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SLIČNOSTI I RAZLIKE KARDIOVASKULARNIH KOMPLIKACIJA COVID-19 INFEKCIJE I COVID-19 VAKCINACIJE

Sažetak: Pacijenti oboleli od COVID-19 infekcije mogu ispoljiti širok spektar kardiovaskularnih komplikacija tokom infekcije: opstruktivnu i neopstruktivnu koronarnu arterijsku bolest – akutni koronarni sindrom (infarkt miokarda tip 1 i tip 2), arterijska ili venska tromboembolijska oboljenja, miokarditis, perikarditis i perikardnu efuziju, stres kardiomiopatiju (Takotsubo sindrom), aritmije, akutnu srčanu insuficijenciju, šok i iznenadnu srčanu smrt, odnosno srčani zastoj (cardiac arrest). Kardiovaskularne komplikacije koje se mogu ispoljiti nakon COVID-19 vakcinacije su: miokarditis, perikarditis, tromboembolijski događaji, hipertenzija, akutni koronarni sindrom, stres kardiomiopatija, aritmije i srčani zastoj. Miokarditis i perikarditis su se u 3/4 svih slučajeva javili nakon druge doze mRNA vakcine protiv SARS-COV2 virusa i većinom kod mlađih odraslih. Vakcinom indukovana imuna trombotička trombocitopenija (VITT) je retko stanje koje se javlja nakon vakcinacije protiv SARS-COV2 sa većom prevalencom kod mlađih žena (mlađih od 50 godina). Incidenca akutnog infarkta miokarda je 0,02% i 0,03% zavisno od tipa mRNA vakcina (Pfizer ili Moderna), češće se javlja kod osoba muškog pola i starijih, sa pojavom simptoma najčešće do 24h nakon aplikacije vakcine. Najčešće aritmije koje se javljaju nakon COVID-19 vakcinacije su sinusna tahikardija, atrijalna fibrilacija i supraventrikularna tahikardija. Odnos korist–rizik COVID-19 vakcinacije na pojavu kardiovaskularnih komplikacija snažno preovladava u korist vakcina za sve starosne grupe (stariji od 12 godina) i za oba pola.

Ključne reči: COVID-19, COVID-19 vakcinacija, kardiovaskularne komplikacije, miokarditis, perikarditis, infarkt miokarda, tromboza, aritmije

Pacijenti oboleli od COVID-19 infekcije mogu ispoljiti širok spektar kardiovaskularnih komplikacija tokom infekcije: opstruktivnu i neopstruktivnu koronarnu

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arterijsku bolest – akutni koronarni sindrom (infarkt miokarda tip 1 i tip 2), arterijska ili venska tromboembolijska oboljenja, miokarditis, perikarditis i perikardnu efuziju, stres kardiomiopatiju (Takotsubo sindrom), aritmije, akutnu srčanu insuficijenciju, šok i iznenadnu srčanu smrt, odnosno srčani zastoj (cardiac arrest) (1).

Postoji više mehanizama kojima se mogu objasniti kardiovaskularne komplikacije tokom COVID-19 infekcije. Endotelna disfunkcija se može posmatrati karakterističnom patološkom lezijom uzrokovanom SARS-COV2 virusom koji se vezuje za ACE-2 receptore na ćelijskim membranama i dovodi do direktnog oštećenja pluća, srca i krvnih sudova. Ulaskom u ćelije domaćina SARS-COV2 virus započinje generalizovani inflamatorni odgovor koji putem više mehanizama narušava homeostazu i imunološki odbrambeni sistem domaćina (2).

Mehanizmi koji mogu dovesti do kardijalnog oštećenja obuhvataju: imunu aktivaciju posredovanu citokinima, direktni kardiotoksični efekti, mikro i makrovaskularna disfunkcija i hiperkoagulabilnost. Ovi mehanizmi mogu dovesti do destabilizacije koronarnog plaka, vazospazma, tromboembolijskih događaja, hipoksičnih lezija koje mogu dovesti do infarkta miokarda tipa 2, kateholaminima indukovane kardiomiopatije, aritmija i miokarditisa. Tokom težih oblika infekcije dolazi i do hemodinamskih poremećaja. Teža pulmonalna infekcija povećava pulmonalne pritiske i opterećenje desne komore (afterload), što dovodi do dilatacije desne komore i povećanja end-dijastolnog volumena, smanjenja preloada u levu komoru, a smanjena kontraktilnost leve komore (hipoksija, inflamacija, koronarni spazam ili miokarditis) dovodi do smanjenja udarnog i minutnog volumena i hipotenzije. Teža inflamacija uzrokuje vazoplegiju (smanjenje sistemske vaskularne rezistencije, povećanje kapilarne permeabilnosti), što dovodi do hipotenzije i razvoja edema. Smanjenje kardijalnog outputa kombinovanog sa hipotenzijom i patološkom aktivacijom renin-angiotenzin-aldosteron sistema (RAAS) može dovesti do smanjenja perfuzije organa i njihovog oštećenja i razvoja cirkulatornog šoka (3).

KARDIOVASKULARNE KOMPLIKACIJE COVID-19 INFEKCIJE

Najčešća kardiovaskularna komplikacija COVID-19 infekcije je akutno miokardno oštećenje, koje se definiše povećanjem kardijalnog troponina > 99-og percentila. Povećanje tropoanina se pojavljuje kod 22% hospitalizovanih pacijenata sa COVID-19 infekcijom, što je značajno više u odnosu na hospitalizovane pacijente od drugih respiratornih infekcija (4). Miokardno oštećenje nije klinička dijagnoza za sebe, ali povećane vrednosti troponina su povezane sa lošijom prognozom i većim mortalitetom obolelih. Preporučuje se merenje troponina kod svih hospitalizovanih pacijenata radi stratifikacije rizika, a potom na svakih 48h kod visokorizičnih pacijenata (5).

