažetak

Diagnostički značaj neinvazivne procene koronarne rezerve protoka transtorakalnom dopler ehokardiografijom kod nedijagnostičkih i inkonkluzivnih stres ehokardiografskih testova

Marija Kotevska, Srđan Dedić, Nikola Bosković, Vojislav Giga, Milorad Tešić, Srđan Aleksandrić, Milan Dobrić, Branko Beleslin, Ana Djordjevic Dikić

Klinika za kardiologiju, Klinički Centar Srbije, Medicinski Fakultet u Beogradu

Uvod: *Nedijagnostički ili inkonkluzivni stres ehokardiografski test (SET) često vodi ka dopunskim ispitivanjima, što rezultuje nepotrebnim invazivnim procedurama i povećanom zdravstvenom trošku.*
Cilj *rada je bio da se utvrdi dijagnostički značaj koronarne rezerve protoka (CFVR) merene putem transtorakalne Dopler ehokardiografije (TTDE) kao dopunske metode, kod nedijagnostičkih i inkonkluzivnih SET.*
Metode*: Studija je obuhvatila 122 pacijenata (73 muškarca, 49 ženae: srednje godine 63±8 godina) sa nedijagnostičkim SET (ciljana srčana frekvenca (SF) nije dostignuta; anginozni bol bez elektrokardiografskih (EKG) i ehokardiografskih promena) i inkonkluzivnim SET (ciljana SF dostignuta, sa anginoznim bolom, bez EKG i ehokardiografskih promena). Svim pacijentima je procenjena CFVR na prednjoj descendetnoj arteriji (LAD) TTDE sa adenozinom. CFVR je bila izračunata kao odnos između maksimalne brzine koronarnog protoka u hiperemiji i maksimalne brzine koronarnog protoka u bazalnim uslovima. CFVR ≤2 je posmatrana kao redukovana vrednost. Kod svih pacijenata je urađena koronarna angiografija..*
Rezultati: *Prosečna vrednost CFVR LAD je bila 2.4 ±0.44. CFVR LAD je bila redukovana kod 22 (18%) i normalna kod 100 (82%) pacijenta. Invazivna koronarografija je detektovala značajne stenoze LAD kod 15 (12.2%) od ukupno 122 pacijenta. Redukovana CFVR LAD ≤ 2.0 je imala senzitivnosti 88%, dok je normalna CFVR LAD imala negativnu prediktivnu vrednost od 95%. Korelaciona analiza je ukazala na značajnu povezanost između nalaza koronarografije i CFVR LAD (r = -0.356; p<0.0001).*
Zaključak: *Redukovana CFVR LAD ≤ 2.0 ima dodatni dijagnostički značaj kod nedijagnostičkih i inkonkluzivnih SET u otkrivanju značajnih stenoza na LAD.*

Ključne reči: *koronarna rezerva protoka, nedijagnostički stres ehokardiografski test*

Srce i krvni sudovi 2019; 38(2): 101-106

Authorship: From Credit to Accountability. Reflections From the Editors´ Network

Fernando Alfonso MD[1]*, Parounak Zelveian MD[2], Jean-Jacques Monsuez MD[3], Michael Aschermann MD[4], Michael Boehm MD[5], Alfonso Buendia Hernandez MD[6], Tzung-Dau Wang MD[7], Ariel Cohen MD[8], Sebija Izetbegovic MD[9], Anton Doubell MD[10], Dario Echeverri MD[11], Nuray Enç MD[12], Ignacio Ferreira-González MD[13], Anetta Undas MD[14], Ulrike Fortmüller MD[15], Plamen Gatzov MD[16], Carmen Ginghina MD[17], Lino Goncalves MD[18], Faouzi Addad MD[19], Mahmoud Hassanein MD[20], Gerd Heusch MD[21], Kurt Huber MD[22], Robert Hatala MD[23], Mario Ivanusa MD[24], Chu-Pak Lau MD[25], Germanas Marinskis MD[26], Livio Dei Cas MD[27], Carlos Eduardo Rochitte MD[28], Kjell Nikus MD[29], Eckart Fleck MD[30], Luc Pierard MD[31], Slobodan Obradović MD[32], María del Pilar Aguilar Passano MD[33], Yangsoo Jang MD[34], Olaf Rødevand MD[35], Mikael Sander MD[36], Evgeny Shlyakhto MD[37], Çetin Erol MD[38], Dimitris Tousoulis MD[39], Dilek Ural MD[40], Jan J. Piek MD[41], Albert Varga MD[42], Andreas J. Flammer /François Mach MD[43], Alban Dibra MD[44], Faiq Guliyev MD[45], Alexander Mrochek MD[46], Mamanti Rogava MD[47], Ismael Guzman Melgar MD[48], Giuseppe Di Pasquale MD[49], Kanat Kabdrakhmanov MD[50], Laila Haddour MD[51], Zlatko Fras MD[52], Claes Held MD[53], Valentyn Shumakov MD[54]

On behalf of the Editors' Network, European Society of Cardiology (ESC) Task Force.

Running Title: "*Authorship and Accountability*"

Disclosures: None of the Editors authors of this paper have any potential conflict of interest that needs to be disclosed in relation to this manuscript.

This is a joint simultaneous publication initiative involving all interested National and Affiliated Cardiovascular Journals of the European Society of Cardiology (ESC).

Affiliations:

[1]Chairman Editors´Network; [2]Editor in Chief Scientific Medical Journal, [3]Editor in Chief Archives des maladies du cœur et des vaisseaux-Pratique, [4]Editor in Chief Cor et Vasa, [5]Editor in Chief Clinical Research in Cardiology, [6]Editor in Chief Archivos de Cardiologia de Mexico, [7]Editor in Chief Acta Cardiologica Sinica, [8]Editor in Chief Archives of Cardiovascular Diseases, [9]Editor in Chief Medicinski Zurnal, [10]Editor in Chief SA Heart, [11]Editor in Chief Revista Colombiana de Cardiologia, [12]Editor in Chief Kardiyovaskuler Hemsirelik Dergisi, [13]Editor in Chief Revista Española de Cardiología, [14]Editor in Chief Kardiologia Polska, [15]Editor in Chief Cardio News, [16]Editor in Chief Bulgarian Journal of Cardiology, [17]Editor in Chief Romanian Journal of Cardiology, [18]Editor in Chief Revista Portuguesa de Cardiologia, [19]Editor in Chief Revue Tunisienne de Cardiologie, [20]Editor in Chief The Egyptian Heart Journal, [21]Editor in Chief Basic Research in Cardiology, [22]Editor in Chief Austrian Journal fo Cardiology, [23]Editor in Chief Cardiology Letters, [24]Editor in Chief Cardiologia Croatica, [25]Editor in Chief Journal of the Hong Kong Colleage of Cardiology, [26]Editor in Chief Seminars in Cardiovascular Medicine, [27]Editor in Chief Journal of Cardiovascular Medicine, [28]Editor in Chief Arquivos Brasileiros de Cardiologia, [29]Editor in Chief Sydänääni (Heart Beat), [30]Editor in Chief Der Kardiologe, [31]Editor in Chief Acta Cardiologica, [32]Editor in Chief Heart and Blood Vessels, [33]Editor in Chief Revista Uruguaya de Cardiologia, [34]Editor in Chief Korean Circulation Journal, [35] Editor in Chief Hjerteforum, [36]Editor in Chief Cardiologisk Forum, [37]Editor in Chief Russian Journal of Cardiology, [38]Editor in Chief Anatolian Journal of Cardiology, [39]Editor in Chief Hellenic Journal of Cardiology, [40]Editor in Chief Archives of the Turkish Society of Cardiology, [41]Editor in Chief Netherlands Heart Journal, [42]Editor in Chief Cardiologia Hungarica, [43]Editor in Chief Cardiovascular Medicine, [44]Editor in Chief Revista Shqiptare e Kardiologjisë, [45]Editor in Chief Azerbaijan Journal of Cardiology, [46]Editor in Chief Cardiology in Belarus, [47]Editor in Chief Cardiology and Internal Medicine (Georgian International Society of Cardiomyopathy), [48]Editor in Chief Revista Guatemalteca de cardiologia, [49]Editor in Chief Giornale Italiano di Cardiologia, [50]Editor in Chief Journal Terapevticheskiy vestnic, [51]Editor in Chief Revue Marocaine de Cardiologie, [52]Editor in Chief Slovenska kardiologija, [53]Editor in Chief Svensk Kardiologi, [54]Editor in Chief Ukrainian Journal of Cardiology

Abstract

The Editors´ Network of the European Society of Cardiology (ESC) provides a dynamic forum for editorial discussions and endorses the recommendations of the International Committee of Medical Journal Editors (ICMJE) to improve the scientific quality of biomedical journals. Authorship confers credit and important academic rewards. Recently, however, the ICMJE emphasized that authorship also requires responsibility and accountability. These issues are now covered by the new (fourth) criterion for authorship. Authors should agree to be accountable and ensure that questions regarding the accuracy and integrity of the entire work will be appropriately addressed. This review discusses the implications of this paradigm shift on authorship requirements with the aim of increasing awareness on good scientific and editorial practices.

Key Words Editorial ethics. Scientific Process. Authorship. Accountability. Scientific Journals. Journals.

