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ULOGA CIRKADIJALNOG SISTEMA U NASTANKU KARDIOVASKULARNIH BOLESTI I KLINIČKE IMPLIKACIJE

Abstract: Circadian rhythm, an internal 24-hour cycle biological clock, regulates important biologic functions such as metabolism, body temperature, heart and respiratory rate, circulating levels of hormones, sleep-wake pattern, behaviour. It is also a very important in regulation of the cardiovascular (CV) system components such as arterial blood pressure, pulse, endothelial function. In this comprehensive review of the literature, we will discuss how interaction between environment/behavior stressors and circadian phases modulate individual cardiovascular risk. Potential therapeutical targets will be also discussed.

Keywords: circadian rhythm; cardiovascular system; cardiovascular diseases

Uvod

Poznato je da višećelijski organizmi, uključujući čoveka, poseduju unutrašnji, biološki časovnik, koji kontroliše metaboličke funkcije, telesnu temperaturu, frekvenciju srca i disanja, nivo hormona, ciklus budnost/spavanje, ponašanje i druge bitne funkcije i time pomaže da se ti procesi odvijaju u vreme koje je odgovarajuće za optimalno funkcionisanje organizma (1). Nobelova nagrada za fiziologiju ili medicinu za 2017. godinu pripala je naučnicima koji su, na modelu voćne mušice (*Drosophila*), 1984.godine izolovali gene koji kontrolišu normalan dnevni biološki ritam. Naime, Jeffrey C. Hall i Michael Rosbash pokazali su da gen, koji su nazvali *period,* kodira protein nazvan *PER* koji se nakuplja u ćeliji tokom noći, a razlaže tokom dana. Nivoi PER proteina osciliraju tokom 24 sata, sinhrono sa cirkadijalnim ritmom. Michael Young je deceniju kasnije, 1994. godine, otkrio i drugi gen, nazvan *timeless,* koji kodira *TIM* protein. Navedeni proteini vezivanjem i ulaskom u jedro blokiraju aktivnost *period* gena mehanizmom negativne povratne sprege. *Young* je identifikovao i gen *doubletime*, koji kodira

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DBT protein čija je uloga da odlaže akumulaciju *PER* proteina (2). S obzirom na kompleksne i precizne molekularne mehanizme, klinički značaj ovih otkrića jeste da je hronična neusklađenost stila života i biološkog ritma povezana sa povećanim rizikom za nastanak različitih bolesti, u prvom redu kardiovaskularnih, a zatim endokrinoloških i malignih.

Cirkadijalni ritam

Jedan od začetnika hronobiologije, Franc Halberg je, još davne 1959. godine, uveo u nauku pojam cirkadijalni ritam (latin. *circa*-okolo; *dien*-dan), koji je definisao kao cikličnu izmenu određene biološke funkcije sa trajanjem jednog ciklusa oko 24 sata, nezavisno od oscilacija spoljašnjih faktora (Halberg, 1959). Molekularne analize su pokazale da je svaka ćelija u telu kompetentni cirkadijalni sat sa glavnim biološkim časovnikom, odnosno cirkadijalnim pejsmejkerom, suprahijazmatičnim nukleusom (SCN) u hipotalamusu, koji sinhronizuje i koordiniše druge oscilatore u organizmu. Parvocelularni neuroni SCN dobijaju informacije sa retine, retinohipotalamičkim putem. Pored brojnih drugih uloga, kontrola sinteze i sekrecije melatonina je glavna izlazna funkcija SCN-a. Svetlost koja pada na retinu šalje signale do epifize (lat. *glandula pinealis*), inhibira sintezu melatonina i stimuliše budnost (3). Melatonin, glavni produkt pinealne žlezde, i primarni hormon cirkadijalnog sistema, ispoljava brojne antioksidativne, antiinflamatorne, antidepresivne, imunomodulatorne i kardioprotektivne efekte. Biosinteza melatonina se uglavnom događa u epifizi. Iako se sintetiše i u retini, digestivnom traktu, kostnoj srži i limfocitima, u ovim tkivima sinteza nije regulisana signalom svetlost/tama. Početak sekrecije melatonina je obično oko 21.00-22.00 h, sa maksimumom između ponoći i 03.00 h, dok se najniža koncentracija beleži u ranim jutarnjim časovima, između 07.00 i 09.00 h (4).