Dijagnoza miokarditisa se uspostavlja na osnovu simptoma, elektrokardiograma (ECG), povećanja troponina i „imidžinga“ (ehokardiografija i/ili kardijalna magnetna

rezonanca). Koronarno oboljenje bi trebalo isključiti kod svih pacijenata sa suspektnim miokarditisom, a endomiokardna biopsija (EMB) predstavlja klasu I preporuka za dijagnozu perzistentne teške srčane insuficijencije i fulminantnog miokarditisa. Najčešći simptomi su groznica, dispnea i bol u grudima, što se može preklapati sa simptomima drugih oboljenja, što otežava dijagnozu. EKG promene se prezentuju ST-T promenama (ST elevacija, negativni T talasi) i/ili poremećajima ritma. Kod težih oblika miokarditisa ehokardiografski se registruje disfunkcija leve komore (smanjenje ejekcione frakcije), kao i regionalna hipokinezija/akinezija. Disfunkcija leve komore prati teže oblike COVID-19 oboljenja i smatra se da je prevalenca miokarditisa značajno veća nego što je registrovana, posebno kod težih oblika COVID-19 infekcije, a simptomi mogu perzistirati i nekoliko nedelja nakon preležane infekcije. COVID-19 miokarditis najverovatnije nastaje aktiviranjem T ćelija i makrofaga koji infiltriraju miokard i/ili direktnim oštećenjem kardiomiocita SARS-COV2 virusima, posebno kod fulminantnih formi miokarditisa (6, 7).

Izolovani perikarditis retko se registruje u korelaciji sa COVID-19 infekcijom, ali su perikardna efuzija i pridruženi mioperikarditis registrovani u oko 50% slučajeva miokarditisa registrovanih u okviru infekcije. Mehanizmi koji dovode do perikardne efuzije su povezani sa direktnim miokardnim i perikardnim oštećenjem SARS-COV2 virusima, inflamacijom tokom razvoja ARDS-a i „citokinskom olujom". Izolovani perikarditis se manifestuje bolom u grudima i ima najčešće benigni tok. Perikardna efuzija može komplikovati kliničku sliku infekcije i produžiti period kliničkog oporavka. Nema jasnog vodiča za tretman perikardnog izliva u okviru COVID-19 infekcije, ali na osnovu više kliničkih studija u terapiji se može koristiti colchicine, kortikosteroidi i NSAIL. Kod velikih izliva i pacijenata koji su hemodinamski nestabilni indikovana je hitna drenaža (perikardiocenteza ili hirurškim putem) (8, 9).

Multiple kohortne studije su pokazale da COVID-19 infekcija može biti okidač za razvoj akutnog koronarnog sindroma (AKS). Pacijenti sa COVID-19 infekcijom imaju 3,4 puta veći rizik za razvoj akutnog koronarnog sindroma tokom prve 2 nedelje od pojave simptoma. Akutni infarkt miokarda (AIM) može se javiti kao inicijalna prezentacija COVID-19 infekcije ili komplikovati njen klinički tok. Jedna danska studija, koja je obuhvatila 5.119 pacijenata sa COVID-19 infekcijom, pokazala je da je incidenca za razvoj AIM pet puta veća tokom 14 dana nakon uspostavljene dijagnoze COVID-19 oboljenja (10). Druga studija u Švedskoj, koja je analizirala 86.742 pacijenta sa simptomima COVID-19 infekcije, pokazala je da je incidenca za razvoj AIM 2,9 puta veća tokom prve nedelje nakon pojave simptoma infekcije (11). Infekcija i posledična inflamacija mogu započeti koronarnu trombozu putem multiplih mehanizama: infiltracija inflamatornim ćelijama aterosklerotičnog plaka (nestabilnost i ruptura plaka), sistemska aktivacija trombocita, koronarna vazokonstrikcija i endotelna disfunkcija. Klinička prezentacija akutnog koronarnog sindroma kod COVID-19 pacijenata može biti: AIM sa ST elevacijom (AIM tip 1), AIM sa

neopstruktivnim koronarnim arterijama (MINOCA), AIM tipa 2 (zbog neusklađenosti između snabdevanja miokarda kiseonikom i zahteva miokarda, a bez opstrukcije koronarne cirkulacije). Na osnovu angiografskih nalaza, nekoliko studija je pokazalo visoku prevalencu neopstruktivne koronarne bolesti kod pacijenata sa COVID-19 infekcijom – od 33% do 44% od onih koji su imali koronarografiju zbog suspektnog AIM sa ST elevacijom. Terapija AKS trebalo bi da se sprovodi po važećim ESC preporukama za lečenje AKS sa ST elevacijom i bez ST elevacije (12).

Venske tromboze su česta komplikacija COVID-19 infekcije sa incidencom od 7,4% (13). Hipoksija i imobilizacija predstavljaju glavne etiološke faktore razvoja venskog tromboembolizma (VTE). SARS-COV2 preko ACE2 receptora oštećuje vaskularni endotel i započinje endotelnu inflamaciju i izloženost von Willebrandovom faktoru (vWF) koji ima značajnu ulogu u adheziji i agregaciji trombocita, što doprinosi razvoju tromboze. Neutrofili aktivirani virusom preko ACE2 receptora oslobađaju medijator zapaljenja (NETs), koji je ključni medijator imunotromboze i preko aktivacije faktora XII započinje se koagulaciona kaskada (14).