Ovaj tekst je preuzet sa dozvolom ESC i u vidu saradnje urednika nacionalnih kardiovaskularnih časopisa.

*Address for Correspondence: Fernando Alfonso MD, PhD, FESC. Cardiology Department. Hospital Universitario de La Princesa. Instituto de Investigación sanitaria IIS-IP. Universidad Autónoma de Madrid. C/ Diego de León 62. Madrid 28006. Spain. Email: falf@hotmail.com

The Editors´ Network of the European Society of Cardiology (ESC) is committed to foster implementation of high-quality editorial standards among ESC National Societies Cardiovascular Journals (NSCJ[1-6]. NSCJ play a major role in disseminating original scientific research worldwide, but also in education and harmonization of clinical practice[2-6]. Promoting editorial excellence is paramount to increasing the scientific prestige of NSCJ[1-6]. In this regard, the Editors´ Network endorses the recommendations of the International Committee of Medical Journal Editors (ICMJE)(1). The ICMJE continuously updates its document on uniform requirements (previously known as the Vancouver guidelines) for manuscripts submitted to biomedical journals. These include recommendations for the conduct, reporting, editing and publication of scholarly work. Notably, vexing ethical issues are gaining increasing editorial relevance[1].

Biomedical research relies on trust and transparency of the scientific process where authors remain centre stage[1,7-9]. This review will discuss the new recommendations on authorship issued by the ICMJE[1,10,11] with the aim of providing further editorial insight to be progressively implemented by the NSCJ.

New Authorship Requirements

In August 2013 an important revision of the ICMJE recommendations included a fourth criterion for authorship to emphasize each author's responsibility to stand by the integrity of the entire work[1,10,11]. Classically, the ICMJE requirements for authorship included: 1) Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; *and,* 2) Drafting the work or revising it critically for important intellectual content; *and,* 3) Final approval of the version to be published. In the updated ICMJE requirements a new (fourth) criterion also should be met[1]. This novel requirement for authorship includes agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved[1]. The essence of this new requirement is that it helps to balance credit with responsibility[10]. With this revision the ICMJE emphasizes that authorship is a serious commitment to accountability. Now all 4 conditions must be met by each individual author[1]. The addition of a fourth criterion was motivated by situations in which some authors were unable to, or refused to, respond to inquiries on potential scientific misconduct regarding certain aspects of the study or by denying any responsibility[1,10-14]. Editors occasionally face reluctant authors who try to distance themselves from a conflictive publication and shift responsibilities elsewhere[11]. The main novel idea is to emphasize the responsibility of each author to stand for the integrity of the entire work. Each author of a scientific paper needs to understand the full scope of the work, know which co-authors are responsible for specific contributions and have confidence in co-authors' ability and integrity[1,10-14]. Should questions arise regarding any aspect of a study, the onus is on all authors to investigate and ensure resolution of the issue, which is then to be presented to the corresponding Editor[1,10-14].

To better appraise this 4th criterion the precise meaning of responsibility and accountability should be revisited. *Responsibility* is defined as the moral obligation to ensure that a particular task is adequately performed[15-16]. Accordingly, responsibility relates to tasks that have been assigned to an individual[15,16]. By contrast, *accountability* denotes the duty to justify a given action to others and to respond for the results of that action(15,16). Therefore, accountability mainly relates to the awareness and assumption of the role of being the one to blame if things go wrong[15,16]. Nevertheless, oftentimes responsibility is used interchangeably with accountability[15,16].

Claiming that each individual author is held morally responsible in every case that misconduct is detected would appear unreasonable considering the complexity of current research. Rather, the fourth criterion suggests that each author must cooperate to clarify misconduct related issues if the paper is called into question[1,16].

Research Credits

Acceptance and publication of a scientific paper is always a cause of major celebration among authors[11]. Authorship provides prestige, credit and scientific recognition. Authorship has important academic, social and financial implications[1,11]. Currently, authorship remains a major criterion for promotion and career advancement among scholars. Publication records are revised in depth for university tenures and job appointments. Total number of publications and citations remain currencies widely used to ascertain the academic value of individual investigators. In this regard, the ICMJE recommendations on authorship are intended to ensure that anybody who has made a "substantive" intellectual contribution to a paper is given credit as an author[1].

Potential Problems Derived From Publication of Research

Publication of a scientific paper usually marks the end of a research project and opens a time for discussion and criticism or acceptance by the scientific community[11]. Occasionally, the healthy scientific debate fuelled by the publication of the paper raises serious concerns. In rare cases, even the integrity of the research or published paper is brought into question[11]. In these situations authors may try to escape from the embarrassment of publishing a scientifically flawed study. This explains why the new fourth criterion is so pertinent to address issues related to scientific misconduct. Should irregularities be confirmed, editors must report to the authors´ academic institution and, eventually, to the readers, with expressions of concern, or, in the worst case scenario, with a retraction of the published paper[1].

Considerations on Classical Authorship Criteria

Any researcher listed as an author should have made a "substantive" intellectual contribution to the study and

be prepared to take public responsibility for the work, ensure its accuracy, and be able to identify his/her contribution to the study[1]. However, a problem with the definition of authorship involves the subjectivity in what constitutes a '*substantial*' contribution to the research or the manuscript. In fact, the precise threshold of involvement required to qualify for authorship remains unclear. As the real problem lies in defining what represents a "substantial" contribution, means to quantify the actual work performed by individual authors have been proposed. In this regard it has been suggested[17] that substantial contribution to a publication consists of an important intellectual contribution without which, a part of the work or even the entire work, could not have been completed or the manuscript could not have been written[17].

According to the ICMJE[1] persons who *do not* qualify as an author include those who "*only"* provide: 1) recruitment of patients to a trial, 2) general data collection, 3) obtaining samples for a study, 4) acquisition of funding, 5) general supervision of the research group by the department chairperson. Conversely, persons who significantly contributed to the paper but do not meet the 4 criteria for authorship should be listed in the acknowledgement section after obtaining their consent.

Publishing Individual Contributions

The ICMJE authorship guidance is intentionally broad and open to accommodate the diversity of scientific research and allow space for the specific editorial policies of individual journals[1]. However, many have requested a more structured authorship framework to improve consistency and clarity in authorship requirements. The best means to present the relationship between authorship and intellectual involvement in research remains an issue of ongoing debate. Currently, the ICMJE does not mandate that all authors communicate exactly what "contributions" qualify them to be an author[1]. However, unless authorship reflects to what extent individual researchers have been intellectually involved in the work it will remain misleading regarding relative research merits. Honesty and openness in attribution ensures fairness in credit. Many editors argue that authorship criteria should be revised to request a contribution declaration, in order to fully capture deserving authorship and credit. Accordingly, to promote transparency and remove ambiguity on specific contributions, editors are now strongly encouraged to develop and implement contributorship policies in their journals[1]. As discussed, however, the question regarding the quality and quantity of contribution required to qualify an individual for authorship remain unresolved[1]. An interesting proposal in this regard suggests including contributorship badges. These badges are designed to fully capture the different types of collaboration in the submitted work that, otherwise, will be difficult to recognise with traditional credentials. Contributors listing allows a more accurate and granular assessment of credit. In addition, this strategy provides additional insight on contributor-adjusted productivity[18]. Ideally, each ICMJE criterion should have at least one badge. Each badge includes a list of authors making a contribution to that specific role[18-20]. Others have proposed the value of assigning a numerical value to better evaluate the degree of relative contributions and, eventually, to create a contribution-specific index for each author to better assess research productivity[18-20].

Detailing authors´ contributions inform the readers of the nature of the individual work and avoids diluting credits by precisely allocating merits. In multi-authored papers it is particularly important that authors state the specific role they played in the research. Each research represents a significant amount of effort and, on average, the larger the number of authors the smaller percentage of effort for a given author. Other forms of contributions, not fulfilling criteria for authorship, may be recognized in the acknowledgement section or by listing these people as collaborators. This is an important issue considering the ever increasing number of authors seen in recent publications that represents a paradigm shift resulting from team-work research[18-24]. Contributors credited as authors should take full responsibility and remain accountable for what is published[1,18]. In this regard, contribution-adjusted credits can be further weighted by other factors to derive more effective parameters for measuring research productivity. Currently, every co-author gets the exact amount of citation credit regardless of their contribution. Therefore, an "author matrix" (including participation in ideas, work, writing and stewardship), has been proposed to "quantify" individual contributions and roles in multi-authored papers[18-24].

By-line Location and Hierarchy

There is no adequate guidance for author sequence in the by-line. In fact, practices to clarify the relative merit of the different coauthors in a manuscript vary significantly among scientific disciplines[18-22]. For biomedical journals, the first author is the most important position, followed by the last author and then the second author. The first author is reserved for the person who made the largest contribution (investing most time in the project) usually the author who wrote the first draft of the paper. Then the sequence of authors tends to represent progressively lesser contributions[18]. Following this approach, where the sequence determines credit, the last author receives the least. Accordingly, the last position might be considered as a rather generous option. Actually, the last position is currently considered as very important in biomedical research and, in fact, it is frequently associated with the corresponding author or the guarantor of the entire work[18]. However, many argue that senior scientists should grab the pen (keyboard) more often as writing remains essential for advancement in knowledge[19]. Senior authors have the responsibility to promote the academic career of new generation scientists.

