Aleksandar Đenić¹, Nataša Vidić²

POREMEĆAJI KARDIOVASKULARNE FUNKCIJE I EHOKARDIOGRAFSKIH PARAMETARA SRCA U MANIFESTNOM I SUBKLINIČKOM HIPOTIREOIDIZMU

Sažetak: Smanjenje tireoidne funkcije dovodi do promena u kardiovaskularnoj hemodinamici, promena u kontraktilnosti miokarda i ubrzane ateroskleroze. Periferna cirkulacija u hipotireoidizmu se karakteriše povećanom vaskularnom rezistencijom i prolongiranim cirkulatornim vremenom. Endotelna disfunkcija koja se javlja kod hipotireoidnih pacijenata predisponira razvoj ateroskleroze i povećava arterijski stiffness. Uticaj subkliničkog hipotireoidizma na kardiovaskularni sistem ispoljava se kroz sistolnu i dijastolnu srčanu funkciju, miokardnu anatomiju i toleranciju napora. Subklinička hipotireoza u akutnom infarktu miokarda povećava 3.6 puta kardijalni mortalitet i 2.3 puta sveukupni mortalitet. Manifestni hipotireoidizam se karakteriše hiperholesterolemijom, značajno povišenim LDL holesterolom i apolipoproteinom B. Subklinička hipotireoza je udružena sa malim porastom LDL holesterola, smanjenjem HDL holesterola, povećavajući rizik za razvoj ateroskleroze i koronarne arterijske bolesti. Izovolumsko relaksacijsko vreme (IVRT) je značajno produženo u hipotireoidnih pacijenata, što ukazuje na oštećenu pasivnu relaksaciju leve komore. Globalni "strain" desne komore i "strain" slobodnog zida desne komore su sniženi kod hipotireoidnih pacijenata u odnosu na zdrave subjekte. Ove promene su kompletno reverzibilne nakon primene tireosupstitucione terapije i većinom nakon 6 meseci primene L-tiroksina.

Ključne reči: hipotireoidizam, L-tiroksin, subklinička hipotireoza, hiperholesterolemija, ateroskleroza, dijastolna disfunkcija

Tireoidni hormoni ispoljavaju efekte na srce i periferni vaskularni sistem smanjenjem sistemske vaskularne rezistencije (SVR), povećanjem srčane frekvence

¹ Aleksandar Đenić, Specijalna bolnica za bolesti štitaste žlezde i bolesti metabolizma Zlatibor, djenic.cigota@gmail.com

² Nataša Vidić, Opšta bolnica Užice, natasa.neskovic977@gmail.com

u miru (pozitivno hronotropno dejstvo), pojačanjem kontraktilnosti leve komore (pozitivno inotropno dejstvo) i povećanjem volumena krvi i cirkulišuće tečnosti. (1)

Dejstvom tireoidnih hormona na krvne sudove dolazi do smanjenja rezistencije perifernih arteriola kroz direktne efekte na glatke mišiće krvnih sudova i smanjenjem srednjeg arterijskog pritiska koji u bubrežima dovodi do aktivacije sistema renin-angiotenzin-aldosteron (RAAS) i povećanja renalne apsorpcije natrijuma. Trijodtironin povećava i sintezu eritropoetina, što dovodi do povećanja mase eritrocita. Ove promene kombinovano dovode do povećanja volumena krvi i preload-a. U hipertireozi ovi efekti dovode do povećanja cardiac outputa za 50-300%, a u hipotireozi do smanjenja cardiac outputa za 30-50%. (2)

Tireoidni hormoni ispoljavaju uticaj na metabolizam lipida putem nekoliko mehanizama. Trijodtironin indukuje povećanu LDL degradaciju posredovanu povećanjem broja LDL receptora, bez promena u afinitetu LDL-a za svoj receptor. (3) Nekoliko ključnih enzima jetre uključenih u metabolizam lipida pod direktnim su uticajem trijodtironina koji ispoljava transkripcione efekte posredstvom tireoidnih receptora (TR), vezujući se za T3 element (TREs) kao vezujuće mesto tireoidnog receptora (TR) za trijodtironin (T3). TREs predstavlja promotor region hepatične lipaze i gena apolipoproteina A1. Sterol-regulatorni-element vezujućeg proteina 2 je pod regulatornom ulogom tireoidnih hormona koji indukuju porast ekspresije LDL receptora. Trijodtironin je važan u hepatičkoj degradaciji holesterola u žučne kiseline povećavajući transkripciju enzima holesterol-7alfa-hidroksilaze koja je uključena u taj proces. (4)

Hipotireoidizam i kardiovaskularna funkcija

Smanjenje tireoidne funkcije dovodi do promena u kardiovaskularnoj hemodinamici, promena u kontraktilnosti miokarda i ubrzane ateroskleroze. U izraženoj hipotireozi smanjen je cardiac output kao rezultat smanjenja udarnog volumena i srčane frekvence. (5)

Preload zavisi od ukupnog volumena krvi i venskog punjenja, kao i od kontraktilne aktivnosti pretkomora i mogućnosti punjenja komora. U hipotireoidnih pacijenata preload je smanjen, što je u korelaciji sa smanjenjem volumena krvi u hipotireozi. (2)

Periferna cirkulacija u hipotireoidizmu karakteriše se povećanom vaskularnom rezistencijom i prolongiranim cirkulatornim vremenom. To rezultira u redistribuciji cirkulišuće tečnosti i smanjenju renalnog protoka. Plazma reninska aktivnost i nivoi aldosterona su smanjeni u hipotireozi, što sugeriše da renin-angiotenzin-aldosteron sistem (RAAS) ima manju ulogu u razvoju hipertenzije indukovanoj hipotireoidizmom. S obzirom na to da je volumen plazme smanjen u hipotireozi najveći doprinos razvoju hipertenzije povećana je periferna vaskularna rezistencija. Povećan afterload može dalje redukovati cardiac output, što doprinosi prolongiranom cirkulacionom

vremenu. Miokard u hipotireozi karakteriše povećanje afterload-a koje je energetski neefikasno uprkos niskom stepenu ukupne potrošnje kiseonika. Afterload je povećan kao rezultat povećane sistemske vaskularne rezistencije i arterijskog stiffness-a i jedan je od važnih determinišućih faktora miokardne potrošnje kiseonika. (6)

Povećanje dijastolnog krvnog pritiska je često u hipotireozi sa sniženjem vrednosti postizanjem eutireoidnog stanja. U izraženom hipotireoidizmu sistemska arterijska hipertenzija je prisutna kod oko 30% pacijenata, povišen je srednji arterijski pritisak i oko 20% pacijenata ima dijastolnu hipertenziju. (7)