Uloga cirkadijalnog ritma u kardiovaskularnom sistemu

Centralni oscilatori su prisutni u centralnom nervnom sistemu, dok se periferni nalaze u različitim organima, uključujući i srce. Geni, receptori, ćelije, organi i fiziološki procesi u kardiovaskularnom sistemu ispoljavaju cirkadijalnu ritmičnost. U organizmu postoji konstantna interakcija između bihejvioralnih stresora (npr. nagla promena položaja tela nakon ustajanja, skok pritiska, smena noći i dana, unos hrane i dr.), cirkadijalnih faza i individualnog kardiovaskularnog rizika. Parametri kardiovaskularnog sistema,kao što su arterijski krvni pritisak, srčana frekvencija, funkcija vaskularnog endotela, faktora koagulacije, nivo cirkulišućih kateholamina i drugi, pokazuju fiziološke dvadesetčetvoročasovne varijacije, shodno potrebama organizma (5).

Cirkadijalne varijacije krvnog pritiska

Krvni pritisak odlikuju cirkadijalne varijacije, sa najizraženijim padom vrednosti tokom noći za 10 do 20%, kako kod zdravih osoba tako i kod hipertoničara. "Non--dipping" fenomen predstavlja pad krvnog pritiska tokom noći za manje od 10% i povezan je sa povećanim kardiovaskularnim rizikom (6). Krvni pritisak, takođe, karakteriše i porast nakon buđenja. Kod starijih pacijenata sa hipertenzijom porast sistolnog krvnog pritiska od 10mmHg dva sata nakon ustajanja povezan je sa 22% većim rizikom od moždanog udara, bez obzira na prosečnu vrednost krvnog pritiska u toku dana (7). Regulatori krvnog pritiska – adrenalin, noradrenalin, kortizol, tonus vagusa i srčana frekvencija, pokazuju cirkadijalni ritam. Burgess i saradnici su poredili funkciju autonomnog nervnog sistema kod ispitanika koji su spavali tokom noći i onih koji su bili lišeni spavanja. Uočeno je da ritmovi simpatičkog tonusa nisu zavisili od spavanja, a da ritmovi kardijalnog tonusa vagusa pokazuju cirkadijalnu ritmičnost. Ipak, nije bila kontrolisana izloženost svetlosti tokom deprivacije spavanja, što je moglo da utiče na simpatičku aktivnost (8). Radnici u noćnim smenama ostaju budni i aktivni i po 24h, u periodu kada su njihove psihofiziološke funkcije podešene na neaktivnost. Kod tih osoba zabeležen je povećan nivo proinflamatornih citokina (IL-6, TNF-α, C-reaktivnog proteina i rezistina). Takođe, često nastaje poremećaj metabolizma glukoze, što sve doprinosi nastanku kardiovaskularnih događaja (9).

Melatonin – imamo li novi antihipertenziv?

Melatonin se, osim kao hormon spavanja, pokazao i kao potencijalan antihipertenzivni agens. U dvostruko slepoj, placebo kontrolisanoj studiji, sprovedenoj na 14 zdravih muškaraca, administracija 1 mg melatonina redukovala je sistolni, dijastolni i srednji arterijski pritisak, kao i nivo kateholamina (10). U drugoj, takođe dvostruko slepoj, placebo kontrolisanoj studiji, tronedeljna peroralna primena ovog hormona (2,5 mg dnevno) sat vremena pre spavanja kod pacijenata sa prethodno nelečenom esencijalnom hipertenzijom značajno je redukovala i sistolni i dijastolni krvni pritisak (11). U navedenim studijama razlika u pritiscima kod primene melatonina i placeba je iznosila oko 5 do 10 mmHg, a poznato je da je upravo ta redukcija dijastolnog pritiska povezana sa smanjenjem kardiovaskularnog mortaliteta za 20% (12). Pokazano je da melatonin hipotenzivne efekte ostvaruje centralnim i perifernim mehanizmima, kao i da se receptori nalaze u centralnom i perifernom nervnom sistemu, endokrinom, reproduktivnom, gastrointestinalnom, imunskom, kao i u kardiovaskularnom sistemu, uključujući koronarne arterije, moždane arterije, aortu i arterije sistemske cirkulacije, kao i miokard komora (13, 14). U organizmu melatonin deluje preko tri tipa receptora, od kojih MT1 i MT2 imaju ključnu ulogu u kardiovaskularnoj regulaciji (15). Pretpostavlja se da svoje hipotenzivne efekte ostvaruje na tri načina: vazodilatatornim