Many journals allow authors to declare that 2 or more individuals have made "equal contribution" to the research[25-29]. In the last decade the percentage of articles with equal contribution statements has increased dra-

matically both in basic and medical scientific journals[25]. Notably, the designation of "joint first-authors" should be based on the quality and quantity of the work[25-29]. Thus the "contributed equally" designation should be reserved to honestly reflect similar scientific contributions and not to inflate a *curriculum vitae*[25-29]. Interestingly, the practice of listing two individuals as "joint last author" is used less frequent but steadily increasing. These publications should include a foot note clearly indicating that both authors equally contributed to the work[25-29].

The corresponding author takes primary responsibility for communication with the journal during the submission, peer-review, publication and post-publication periods[1]. Currently, most journals require contact e-mail addresses from all listed authors who then will be contacted to inform that the corresponding author submitted the paper. This ensures that they are aware that the paper has been submitted in their name. The systematic implementation of this electronic warning system paves the way to guarantee that the 3rd authorship criterion has been met. Therefore, the policy now may be considered as a mere administrative requirement similar to signing of a copyright transfer.

The "guarantor" of the study may be different from the first or corresponding author and frequently is the principal investigator or more senior person in the group. The guarantor takes full responsibility for the integrity of the work as a whole from inception to the published paper. Accordingly, the guarantor must be fully prepared to defend all parts of the research project and final manuscript. Guarantors vouching for the integrity of the entire work are of special value for multi-author articles particularly when many institutions are involved. All authors should also disclose potential conflicts of interest[1,5]. The ICMJE uniform conflict of interest disclosure has been recently updated and all authors should complete the corresponding standardized individual electronic document[1,5]. In particular, authors of sponsored studies should indicate that they had full access to the data and take complete responsibility for the accuracy and integrity of the analysis. This is important as roles and interests of different stakeholders may remain elusive or misleading in this type of study[1].

The subjectivity and emotionality of authorship may explain why disputes among investigators are not uncommon. Authorship disputes amongst research teams should be avoided by deciding roles and responsibilities beforehand. Ideally, the order of authors should be collectively decided by the research team at the onset of the project[30]. Then, the definitive author order should be revised when the work is completed, taking into account the actual level of individual contributions[17]. Editors are unable to judge whether authors have met the authorship criteria. The COPE (Committee on Publication Ethics; www.publicationethics.org) guidelines are useful to solve publication disputes[9]. Editors should seek explanations and signed agreement of all authors in case of a request for a change in the author list[1].

Multi-Authored Articles

Scientific collaboration has become increasingly important because the complexity of modern research involves different competencies[16]. Moreover, a large number of patients and centres may be required to adequately address clinically relevant questions[16]. In addition, multidisciplinary research groups offer the opportunity of cross-pollination[16]. Therefore, team-work is currently common place in biomedical research. Co-authorship is the most tangible result of multilateral scientific collaboration. Group (corporate) authorship has become increasingly common with variations in how individual authors and research group names are listed in the by-line. Notably, citation impact is greater in papers with multiple authors coming from international cooperation. The problem of inflating publication and citation records of authors participating in multicenter studies has been a cause of concern[18]. This is due, at least in part, to collaboration-induced self-citation[31]. Salami publications, or least publishable units strategies, are initiatives that inflate the number of publications on the same research project by dividing the work (that could have been presented in a single main paper) into smaller component parts, then publishing them as several different articles. Such strategies may be detected in some multicenter studies[31]. The use of coauthor-adjusted citation indexes have been suggested to account for this phenomenon[31].

There is evidence that the number of coauthors per paper in medical literature has increased exponentially over time[22,32]. The reason for this increase is probably multifactorial and includes, increasing complexity of research, as discussed, but also author inflation. Inappropriate authorship is not ethical and eventually leads to diminish the value of authorship, generating a situation where undeserved coauthors cannot take responsibility for the research[22,32]. Interestingly, the correlation between research quality and number of authors is poor, suggesting that the component of author inflation plays a greater role than that of research complexity[32].

Until now the number of authors in the by-line was not considered in the evaluation of the relative academic merit of individual authors[3]. However, as a research project involves a defined amount of work, the larger the number of authors in a paper the smaller the merit that deserves any given author. Major efforts are made by some individuals whereas others contribute significantly less. The credit received by people doing the work becomes diluted by the inclusion of many authors with little, if any, contributions. Eventually this "free lunch" strategy undermines the value of being named on a scientific paper[33].

Authorship guidelines should be updated to adapt to the growing trend of collaborative research. The larger the number of authors the more opportunities for contentious arguments and disputes. Every author of a "group authorship" work must meet the 4 criteria for authorship. Otherwise they should be identified just as investigators or collaborators rather than authors[1]. Given the complexity and multiple tasks involved in current research it is

clear that most authors cannot participate in every aspect of the work. Accordingly, specific responsibilities should be tied to different research roles. Authors should refrain from collaborating with colleagues whose quality or integrity may inspire concerns[1]. Last, but not least, with a growing number of authors it is increasingly difficult to identify those who may be held morally responsible should scientific misconduct be detected[22,32]. Holding everybody responsible is unfair to the researchers that are not guilty of misconduct.

Breaches in Authorship: From Ghost to Guest Authors

Breaches in authorship are a form of deception. Guest or gift (honorary) and ghost (hidden) authors represent a form of authorship abuse that should not be permitted[34-39]. Ghost authorship is omitting authors that have made relevant contributions to a paper. Ghost authors provide contributions to a manuscript that do merit authorship but, for different reasons, are not included in the author by-line. Some ghost authors may have major conflicts of interest or are paid by a commercial sponsor. This should be differentiated from ghost writing. Ghost writers are writing contributors to a manuscript that do not fulfill authorship criteria, but their contributions are not disclosed in the acknowledgements[17,38]. Ghost writing is also an unethical practice as it keeps hidden the involvement in the manuscript. The concern is that writers hired by the industry might influence the content of the publication or hide unwelcome results, which introduces potential bias that is obscured when relevant academic guest authors are accredited with authorship[17]. Professional medical writers should follow ethical publication practices and should openly disclose their involvement in the acknowledgement section[38].
The inclusion of individuals with minimal or no input reflects ''loose authorship" practices[34-39]. Guest, gift or honorary authorship is defined as co-authorship awarded to people who do not meet the authorship criteria and have not contributed substantially to take public responsibility for the work[1]. This may be offered in the belief that the prestige of a scientifically respected person will increase the likelihood of publication or the impact of the work[30]. Oftentimes, a well-known academic senior name is used to conceal ghost authors with industry-related conflicts of interest[30]. Both, the gift-author and the remaining co-authors may benefit from this practice (a win-win situation) that, nevertheless, remains unethical. The increased pressure for publishing among scholars seeking promotion and career advancement (the "publish or perish" culture) may also help to explain these practices. This pressure explains why some researchers accept the 'gift' authorship in papers to which they have not contributed intellectually. This abuse in authorship devalues the merit of being named as an author in a scientific paper. As previously discussed, quantitative contribution helps to prevent granting undeserved credits to guest authors who take away well-deserved credits from the authors who actually did the work[39-42].

Studies suggest that breaches of authorship guidelines are frequent. In a recent survey one-third of authors believed that they had been excluded from deserved authorship and a similar number declared that they had experienced pressures to include undeserved authors in their papers[20]. Another recent study of journals included in the Journals Citation Reports database suggested that 85% of them included in their policy guidance the requirement that authors should be accountable for the research as a whole, 32% explicitly prohibited guest or ghost authorship but only 5% required authors to describe their individual contributions[25].

Final Remarks

Authorship confers credit but also involves responsibility. Authors should be accountable and vouch for the integrity of the entire work. The Editors´ Network of the ESC endorses the ICMJE recommendations on authorship and encourages individual NSCJ to adapt their editorial policies accordingly.

Acknowledgements:

We are grateful for the support and assistance of Michael Alexander and Margot Bolard, from the ESC Publications Department, at the European Heart House.

References

1. The International Committee of Medical Journals Editors.Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Available: http://www.icmje.org/recommendations
2. Lüscher TF. The codex of science: honesty, precision, and truth-and its violations. Eur Heart J 2013;34:1018–1023.
3. Alfonso F, Ambrosio G, Pinto FJ, Ector H, Vardas P, Kulakowski P, Timmis A; Editors' Network ESC Task Force. European Society of Cardiology national cardiovascular journals: the 'Editors' Network'. Eur Heart J. 2010;31:26-8.
4. Mills P, Timmis A, Huber K, Ector H, Lancellotti P, Masic I, Ivanusa M, Antoniades L, Aschermann M, Laucevicius A, Mustonen P, Artigou JY, Vardas P, Stefanadis C, Chiarello M, Bolognese L, Ambrosio G, van der Wall EE, Kułakowski P, Pinto FJ, Apetrei E, Oganov RG, Kamensky G, Lüscher TF, Lerch R, Haouala H, Sansoy V, Shumakov V, Tajer CD, Lau CP, Márquez M, Krittayaphong R, Arai K, Alfonso F. The role of European national journals in education. Heart. 2009;95:e3.
5. Alfonso F, Timmis A, Pinto FJ, Ambrosio G, Ector H, Kulakowski P, Vardas P; Editors' Network European Society of Cardiology Task Force. Conflict of interest policies and disclosure requirements among European Society of Cardiology National Cardiovascular Journals. Eur Heart J. 2012;33:587-94.
6. Alfonso F, Data Sharing. Editors' Network European Society of Cardiology Task Force ; Editors' Network European Society of Cardiology Task Force. Eur Heart J. 2017;38:1361-1363.
7. Council of Science Editors. White Paper on Publication Ethics. CSE's White Paper on Promoting Integrity in Scientific Journal Publications, 2012 Update Available: http://www.CouncilScienceEditors.org.
8. World Association of Medical Editors. WAME Professionalism Code of Conduct The new WAME Professionalism Code of Conduct for medical journal editors. Available: http://www.wame.org.
9. Committee On Publication Ethics. COPE. Code of Conduct and Best Practice Guidelines for Journal Editors. Available: http://publicationethics.org/resources/guidelines.
10. Stephenson J. ICMJE: All authors of medical Journal articles have "responsibility to stand by the integrity of the entire work". JAMA. 2013;310:1216.