Endotelna disfunkcija, koja se javlja kod hipotireoidnih pacijenata, predisponira razvoj ateroskleroze i povećava arterijski stiffness. Povećani centralni arterijski stiffness može dalje doprineti razvoju hipertenzije u hipotireoidizmu. Aortni stiffness i sistemska vaskularna rezistencija su povećani kod svih pacijenata sa hipotireoidizmom, bez obzira da li imaju ili nemaju hipertenziju; efekti ova dva stanja su aditivna. (8) Aortni stiffness i sistemska vaskularna rezistencija se smanjuju tokom L-tiroksin terapije u hipotireoidnih pacijenata sa normalnim krvnim pritiskom i kod pacijenata sa perzistentnom hipertenzijom. Međutim, pacijenti sa višim bazalnim vrednostima aortnog stiffness-a imaju manju verovatnoću normalizacije sistolnog krvnog pritiska koje korelira sa smanjenjem aortnog stiffness-a. Oštećenje elastičnih svojstava aorte može biti uzrok nepotpune normalizacije krvnog pritiska nakon supstitucione terapije kod 50% pacijenata sa hipotireoidizmom i hipertenzijom, što zahteva potrebu za dodatnom antihipertenzivnom terapijom. (9)

Uticaj subkliničkog hipotireoidizma na kardiovaskularni sistem ispoljava se kroz sistolnu i dijastolnu srčanu funkciju, miokardnu anatomiju i toleranciju napora. Brojne opservacione studije su pokazale da osobe sa tireoidnom disfunkcijom imaju lošiji kardiovaskularni ishod, uključujući i povećan mortalitet. Čak i male promene u koncentraciji tireoidnih hormona mogu se negativno odraziti na kardiovaskularni sistem. Subklinički hipotireoidizam je snažan nezavisni faktor rizika za oboljenje koronarnih krvnih sudova. Prospektivne opservacione studije su pokazale da je subklinička hipotireoza u akutnom infarktu miokarda (AIM) udružena sa lošijim kardiovaskularnim ishodom. Subklinička hipotireoza u akutnom infarktu miokarda povećava 3.6 puta kardijalni mortalitet i 2.3 puta sveukupni mortalitet. (10)

Subklinička hipotireoza u vremenu oko akutnog infarkta miokarda (AIM) predstavlja stanje koje favorizuje srčanu insuficijenciju. AIM dovodi do nižih serumskih nivoa tireoidnih hormona, kao i do nishodne regulacije tireoidnih receptora u miokardu, dovodeći do tkivnog hipotireoidizma. Prospektivna studija Friberga i sarad. je pokazala da se nivo tireoidnih hormona rapidno smanjuje nedelju dana nakon AIM. (11) Druga studija Friberga i sarad. je pokazala da je intrahospitalni mortalitet i mortalitet nakon otpusta iz bolnice veći u pacijenata koji su imali niže vrednosti tireoidnih hormona u serumu nakon AIM, što govori u prilog da je hipotireoidno stanje udruženo sa lošijom prognozom. (12) U poređenju sa drugim organima srce je mnogo vulnerabilnije u

hipotireoidnom stanju, zato što kardiomiociti nemaju sposobnost konverzije prekursora T4 u T3, kao što je to slučaj u drugim organima. Time se može objasniti zašto i blaga tireoidna disfunkcija ima izraženije efekte na srce u odnosu na druge organe. (3)

Rizik za aterosklerotsku kardiovaskularnu bolest u pacijenata sa hipotireoidizmom

Manifestni hipotireoidizam se karakteriše hiperholesterolemijom, značajno povišenim LDL holesterolom i apolipoproteinom B. Zbog smanjenog frakcionog klirensa LDL-a, kao posledice smanjenog broja LDL receptora u jetri, smanjen je katabolizam LDL holesterola i time prolongiran njegov poluživot u cirkulaciji. Primenom tireosupstitucije dolazi do signifikantnog poboljšanja katabolizma LDL partikula u jetri posredstvom aktivacije LDL receptorske mRNA. Opservacione studije su pokazale da hipotireoidizam uzrokuje kvalitativne promene cirkulišućih lipoproteina povećavajući njihovu aterogenost. LDL je osetljiviji na oksidaciju u pacijenata sa hipotireoidizmom sa normalizacijom oksidacije postizanjem eutireoidnog stanja. (4) Hipotireoidizam je udružen sa reverzibilnom redukcijom aktivnosti holesterol-estar transfer proteina, hepatične endotelijalne lipaze, 7-alfa hidroksilaze i hepatičkog LDL receptora. Nivo lipoproteina(a) je povišen u hipotireoidnih pacijenata, ali je nejasan odgovor na tireosupstituciju, mada je nekoliko studija pokazalo smanjenje nivoa lipoproteina(a) na terapiju L-tiroksinom. Trijodtironin i HDL holesterol su u obrnutoj korelaciji sa razvojem koronarne bolesti. Hipotireoidizam je udružen sa nižim nivoom HDL-a. Opservacione studije su pokazale značajan porast HDL holesterola primenom L-T4 terapije i normalizacijom nivoa TSH u serumu. (13)

Hiperhomocisteinemija je nezavisni faktor rizika za okluzivnu vaskularnu bolest, uključujući koronarnu aterosklerozu i predisponira razvoj ateroskleroze stimulišući LDL oksidaciju, endotelnu disfunkciju i vaskularno oštećenje endotelnih ćelija. Hiperhomocisteinemija se javlja kod pacijenata u hipotireoidizmu zbog smanjene glomerularne filtracije homocisteina (smanjen klirens homocisteina), a nedostatak tireoidnih hormona utiče na smanjenu aktivnost enzima uključenih u metabolizam folate, što dovodi do povećanja nivoa kreatinina i smanjenja koncentracije folata i vitamina B12. Nakon postizanja adekvatne tireosupstitucije nivoi homocisteina u krvi se normalizuju. Smanjenje homocisteina u krvi za 2–5 mikromol/L, što se postiže primenom L-tiroksina i postizanjem optimalnih nivoa TSH, značajno se snižava kardiovaskularni rizik. Nasuprot manifestnom hipotireoidizmu, subklinička hipotireoza nije udružena sa hiperhomocisteinemijom i u kliničkim studijama nije primećeno signifikantno sniženje homocisteina u krvi nakon tretmana subkliničke hipotireoze sa L-T4. (14)

Povišeni nivoi C-reaktivnog proteina (CRP), endotelna disfunkcija i abnormalnosti koagulacije predstavljaju dodatni faktor rizika za aterosklerozu u hipotireoidnih pacijenata. (5)

Stepen hipotireoidizma determiniše efekte na koagulacione parametre. U jednoj studiji su poređene žene sa umerenim hipotireoidizmom (TSH 10-50mU/L) i težom hipotireozom (TSH>50 mU/L) u odnosu na žene sa eutireoidnim stanjem i mereni su nivoi hemostatskih parametara u krvi. Žene sa umerenom hipotireozom su imale smanjenje fibrinolitičke aktivnosti, sa smanjenjem nivoa D-dimera, povišenom alfa2-antiplazmin aktivnošću i povišenim nivoom tkivnog plazminogen aktivator antigena i plazminogen aktivator inhibitor antigena. Suprotno, žene sa teškom formom hipotireoze su imale visoke nivoe D-dimera, sniženu alfa2-antiplazmin aktivnost i snižene nivoe tkivnog plazminogen aktivator antigena i plazminogen aktivator inhibitor antigena. Ovi rezultati su sugerisali povećan rizik za trombozu koji može precipitirati pojavu infarkta miokarda i mozga kod umerene forme hipotireoze i povećanom sklonošću ka krvarenju kod pacijenata sa težom formom hipotireoze. (15)