dejstvom posredovanim endotelom, antioksidativnim efektom i simpatiko-vagalnom autonomnom regulacijom. Predstavlja snažan stimulator azot-monoksid sintaze i vazodilatatorni efekat ostvaruje preko MT2 receptora. Takođe, smanjuje koncentraciju cirkulišućeg noradrenalina, a povećava kardijalni tonus vagusa. Melatonin se pokazao kao siguran i efikasan aditivni antihipertenzivni agens. S obzirom na to da su melatoninski receptori široko rasprostranjeni u organizmu, potrebna su dalja istraživanja kako bi se rasvetleli precizni molekularni mehanizmi kojima ostvaruje svoje antihipertenzivne efekte (16, 17).

Disrupcija cirkadijalnog ritma i nastanak kardiovaskularnih događaja

Savremeni način života sa brojnim stresnim situacijama, nedovoljnim spavanjem, kasnim, neredovnim i preobilnim obrocima, izlaganjem veštačkom osvetljenju, posebno plavom spektru svetlosti koju emituju mobilni telefoni i računari, prekookeanski letovi sa promenama vremenskih zona, smenski, naročito noćni rad uvode u nauku jedan novi termin (18). Socijalni *jet lag* se definiše kao hronična neusklađenost cirkadijalnog sistema koja menja socijalno ponašanje. Približno 70% populacije pati od socijalnog *jet lag*-a (npr. njihov biološki i socijalni sat se razlikuju za više od 1h). Istraživanja su pokazala da veći socijalni *jet lag* nosi veći rizik od nastanka metaboličkih poremećaja, kao što su dijabetes melitus i gojaznost, kao i mentalnih poremećaja. Nije u potpunosti ispitana povezanost socijalnog *jet lag*-a i kardiovaskularnih bolesti, ali je poznato da je kod zdravih ispitanika povećana srčana frekvencija i nivo kortizola, dok je kod bolesnika sa dijabetes melitusom tip II zabeležena viša vrednost glikoziliranog hemoglobina (19). Epidemiološke studije su pokazale da se povećana incidencija kardiovaskularnih događaja beleži u jutarnjim časovima između 6h i 12h, upravo zbog disrupcije cirkadijalnih ritmova (20). Razlozi za jutarnje javljanje akutnog infarkta miokarda, moždanog udara, malignih poremećaja ritma, kao i iznenadne srčane smrti nalaze se u povećanom tonusu simpatikusa, vazokonstrikciji, porastu perifernog arterijskog otpora i sledstvenom skoku krvnog pritiska i srčane frekvencije, kao i povećanoj agregaciji trombocita u ranim jutarnjim satima. Nasuprot tome, beleži se smanjenje trombolitičke aktivnosti, parasimpatičkog tonusa i disfunkcija endotela (21–24).

Endotelna disfunkcija

Veoma važnu ulogu u regulaciji preciznih homeostatskih mehanizama u kardiovaskularnom sistemu (npr. vaskularni tonus, agregacija trombocita, fibrinoliza) igra endotel (25). Smanjena ili poremećena endotelna funkcija može provocirati vazokonstrikciju i intravaskularnu trombozu, naročito u slučaju pojačane aktivnosti simpatikusa i povećane senzitivnosti α-receptora u ranim jutarnjim satima (26).