11. No author listed. The Lancet. Authorship and accountability. Lancet. 2013;382:744.
12. Goodman NW. Survey of fulfillment of criteria for authorship in published medical research. BMJ. 1994;309:1482.
13. Rennie D, Flanagin A. Authorship! Authorship! Guests, ghosts, grafters, and the two-sided coin. JAMA. 1994;271:469-71.
14. Rennie D, Yank V, Emanuel L. When authorship fails. A proposal to make contributors accountable. JAMA. 1997;278:579-85.
15. Leonelli S. Locating ethics in data science: responsibility and accountability in global and distributed knowledge production systems. Philos Trans A Math Phys Eng Sci. 2016;374(2083).
16. Helgesson G, Eriksson S. Responsibility for scientific misconduct in collaborative papers. Med Health Care Philos. 2018;21:423-430.
17. Stocks A, Simcoe D, Toroser D, DeTora L. Substantial contribution and accountability: best authorship practices for medical writers in biomedical publications. Curr Med Res Opin. 2018;34:1163-1168
18. Clement TP. Authorship matrix: a rational approach to quantify individual contributions and responsibilities in multi-author scientific articles. Sci Eng Ethics 2014;20:345-361.
19. Fairbairn S, Kelly L, Mahar S, Prosée R. Authorship: an evolving concept. Editorial coordinators. Health Learning, Research & Practice, Wolkers and Kluber. Available: http://wkauthorservices.editage.com/resources/files/An_Evolving_Concept_in_Scientific_and_Medical_Publishing.pdf
20. Nylenna M1, Fagerbakk F, Kierulf P. Authorship: attitudes and practice among Norwegian researchers. BMC Med Ethics. 2014;15:53.
21. Hess CW, Brückner C, Kaiser T, Mauron A, Wahli W, Wenzel UJ, Salathé M. Authorship in scientific publications: analysis and recommendations. Swiss Med Wkly. 2015;145:w14108.
22. Hwang SS, Song HH, Baik JH, Jung SL, Park SH, Choi KH, et al. Researcher contributions and fulfillment of ICMJE authorship criteria: analysis of author contribution lists in research articles with multiple authors published in radiology. International Committee of Medical Journal Editors. Radiology. 2003;226:16- 23.
23. Hoen WP, Walvoort HC, Overbeke AJ. What are the factors determining authorship and the order of the authors' names? A study among authors of the Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine). JAMA. 1998;280:217-8.
24. Wager E: Do medical journals provide clear and consistent guidelines on authorship? Med Gen Med 2007;9:16.
25. Resnik DB, Tyler AM, Black JR, Kissling G. Authorship policies of scientific journals. J Med Ethics. 2016;42:199-202.
26. Akhabue E, Lautenbach E. "Equal" contributions and credit: an emerging trend in the characterization of authorship. Ann Epidemiol. 2010;20:868-871.
27. Dotson B. Equal contributions and credit assigned to authors in pharmacy journals. Am J Pharm Educ. 2013;77:39.
28. Li Z, Sun YM, Wu FX, Yang LQ, Lu ZJ, Yu WF. Equal contributions and credit: an emerging trend in the characterization of authorship in major anaesthesia journals during a 10-yr period. PLoS One. 2013;8:e71430.
29. Hess CW, Brückner C, Kaiser T, Mauron A, Wahli W, Wenzel UJ, Salathé M. Authorship in scientific publications: analysis and recommendations. Swiss Med Wkly. 2015;145:w14108.
30. Tarkang EE, Kweku M, Zotor FB. Publication Practices and Responsible Authorship: A Review Article. J Public Health Afr. 2017;8:723.
31. Ioannidis JP. A generalized view of self-citation: direct, co-author, collaborative, and coercive induced self-citation. J Psychosom Res. 2015;78:7-11.
32. Chow DS1, Ha R, Filippi CG. Increased rates of authorship in radiology publications: a bibliometric analysis of 142,576 articles published worldwide by radiologists between 1991 and 2012. AJR Am J Roentgenol. 2015;204:W52-7.
33. Shapiro DW, Wenger NS, Shapiro MF. The contributions of authors to multiauthored biomedical research papers. JAMA. 1994;271:438-42.
34. Flanagin A, Carey LA, Fontanarosa PB, Phillips SG, Pace BP, Lundberg GD, Rennie D: Prevalence of articles with honorary authors and ghost authors in peer-reviewed medical journals. JAMA 1998,280:222–224.
35. Laine C, Mulrow CD: Exorcising ghosts and unwelcome guests. Ann Intern Med 2005, 143:611–612.
36. Wislar JS, Flanagin A, Fontanarosa PB, Deangelis CD: Honorary and ghost authorship in high impact biomedical journals: a cross sectional survey. BMJ 2011;343:d6128.
37. Wislar JS1, Flanagin A, Fontanarosa PB, Deangelis CD. Honorary and ghost authorship in high impact biomedical journals: a cross sectional survey. BMJ. 2011;343:d6128.
38. Stretton S. Systematic review on the primary and secondary reporting of the prevalence of ghostwriting in the medical literature. BMJ Open. 2014;4:e004777.
39. Smith R. Let's simply scrap authorship and move to contributorship. BMJ. 2012;344:e157.
40. Tilak G, Prasad V, Jena AB. Authorship Inflation in Medical Publications. Inquiry. 2015 29;52.
41. Juyal D, Thawani V, Thaledi S, Prakash A. The fruits of authorship. Educ Health (Abingdon). 2014;27:217-20.
42. Fanelli D. Why growing retractions are (mostly) a good sign. PLoS Med. 2013;10:e1001563

Srce i krvni sudovi 2019; 38(2): 107-114

The year in cardiology: cardiovascular prevention

Kausik K. Ray[1], Ulrich Laufs[2], Francesco Cosentino[3], Melvin D. Lobo[4], and Ulf Landmesser[5,6]

[1]Department of Primary Care and Public Health, Imperial Centre for Cardiovascular Disease Prevention, Imperial College London, Reynolds building, St Dunstan's Road, London W68RP, UK; [2]Klinik und Poliklinik für Kardiologie, Universitätsklinikum Leipzig, Liebigstrasse 20, 04103 Leipzig, Germany; [3]Unit of Cardiology, Department of Medicine, Karolinska Institute and Karolinska University Hospital, SE 171 76, Stockholm, Sweden; [4]Department of Clinical Pharmacology, Barts NIHR Biomedical Research Centre, William Harvey Research Institute, QMUL Charterhouse Square, London EC1M 6BQ, UK; [5]Department of Cardiology, Charite University Medicine Berlin, Berlin, Germany; and [6]Berlin Institute of Health (BIH); German Center of Cardiovascular Research (DZHK); Partner Site Berlin, Berlin, Germany

Ovaj tekst je preuzet sa dozvolom ESC i u vidu saradnje urednika nacionalnih kardiovaskularnih časopisa.

Preamble

Advances in genomics, understanding of the effects of cumulative exposure and various environmental risk factors have moved us closer to better models of care focused at early risk assessment and treatment to prevent cardiovascular (CV) disease. We review relevant contributions in 2019 to the field of CV disease prevention, with a focus on epidemiology, lipids, diabetes, and hypertension.

Evolving concepts in prevention

Current concepts for risk assessment for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) are based on assessments of multiple risk factors and global risk when one high-risk condition such as diabetes, genetic dyslipidaemia, or hypertension is absent. These are usually measured at a specific time point and predict short-term risk (10 years) upon which life-long interventions including lifestyle and pharmacotherapy are then based. Advances in genomics may help identify individuals with genetic vulnerability to ASCVD and the recognition of the importance of duration of exposure to risk factors such as low-density lipoprotein (LDL)-cholesterol (LDL-C), blood pressure[1] or number of cigarettes (pack-years) are helping to reshape the paradigm of risk assessment with greater precision (*Take home figure*). These are likely to move the approach of health systems from ones treating disease to ones which aim to preserve health (*Figure 1*). Central to this aim is the move from shortterm risk assessment to lifetime risk and earlier implementation of preventive strategies.[2] In this article, we highlight some of the key scientific observations in the field of prevention in 2019 from risk assessment, epidemiology with an additional focus on lipids, diabetes, and hypertension.