Plućni embolizam (PE) predstavlja najtežu tromboembolijsku komplikaciju. Procenjuje se da je sveukupna incidenca PE kod COVID-19 pacijenata između 1,1% i 3,4%, sa porastom na 17% do 27% kod težih formi infekcije. Na autopsijskim studijama, plućna embolija (PE) je bila direktan uzrok smrti kod 33% COVID-19 pacijenata (15). Duboke venske tromboze (DVT) predstavljaju jedan od glavnih uzročnika PE, ali i in situ tromboze mikro i makrovaskularne plućne cirkulacije predstavljaju značajan uzročnik plućnih embolija kod COVID-19 pacijenata. Više retrospektivnih studija je pokazalo da rana primena profilaktičkih doza niskomolekularnih heparina (LMWH) kod svih hospitalizovanih pacijenata sa COVID-19 infekcijom bez kontraindikacija za primenu LMWH smanjuje mortalitet za 34%, a bez povećanog rizika od krvarenja (16).

Kardijalne aritmije se javljaju kod 17% pacijenata sa COVID-19 infekcijom, a kod 50% pacijenata smeštenih u jedinice intenzivne nege. COVID-19 infekcija predstavlja 3,83 puta veći rizik za razvoj aritmija. Aritmije se javljaju dva puta češće kod pacijenata sa povećanim troponinom u serumu. Pojava aritmija predstavlja jedan od najznačajnijih rizika lošije prognoze i povećane incidence intrahospitalne smrti. Aritmije variraju od bradiaritmija (ređe se javljaju), preko sinusne tahikardije i atrijalnih artimija, od kojih je najčešća atrijalna fibrilacija (81,8% svih aritmija kod hospitalizovanih COVID-19 pacijenata). Povećan nivo troponina kod pacijenata sa postojećim kardiovaskularnim oboljenjem i COVID-19 infekcijom se javlja kod 54,5% hospitalizovanih i predstavlja dodatni rizik za pojavu malignih aritmija, kao što je ventrikularna tahikardija (VT) i ventrikularna fibrilacija (VF), što može dovesti i do iznenadne srčane smrti i srčanog zastoja – 11,5% pacijenata sa prethodnim kardiovaskularnim oboljenjem razvija maligne aritmije, a 5,2% bez kardiovaskularnog oboljenja. Direktno miokardno oštećenje (ishemija i miokarditis), sistemska inflamacija –„citokinska oluja“, respiratorna insuficijencija, elektrolitni disbalans, hiperaktivnost

adrenergičkog sistema (povećani nivoi kateholamina), hiperkoagulabilno stanje i primena lekova koji produžavaju QT interval (hlorokin, azitromicin) predstavljaju okidače i faktore rizika za razvoj aritmija (17).

Srčana insuficijencija (SI) se češće razvija tokom COVID-19 infekcije kod starijih pacijenata sa komorbiditetima: ishemijsko oboljenje srca, hipertenzija i dijabetes i razvoj SI tokom infekcije udruženo je sa lošijom prognozom. Visoki nivoi NT-pro BNP i BNP-a tokom razvoja srčane insuficijencije su povezani sa većim mortalitetom COVID-19 oboljenja (18).

Stres kardiomiopatija ili Takotsubo sindrom se retko javlja kao komplikacija COVID-19 infekcije. Oba pola su jednako zahvaćena, a prosečne godine života su 57 (19). Većina pacijenata ima redukovanu ejekcionu frakciju uz normalni koronarni angiogram i reverzibilnu ventrikularnu disfunkciju sa većom smrtnošću u odnosu na stres kardiomiopatije koje nisu udružene sa infekcijom i češće su kod postmenopauzalnih žena. Mogući mehanizmi koji uzrokuju stres kardiomiopatiju su visoki nivoi cirkulišućih kateholamina, direktna citotoksičnost i prenaglašen imuni odgovor (20).

Muškarci oboleli od COVID-19 infekcije imaju veći rizik od žena za teže forme infekcije. Većina pacijenata sa AIM sa ST elevacijom (STEMI) tokom COVID-19 infekcije su muškarci i koronarografijom potvrđenom koronarnom opstrukcijom, dok se kod žena AKS manifestuje neopstruktivnom koronarnom bolešću (MINOCA) ili mikrovaskularnom disfunkcijom. Povećani nivoi ACE2 receptora na kardiomiocitima kod muškarca mogu uticati na lakši ulazak virusa u kardiomiocite, veću virulenciju i veću zastupljenost kardijalnih komplikacija kod muškaraca, uključujući i akutne forme virusnog miokarditisa. Uticaj 17-beta estradiola na T-ćelijski fenotip i funkciju dovodi do značajne razlike u smanjenju redukcije hiperinflamatornog odgovora kod muškaraca, što dovodi i do težeg kliničkog ishoda COVID-19 infekcije. Povećani nivoi D-dimera kod muškaraca više nego kod žena predstavljaju nezavisni prediktor prijema u jedinice intenzivne nege, invazivne mehaničke ventilacije i intrahospitalne smrti (21).

KARDIOVASKULARNE KOMPLIKACIJE NAKON COVID-19 VAKCINACIJE

Kardiovaskularne komplikacije koje se mogu ispoljiti nakon COVID-19 vakcinacije su: miokarditis, perikarditis, tromboembolijski događaji, hipertenzija, akutni koronarni sindrom, stres kardiomiopatija, aritmije i srčani zastoj (22).

Miokarditis i perikarditis su se u 3/4 svih slučajeva javili nakon druge doze mRNA vakcine protiv SARS-COV2 virusa i većinom kod mlađih odraslih. Incidenca mioperikarditisa je prosečno 12,6 slučajeva mioperikarditisa na million doza od druge doze mRNA vakcine životnog doba 12–39 godina, bez prethodne istorije o preležanoj COVID-19 infekciji ili komorbiditetima, sa predominacijom kod muškaraca (79%). Prosečna životna dob za pojavu miokarditisa kod oba pola je bila 24 godine, a kod perikarditisa 24 godine za muškarce a 54 godine za žene. Ređa pojava miokarditisa