Mnoge studije su pokazale da su insulinska rezistencija i metabolički sindrom nezavisni faktori rizika za kardiovaskularna oboljenja, čak i kod osoba koje nemaju šećernu bolest. Iako hipotireoidizam nema direktan uticaj na razvoj insulinske rezistencije, smanjeni nivoi tireoidnih hormona u krvi mogu amplifikovati povišen kardiovaskularni rizik udružen sa insulinskom rezistencijom delujući na povišenje nivoa ukupnog i LDL holesterola. (4)

Subklinička hipotireoza je udružena sa malim porastom LDL holesterola, smanjenjem HDL holesterola povećavajući rizik za razvoj ateroskleroze i koronarne arterijske bolesti. Ove promene su zasnovane na značajnom uticaju tireoidnih hormona na lipidni metabolizam. (16) Subklinički hipotireoidizam sa blagim stepenom tireoidne disfunkcije može indukovati razvoj ateroskleroze na različite načine – putem endotelne disfunkcije i poremećenih koagulacionih parametara. Dodatni faktori rizika koji doprinose povećanju prevalence infarkta miokarda u subkliničkom hipotireoidizmu su poznati faktori rizika za razvoj koronarnog arterijskog oboljenja: hiperholesterolemija, hipertenzija, pušenje i diabetes mellitus. Pacijenti u subkliničkoj hipotireozi, koji su imali i niže vrednosti ukupnog holesterola u odnosu na kontrolnu grupu, imali su manifestno aterosklerotsko vaskularno oboljenje, što sugeriše da drugi faktori doprinose povećanom riziku za razvoj ateroskleroze. Smatra se da povišene koncentracije LDL holesterola, povećana LDL oksidacija, povišeni trigliceridi i lipoprotein (a) u serumu mogu objasniti udruženost subkliničke hipotireoze i kardiovaskularnih oboljenja. (17)

Jasan dokaz povećane prevalence aterosklerotskog kardiovaskularnog oboljenja u subkliničkoj hipotireozi pokazan je u velikoj randomizovanoj studiji u kojoj je učestvovalo 1.149 žena koje su živele u Roterdamu starijih od 55 godina (Roterdamska studija). Ova studija je pokazala da žene srednjih godina sa subkliničkom hipotireoidozom imaju veću verovatnoću za razvoj infarkta miokarda i kalcifikacije zida aorte. Žene sa TSH većim od 4 mU/L (a normalnim vrednostima FT4) imale su

veću prevalencu koronarne arterijske bolesti u odnosu na kontrolni uzorak sa TSH manjim od 4 mU/L. Rotterdamskom studijom je utvrđeno da žene sa povišenim titrom antiperoksidaza antitela, a normalnom tireoidnom funkcijom imaju sličnu prevalencu ateroskleroze i infarkta miokarda kao i eutireoidne žene bez povišenih antitela na tireoidnu peroksidazu, što sugerije da je razvoj ateroskleroze posredovan relativnom deficijencijom tireoidnih hormona, pre nego imunološkom disfunkcijom. (18)

Efekat tireosupstitucione terapije na kardiovaskularni sistem

Kod većine pacijenata cilj tireosupstitucione terapije je da TSH bude između 0,5 i 2,5 mU/L, čime se izbegava efekat neadekvatne tireosupstitucije. Optimalna tireosupstituciona terapija mora uzeti u obzir životno doba pacijenta, kao i uzrok hipotireoidizma. Puna doza terapije L-tiroksina može se sa sigurnošću dati mlađim pacijentima sa manifestnim hipotireoidizmom koji nemaju kardiovaskularno oboljenje. Kod starijih pacijenata sa poznatim ili suspektnim koronarnim oboljenjem ili kod pacijenata sa manifestnim srčanim oboljenjem tireosupstitucionu terapiju trebalo bi započeti malim dozama i postepeno povećavati uz monitoring pacijentovog zdravstvenog stanja. (19)

U velikim retrospektivnim studijama novonastala angina pectoris i infarkt miokarda se relativno retko pojavljuju nakon administracije tireoidnih hormona. Korisni efekti tireosupstitucije su mnogo češći u smanjenju anginalnih simptoma (38%) u odnosu na pogoršanja angine (16%). Jednogodišnji kardiovaskularni mortalitet kod ovih pacijenata sa dijagnostikovanom anginom i tretiranim hipotireoidizmom je bio 3%, što je manje u odnosu na jednogodišnji kardiovaskularni mortalitet od 9% do 15% koji je zabeležen kod pacijenata sa anginom tokom istog perioda posmatranja. Administracija tireoidnih hormona dovodi do poboljšanja miokardne kontraktilnosti i dijasolne funkcije i redukuje afterload, što je glavna determinanta potrošnje kiseonika. Ovim se može objasniti kako terapija tireoidnim hormonima poboljšava efikasnost miokarda i dovodi do regresije anginalnih simptoma u hipotireoidnih pacijenata. Pogoršanje angine, infarkt miokarda i smrt se mogu javiti kada se L-tiroksin terapija započne punim dozama kod starijih pacijenata sa ishemijskim oboljenjem miokarda. Suprotno, ventrikularne aritmije se mogu poboljšati ili kompletno rešiti nakon terapije sa L-tiroksinom. (20)

Najnoviji konsenzusi formulisani za vodiče za terapiju pacijenata sa subkliničkim hipotireoidizmom preporučuju započinjanje terapije L-tiroksinom kod pacijenata sa subkliničkom hipotireoidozom sa vrednostima TSH iznad 10 mU/L u cilju prevencije progresije u manifestni hipotireoidizam. Tireosupstituciona terapija poboljšava lipidni profil i smanjuje kardiovaskularni rizik kod pacijenata koji su bili uključeni u više selektovanih studija, a koji su imali TSH veći od 10 mU/L, što je dalo podršku u stavu da treba tretirati pacijente sa subkliničkim hipotireoidizmom. (21)

Promene ehokardiografskih parametara u manifestnom i subkliničkom hipotireoidizmu

Tokom razvoja tireoidne disfunkcije dolazi do promena u strukturi i funkciji miokarda što se može ispoljiti: 1. strukturalnim i funkcionalnim remodelingom leve komore koji mogu dovesti do oslabljene sistolne, dijastolne i globalne funkcije leve komore; 2. poremećenom mehanikom leve komore; 3. poremećenom strukturom, dijastolnom i globalnom funkcijom desne komore; 4. poremećenom mehanikom desne komore. (17)