Najveći stepen agregacije trombocita i najveća koncentracija inhibitora aktivacije plazminogena-1 (eng. *plasminogen activator inhibitor*-1, PAI-1), glavnog regulatora endogene fibrinolize, beleži se ujutru. Između ostalog, povišen nivo PAI-1 je povezan sa rizikom za aterosklerozu i trombozu (27). Takođe, postoji jutarnji pik aktivacije glikoproteinskih IIb/IIIa receptora na površini trombocita, koji su uključeni u završni zajednički put agregacije trombocita (28). Klinički značaj je da se lekovima inhibitorima glikoproteinskih IIb/IIIa receptora može blokirati agregacija trombocita koja je stimulisana trombinom, ADP, kolagenom, serotoninom i drugim medijatorima.

Uloga cirkadijalnog sistema i melatonina u akutnom infarktu miokarda

Istraživanja su pokazala da je nastanak akutnog infarkta miokarda povezan sa smanjenom nokturalnom sekrecijom melatonina. Smanjena sekrecija melatonina tokom noći kod bolesnika sa infarktom miokarda sa ST elevacijom (STEMI) korelirala je sa porastom C-reaktivnog proteina, markera akutne faze zapaljenskog procesa, i bila je prediktor nepovoljnih događaja u narednih 6 meseci (29). Kod bolesnika sa koronarnom bolešću ili srčanom insuficijencijom uočen je pad noćne sekrecije melatonina ili njegovog metabolita 6-sulfatoksimelatonina (aMT6S) koji se izlučuje urinom (30, 31). Na izolovanom srcu pacova melatonin je delovao protektivno na ishemijsko-reperfuziono oštećenje miokarda i redukovao je nekrozu i veličinu infarktne zone (32). Studija Reiter-a i saradnika, iz 2011. godine, po prvi put je pokazala na humanoj populaciji da veličina infarktne zone i ejekciona frakcija leve komore kod bolesnika sa infarktom miokarda sa elevacijom ST segmenta (STEMI) imaju cirkadijalnu zavisnost, odnosno da zavise od doba dana. U njihovoj studiji najveće oštećenje miokarda zabeleženo je jedan sat od početka ishemije i pet sati nakon reperfuzije (33). Istraživanje Mahmoud-a i saradnika pokazalo je da je i najveća incidencija tromboze stenta zabeležena u ranim jutarnjim satima (34). Interesantno je da se pomeranje kazaljki časovnika jedan sat unapred zbog letnjeg računanja vremena dovodi u vezu sa tranzitornim porastom incidencije akutnog infarkta miokarda u proleće, između ostalog, zbog deprivacije spavanja i lošijeg kvaliteta sna, dok su podaci o incidenciji usled zimskog računanja vremena kontroverzni (35). U prospektivnoj, randomizovanoj studiji Domínguez-Rodríguez i saradnici su pokazali da je intravenska primena melatonina kod bolesnika sa STEMI, lečenih primarnom perkutanom koronarnom intervencijom, korelirala sa redukcijom mortaliteta i rehospitalizacije zbog srčane slabosti, u dvogodišnjem periodu praćenja. Efekat melatonina se ogledao u atenuaciji matriksne metaloproteinaze-9, ključnog enzima uključenog u remodelovanje miokarda usled akutnog infarkta miokarda (36). Studija publikovana u *Lancet*-u 2018. godine pokazala je značaj hronobiologije i u kardiohirurgiji. Perioperativna ozleda miokarda usled zamene aortne valvule bila je statistički značajno niža kod pacijenata koji su operisani u popodnevnim satima,

u poređenju sa operacijama izvedenim u jutarnjim satima. Razlog je cirkadijalna ekspresija miokardnog gena sa nuklearnim receptorom Rev-Erbα koja je najviša prepodne. Kardioprotekciju bi omogućila eventualna farmakološka primena antagonista Rev-Erbα receptora (37).