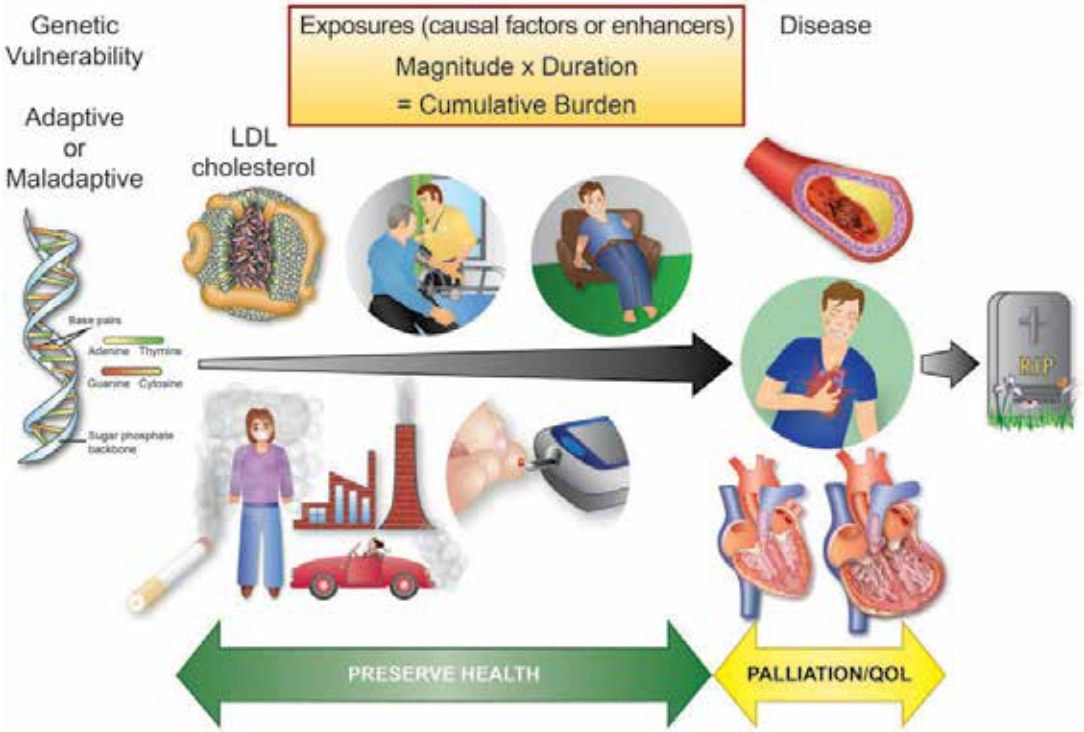
A recurring observation is that conventional risk assessment is imprecise and the addition of information from imaging consistently helps to correctly reclassify individuals. As a result, the use of imaging and in particular coronary artery calcification (CAC) has been shown to be superior to other modalities and is therefore encouraged among those at intermediate risk and the presence of subclinical atherosclerotic disease supports earlier and more targeted CV prevention strategies in the new ESC/EAS and ESC/EASD 2019 guidelines.[3,4] Moreover, absence of CAC may also reclassify risk down and that should be considered in a shared decision environment. Imaging modalities which lend themselves to machine learning such as evaluation of perivascular fat in cardiac computer tomography may well allow imaging to be scaled up, become reproducible and cost-effective as part of the risk assessment tool.[5]

Whilst imaging is clearly important its use is likely to be useful after decades of exposure to risk factors and still provides assessment for shortto intermediate-term risk. Recently, a lifetime-perspective CardioVascular Disease (LIFE-CVD) model for the estimation of treatment-effects of cholesterol-lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people has been developed. This freely accessible on line calculator (www.U-Prevent.com) estimates risk and treatment-effects in terms of improved 10-year risk, lifetime risk, and life-expectancy free of CVD and is designed to facilitate doctor–patient communication.[6]

Largetrialsofpharmacologicalinterventionassessingoutcomesover a time horizon of 50 years will never occur. However, the importance of early and sustained reduction in risk factors notably LDL-C and blood pressure were highlighted in analyses from UK Biobank where a 1 mmol/L lower LDL-C and a 10 mmHg lower blood pressure were associated with an 80% lower risk of CV disease.[1] Put more simply small differences maintained over a long time produce cumulative benefits.[1] Moreover, higher levels of CV risk factors are associated with worse brain health across grey and white matter macrostructure and microstructure in relatively healthy middle and older age individuals suggesting that common risk factor modification could improve a current health burden in late-life namely dementia.[7]

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

* Corresponding author. Tel: þ44 207 594 0716, Email: k.ray@imperial.ac.uk,



Take home figure. Life time trajectory of gene-environment interactions towards cardiovascular disease and death. The figure illustrates the impact of life time exposure to both genetic and life style/environmental causal risk factors that determine the development and clinical course of cardiovascular disease. A better understanding of opportunities for a more effective preservation of health is described in the article that is gaining an increasing attention. QOL, quality of life.

Digital health technology is rapidly advancing and sensors may allow earlier detection of conditions associated with increased CV risk, such as atrial fibrillation (AF).[8] Whilst compelling evidence for their effectiveness is largely lacking, large scale studies have been initiated. The HEARTLIVE study enrolling ~150 000 participants (>65 years of age) is assessing whether earlier detection of AF by a smartwatch sensing technology reduces the risk of CV events. However, there are also concerns that widespread use of such approaches, particularly in the low risk, younger populations using such devices, may lead to unnecessary medical consultations,[9] making an assessment of studies such as HEARTLIVE in appropriate populations important.

Behaviour and environmental factors

Genetics

Considerable amounts of data have emerged from UK Biobank. However data is needed on non-European populations as ~10 000 of the 500 000 cohort are from south Asian or Afrocarribean ancestry.

Behaviour may, in part, have a genetic basis. In a Mendelian randomization analysis from UK Biobank genetic variants known to affect educational attainment were associated with health-conscious lifestyle later in life and which in turn may subsequently affect the risk of coronary artery disease.[10]

Nutrition

Red meat

Data are conflicting with different recommendations regarding red meat consumption. Observational studies suggested potential carcinogenic effects of processed meat.[11] Four systematic reviews on the health effects of red meat and one systematic review on individual health-related values and preferences regarding meat consumption have been published,[12] where the magnitudes of any effect were small. Additionally, these studies report only very low to low certainty for any association of unprocessed or processed red meat intake with CV mortality, diabetes, or cancer. The authors conclude that individuals continue their current consumption of both processed and unprocessed meat, albeit with a weak recommendation because of the low certainty around the evidence.[12] Of note, a recent randomized dietary study suggests that chronic dietary red meat consumption increases systemic levels of trimethylamine N-oxide (TMAO), a microbiome-dependent metabolite, that has been associated with increased CV risk[13] but larger studies are needed.

Carbohydrates

Conflicting data on the role of carbohydrates for ASCVD risk have led to different recommendations. For example, the large Prospective Urban Rural Epidemiology (PURE) study reported that high carbohydrate intake was associated with higher risk of total mortality[14] In contrast, a recent analysis of the National Health and Nutrition Examination Survey (NHANES; 1999–2010) suggests exactly the opposite with low carbohydrate diets associated with excess overall and cause-specific mortality.[15] Nutritional epidemiology carries the risk of confounding by social and economic factors. The underlying causal association (if any) of behaviour, such as 'skipping breakfast', with ASCVD may be unrelated to discussions about

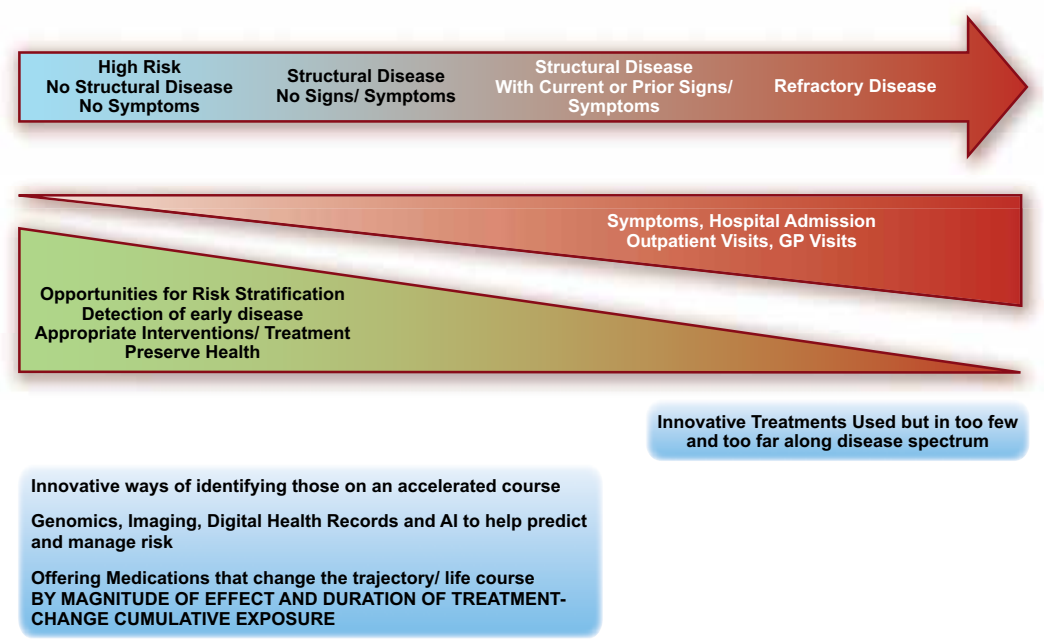


Figure 1. Missed OPPORTUNITIES in reducing the health care burden, improving quality of life, delaying death—exemplar for common conditions. The figure shows potential opportunities for more effective prevention strategies during the course of subclinical and clinical cardiovascular disease development; e.g. atherosclerotic cardiovascular disease develops and progresses over several decades providing numerous opportunities for prevention before clinical manifestations of the disease.