Smanjena dijastolna funkcija je detektibilna u ranoj fazi razvoja hipotireoidoze. Izovolumsko relaksacijsko vreme (IVRT) je značajno produženo u hipotireoidnih pacijenata, što ukazuje na oštećenu pasivnu relaksaciju leve komore, što dovodi do smanjenog ranog punjenja u dijastoli. Dopler ehokardiografijom registrovan odnos rani/kasni (E/A) dijastolni transmitralni protok je već snižen u ranim fazama razvoja hipotireoidizma. Ova stanja su kompletno reverzibilna nakon 3–6 meseci adekvatne tireosupstitucione terapije. Dijastolna disfunkcija može da dovede do povećanog morbiditeta, smanjene tolerancije napora i dijastolne srčane insuficijencije. Pojedine studije su ukazale na redukciju dijametra korena aorte nakon primene tireosupstitucione terapije, što se reflektuje poboljšanjem aortne komplijanse i može biti udruženo sa poboljšanjem dijastolne funkcije. U hipotireozu se može detektovati asimetrična septalna hipertrofija koja je u određenom stepenu reverzibilna postizanjem eutireoidnog stanja. Ovo stanje se može posmatrati i kao jedan od uzroka dijastolne disfunkcije leve komore, ali i kao adaptivni odgovor na povećani afterload, pogotovo u starijih. (22) Monzani i sarad. su pokazali porast indeksa mase leve komore u subkliničkom hipotireoidizmu u odnosu na kontrolu, a primena L-tiroksin terapije dovodi do redukcije mase i debljine zida leve komore. Mehanizam koji dovodi do hipertrofije leve komore u tireoidnoj disfunkciji je porast sistemske vaskularne rezistencije i aktivacija simpatičkog nervnog sistema i renin-angiotenzin-aldosteron sistema (RAAS), koji imaju značajnu ulogu u hemodinamici i strukturnim promenama leve komore. (23)

Redukcija mase leve komore nakon primene L-tiroksina ima pozitivne efekte na poboljšanje dijastolne disfunkcije. Pulsnim tkivnim Doplerom se može detektovati prolongirano miokardno prekontrakcijsko vreme i miokardno relaksacijsko vreme na nivou posteriornog septuma i mitralnog anulusa, što ukazuje na oštećenu sistolnu i dijastolnu funkciju u hipotireoidizmu. (24)

Uticaj manifestne i subkliničke hipotireoze na sistolnu funkciju je kontroverzan. Senzitivne ehokardiografske metode, posebno tokom fizičkog stresa, pokazale su promene sistolne funkcije kod pacijenata sa tireoidnom disfunkcijom u odnosu na kontrolne subjekte. Oštećena sistolna funkcija leve komore u miru, definisana kroz porast odnosa preejekcioni period (PEP)/ejekciono vreme leve komore (LVET) i produženje vremena preejekcionog perioda leve komore (PEP) prikazana je u nekoliko

studija koje su obuhvatile pacijente sa subkliničkim hipotireoidizmom u odnosu na kontrolne grupe. Ove promene su kompletno reverzibilne nakon primene tireosupstitucione terapije i većinom nakon 6 meseci primene L-tiroksina. (25)

Pojedine studije ukazuju i na depresiju globalnog longitudinalnog "strain"-a leve komore i "strain"-a lateralnog zida i interventrikularnog septuma leve komore kod pacijenata sa subkliničkim hipotireoidizmom. Promene mehanike leve komore se povlače nakon primene tireosupstitucione terapije. Ovi rezultati ukazuju da hipertrofija leve komore nije jedini mehanizam odgovoran za disfunkciju leve komore u subkliničkoj hipotireozii. Hemodinamske promene u subkliničkom hipotireoidizmu dovode do porasta sistemske vaskularne rezistencije, što ima veoma važnu ulogu u odnosu između tireoidnih hormona i mehanike leve komore. U subkliničkom hipotireoidizmu oštećena funkcija leve komore i kardiorespiratorna adaptacija na napor postaju manifestni tokom opterećenja. Ove promene su reverzibilne nakon uspostavljanja eutireoidnog stanja. (26)

Desna komora je ehokardiografski manje proučavana, uglavnom zbog komplikovanije anatomije i nedostatka pouzdanih i dostupnih tehnika snimanja. Postoje oprečne studije o uticaju tireoidne disfunkcije na debljinu zida desne komore. U nekoliko studija pokazano je da tireoidna disfunkcija nije dovela do promena u debljini zida desne komore, a nekoliko kontrolisanih studija je pokazalo da je došlo do porasta debljine zida desne komore, oštećene globalne i dijasolne funkcije desne komore kod pacijenata sa subkliničkim hipotireoidizmom u odnosu na kontrolne zdrave subjekte, pri čemu u tim studijama nije došlo do redukcije debljine zida desne komore nakon primene tireosupstitucione terapije, za razliku od poboljšanja globalne i dijasolne funkcije desne komore nakon uvođenja L-tiroksina. Pokazano je da je mehanika desne komore primenom "speckle tracking imaging" signifikantno oštećena u subkliničkom hipotireoidizmu. Globalni "strain" desne komore i "strain" slobodnog zida desne komore su sniženi kod hipotireoidnih pacijenata u odnosu na zdrave subjekte. Interakcija između desne i leve komore je jedan od najvažnijih uzroka oštećene funkcije desne komore koja nastaje povećanjem pritiska punjenja leve komore i posledičnog povećanja plućnog protoka i pritiska u desnoj komori. Mehanizam koji dovodi do remodelovanja desne komore je povišen pritisak punjenja, što se reflektuje povišenim odnosom E/e'. Drugi mogući mehanizmi hipertrofije desne komore u hipotireoidizmu su endotelna disfunkcija pulmonalne cirkulacije, povišena simpatička i RAAS aktivnost, kao i neadekvatno preuzimanje kalcijuma, što dovodi do povećane plućne vaskularne rezistencije. Velikim brojem studija dokazano je da se oštećena mehanika desne komore kompletno popravlja nakon adekvatne tireosupstitucije. (25, 26)

Literatura

1. Jabbar A, Razvi S. Thyroid disease and vascular risk. *Clinical Medicine*. 2014; 14(6): 29–32.
2. Grais IM, Sowers JR. Thyroid and the heart. *Am J Med*. 2014; 127(8): 691–98.
3. Klein I, Danzi S. Thyroid disease and the heart. *Circulation* 2007; 116: 1725–35.
4. Vargas-Uricoechea H, Bonelo-Perdomo A, Sierra-Torres CH. Effects of thyroid hormones on the heart. *Clin Investig Arterioscler*. 2014; 26(6): 296–309.
5. Udovcic M, Pena RH, Patham B, Tabatabai L, Kansara A. Hypothyroidism and the heart. *Methodist Deakey Cardiovasc J*. 2017; 13(2): 55–59.
6. Ichiki T. Thyroid hormone and vascular remodeling. *J Atheroscler Thromb*. 2016; 23(3): 266–75.
7. Owen PJ, Sabit R, Lazarus JH. Thyroid disease and vascular function. *Thyroid*. 2007; 17(6): 519–24.
8. Delitala AP, Orru M, Filigheddu F, Pilia MG, Delitala G, Ganau A, et al. Serum free thyroxine levels are positively associated with arterial stiffness in the SardiNIA study. *Clin Endocrinol*. 2015; 82(4): 592–7.
9. Wang J, Zheng X, Sun M, Wang Z, Fu Q, Shi Y, et al. Low serum free thyroxine concentrations associate with increased arterial stiffness in euthyroid subjects: a population-based cross-sectional study. *Endocrine*. 2015; 50(2): 465–73.
10. Molinaro S, Iervasi G, Lorenzoni V, Landi P, Srebot V, Mariani F, et al. Persistence of mortality risk in patients with acute cardiac diseases and mild thyroid dysfunction. *Am J Med Sci*. 2012; 343: 65–70.
11. Friberg L, Werner S, Eggertsen G, Ahnve S. et al. Rapid down-regulation of thyroid hormones in acute myocardial infarction: is it cardioprotective in patients with angina? *Arch Intern Med*. 2002; 162: 1388–94.
12. Friberg L, Drvota V, Bjelak AH, Eggertsen G, Ahnve S. Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. *Am J Med*. 2001; 111: 699–703.
13. Bansal SK, Yadav R. A Study of Extended Lipid Profile Including Oxidized LDL, Small Dense LDL, Lipoproteins (a) and Apolipoproteins in the Assessment of Cardiovascular Risk in Hypothyroidism Patients. *J Clin Diagn Res*. 2016; 10(6): BC04-BC08.
14. Zhou Y, Chen Y, Cao X, Liu C, Xie Y Association between plasma homocysteine status and hypothyroidism: a meta-analysis. *Int J Clin Exp Med*. 2014; 7(11): 4544–53.
15. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. *J Clin Endocrinol Metab*. 2003; 88(6): 2438–44.
16. Liu XL, He S, Zhang SF, Wang J, Sun XF, Gong CM, et al. Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis. *Med Sci Monit*. 2014; 20: 1432–41.
17. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, et al. Thyroid hormones and cardiovascular function and diseases. *J Am Coll Cardiol*. 2018; 71:1781–96.
18. Hak AE, Pols HAP, Visser TJ, Drexhage HA, Hofman A, Witteman JCM. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam study. *Ann Intern Med*. 2000; 132: 270–78.

19. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid*. 2014; 24(12): 1670–1751.
20. Gerdes AM, Iervasi G. Thyroid replacement therapy and heart failure. *Circulation*. 2010; 122(4): 385–93.
21. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. *Eur Thyroid J*. 2013; 2(4): 215–28.
22. Masaki M, Komamura K, Goda A, Hirotani S, Otsuka M, Nakabo A, et al. Elevated arterial stiffness and diastolic dysfunction in subclinical hypothyroidism. *Circ J*. 2014; 78: 1494–1500.
23. Monzani F, Di Bello V, Caraccio N, Bertini A, Giorgi D, Giusti C, et al. Effect of levotroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2001; 86(3): 1110–15.
24. Kosar F, Sahin I, Aksoy Y, Uzer E, Turan N. Usefulness of pulsed wave tissue Doppler echocardiography for the assessment of the left and right ventricular function in patients with clinical hypothyroidism. *Echocardiography*. 2006; 23(6): 471–77.
25. Turhan S, Tulunay C, Ozduman Cin M, Gursay A, Kilickap M, Dincer I, et al. Effects of thyroxine therapy on right ventricular systolic and diastolic function in patients with subclinical hypothyroidism: a study by pulsed wave tissue Doppler imaging. *J Clin Endocrinol Metab*. 2006; 91(9): 3490–93.
26. Tiryakioglu SK, Tiryakioglu O, Ari H, Basel MC, Ozkan H, Bozat T. Left ventricular longitudinal myocardial function in overt hypothyroidism: a tissue Doppler echocardiographic study. *Echocardiography*. 2010; 27(5): 505–11.

Aleksandar Djenic¹, Natasa Vidic²

DISORDERS OF CARDIOVASCULAR FUNCTION AND ECHOCARDIOGRAPHIC PARAMETERS OF THE HEART IN OVERT AND SUBCLINICAL HYPOTHYROIDISM

Summary: Decreased thyroid function leads to changes in cardiovascular hemodynamics, changes in myocardial contractility and accelerated atherosclerosis. Peripheral circulation in hypothyroidism is characterized by increased vascular resistance and prolonged circulatory duration. Endothelial dysfunction that occurs in hypothyroid patients predisposes to the development of atherosclerosis, and increases arterial stiffness. The influence of subclinical hypothyroidism on the cardiovascular system is manifested through systolic and diastolic cardiac function, myocardial anatomy and effort endurance. Subclinical hypothyroidism in acute myocardial infarction increases cardiac mortality 3.6-fold and 2.3-fold overall mortality. Overt hypothyroidism is characterized by hypercholesterolemia, significantly elevated LDL cholesterol and apolipoprotein B. Subclinical hypothyroidism is associated with a small increase in LDL cholesterol, a decrease in HDL cholesterol, increasing the risk of developing atherosclerosis and coronary artery disease. Isovolumic relaxation time (IVRT) is significantly prolonged in hypothyroid patients, which indicates impaired passive relaxation of the left ventricle. Global right ventricular strain and right ventricular free wall strain are reduced in hypothyroid patients compared to healthy subjects. These changes are completely reversible after the application of thyroid replacement therapy and mostly after 6 months of L-thyroxine administration.

Keywords: hypothyroidism, L-thyroxine, subclinical hypothyroidism, hypercholesterolemia, atherosclerosis, diastolic dysfunction.

Thyroid hormones have effects on the heart and peripheral vascular system by reducing systemic vascular resistance (SVR), increasing resting heart rate (positive

¹ Aleksandar Djenic, Special Hospital for Thyroid and Metabolism Disorders Zlatibor, djenic.cigota@gmail.com

² Natasa Vidic, Health Center Uzice, natasa.neskovic977@gmail.com

chronotropic effect), increasing left ventricular contractility (positive inotropic effect) and increasing blood volume. (1)

The action of thyroid hormones on blood vessels reduces peripheral arteriole resistance through direct effects on vascular smooth muscle and reduces mean arterial pressure, which leads to activation of the renin-angiotensin-aldosterone system (RAAS) in the kidneys and increased renal sodium absorption. Triiodothyronine also increases the synthesis of erythropoietin, which leads to an increase in the mass of erythrocytes. These changes combined lead to an increase in blood volume and preload. In hyperthyroidism these effects lead to an increase of cardiac output by 50-300%, and in hypothyroidism to a decrease of cardiac output by 30-50%. (2)

Thyroid hormones affect lipid metabolism through several mechanisms. Triiodothyronine induces increased LDL degradation mediated by an increase in the number of LDL receptors, with no change in LDL affinity for its receptor. (3) Several key liver enzymes involved in lipid metabolism are directly influenced by triiodothyronine, which exhibits transcription effects through thyroid receptors (TRs) by binding to the T3 element (TREs) as a thyroid receptor (TR) binding site to triiodothyronine (T3). TREs represent a promoter of the hepatic lipase region and the apolipoprotein A1 gene. The sterol-regulatory-element of binding protein 2 is under the regulatory role of thyroid hormones that induce an increase in LDL receptor expression. Triiodothyronine (T3) is important in the hepatic degradation of cholesterol to bile acids by increasing the transcription of the enzyme cholesterol-7 α -hydroxylase which is involved in this process. (4)

HYPOTHYROIDISM AND CARDIOVASCULAR FUNCTION

Decreased thyroid function leads to changes in cardiovascular hemodynamics, changes in myocardial contractility and accelerated atherosclerosis. In severe hypothyroidism, cardiac output is reduced as a result of a decrease in stroke volume and heart rate. (5)