Cirkadijalna distribucija kardiovaskularnih događaja kod bolesnika sa poremećajima disanja tokom spavanja

Bolesnici sa srčanom insuficijencijom sa redukovanom ejekcionom frakcijom (engl. *Heart failure with reduced ejection fraction* – HFrEF) često kao komorbiditet imaju poremećaje disanja tokom spavanja, kao što su opstruktivna (OSA) i centralna sleep apnea (CSA). Disrupcija cirkardijalnog ritma nastaje usled narušene arhitektonike spavanja usled prisutnog poremećaja disanja, sa posledičnim disbalansom autonomne, hemodinamske, humoralne i vaskularne regulacije (38). Zapaženo je da se naprasna srčana smrt dešava najčešće tokom spavanja, u periodu od ponoći do šest časova ujutru, za razliku od opšte populacije, gde je incidencija najveća ujutru nakon buđenja (39). U prilog tome govori podatak iz studije Bitter-a u kojoj su aktivacije implantibilnog kardioverter defibrilatora usled ventrikularne tahikadije kod bolesnika sa OSA i HFrEF registrovane najčešće tokom noći, u periodu od 00.00 do 05.59h, dok su se kod bolesnika sa CSA javljale u bilo koje doba dana ili noći (40). Poznato je da se opstruktivna apnea javlja samo tokom spavanja, dok se Čejn Štoksovo (engl. *Cheyne-Stokes*) disanje, kao centralni poremećaj respiracije, može javiti i u budnom stanju (41). Naime, epizode apnee dovode do hipoksemije, hiperkapnije, povećanog tonusa simpatikusa, povećanog intratorakalnog pritiska i nastanka srčanih aritmija (38). Stoga je potrebna pažljiva, multidisciplinarna evaluacija ovih vulnerabilnih grupa bolesnika.

Zaključak

Iako su brojne studije pokazale uticaj izmene cirkadijalnih ritmova na kardiovaskularni sistem, treba naglasiti da je većina sprovedena na zdravim ispitanicima. Stoga, potencijalna ispitivanja cirkadijalnih ritmova treba izvršiti na osobama obolelim od kardiovaskularnih bolesti. Poznato je da se i kardiovaskularni lekovi primenjuju u određeno doba dana, kako bi se ostvarili maksimalni efekti, a minimizirale nuspojave. Značaj budućih studija ogledaće se u detaljnijem razjašnjenju uloge cirkadijalnog sistema na kardiovaskularne komplikacije kod ljudi, kao i boljem razumevanju i razvoju hronoterapije, koja može biti implementirana ne samo u medikamentnom lečenju, već i u elektivnim kardiovaskularnim intervencijama, uz prilagođavanje biološkom ritmu individualnog pacijenta.

Ne postoji konflikt interesa.

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THE ROLE OF THE CIRCADIAN SYSTEM IN CARDIOVASCULAR DISEASES AND CLINICAL IMPLICATIONS

Abstract: Circadian rhythm, an internal 24-hour cycle biological clock, regulates important biologic functions such as metabolism, body temperature, heart and respiratory rate, circulating levels of hormones, sleep-wake pattern, behaviour. It is also a very important in regulation of the cardiovascular (CV) system components such as arterial blood pressure, pulse, endothelial function. In this comprehensive review of the literature, we will discuss how interaction between environment/behavior stressors and circadian phases modulate individual cardiovascular risk. Potential therapeutical targets will be also discussed.

Keywords: circadian rhythm; cardiovascular system; cardiovascular diseases

Introduction

It is well known that all multicellular organisms, including humans, have an internal, biological clock that regulates important biologic functions such as metabolism, body temperature, heart and respiratory rate, circulating levels of hormones, sleep/wake pattern, behavior. The biological clock provides that the body's processes are optimized at various points during a 24-hour period (1). The 2017 Nobel Prize in Physiology or Medicine is awarded to the scientists for their discoveries of genes that regulate circadian rhythm, described in 1984, in the fruit fly model (*Drosophila*). Jeffrey C. Hall and Michael Rosbash showed that clock gene, called *period*, encoding protein called PER, accumulates in the cell during the night, and degrades during the day. PER protein levels oscillate during 24h, synchronously to the circadian rhythm. A decade later, in 1994, Michael W. Young discovered *timeless*, an additional gene influencing the circadian clock, that encodes TIM protein. Upon entering the nucleus, the mentioned proteins block the activity of the period gene by a negative feedback mechanism. Young also identified the *doubletime* gene, which encodes a DBT protein

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whose role is to delay the accumulation of PER protein (2). Considering the complex and precise molecular mechanisms, the clinical significance of these findings is that chronic disturbance of the biological rhythm is associated with an increased risk for various diseases, primarily cardiovascular, then endocrinological and malignant.