the benefit of fat vs. carbohydrates,[16] therefore, the evidence to support population-level interventions such as increasing the price of high sugar snacks appears incomplete, especially since this would differentially affect low-income individuals.[17] More recently, the totality of the literature of this topic was summarized by a U-shaped relationship between carbohydrate intake and mortality.[18] The authors conclude that 'taking all the studies into account, the message of moderation is perhaps the most convincing one of all —diets that focus too heavily on a single macronutrient, whether extreme protein, carbohydrate, or fat intake, may adversely impact health —the best advice seems to be to select whole foods from a variety of sources and avoid dietary extremism. For now, for carbohydrates, everything in moderation seems to carry the day'.[18]

Body weight

The notion that the effect of any diet on body weight is in turn proportional to risk of ASCVD may be over-simplistic.[19] In the Women's Health Initiative, during a median of 17.9 years of followup, whole body fat mass was not associated with incident ASCVD among normal weight post-menopausal women. Interestingly, the distribution of fat was; with higher trunk fat associated with higher risk of ASCVD, while higher leg fat predicted lower risk.[20] These data suggest an adverse fat distribution and risk can be characterized by increased (unfavourable) abdominal/visceral (trunk) and decreased (beneficial) lower body (leg) fat that is independent of body fat mass. Future research should address potential mechanisms for the development of adverse fat distribution and how it is may be linked to atherosclerosis.[19,20]

Sleep duration

Data from the Prospective Urban Rural Epidemiology (PURE) study on 116 632 with follow-up of 7.8 years that show that estimated total sleep duration of 6–8 h per day is associated with the lowest risk of deaths and major CV events.[21] Interestingly, a neuro-immune axis that links sleep to haematopoiesis and atherosclerosis has been identified and provides a mechanistic rationale for disturbed sleep and increased CV risk.[22]

Smoking

Recent data from the Framingham Heart Study provide quantitative information on the positive health effects of smoking cessation based on >25 years of follow-up showing that quitting within 5 years was associated with 39% lower risk of incident CVD compared with current smokers. Also, among heavy smokers, smoking cessation was associated with lower risk of CVD relative to current smokers.[23] The health effects of e-cigarettes (so-called 'vaping') are still uncertain, recent case reports suggest potential emerging clinical syndromes that are not yet completely understood.[24]

Exercise

Increased physical activity, at any intensity and less time spent sedentary, is associated with substantially reduced risk for premature mortality.[25] However, translation into patient care and individualized training recommendations remain a challenge. A randomized controlled trial showed that endurance and interval training but not resistance training-induced effects on circulating blood cells that are important for cellular senescence and regenerative capacity showing that different training modalities exert differential cellular and vascular effects contributing to vascular health.[26]

Noise, pollution, and workplace

There is increasing awareness of associations between our environment and health. For instance, ambient air pollution has been linked to an excess annual mortality rate of 659 000 in the European Union (EU-28), with the majority attributable to CV causes.[27] Estimates put attributable per capita annual mortality rate in Europe at 133/100 000, but considerable uncertainty around this estimate remain.[27] In this regard, a nationwide cohort study from Switzerland modelled long-term exposure to noise levels as well as environmental pollutants for each address of four million adults.[28] The data suggest that road traffic, aircraft, and railway noise are each associated with excess mortality from myocardial infarction (MI), independent of air pollution. The authors suggest that air pollution studies not adequately adjusting for noise exposure may overestimate the attributable burden of risk from air pollution.[28,29]

Finally, large cohort studies from Sweden and Denmark reveal that 9% reported being bullied at work and 13% recorded exposure to workplace violence during the preceding year. After adjustment, being bullied at work was associated 59% increased risk of ASCVD. The population attributable risk was dose-dependent and overall 5.0% for workplace bullying and 3.1% for workplace violence.[30]

Dyslipidaemia and lipids

Several clinical trial programmes have studied novel treatment options for modification of lipoprotein-related risk of ASCVD that are described below, e.g. new options for lowering LDL-cholesterol and triglyceride-rich lipoproteins. These novel therapeutic approaches will allow a more effective and targeted strategy for management of lipoprotein-related risk in the future (*Figure 2*).

Low-density lipoprotein-cholesterol

ATP citrate lyase is an enzyme in the cholesterol-biosynthesis pathway upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the target of statins. Genetic variants that mimic the effect of ATP citrate lyase inhibitors and statins appeared to lower plasma LDL-cholesterol levels by the same mechanism of action and were associated with similar effects on the risk of CV disease per unit decrease in the LDL-cholesterol level.[31] Bempedoic acid, an inhibitor of ATP citrate lyase, reduced levels of LDL cholesterol by 16.5% when added to maximally tolerated statin therapy,[32] and a clinical outcomes study is ongoing.

Recent data from trials of ezetemibe and PCSK9 monoclonal antibodies demonstrating consistent evidence of benefit with the achievement of lower risk among patients with lower LDL-C levels have now been incorporated into the new ESC/EAS treatment guidelines in 2019 with 55 mg/dL the new goal for very high-risk patients.[3]

Triglyceride-rich lipoproteins

In a genetic study, it was observed that triglyceride-lowering lipoprotein lipase variants and LDL-C-lowering LDL-receptor variants were associated with a similar lower risk of coronary heart disease per unit difference in ApoB, suggesting that the clinical benefit of lipid lowering *per se* is proportional to the absolute change in ApoB.[33] Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowered triglyceride levels, and reduced ischaemic events by 26% in the recent REDUCE-IT trial in patients with elevated triglyceride levels compared to mineral oil.[34] The magnitude of benefit was greater than that expected by ApoB changes alone suggesting mechanisms beyond ApoB lowering.[34,35]

Lipoprotein (a)

A recent analysis of > 65 000 subjects suggested that lipoprotein(a) levels >93 mg/dL (199 nmol/L; 96th–100th percentiles) vs. <10 mg/ dL (18 nmol/L; 1st–50th percentiles) was associated with a 50% excess risk for CV mortality and of 20% for all-cause mortality.[36] The authors hypothesize that elevated lipoprotein(a), (through corresponding low LPA KIV-2 number of repeats) rather than through Lp(a) cholesterol content were the drivers of this excess risk.[36]

Hypertension

Epidemiology

Hypertension is a very important risk factor for CV disease and five decades of trials have demonstrated the benefits of pharmacotherapy in reducing CV morbidity and mortality. However, contemporary data reinforce the need for improvement in hypertension healthcare globally. In 12 high-income countries, data from more than half a million participants indicated greatly improved hypertension awareness, treatment, and control since the 1980s but substantial variations in hypertension prevalence and treatment across countries.[37] Control rates have plateaued in recent decades with rates of treatment coverage ~80% and control ~70% in best performing countries. Conversely, in 44 low-income and middle-income countries, only 40% of those with hypertension were diagnosed, with 30% receiving antihypertensive medication, and 10% controlled with disparity across countries and sub-Saharan Africa performing the worst.[38]

Blood pressure measurement

A study from 1.3 million North American patients has shown that both systolic blood pressure (SBP) and diastolic blood pressure (DBP) independently predicted MI, ischaemic/haemorrhagic stroke with a greater effect of systolic hypertension.[39] Importantly, the relationship between SBP, DBP, and events is independent of treatment threshold (>_ 140/90 vs. >_ 130/80 mmHg) supporting the more proactive management of hypertension in high-risk individuals in recent guidelines.[40–42] The IDACO investigators observed in a study of 11 135 adults, that higher 24-h and night-time SBP were significantly associated with greater risks of death and CV events even after adjusting for other office-based or ambulatory BP measurements,[43] reinforcing recent guidelines, recommending the routine use of ambulatory BP monitoring (ABPM) for BP assessment.