Preload depends on the total volume of blood and venous filling, as well as of the contractile activity of the atria and the possibility of filling the ventricles. In hypothyroid patients, preload is reduced, which is correlated with a decrease in blood volume in hypothyroidism. (2)

Peripheral circulation in hypothyroidism is characterized by increased vascular resistance and prolonged circulatory duration. This results in redistribution circulating fluids and decreased renal flow. Plasma renin activity and aldosterone levels are reduced in hypothyroidism, suggesting that the renin-angiotensin-aldosterone system (RAAS) plays a minor role in the development of hypothyroidism-induced hypertension. Since plasma volume is reduced in hypothyroidism, the greatest contribution to the development of hypertension is increased peripheral vascular resistance. Increased afterload

can further reduce cardiac output which contributes to prolonged circulation duration. The myocardium in hypothyroidism is characterized by an increase in afterload, which is energy inefficient despite the low level of total oxygen consumption. Afterload is increased as a result of increased systemic vascular resistance and arterial stiffness and it is one of the important determining factors of myocardial oxygen consumption. (6)

An increase in diastolic blood pressure is often in hypothyroidism which is normalized reaching the euthyroid state. In severe hypothyroidism, systemic arterial hypertension is present in about 30% of patients, mean arterial pressure is elevated, and about 20% of patients have diastolic hypertension. (7)

Endothelial dysfunction that occurs in hypothyroid patients predisposes to the development of atherosclerosis and increases arterial stiffness. Increased central arterial stiffness may further contribute to the development of hypertension in hypothyroidism. Aortic stiffness and systemic vascular resistance are increased in all patients with hypothyroidism, whether or not they have hypertension; the effects of these two conditions are additive. (8) Aortic stiffness and systemic vascular resistance are reduced during L-thyroxine therapy in hypothyroid patients with normal blood pressure and in patients with persistent hypertension. However, patients with higher basal aortic stiffness are less likely to normalize systolic blood pressure, which correlates with a decrease in aortic stiffness. Impairment of the elastic properties of the aorta may be the cause of incomplete normalization of blood pressure after replacement therapy in 50% of patients with hypothyroidism and hypertension, which requires the need for additional antihypertensive therapy. (9)

The influence of subclinical hypothyroidism on the cardiovascular system is manifested through systolic and diastolic cardiac function, myocardial anatomy and effort endurance. Numerous observational studies have shown that people with thyroid dysfunction have a worse cardiovascular outcome, including increased mortality. Even small changes in the concentration of thyroid hormones can have a negative effect on the cardiovascular system. Subclinical hypothyroidism is a strong independent risk factor for coronary artery disease. Prospective observational studies have shown that subclinical hypothyroidism in acute myocardial infarction (AIM) is associated with poorer cardiovascular outcome. Subclinical hypothyroidism in acute myocardial infarction increases cardiac mortality 3.6-fold and overall mortality 2.3-fold. (10)

Subclinical hypothyroidism in the time around acute myocardial infarction (AIM) is a condition that favors heart failure. AIM leads to lower serum levels of thyroid hormones as well as to downstream regulation of thyroid receptors in the myocardium, leading to tissue hypothyroidism. Prospective study by Friberg et al. has shown that thyroid hormone levels decline rapidly one week after AIM. (11) Second study by Friberg et al. showed that in-hospital mortality and post-hospital mortality were higher in patients who had lower serum thyroid hormone levels after AIM, suggesting that hypothyroidism was associated with a poorer prognosis. (12)

Compared with other organs, the heart is much more vulnerable in the hypothyroid state, because cardiomyocytes do not have the ability to convert T4 precursors to T3, as is the case in other organs. This may explain why even mild thyroid dysfunction has more pronounced effects on the heart than other organs. (3)

RISK FOR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN PATIENTS WITH HYPOTHYROIDISM

Overt hypothyroidism is characterized by hypercholesterolemia, significantly elevated LDL cholesterol, and apolipoprotein B. Due to the reduced fractional clearance of LDL cholesterol as a consequence of the reduced number of LDL receptors in the liver, the catabolism of LDL cholesterol is reduced and thus its half-life in circulation is prolonged. The application of L-thyroxine significantly improves the catabolism of LDL particles in the liver by activating LDL receptor mRNA. Observational studies have shown that hypothyroidism causes qualitative changes in circulating lipoproteins by increasing their atherogenicity. LDL cholesterol is more sensitive to oxidation in patients with hypothyroidism with normalization of oxidation by achieving a euthyroid state. (4) Hypothyroidism is associated with a reversible reduction in the activity of cholesterol-ester transfer protein, hepatic endothelial lipase, 7-alpha hydroxylase and hepatic LDL receptor. Lipoprotein(a) levels are elevated in hypothyroid patients, but the response to thyroid replacement therapy is unclear, although several studies have shown a decrease in lipoprotein(a) levels to L-thyroxine therapy. Triiodothyronine and HDL cholesterol are inversely correlated with the development of coronary heart disease. Hypothyroidism is associated with lower HDL cholesterol levels. Observational studies have shown a significant increase in HDL cholesterol with L-thyroxine (L-T4) therapy and normalization of serum TSH levels. (13)

Hyperhomocysteinemia is an independent risk factor for occlusive vascular disease, including coronary atherosclerosis, and predisposes to the development of atherosclerosis by stimulating LDL cholesterol oxidation, endothelial dysfunction and vascular damage of endothelial cells. Hyperhomocysteinemia occurs in patients with hypothyroidism due to reduced glomerular filtration of homocysteine (decreased clearance of homocysteine), and lack of thyroid hormones affects the activity of enzymes involved in folate metabolism, which leads to increased creatinine levels and reduced folate and vitamin B12. After achieving adequate thyrosubstitution, homocysteine levels in the blood return to normal. Reduction of homocysteine in the blood by 2-5 micromol/L, which is achieved by using L-thyroxine and achieving optimal TSH levels, significantly reduces cardiovascular risk. In contrast to overt hypothyroidism, subclinical hypothyroidism is not associated with hyperhomocysteinemia and no significant reduction in blood homocysteine has been observed in clinical studies after treatment of subclinical hypothyroidism with L-T4. (14)

Elevated levels of C-reactive protein (CRP), endothelial dysfunction, and coagulation abnormalities are additional risk factors for atherosclerosis in hypothyroid patients. (5)

The degree of hypothyroidism determines the effects of coagulation parameters. One study compared women with moderate hypothyroidism (TSH 10-50mU/L) and severe hypothyroidism (TSH > 50 mU/L) compared to euthyroid women and measured blood hemostatic parameters. Women with moderate hypothyroidism had decreased fibrinolytic activity, with decreased D-dimer levels, elevated alpha2-antiplasmin activity, and elevated levels of tissue plasminogen antigen activator and plasminogen activator antigen inhibitor. In contrast, women with severe hypothyroidism had high levels of D-dimer, decreased alpha2-antiplasmin activity, and decreased levels of tissue plasminogen antigen activator and plasminogen activator antigen inhibitor. These results suggested an increased risk of thrombosis that may precipitate myocardial and cerebral infarction in moderate hypothyroidism and an increased tendency for bleeding in patients with severe hypothyroidism. (15)