kod osoba ženskog pola može se objasniti inhibitornom ulogom estrogena na proinflamatorne T ćelije (23). Pojava miokarditisa kod obolelih od COVID-19 se javlja prosečno kod 11 osoba na 100.000 obolelih, a pojava miokarditisa nakon druge doze mRNA vakcine je 1–5/100.000 osoba, a kod muškaraca od 16-30 godina prevalenca miokarditisa je 5 puta češća (1/20000). Najčešća prezentacija mioperikarditisa je pojava bola u grudima i groznice u periodu od 7 dana (najčešće dva do tri dana) od druge doze mRNA vaccine, udružena sa povišenim troponinom i CRP-om, ST elevacijom na EKG-u i kardijalnom magnetnom rezonancom (CMR) koja ukazuje na miokarditis. Mehanizam nastanka ovih komplikacija nije sasvim jasan, ali molekularna mimikrija može biti potencijalni mehanizam. Antitela na SARS-COV2 "spike" protein ukršteno reaguju sa sličnim sekvencama proteina srca uključujući alfa-miozin (autoimuna reakcija) i dovode do aktivacije imunoloških puteva i disregulacije ekspresije citokina. U nekim slučajevima miokardni mikrotrombi bez infiltracije inflamatornim ćelijama mogli bi biti mogući mehanizam. Lipidne nanopartikule i drugi adjuvansi koji su u sastavu mRNA vakcine ne utiču na imuni i inflamatorni odgovor (24). U većini slučajeva mioperikarditisi imaju benigni tok nezavisno od terapije (povlačenje simptoma i znakova i normalizacija dijagnostičkih markera), a hospitalizuju se pacijenti sa miokardnim oštećenjem, aritmijama ili hemodinamskom nestabilnošću. U nekoliko slučajeva kod patohistološki potvrđenog miokarditisa koji se razvio tokom 2 nedelje nakon COVID-19 mRNA vakcine tok je bio fulminantan i završio se letalno. Sadašnje preporuke savetuju odlaganje druge doze mRNA vakcine u slučaju pojave mioperikarditisa nakon prve doze, uz moguće razmatranje aplikacije druge doze vakcine nakon potpune rezolucije simptoma (25).

Vakcinom indukovana imuna trombotička trombocitopenija (VITT) je retko stanje koje se javlja nakon vakcinacije protiv SARS-COV2, posebno nakon aplikacije adenovirusne vektorske vakcine AstraZeneca i Janssen/Johnson&Johnson vakcine. VITT ima nisku incidencu (1/100.000–150.000), sa većom prevalencom kod mlađih žena (mlađih od 50 godina) i pojavom simptoma 4-28 dana nakon vakcinacije (najčešće 8–10. dana) i može imati letalni ishod – stopa mortaliteta je 20–30% (26). VITT se javlja kod osoba bez prethodno poznate predispozicije i poznatih faktora rizika za trombozu, a karakteriše se stvaranjem imunih kompleksa koji se sastoje od antitela usmerenih na trombocitni faktor 4 (PF4), što dovodi do aktivacije trombocita, njihove agregacije i stvaranja tromba – po mehanizmu, kliničkoj slici i biohemijskim parametrima stanje slično heparinom indukovanoj trombocitopeniji (HIT). VITT se najčešće klinički prezentuje trombozom cerebralnih venskih sinusa, ali se često mogu javiti i splanhničke venske tromboze, duboke venske tromboze (DVT), plućne embolije (PE) i arterijske tromboze (27). Tretman tromboza u okviru VITT stanja sastoji se u primeni intravenskih imunoglobulina (IVIG) – 1g/kg tokom 2 dana, primeni kortikosteroida i neheparinskih antikoagulanasa (fondaparinux, argatroban) (28).

Akutni infarkt miokarda (AIM) predstavlja retku, ali potencijalno visoko letalnu komplikaciju nakon primene COVID-19 vakcina. Incidenca AIM je 0,02% i 0,03% zavisno od tipa mRNA vakcina (Pfizer ili Moderna), češće se javlja kod osoba muškog pola i starijih, sa pojavom simptoma najčešće do 24h nakon aplikacije vakcine (češće nakon druge doze vakcine). Za sada su nejasni mehanizmi koji dovode do razvoja infarkta miokarda nakon aplikacije vakcine. Slični mehanizmi koji dovode do vakcinom indukovane tromboze (VITT) mogli bi objasniti većinu slučajeva AIM (29). Kounis sindrom, koji predstavlja alergijsku ili anafilaktičku reakciju na vakcinu, mogao bi biti jedan od mehanizama razvoja AIM – putem različitih mehanizama kao što je alergijski vazospazam i okluzija krvnog suda sa stvaranjem tromba koji je infiltrovan eozinofilima i/ili mast ćelijama. Stres tokom primene vakcine kod starijih osoba sa pridruženim komorbiditetima može dovesti do ishemije i razvoja AIM tipa 2 (nesklad između snabdevanja kiseonikom i zahteva miokarda). Pacijenti kojima je nakon ispoljavanja kliničke slike AIM i potvrde dijagnoze urađena koronarna angiografija (primarna PCI) imali su u 60% slučajeva kulprit leziju na prednjoj desendentnoj arteriji (LAD) (30).

Stres kardiomiopatija (Takotsubo sindrom) je retka komplikacija nakon primene COVID-19 vakcine uz medijanu ispoljavanja jedan do tri dana nakon aplikacije prve ili druge doze vakcine, sa većom incidencom kod osoba ženskog pola (31). Manifestuje se bolom u grudima, neopstruktivnim koronarnim angiogramom uz znake ST elevacije na EKG-u i apikalne hipokinezije na ehokardiografiji. Faktori rizika za razvoj stres kardiomiopatije su pol, životna dob, anksioznost povezana sa aplikacijom vakcine i vrsta vakcine (32).