Treatment

Pharmacotherapy

Whilst there have been no developments in novel therapies for hypertension, an increasing focus is use of mul-

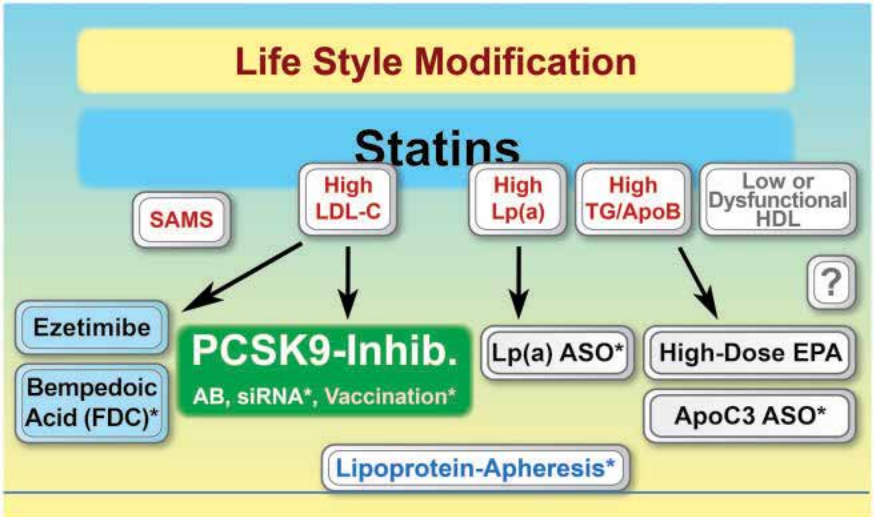


Figure 2. Developments in lipid-targeted therapies. Genetic studies have provided important insights into causal genes and related lipoproteins for development and progression of atherosclerotic vascular disease. Whereas initial management steps will remain life style optimization and statin therapy, a more focused treatment depending on the lipoprotein profile is currently being developed in addition to these treatment options, focusing on low-density lipoprotein-cholesterol-related risk, lipoprotein(a), and triglyceride-rich lipoproteins. *no outcomes data available. AB, antibody; ASO, anti sense oligonuceotide; EPA; eicosapentanoeic acid; FDC, fixed dose combination; SAMS, statin associated muscle symptoms; si, small interfering.

tidrugcombinations, even as an initial step in treatment. Most recently, the WHO added fixed dose combination antihypertensive medications to the Essential Medicines List with the aim of addressing inequalities in treatment and control in low to middle income countries (LMIC).[44] This approach has already demonstrated cost-effectiveness in patients in Sri Lanka with mild-moderate hypertension treated with a triple pill strategy vs. usual care; providing the first economic evaluation of a triple-pill approach.[45]

Evidence is accumulating to support nocturnal dosing of antihypertensive medication, with the Hygia Chronotherapy trial, the first ABPM-based outcome study providing evidence that bed-time dosing of $\geq$ 1 antihypertensive drug, vs. morning, results in better ambulatory BP control lower sleep-time BP and improved nocturnal dipper status.[46] Despite modest differences in BP,[46] there was a disproportionate reduction in CVD morbidity and mortality with bedtime dosing with no safety signal noted. Whether this is real requires independent confirmation.

Device therapy

Endovascular renal denervation (RDN) aims to achieve durable hypertension control through interruption of renal sympathetic nervous system signalling. The open label, single arm Global Symplicity Registry have reported significant and sustained reductions in ambulatory and office BP (-16.5 ± 28.6 and -8.0 ± 20.0 mmHg, respectively) 3 years post-radiofrequency ablation with no safety signal and preserved renal function in 1742 patients.[47] Furthermore, the RADIANCE-HTN SOLO investigators have now shown that the effects of endovascular ultrasound RDN in patients with mildmoderate hypertension are preserved at 6 months with less medication burden compared with sham control.[13,48] It is unclear which, if any, of the technologies to achieve RDN is superior: radiofrequency (RF) vs. ultrasound (US) vs. alcohol chemical ablation. However the RADIOSOUND-HTN investigators have shown in patients with resistant hypertension, endovascular US-based RDN achieved similar BP reduction to RF ablation of the main arteries, accessories, and side branches but was superior to RF ablation of the main renal arteries only.[49] Furthermore, whilst the search for marker of procedural success and predictors of response to RDN is on-going, the SPYRAL HTN-OFF MED investigators have demonstrated that RF RDN in patients with mild-moderate hypertension resulted in significant heart rate reduction compared to sham and that hypertensive patients with higher heart rates may be more likely to respond.[48]

Diabetes

The prevalence of diabetes is increasing, with >425 million already affected globally potentially growing to 629 million by 2045.[4] As diabetes doubles the risk of CVD, the increase in prevalence will increase the population attributable risk disproportionately in lowmiddle income countries where the disposable income and economic growth coupled with sedentary lifestyle are seeing the greatest rise in diabetes prevalence. Novel therapeutic options now offer a chance to move away from prior glucose centric approaches in diabetes care to those aimed at preventing cardio-renal complications as evidenced by the 2019 ESC guidelines on diabetes, prediabetes, and CV diseases developed in collaboration with the European Association for the Study of Diabetes (EASD).[4] A key premise of these is the classification of absolute CV risk as the first step, into *Very high*, *High, and Moderate risk.* Based on the results of recent trials, using both GLP1RAs and SGLT2 inhibitors, in the 2019 guidelines, these drug classes are recommended as first-line therapy in patients with T2DM and established ASCVD or at high/very high CV risk, such as those with target-organ damage or multiple risk factors instead of metformin.[4] Among those already on metformin GLP1-RAs

and SGLT2 inhibitors should be added for CV risk reduction with the aim of moving away from a HbA1c centric approach to one which prevents CV disease.

Notable contributions from several large trials in 2019 include the REWIND trial[50] assessing the effect of once weekly subcutaneous dulaglutide vs. placebo on three-point major adverse cardiac events (MACE) in 9901 patients with T2DM, who had either a previous CV event or multiple risk factors. Over 5.4 years of follow-up, the primary composite outcome occurred in 12.0% of participants in the dulaglutide group and in 13.4% in the placebo group reflecting a significant 12% relative risk reduction. The DECLARE-TIMI 58 trial[51] investigated the effect of dapagliflozin vs. placebo in 17 160 patients with DM and established CVD or multiple risk factors. After 4.2 years of follow-up, the pre-specified criterion for non-inferiority for the composite MACE was met by dapagliflozin compared with placebo. In two primary efficacy analyses, dapagliflozin did not significantly reduce 3P-MACE but resulted in a lower rate of the combined endpoint of CV death or HF hospitalization by 17% (4.9 vs. 5.8% absolute difference). The benefit on heart failure was similar in patients with CVD as well as those with multiple risk factors only. A recent meta-analysis of the SGLT2i trials suggested consistent benefits on reducing the composite of HF hospitalization or CV death, as well as on the progression of kidney disease, regardless of presence of established CVD, while the reduction in MACE was only apparent in ASCVD patients.[52] Previous CVOTs with SGLT2 inhibitors demonstrated renal benefit as a secondary endpoint, but the CREDENCE trial[53] was the first dedicated study assessing renal preservation with SGLT2i in chronic kidney disease and diabetes (estimated glomerular filtration rate 30 to <90 mL/min/1.73 m^2). Individuals randomized to canagliflozin had a relative reduction in the primary renal outcome of 30% compared to placebo. In addition, canagliflozin significantly reduced the prespecified secondary CV outcomes of 3P-MACE by 20% and hospitalization for heart failure by 29% compared with placebo. More recently, there is now compelling evidence that SGLT2 inhibition reduces heart failure in populations with heart failure and reduced ejection fraction equally among those with or without diabetes in the DAPA CHF trial.[54]

Inflammation and thrombosis

The CANTOS trial provided the first evidence that targeting inflammation reduced CV outcomes in those with established disease. Ultimately cost, questions regarding duration of therapy and efficacy vs. safety 'trade off ' with increased infections have not seen the development of IL-1beta antagonism. Targeting inflammation indirectly, with low-cost safe alternatives have been sought with methotrexate showing no benefit. Among patients with a recent MI low-dose colchicine reduced a broad composite CV endpoint including revascularization by 23% (1.6% absolute benefit) in the COLCOT trial.[55] Colchicine use was associated with an absolute excess of 0.8% in diarrhoea (NS) and 0.5% in pneumonia ($P = 0.03$).

Finally, aspirin clearly has net benefit (more CV events voided than significant bleeds caused) in the setting of established CV disease or secondary prevention. However, the observation that in over 100 000 patients in primary prevention trials of aspirin demonstrated an excess of about 2.5 excess major bleeds for each non-fatal MI averted and no mortality benefit over 5 years.[56] As such aspirin is not routinely recommended in the ESC guidelines in the setting of primary prevention.[57]

Summary and conclusions

The present article summarizes important advances in the field of CV prevention in 2019. We have highlighted the increasing role of considering lifetime CV risk for maintaining CV health, as well as the need for risk assessment in patients with established ASCVD or diabetes, for which novel and more targeted preventive therapies have been developed and proven effective.

Acknowledgements

The authors are grateful to Mrs Jennifer Landmann for her editorial support (Imperial College London). K.R. acknowledges support of the NIHR Imperial Biomedical Research Centre. Imperial College London is grateful for support from the NW London NIHR Applied Research Collaboration. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. U.L. acknowledges support from the Leducq Foundation, Berlin Institute of Health, German Center of Cardiovascular Research (DZHK).