Many studies have shown that insulin resistance and metabolic syndrome are independent risk factors for cardiovascular disease, even in people without diabetes disease. Although, hypothyroidism has no direct effect on the development of insulin resistance, decreased levels of thyroid hormones in the blood may amplify the increased cardiovascular risk associated with insulin resistance by acting to increase total and LDL cholesterol levels. (4)

Subclinical hypothyroidism is associated with a small increase in LDL cholesterol, a decrease in HDL cholesterol, increasing the risk of developing atherosclerosis and coronary artery disease. These changes are based on the significant influence of thyroid hormones on lipid metabolism. (16) Subclinical hypothyroidism with a mild degree of thyroid dysfunction can induce the development of atherosclerosis in various ways - through endothelial dysfunction and impaired coagulation parameters. Additional risk factors that contribute to the increased prevalence of myocardial infarction in subclinical hypothyroidism are known risk factors for the development of coronary artery disease: hypercholesterolemia, hypertension, smoking and diabetes mellitus. Patients with subclinical hypothyroidism, who also had lower total cholesterol values compared to the control group, had manifest atherosclerotic vascular disease, suggesting that other factors contribute to an increased risk of developing atherosclerosis. Elevated serum LDL cholesterol, increased LDL oxidation, elevated serum triglycerides, and lipoprotein(a) are thought to explain the association of subclinical hypothyroidism and cardiovascular disease. (17)

Clear evidence of an increased prevalence of atherosclerotic cardiovascular disease in subclinical hypothyroidism was shown in a large randomized study involving 1,149 women living in Rotterdam over the age of 55 (Rotterdam study). This study showed that middle-aged women with subclinical hypothyroidism are more likely to

develop myocardial infarction and aortic wall calcification. Women with TSH greater than 4 mU/L (and normal FT4 values) had a higher prevalence of coronary artery disease compared to a control subjects with TSH less than 4 mU/L. A Rotterdam study found that women with elevated levels of antiperoxidase antibodies and normal thyroid function had a similar prevalence of atherosclerosis and myocardial infarction as euthyroid women without elevated levels of antibodies to thyroid peroxidase, suggesting that the development of atherosclerotic is mediated by a relative deficiency of thyroid hormones, rather than by immune dysfunction. (18)

EFFECTS OF THYROID REPLACEMENT THERAPY ON CARDIOVASCULAR SYSTEM

In most patients, the goal of thyroid replacement therapy is the TSH values between 0.5 and 2.5 mU/L, thus avoiding the effect of inadequate thyro-substitution. Optimal thyroid replacement therapy must take into account the patient's lifespan as well as the cause of hypothyroidism. The full dose of L-thyroxine therapy can be given with certainty to younger patients with overt hypothyroidism who do not have cardiovascular disease. In elderly patients with known or suspected coronary heart disease or in patients with manifest heart disease, thyroid replacement therapy should be initiated in small doses and gradually increased with monitoring of the patient's health. (19)

In large retrospective studies, new-onset angina pectoris and myocardial infarction occur relatively rarely after thyroid hormone administration. The beneficial effects of thyrosubstitution are much more common in reducing anginal symptoms (38%) compared to worsening angina (16%). One-year cardiovascular mortality in these patients diagnosed with angina and treated hypothyroidism was 3%, which is less than the one-year cardiovascular mortality of 9-15% observed in patients with angina during the same observation period. Administration of thyroid hormones leads to improved myocardial contractility and diastolic function and reduces afterload, which is the main determinant of oxygen consumption. This may explain how thyroid hormone therapy improves myocardial efficacy and leads to regression of anginal symptoms in hypothyroid patients. Worsening of angina, myocardial infarction and death may occur when L-thyroxine therapy is initiated at full doses in elderly patients with ischemic myocardial disease. Conversely, ventricular arrhythmias may improve or resolve completely after L-thyroxine therapy. (20)

The latest consensus formulated for guidelines for the treatment of patients with subclinical hypothyroidism recommends initiating L-thyroxine therapy in patients with subclinical hypothyroidism with TSH values above 10 mU/L in order to prevent progression to overt hypothyroidism. Thyroid replacement therapy improves the lipid profile and reduces cardiovascular risk in patients enrolled in multiple selected studies

who had a TSH greater than 10 mU/L, which supported the view that patients with subclinical hypothyroidism should be treated. (21)

CHANGES OF ECHOCARDIOGRAPHIC PARAMETERS IN OVERT AND SUBCLINICAL HYPOTHYROIDISM

During the development of thyroid dysfunction, there are changes in the structure and function of the myocardium, which can be manifested by: 1. structural and functional remodeling of the left ventricle, which can lead to impaired systolic, diastolic and global function of the left ventricle; 2. impaired left ventricular mechanics; 3. impaired structure, diastolic and global function of the right ventricle; 4. impaired right ventricular mechanics. (17)

Decreased diastolic function is detectable in the early stages of hypothyroidism. Isovolumic relaxation time (IVRT) is significantly prolonged in hypothyroid patients, which indicates impaired passive relaxation of the left ventricle, which leads to reduced early filling in diastole. Early/late (E/A) ratio of diastolic transmitral flow registered by Doppler echocardiography is already reduced in the early stages of hypothyroidism. These conditions are completely reversible after 3-6 months of adequate thyroid replacement therapy. Diastolic dysfunction can lead to increased morbidity, decreased exercise endurance and diastolic heart failure. Some studies have indicated a reduction in aortic root diameter after the application of L-thyroxine therapy, which is reflected in an improvement in aortic compliance and may be associated with an improvement in diastolic function. In hypothyroidism, asymmetric septal hypertrophy can be detected, which is reversible upon reaching the euthyroid state. This condition can be seen as one of the causes of left ventricular diastolic dysfunction, but also as an adaptive response to increased afterload, especially in the elderly. (22) Monzani et al. are showed an increase in left ventricular mass index in subclinical hypothyroidism relative to control, and the application of L-thyroxine therapy leads to a reduction in left ventricular mass and wall thickness. The mechanism leading to left ventricular hypertrophy in thyroid dysfunction is an increase in systemic vascular resistance and activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) which play a significant role in left ventricular hemodynamics and structural changes. (23) Reduction of left ventricular mass after L-thyroxine administration has positive effects on the improvement of diastolic dysfunction. Pulsed tissue Doppler can detect prolonged myocardial precontraction time and myocardial relaxation time at the level of the posterior septum and mitral annulus, which indicates impaired systolic and diastolic function in hypothyroidism. (24)

The influence of overt and subclinical hypothyroidism on systolic function is controversial. Sensitive echocardiographic methods, especially during physical stress, showed changes in systolic function in patients with thyroid dysfunction in relation

to control subjects. Impaired systolic function of the left ventricle at rest, defined by an increase in the ratio of preejection period (PEP) / left ventricular ejection time (LVET) and prolongation of left ventricular preejection period (PEP) has been shown in several studies involving patients with subclinical hypothyroidism. These changes are completely reversible after the application of thyroid replacement therapy and mostly after 6 months of L-thyroxine administration. (25)