Najčešće aritmije koje se javljaju nakon COVID-19 vakcinacije su sinusna tahikardija, atrijalna fibrilacija i supraventrikularna tahikardija. Klinički se najčešće manifestuju palpitacijama. Nejasno je da li su aritmije povezane sa COVID-19 vakcinacijom ili prisutnim komorbiditetima i koencidencijom vremena pojave aritmija nakon aplikacije vakcina. Prevalenca palpitacija nakon vakcinacije je 0,006%, a prevalenca atrijalne fibrilacije je 0,0009% (22). Zabeleženo je nekoliko slučajeva posturalne ortostatske tahikardije koja se javila kod zdravih pacijenata tokom narednih 6 dana od prve doze Pfizer vakcine. Mogući mehanizam nastanka je autoimuna reakcija na adrenergičke receptore u kardiovaskularnom sistemu koji dovode do oštećene vazokonstrikcije koja uzrokuje posturalnu tahikardiju (33).

Hipertenzivna reakcija nakon COVID-19 vakcinacije predstavlja 5,82% svih kardiovaskularnih komplikacija vakcinacije (22). Od svih slučajeva hipertenzivnih reakcija, incidenca hipertenzivnih kriza je 1,3%, a 0,8% je incidenca epizoda "hypertensive urgency". Hipertenzija nakon aplikacije vakcina se javlja kod oba pola i u svim starosnim grupama, a prosečna starosna dob je 73 godine. Stres i efekat „belog mantila" su doprinoseći faktori u ispoljavanju hipertenzije uz postojeće komorbiditete (34).

Zaključci

COVID-19 vakcinacija ne prevenira samo hospitalizaciju i smanjuje mortalitet COVID-19 infekcije, već smanjuje i komplikacije nastale tokom i nakon infekcije. Rizik za pojavu miokarditisa nakon COVID-19 vakcinacije je 3,24 puta veći tokom 42 dana od prve doze Pfizer-BioNTech mRNA vakcine u kontrastu sa pojavom miokarditisa tokom COVID-19 infekcije gde je rizik 18,28 puta veći u odnosu na populaciju svih starosnih grupa. Pacijenti sa miokarditisom nakon mRNA vakcine imali su kratko vreme hospitalizacije (3–5 dana) i oporavak srčane funkcije tokom 1–5 nedelja nakon inicijalne hospitalizacije (35). COVID-19 vakcinacija značajno redukuje rizik od razvoja tromboza, aritmija i akutne bubrežne insuficijencije tokom SARS-COV2 infekcije i smanjuje rizik od razvoja miokardnog oštećenja i miokarditisa za 1.000 puta u svim starosnim grupama, sa nešto većim rizikom razvoja blažih formi miokarditisa (1–5 puta veći rizik) kod mlađih odraslih osoba. Prevalenca tromboza kod COVID-19 pacijenata je 22%, sa porastom incidence na 43% nakon prijema u jedinice intenzivne nege, dok je incidenca trombotičnih događaja nakon COVID-19 vakcinacije mala (manja od 0,001%) (36).

Većina ljudi starijeg životnog doba koji su primili vakcinu imaju komorbiditete i očekivano je da imaju kardivaskularne događaje kao što je infarkt miokarda, hipertenzija i poremećaji ritma i verovatno neki od kardiovaskularnih događaja nakon aplikacije COVID-19 vakcine se javljaju nezavisno od vakcine, ali se prikazuju kao neželjeni efekti vakcine.

Odnos korist–rizik COVID-19 vakcinacije na pojavu kardiovaskularnih komplikacija snažno preovladava u korist vakcina za sve starosne grupe (stariji od 12 godina) i za oba pola.

Ne postoji sukob interesa.

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SIMILARITIES AND DIFFERENCES OF CARDIOVASCULAR COMPLICATIONS OF COVID-19 INFECTION AND COVID-19 VACCINATION

Summary: COVID-19 patients may experience with a wide range of cardiovascular complications during infection: obstructive and non-obstructive coronary artery disease-acute coronary syndrome (myocardial infarction type 1 and type 2), arterial or venous thromboembolic diseases, myocarditis, pericarditis, pericardial effusion, stress cardiomyopathy (Takotsubo syndrome), arrhythmias, acute heart failure, shock and sudden cardiac death (cardiac arrest). Cardiovascular complications that may occur after COVID-19 vaccination are: myocarditis, pericarditis, thromboembolic events, hypertension, acute coronary syndrome, stress cardiomyopathy, arrhythmias and cardiac arrest. Myocarditis and pericarditis occurred in 3/4 of all cases after the second dose of mRNA vaccine against SARS-COV2 virus, most often in young adults. Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare condition that occurs after vaccination against SARS-COV2, more prevalently in young women (under 50 years of age). The incidence of acute myocardial infarction is 0.02% and 0.03% depending on the type of mRNA vaccine (Pfizer or Moderna), more common in males and the elderly, with symptoms onset the most frequently up to 24 hours after vaccine application. The most common arrhythmias that occur after COVID-19 vaccination are sinus tachycardia, atrial fibrillation, and supraventricular tachycardia. The benefit-risk ratio of COVID-19 vaccination to the occurrence of cardiovascular complications strongly prevails in favor of vaccines for all age groups (older than 12 years) and for both sexes.

Key words: COVID-19, COVID-19 vaccination, cardiovascular complications, myocarditis, pericarditis, myocardial infarction, thrombosis, arrhythmias.

COVID-19 patients may experience with a wide range of cardiovascular complications during infection: obstructive and non-obstructive coronary artery disease-acute coronary syndrome (myocardial infarction type 1 and type 2), arterial or

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venous thromboembolic diseases, myocarditis, pericarditis, pericardial effusion, stress cardiomyopathy (Takotsubo syndrome), arrhythmias, acute heart failure, shock and sudden cardiac death (cardiac arrest) (1).

There are several mechanisms that can explain cardiovascular complications during COVID-19 infection. Endothelial dysfunction can be observed as a characteristic pathological lesion caused by the SARS-COV2 virus, which binds to ACE-2 receptors on cell membranes and leads to direct injury of the lungs, heart and blood vessels. By entering the host cells, the SARS-COV-2 virus triggers a generalized inflammatory response that disrupts homeostasis and the host's immune defense system through multiple mechanisms (2).