Circadian rhythm

Franz Halberg, one of the founders of chronobiology, introduced the term circadian rhythm to science in 1959 (latin. *Circa* – around, and *dies* – day), which he defined as a cyclic change of a certain biological function with duration of one cycle about 24 hours, independent of external factors oscillations (Halberg, 1959). Molecular analyzes have shown that every cell in the body underogoes circadian clock with a master biological clock, that is, the circadian pacemaker, the suprachiasmatic nucleus (SCN) in the hypothalamus, which synchronizes and coordinates other oscillators in the body. Parvocellular neurons of the SCN receive information from the retina, via the retinohypothalamic pathway. In addition to numerous roles, melatonin synthesis and secretion control is a major output function of the SCN. The light falling on the retina sends signals to the pineal gland (latin. *glandula pinealis*), inhibits melatonin synthesis and stimulates wakefulness (3). Melatonin the main product of the pineal gland, and the primary hormone of the circadian system, exhibits numerous antioxidant, anti-inflammatory, antidepressant, immunomodulatory and cardioprotective effects. Biosynthesis of melatonin mainly occurs in the pineal gland. Although it is also synthesized in the retina, digestive tract, bone marrow and lymphocytes, synthesis in these tissues is not regulated by the light/dark signal. The start of melatonin secretion is usually around 09:00-10:00 p.m. with a maximum between midnight and 03:00 a.m. while the lowest concentration is in the early morning hours, between 07:00 and 09:00 a.m. (4).

The role of the circadian rhythm in the cardiovascular system

Central oscillators are present in the central nervous system, while peripheral oscillators are found in various organs, including the heart. Genes, receptors, cells, organs and physiological processes in the cardiovascular system have circadian rhythmicity. In the body, there is a constant interaction between behavioral stressors (for example, a sudden change in body position after getting up, sudden rise in blood pressure, change of night and day, food intake), circadian phases and individual cardiovascular risk. Parameters of the cardiovascular system such as arterial blood pressure, heart rate, vascular endothelium function, coagulation factors, level of circulating catecholamines and others, show physiological 24-hour variations (5).

Circadian variations in blood pressure

Blood pressure is characterized by circadian variations, with the most pronounced drop in values during the night by 10 to 20%, both in healthy individuals and in hypertensive patients. The "non-dipping" phenomenon is a drop in blood pressure during the night by less than 10% and is associated with an increased cardiovascular risk (6). Similarly, in elderly patients with hypertension, an increase in systolic blood pressure more than 10 mmHg two hours after waking up was associated with a 22% higher risk of stroke, regardless of the average value of blood pressure during the day (7). Blood pressure regulators (adrenaline, noradrenaline, cortisol, vagus tone and heart rate) are also under circadian rhythm regulation. Burgess et al. compared the autonomic nervous system function in subjects who slept through the night and those who were sleep deprived. It was observed that the rhythms of the sympathetic tone did not depend on sleep, while the vagus mediated cardiac tone showed circadian rhythmicity. However, exposure to light during sleep deprivation, which could affect sympathetic activity, was not controlled (8). Dysregulated circadian rhythm may consequently result in increase of proinflammatory cytokines. Namely, it was observed that night shift workers who stay awake up to 24 hours have increase of some markers of inflammation such as IL-1β, IL-6, TNF-α. They were also associated with impaired glucose metabolism. – resulting in higher presence of cardiovascular events in this population (9).

Melatonin-do we have a new antihypertensive agent?