Some studies also indicate depression of the global longitudinal strain of the left ventricle and the strain of the lateral wall and the interventricular septum of the left ventricle in patients with subclinical hypothyroidism. Changes in the mechanics of the left ventricle are mostly reduced after the application of L-thyroxine therapy. These results indicate that left ventricular hypertrophy is not the only mechanism responsible for left ventricular dysfunction in subclinical hypothyroidism. Hemodynamic changes in subclinical hypothyroidism lead to an increase in systemic vascular resistance, which plays a very important role in the relationship between thyroid hormones and left ventricular mechanics. In subclinical hypothyroidism, impaired left ventricular function and cardiorespiratory adaptation to exertion become manifest during exercise. These changes are reversible after the restitution of the euthyroid state. (26)

The right ventricle has been less studied echocardiographically, mainly due to the more complicated anatomy and the lack of reliable and accessible imaging techniques. There are conflicting studies on the effect of thyroid dysfunction on the thickness of the right ventricular wall. Several studies have shown that thyroid dysfunction did not lead to changes in right ventricular wall thickness. In contrast, several controlled studies showed that there was an increase in right ventricular wall thickness, impaired global and diastolic right ventricular function in patients with subclinical hypothyroidism compared to controls healthy subjects. There were no reduction in right ventricular wall thickness after thyroid replacement therapy in these studies, in contrast to improvements in global and diastolic right ventricular function after L-thyroxine administration. It has been shown that the mechanics of the right ventricle using "speckle tracking imaging" are significantly impaired in subclinical hypothyroidism. Global right ventricular strain and right ventricular free wall strain are reduced in hypothyroid patients compared to healthy subjects. The interaction between the right and left ventricles is one of the most important causes of impaired right ventricular function resulting from an increase in left ventricular filling pressure and a consequent increase in pulmonary flow and right ventricular pressure. The mechanism that leads to the remodeling of the right ventricle is the increased filling pressure, which is reflected in the increased E/e ratio. Other possible mechanisms of right ventricular hypertrophy in hypothyroidism are endothelial dysfunction of the pulmonary circulation, increased sympathetic and RAAS activity, as well as inadequate calcium uptake, leading to increased pulmonary vascular resistance. A large number

of studies have shown that disturbed mechanics of the right ventricle are completely repaired after adequate thyrosubstitution. (25,26)

References:

1. Jabbar A, Razvi S. Thyroid disease and vascular risk. *Clinical Medicine*. 2014; 14(6): 29–32.
2. Grais IM, Sowers JR. Thyroid and the heart. *Am J Med*. 2014; 127(8): 691–98.
3. Klein I, Danzi S. Thyroid disease and the heart. *Circulation* 2007; 116: 1725–35.
4. Vargas-Uricoechea H, Bonelo-Perdomo A, Sierra-Torres CH. Effects of thyroid hormones on the heart. *Clin Investig Arterioscler*. 2014; 26(6): 296– 309.
5. Udovicic M, Pena RH, Patham B, Tabatabai L, Kansara A. Hypothyroidism and the heart. *Methodist Debaque Cardiovasc J*. 2017; 13(2): 55–59.
6. Ichiki T. Thyroid hormone and vascular remodeling. *J Atheroscler Thromb*. 2016; 23(3): 266–75.
7. Owen PJ, Sabit R, Lazarus JH. Thyroid disease and vascular function. *Thyroid*. 2007; 17(6): 519–24.
8. Delitala AP, Orru M, Filigheddu F, Pilia MG, Delitala G, Ganau A, et al. Serum free thyroxine levels are positively associated with arterial stiffness in the SardiNIA study. *Clin Endocrinol*. 2015; 82(4): 592–7.
9. Wang J, Zheng X, Sun M, Wang Z, Fu Q, Shi Y, et al. Low serum free thyroxine concentrations associate with increased arterial stiffness in euthyroid subjects: a population-based cross-sectional study. *Endocrine*. 2015; 50(2): 465–73.
10. Molinaro S, Iervasi G, Lorenzoni V, Landi P, Srebot V, Mariani F, et al. Persistence of mortality risk in patients with acute cardiac diseases and mild thyroid dysfunction. *Am J Med Sci*. 2012; 343: 65–70.
11. Friberg L, Werner S, Eggertsen G, Ahnve S. et al. Rapid down-regulation of thyroid hormones in acute myocardial infarction: is it cardioprotective in patients with angina? *Arch Intern Med*. 2002; 162: 1388–94.
12. Friberg L, Drvota V, Bjelak AH, Eggertsen G, Ahnve S. Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. *Am J Med*. 2001; 111: 699–703.
13. Bansal SK, Yadav R. A Study of Extended Lipid Profile Including Oxidized LDL, Small Dense LDL, Lipoproteins (a) and Apolipoproteins in the Assessment of Cardiovascular Risk in Hypothyroidism Patients. *J Clin Diagn Res*. 2016; 10(6): BC04-BC08.
14. Zhou Y, Chen Y, Cao X, Liu C, Xie Y Association between plasma homocysteine status and hypothyroidism: a meta-analysis. *Int J Clin Exp Med*. 2014; 7(11): 4544–53.
15. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. *J Clin Endocrinol Metab*. 2003; 88(6): 2438–44.
16. Liu XL, He S, Zhang SF, Wang J, Sun XF, Gong CM, et al. Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis. *Med Sci Monit*. 2014; 20: 1432–41.

17. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, et al. Thyroid hormones and cardiovascular function and diseases. *J Am Coll Cardiol*. 2018; 71:1781–96.
18. Hak AE, Pols HAP, Visser TJ, Drexhage HA, Hofman A, Witteman JCM. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam study. *Ann Intern Med*. 2000; 132: 270–78.
19. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid*. 2014; 24(12): 1670–1751.
20. Gerdes AM, Iervasi G. Thyroid replacement therapy and heart failure. *Circulation*. 2010; 122(4): 385–93.
21. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. *Eur Thyroid J*. 2013; 2(4): 215–28.
22. Masaki M, Komamura K, Goda A, Hirotani S, Otsuka M, Nakabo A, et al. Elevated arterial stiffness and diastolic dysfunction in subclinical hypothyroidism. *Circ J*. 2014; 78: 1494–1500.
23. Monzani F, Di Bello V, Caraccio N, Bertini A, Giorgi D, Giusti C, et al. Effect of levotroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2001; 86(3): 1110–15.
24. Kosar F, Sahin I, Aksoy Y, Uzer E, Turan N. Usefulness of pulsed wave tissue Doppler echocardiography for the assessment of the left and right ventricular function in patients with clinical hypothyroidism. *Echocardiography*. 2006; 23(6): 471–77.
25. Turhan S, Tulunay C, Ozduman Cin M, GURSOY A, Kilickap M, Dincer I, et al. Effects of thyroxine therapy on right ventricular systolic and diastolic function in patients with subclinical hypothyroidism: a study by pulsed wave tissue Doppler imaging. *J Clin Endocrinol Metab*. 2006; 91(9): 3490–93.
26. Tiryakioglu SK, Tiryakioglu O, Ari H, Basel MC, Ozkan H, Bozat T. Left ventricular longitudinal myocardial function in overt hypothyroidism: a tissue Doppler echocardiographic study. *Echocardiography*. 2010; 27(5): 505–11.