Mechanisms that can lead to cardiac injury include: cytokine-mediated immune activation, direct cardio-toxic effects, micro and macro vascular dysfunction, and hypercoagulability. These mechanisms can lead to coronary plaque destabilization, vasospasm, thromboembolic events, hypoxic lesions that can lead to type 2 myocardial infarction, catecholamines-induced cardiomyopathy, arrhythmias, and myocarditis. During severe forms of infection, hemodynamic disorders also occur. Severe pulmonary infection increases pulmonary pressures and right ventricular load (afterload), leading to the right ventricular dilatation and increased end-diastolic volume, decreased left ventricular preload, and decreased left ventricular contractility (hypoxia, inflammation, coronary spasm, or myocarditis), leads to a decrease in stroke and minute volume and hypotension. Severe inflammation causes vasoplegia (decrease in systemic vascular resistance, increase in capillary permeability), which leads to hypotension and the development of edema. Decreased cardiac output combined with hypotension and pathological activation of the renin-angiotensin-aldosterone system (RAAS) can lead to decreased perfusion of organs, their damage and the development of circulatory shock (3).

CARDIOVASCULAR COMPLICATIONS OF COVID-19 INFECTION

The most common cardiovascular complication of COVID-19 infection is acute myocardial injury, defined by an increase in cardiac troponin > 99th percentile. Troponin elevation occurs in 22% of hospitalized patients with COVID-19 infection, which is significantly higher than in hospitalized patients than other respiratory infections (4). Myocardial injury is not a clinical diagnosis per se, but increased troponin values are associated with a worse prognosis and higher mortality. It is recommended to measure troponin at baseline for all hospitalized patients for risk stratification, and then every 48 hours in high risk patients (5).

The diagnosis of myocarditis is made on the basis of symptoms, electrocardiogram (ECG), troponin elevation and imaging (echocardiography and cardiac magnetic resonance). Coronary disease should be excluded in all patients with suspected

myocarditis, and endomyocardial biopsy (EMB) is a class I recommendations for diagnosis of persistent severe heart failure and fulminant myocarditis. The most common symptoms are fever, dyspnea and chest pain, which may overlap with the symptoms of other diseases and complicate the diagnostic process. ECG changes are represented by ST-T changes (ST elevation, negative T waves) and /or arrhythmias. In severe forms of myocarditis, left ventricular dysfunction (reduction of the ejection fraction), as well as regional hypokinesia/akinesia are registered by echocardiography. Left ventricular dysfunction accompanies more severe forms of COVID-19 disease and the prevalence of myocarditis is thought to be significantly higher than registered, especially in more severe forms of COVID-19 infection, and symptoms may persist for several weeks after infection. COVID-19 myocarditis is most likely caused by activation of T cells and macrophages that infiltrate the myocardium and / or direct injury to cardiomyocytes by SARS-COV2 viruses, especially in fulminant forms of myocarditis (6,7).

Isolated pericarditis is rarely registered in correlation with COVID-19 infection, but pericardial effusion and associated myopericarditis have been reported in about 50% of cases of myocarditis registered within the infection. The mechanisms leading to pericardial effusion are associated with direct myocardial and pericardial injury by SARS-COV2 viruses, inflammation during ARDS development, and "cytokine storm". Isolated pericarditis is manifested by chest pain and usually has a benign course. Pericardial effusion can complicate the clinical presentation of infection and prolong the period of clinical recovery. There is no clear guide to the treatment of pericardial effusion within COVID-19 infection, but colchicine, corticosteroids and NSAIDs may be used in therapy based on several clinical studies. In large effusions and patients who are hemodynamically unstable, emergency drainage is indicated (pericardiocentesis or surgery) (8,9).

Multiple cohort studies have shown that COVID-19 infection may be a trigger for the development of acute coronary syndrome (ACS). Patients with COVID-19 infection have a 3.4 times higher risk of developing acute coronary syndrome during the first 2 weeks after the onset of symptoms. Acute myocardial infarction (AIM) may occur as an initial presentation of COVID-19 infection or complicate its clinical course. A Danish study of 5119 patients with COVID-19 infection found that the incidence of developing AIM was five times higher during the 14 days after COVID-19 diagnosis (10). Another study in Sweden that analyzed 86742 patients with symptoms of COVID-19 infection showed that the incidence of AIM development was 2.9 times higher during the first week after the onset of symptoms COVID-19 (11). Infection and subsequent inflammation may trigger coronary thrombosis through multiple mechanisms: infiltration of atherosclerotic plaque by inflammatory cells (plaque instability and rupture), systemic platelet activation, coronary vasoconstriction, and endothelial dysfunction. Clinical presentation of acute coronary syndrome in COVID-19 patients

may range from AIM with ST elevation (AIM type 1) to AIM with non-obstructive coronary arteries (MINOCA) and type 2 AIM (due to mismatch between myocardial oxygen supply and myocardial demand, without obstruction of coronary circulation). Based on angiographic findings, several studies have shown a high prevalence of non-obstructive coronary heart disease in patients with COVID-19 infection - from 33% to 44% of those who had coronary angiography due to suspected ST elevation AIM. ACS therapy should be performed according to current ESC recommendations for the treatment of ACS with ST elevation and without ST elevation (12).

Venous thrombosis is a common complication of COVID-19 infection with an incidence of 7.4% (13). Hypoxia and immobilization are the main etiological factors in the development of venous thromboembolism (VTE). SARS-COV2 through ACE2 receptors enters the vascular endothelium, triggering endothelial inflammation and the exposure of von Willebrand factor (vWF) with a significant role in platelet adhesion and aggregation causing thrombosis development. Neutrophils activated by the virus via the ACE2 receptor release an inflammatory mediator (NETs), which is a key mediator of immunothrombosis that activate factor XII and trigger the coagulation cascade (14) .