Conflict of interest: K.R. reports personal fees from The Medicines Company Aegerion, Astra Zeneca, Cerenis, Akcea, Medicines Company, Kowa, Novartis, Cipla, Lilly, Algorithm, Takeda, Boehringer Ingelheim, Abbvie, Silence Therapeutics, Dr Reddys, Bayer, Daiichi Sankyo, Esperion, Abbvie, Zuelling Pharma, Resverlogix, outside the submitted work; grants and personal fees from Amgen, Sanofi/Regeneron, Pfizer, MSD. F.C. reports personal fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, Merck, Mundipharma, Novo Nordisk, Pfizer; grants from Swedish Research Council VR 2016-02706; Swedish Heart and Lung Foundation 20170717; and Konung Gustav: Vs och Drottning Victorias Frimurarestiftelse. M.D.L. is funded by the Barts Charity and is a consultant to Medtronic, Ablative Solutions, ReCor Medical, Vascular Dynamics, ROX Medical, and Tarilian Laser Technologies and has received speaker fees from CVRx. U.L. reports personal lecture and advisory fees from The Medicines Company, Bayer, Sanofi, Amgen, Berlin Chemie, Abbott, Boston Scientific, and Novartis. U.L. reports personal lecture or advisory fees from Amgen, Bayer, Boehringer, Sanofi, Amgen, and Novartis.

References

1. Ference BA, Bhatt DL, Catapano AL, et all. Association of genetic variants related to combined exposure to lower low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease. JAMA 2019;322:1381.
2. Leistner DM, Landmesser U. Maintaining cardiovascular health in the digital era. Eur Heart J 2019;40:9–12.
3. Mach F, Baigent C, Catapano AL, et all. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2019;doi:10.1093/eurheartj/ehz455.
4. Cosentino F, Grant PJ, Aboyans V, et all. ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019;doi:10.1093/eurheartj/ehz486.
5. Oikonomou EK, Williams MC, Kotanidis CP, et all. A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography. Eur Heart J 2019;doi: 10.1093/eurheartj/ehz592.
6. Jaspers NEM, Blaha MJ, Matsushita K, et all. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessa-

tion in apparently healthy people. Eur Heart J 2019;doi: 10.1093/eurheartj/ehz239.
7. Cox SR, Lyall DM, Ritchie SJ, et all. Associations between vascular risk factors and brain MRI indices in UK Biobank. Eur Heart J 2019;40:2290–2300.
8. Sim I. Mobile devices and health. N Engl J Med 2019;381:956–968.
9. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med 2019;25:44–56.
10. Zeng L, Ntalla I, Kessler T, et all. Genetically modulated educational attainment and coronary disease risk. Eur Heart J 2019; 40:2413–2420.
11. Bouvard V, Loomis D, Guyton KZ, et all. Carcinogenicity of consumption of red and processed meat. Lancet Oncol 2015; 16:1599–1600.
12. Johnston BC, Zeraatkar D, Han MA, et all. Unprocessed red meat and processed meat consumption: dietary guideline recommendations from the Nutritional Recommendations (NutriRECS) Consortium. Ann Intern Med 2019;171:756.
13. Azizi M, Schmieder RE, Mahfoud F, et all. RADIANCEHTN Investigators. Six-month results of treatment-blinded medication titration for hypertension control following randomization to endovascular ultrasound renal denervation or a Sham procedure in the RADIANCE-HTN SOLO trial. Circulation 2019;139:2542.
14. Dehghan M, Mente A, Zhang X, et all. Prospective Urban Rural Epidemiology (PURE) study investigators. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet 2017;390:2050–2062.
15. Mazidi M, Katsiki N, Mikhailidis DP, et all. Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies. Eur Heart J 2019;40:2870–2879.
16. Rong S, Snetselaar LG, Xu G, et all. Association of skipping breakfast with cardiovascular and all-cause mortality. J Am Coll Cardiol 2019;73:2025–2032.
17. Scheelbeek PFD, Cornelsen L, Marteau TM, et all. Potential impact on prevalence of obesity in the UK of a 20% price increase in high sugar snacks: modelling study. BMJ 2019;366:l4786.
18. de Souza RJ, Dehghan M, Anand SS. Low carb or high carb? Everything inmoderation… until further notice. Eur Heart J 2019; 40:2880–2882.
19. Bluher M, Laufs U. New concepts for body shape-related cardiovascular risk: role of fat distribution and adipose tissue function. Eur Heart J 2019;40: 2856–2858.
20. Chen G-C, Arthur R, Iyengar NM, et all. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. Eur Heart J 2019;40:2849–2855.
21. Wang C, Bangdiwala SI, Rangarajan S, et all. Association of estimated sleep duration and naps with mortality and cardiovascular events: a study of 116 632 people from 21 countries. Eur Heart J 2019;40:1620–1629.
22. McAlpine CS, Kiss MG, Rattik S, et all. Sleep modulates haematopoiesis and protects against atherosclerosis. Nature 2019; 566:383–387.
23. Duncan MS, Freiberg MS, Greevy RA Jr, et all. Association of smoking cessation with subsequent risk of cardiovascular disease. JAMA 2019;322:642–650.
24. Layden JE, Ghinai I, Pray I, et all. Pulmonary illness related to ecigarette use in Illinois and Wisconsin—preliminary report. N Engl J Med 2019.
25. Ekelund U, Tarp J, Steene-Johannessen J, et all. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. BMJ 2019;366:l4570.
26. Werner CM, Hecksteden A, Morsch A, et all. Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study. Eur Heart J 2019; 40:34–46.
27. Lelieveld J, Klingmüller K, Pozzer A, et all. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. Eur Heart J 2019;40:1590–1596.
28. Héritier H, Vienneau D, Foraster M, et all. A systematic analysis of mutual effects of transportation noise and air pollution exposure on myocardial infarction mortality: a nationwide cohort study in Switzerland. Eur Heart J 2019;40:598–603.
29. Sorensen M, Pershagen G. Transportation noise linked to cardiovascular disease independent from air pollution. Eur Heart J 2019;40:604–606.
30. Xu T, Magnusson Hanson LL, Lange T, et all. Workplace bullying and workplace violence as risk factors for cardiovascular disease: a multi-cohort study. Eur Heart J 2019;40:1124–1134.
31. Ference BA, Ray KK, Catapano AL, et all. Mendelian randomization study of ACLY and cardiovascular disease. N Engl J Med 2019;380:1033–1042.
32. Ray KK, Bays HE, Catapano AL, et all. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med 2019;380: 1022–1032.
33. Ference BA, Kastelein JJP, Ray KK, et all. Association of triglyceridelowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. JAMA 2019;321:364–373.
34. Bhatt DL, Steg PG, Miller M, et all. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380: 11–22.
35. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J 2019;doi: 10.1093/eurheartj/ehz785.
36. Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. Eur Heart J 2019;40:2760–2770.
37. NCD Risk Factor Collaboration (NCD-RisC). Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. Lancet 2019;394:639–651.
38. Geldsetzer P, Manne-Goehler J, Marcus M-E, et all. The state of hypertension care in 44 low-income and middle-income countries:a cross-sectional study of nationally representative individual-level data from 1.1 million adults. Lancet 2019;394:652–662.
39. Flint AC, Conell C, Ren X, et all. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. NEngl J Med 2019; 381:243–251.
40. Whelton PK, Carey RM, Aronow WS, et all. 2017ACC/AHA/AAPA/ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127–e248.
41. Williams B, Mancia G, Spiering W, et all. ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;313:603–698.
42. Williams B, Mancia G, Spiering W, et all. ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–3104.
43. Yang W-Y, Melgarejo JD, Thijs L, et all. Association of office and ambulatory blood pressure with mortality and cardiovascular outcomes. JAMA 2019;322:409–420.
44. Benjamin IJ, Kreutz R, Olsen MH, et all. Lancet 2019;394:637–638.
45. Lung T, Jan S, de Silva HA, et all. Fixed-combination, low-dose, triple-pill antihypertensive medication versus usual care in patients with mild-to-moderate hypertension in Sri Lanka: a within-trial and modelled economic evaluation of the TRIUMPH trial. Lancet Glob Health 2019;7:e1359–e1366.
46. Hermida RC, Crespo JJ, Domínguez-Sardiña M, et all. Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J 2019;doi: 10.1093/eurheartj/ehz754.
47. Mahfoud F, Böhm M, Schmieder R, et all. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. Eur Heart J 2019; doi: 10.1093/eurheartj/ehz118.
48. Böhm M, Mahfoud F, Townsend RR, et all. Ambulatory heart rate reduction after catheter-based renal denervation in hypertensive patients not receiving anti-hypertensive medications: data from SPYRAL HTN-OFF MED, a randomized, sham-controlled, proof-of-concept trial. Eur Heart J 2019;40:743–751.
49. Fengler K, Rommel K-P, Blazek S, et all. A three-arm randomized trial of different renal denervation devices and techniques in

patients with resistant hypertension (RADIOSOUND-HTN). Circulation 2019;139:590–600.
50. Gerstein HC, Colhoun HM, Dagenais GR, et all. REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019; 394:121–130.
51. Wiviott SD, Raz I, Bonaca MP, et all. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–357.
52. Zelniker TA, Wiviott SD, Raz I, et all. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and metaanalysis of cardiovascular outcome trials. Lancet 2019;393:31–39.
53. Perkovic V, Jardine MJ, Neal B, et all. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380: 2295–2306.
54. McMurray JJV, Solomon SD, Inzucchi SE, et all. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381: 1995–2008.
55. Tardif JC, Kouz S, Waters DD, et all. Efficacy and safetyof low-dose colchicine after myocardial infarction. N Engl J Med 2019.
56. Seshasai SR, Wijesuriya S, Sivakumaran R, et all. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med 2012;172:209–216.
57. Authors/Task Force Members: Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, Bart van der Worp H, van Dis I, Verschuren WMM. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–2381.