Pulmonary embolism (PE) is the most severe thromboembolic complication. The overall incidence of PE in COVID-19 patients is estimated to be between 1.1% and 3.4%, with an increase to 17% to 27% in more severe forms of infection. In autopsy studies, pulmonary embolism (PE) was the direct cause of death in 33% of COVID-19 patients (15). Deep venous thrombosis (DVT) is one of the main causes of PE, but also in situ thrombosis of micro and macrovascular pulmonary circulation is a significant cause of pulmonary embolism in COVID-19 patients. Several retrospective studies have shown that early administration of prophylactic doses of low molecular weight heparin (LMWH) in all hospitalized patients with COVID-19 infection without contraindications to LMWH, reduces mortality by 34% and without increased risk of bleeding (16).

Cardiac arrhythmias occur in 17% of patients with COVID-19 infection, and in almost 50% of patients in the intensive care units. COVID-19 infection present a 3.83-fold higher risk for developing arrhythmias. Cardiac arrhythmias occur two-fold more frequently in patients with increased serum troponin. The occurrence of arrhythmias is one of the most significant risks of adverse outcomes, with an increased incidence of in-hospital death. Arrhythmias vary from bradyarrhythmias (less common), through sinus tachycardia and atrial arrhythmias, of which atrial fibrillation is the most common (81.8% of all arrhythmias in hospitalized COVID-19 patients). Increased troponin levels in patients with pre-existing cardiovascular disease and COVID-19 infection occur in 54.5% of patients and present an additional risk of malignant arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF), which can lead to sudden cardiac death and cardiac arrest - 11.5% of patients with

previous cardiovascular disease develop malignant arrhythmias, and 5.2% without cardiovascular disease. Direct myocardial injury (ischemia and myocarditis), systemic inflammation (cytokine storm), respiratory failure, electrolyte imbalance, hyperactivity of the adrenergic system (increased levels of catecholamines), hypercoagulable status and the use of drugs that prolong the QT interval (chloroquine and azithromycin) may source the development of arrhythmias (17).

Heart failure (HF) is more common during COVID-19 infection in elderly patients with comorbidities: ischemic heart disease, hypertension and diabetes, and the development of HF during infection is associated with a poorer prognosis. High levels of NT-pro BNP and BNP during the development of heart failure are associated with higher mortality of COVID-19 disease (18).

Stress cardiomyopathy or Takotsubo syndrome rarely occurs as a complication of COVID-19 infection. Both sexes are equally affected, and the mean age is 57 years (19). Most patients have a reduced ejection fraction with normal coronary angiogram and reversible ventricular dysfunction with higher mortality compared to stress cardiomyopathies that are not associated with infection and are more common in postmenopausal women. Possible mechanisms that cause stress cardiomyopathy are high levels of circulating catecholamines, direct cytotoxicity, and an overemphasized immune response (20).

Men with COVID-19 infection have a higher risk than women with more severe forms of the infection. The majority of patients with ST elevation AIM (STEMI) during COVID-19 infection are men and coronary angiography confirmed coronary obstruction, while in women ACS is manifested by non-obstructive coronary heart disease (MINOCA) or microvascular dysfunction. Increased levels of ACE2 receptors on cardiomyocytes in men may lead to easier entry of the virus into cardiomyocytes, higher virulence and increased prevalence of cardiac complications in men, including acute forms of viral myocarditis. The effect of 17-beta estradiol on T-cell phenotype and function leads to a significant difference in the reduction of the hyperinflammatory response in men, which leads to a more severe clinical outcome of COVID-19 disease. Increased levels of D-dimer in men more than in women are an independent predictor of admission to intensive care units, invasive mechanical ventilation and in-hospital death (21).

CARDIOVASCULAR COMPLICATIONS AFTER COVID-19 VACCINATION

Cardiovascular complications that may occur after COVID-19 vaccination are: myocarditis, pericarditis, thromboembolic events, hypertension, acute coronary syndrome, stress cardiomyopathy, arrhythmias and cardiac arrest (22).

Myocarditis and pericarditis occurred in 3/4 of all cases after the second dose of mRNA vaccine against SARS-COV2 virus and mostly in younger adults. The

incidence of myopericarditis is an average of 12.6 cases of myopericarditis per million doses of the second dose of mRNA vaccine aged 12-39 years, with no previous history of COVID-19 infection or comorbidities, with a predominance in men (79%). The median age for myocarditis was approximately 24 years in both sexes, while the median age for pericarditis was 24 years in males and 54 years in women. The rare occurrence of myocarditis in females can be explained by the inhibitory role of estrogen on proinflammatory T cells (23). The incidence of myocarditis in patients with COVID-19 occurs in an average of 11 people per 100,000 patients, and the incidence of myocarditis after the second dose of mRNA vaccine is 1-5 /100.000 people, and in men aged 16-30 myocarditis is 5 times more common (1/20000). The most common presentation of myopericarditis is chest pain and fever within 7 days (usually 2 to 3 days) of the second dose of mRNA vaccine associated with elevated troponin and CRP, ST elevation on ECG and cardiac magnetic resonance imaging (CMR) which indicates myocarditis. The mechanism of these complications is not entirely clear, but molecular mimicry may be a potential mechanism. Antibodies to the SARS-COV2 "spike" protein cross-react with similar cardiac protein sequences including alpha-myosin (autoimmune reaction) and lead to activation of immune pathways and dysregulation of cytokine expression. In some cases, myocardial microthrombi without infiltration by inflammatory cells could be a possible mechanism. Lipid nanoparticles and other adjuvants that are part of the mRNA vaccine do not affect the immune and inflammatory response (24). In most cases, myopericarditis has a benign course independent of therapy (withdrawal of symptoms and signs and normalization of diagnostic markers), and patients with myocardial damage, arrhythmias or hemodynamic instability are hospitalized. In several cases of pathohistologically confirmed myocarditis that developed within 2 weeks after the COVID-19 mRNA vaccine, the course was fulminant and ended lethally. Current recommendations advise delaying the second dose of mRNA vaccine in case of myopericarditis after the first dose, with possible consideration of the application of the second dose of vaccine after complete resolution of symptoms (25).

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare condition that occurs after vaccination against SARS-COV2, especially after administration of the adenoviral vector vaccine Astra Zeneca and Janssen / Johnson & Johnson vaccine. VITT has a low incidence (1/100000-150000), more prevalently in young women (under 50 years of age) with median onset of symptoms 4-28 days after vaccination (usually 8-10 days) and can be fatal - mortality rate is 20 -30% (26). VITT occurs in people without a previously known predisposition and known risk factors for thrombosis, and is characterized by the formation of immune complexes consisting of antibodies directed to platelet factor 4 (PF4) which leads to platelet activation, aggregation and thrombus formation by mechanism, clinical presentation and biochemical parameters of a condition similar to heparin-induced thrombocytopenia (HIT). VITT

is most often clinically present with cerebral venous sinus thrombosis, but splanchnic venous thrombosis, deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis can also occur frequently (27). Treatment of thrombosis within the VITT condition consists of the use of intravenous immunoglobulins (IVIG) -1g/kg for 2 days, the use of corticosteroids and non-heparin anticoagulants (fondaparinux, argatroban) (28).

Acute myocardial infarction (AIM) is a rare but potentially highly lethal complication following COVID-19 vaccines. The incidence of acute myocardial infarction is 0.02% and 0.03% depending on the type of mRNA vaccine (Pfizer or Moderna), more common in males and the elderly, with symptoms onset the most frequently up to 24 hours after vaccine application (more often after the second dose of vaccine). For now, the mechanisms that lead to the development of myocardial infarction after vaccine administration are unclear. Similar mechanisms leading to vaccine-induced thrombosis (VITT) could explain most cases of AIM (29). Kounis syndrome, which is an allergic or anaphylactic reaction to the vaccine, could be one of the mechanisms of AIM development - through various mechanisms such as allergic vasospasm and occlusion of a blood vessel with the formation of a thrombus infiltrated by eosinophils and/or mast cells. Stress during vaccine administration in the elderly with associated comorbidities may lead to ischemia and the development of type 2 AIM (mismatch between oxygen supply and myocardial demand). Patients who underwent coronary angiography (primary PCI) after the clinical presentation of AIM and confirmation of the diagnosis had a culprit lesion in the anterior descending artery (LAD) in 60% of cases (30).

Stress cardiomyopathy (Takotsubo syndrome) is a rare complication after administration of COVID-19 vaccine with a median manifestation 1 to 3 days after administration of the first or second dose of vaccine, with a higher incidence in females (31). It is manifested by chest pain, non-obstructive coronary angiogram with signs of ST elevation on the ECG and apical hypokinesia on echocardiography. Risk factors for the development of stress cardiomyopathy are gender, age, anxiety associated with the application of the vaccine and the type of vaccine (32).

The most common arrhythmias that occur after COVID-19 vaccination are sinus tachycardia, atrial fibrillation, and supraventricular tachycardia. Clinically, they are most often manifested by palpitations. It is unclear whether the arrhythmias are related to COVID-19 vaccination or to the presence of comorbidities and the coincidence of the time of onset of arrhythmias after vaccine administration. The prevalence of palpitations after vaccination is 0.006% and the prevalence of atrial fibrillation is 0.0009% (22). Several cases of postural orthostatic tachycardia have been reported in healthy patients within 6 days of the first dose of Pfizer vaccine. A possible mechanism of occurrence is an autoimmune reaction to adrenergic receptors in the cardiovascular system that lead to impaired vasoconstriction that causes postural tachycardia (33).

The hypertensive reaction after COVID-19 vaccination represents 5.82% of all cardiovascular complications of vaccination (22). Of all cases of hypertensive reactions, the incidence of hypertensive crises is 1.3%, and 0.8% is the incidence of episodes of "hypertensive urgency". Hypertension after vaccine application occurs in both sexes and in all age groups, and the median age is 73 years. Stress and the effect of the "white coat" are contributing factors in the manifestation of hypertension with existing comorbidities (34).

Conclusions

COVID-19 vaccination prevents hospitalization and reduces the mortality of COVID-19 infection and reduces complications that occur during and after infection. The risk of myocarditis after COVID-19 vaccination is 3.24 times higher within 42 days after the first dose of Pfizer-BioNTech mRNA vaccine as opposed to the occurrence of myocarditis during COVID-19 infection where the risk is 18.28 times higher than the population of all age groups. Patients with myocarditis after mRNA vaccine had a short hospital stay (3-5 days) and recovery of cardiac function during 1-5 weeks after initial hospitalization (35). COVID-19 vaccination significantly reduces the risk of thrombosis, arrhythmias and acute renal failure during SARS-COV2 infection and reduces the risk of myocardial damage and myocarditis by 1000 times in all age groups, with a slightly higher risk of mild myocarditis (1-5 times higher risk) in younger adults. The prevalence of thrombosis in COVID-19 patients is 22%, with an increase in incidence to 43% after admission to intensive care units, while the incidence of thrombotic events after COVID-19 vaccination is low (less than 0.01%) (36).

Most elderly people who have received the vaccine have comorbidities and are expected to have cardiovascular events such as myocardial infarction, hypertension and arrhythmias, and probably some of the cardiovascular events after COVID-19 administration occur independently of the vaccine but are presented as vaccine side effects.

The benefit-risk ratio of COVID-19 vaccination to the occurrence of cardiovascular complications strongly prevails in favor of vaccines for all age groups (older than 12 years) for both sexes.

There is no conflict of interest.

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