Melatonin, in addition to being a sleep hormone, has also been shown to be a potential antihypertensive agent. In a double-blind, placebo-controlled study conducted on 14 healthy men, administration of 1 mg of melatonin reduced systolic, diastolic and mean arterial pressure, as well as catecholamine levels (10). In another, also double-blind, placebo-controlled study, three-week oral administration of this hormone (2.5 mg daily) one hour before bedtime in patients with previously untreated essential hypertension significantly reduced both systolic and diastolic blood pressure (11). In these studies, the difference in blood pressure when using melatonin versus placebo was about 5 to 10 mmHg, and it is known that this reduction in diastolic pressure is associated with a 20% reduction in cardiovascular mortality (12). It has been shown that melatonin achieves hypotensive effects through central and peripheral mechanisms, as well as that receptors are located in the central and peripheral nervous system, endocrine, reproductive, gastrointestinal, immune and cardiovascular systems, including coronary arteries, cerebral arteries, aorta and systemic circulation arteries, as well as the myocardial ventricles (13,14). In the body, melatonin acts through three types of receptors, of which MT1 and MT2 play a key role in cardiovascular regulation (15).

It is assumed that hypotensive effects of melatonin are achieved through endothelium mediated vasodilatatory effect, antioxidant effect and sympathetic-vagal autonomic regulation. It is a strong stimulator of nitric oxide synthase and has a vasodilatory effect through the MT2 receptor. Also, it reduces the concentration of circulating noradrenaline, and increases the cardiac tone of the vagus. Melatonin has been shown to be a safe and effective additive antihypertensive agent. The melatonin receptors are widely distributed in the body and further research is needed to elucidate all precise molecular mechanisms of its antihypertensive effects (16,17).

Disruption of the circadian rhythm and the occurrence of cardiovascular events

The modern way of life with numerous stressful situations, insufficient sleep, late, irregular and excessive meals, exposure to artificial lighting, especially the blue spectrum of light emitted by mobile phones and computers, transoceanic flights with time zones changes, shift work, especially night work, introduce a new field in science and medicine (18). Social jet lag is defined as a chronic misalignment of the circadian system that alters social behavior. Approximately 70% of the population suffers from social jet lag (for example, their biological and social clocks differ by more than one hour). Research has shown that greater social jet lag carries a greater risk of developing metabolic disorders, such as diabetes mellitus and obesity, as well as mental disorders. The assosication between social jet lag and cardiovascular diseases has not been fully investigated, but it is known that heart rate and cortisol levels are increased in healthy subjects, while a higher value of glycosylated hemoglobin was noticed in patients with type II diabetes mellitus (19). Epidemiological studies have shown the increased incidence of cardiovascular events in the morning hours between 6 a.m. and noon because of disrupted circadian rhythms (20). The reasons for the morning occurrence of acute myocardial infarction, stroke, malignant arrhythmias, as well as sudden cardiac death are found in increased sympathetic tone, vasoconstriction, an increase in peripheral arterial resistance and a consequent raise in blood pressure and heart rate, as well as increased platelet aggregation in the early morning hours. In contrast, a decrease in thrombolytic activity and parasympathetic tone as well as endothelial dysfunction is noted (21-24).

Endothelial dysfunction

The endothelium plays a very important role in the regulation of precise homeostatic mechanisms in the cardiovascular system (for example, vascular tone, platelet aggregation, fibrinolysis) (25). Impaired endothelial function results in vasoconstriction and intravascular thrombosis. This is particulartly prominent event in the early

morning hours when increased sympathetic activity and sensitivity of α-receptors are present (26). The highest platelet aggregation and the highest concentration of plasminogen activation inhibitor-1 (PAI-1), the main regulator of endogenous fibrinolysis, is in the morning. An elevated PAI-1 is associated with the risk for atherosclerosis and thrombosis (27). Similarly, there is a morning peak of glycoprotein IIb/IIIa receptors activation on the platelet surface, which are involved in the final common pathway of platelet aggregation (28). The clinical significance is that platelet aggregation stimulated by thrombin, ADP, collagen, serotonin and other mediators can be blocked with glycoprotein IIb/IIIa receptor inhibitor drugs.

The role of the circadian system and melatonin in acute myocardial infarction

Studies have shown that the onset of acute myocardial infarction is associated with reduced nocturnal melatonin secretion. Decreased secretion of melatonin during the night in patients with ST-elevation myocardial infarction (STEMI) correlated with an increase in C-reactive protein, a marker of the acute phase of the inflammatory process, and was a predictor of adverse events in the following 6 months (29). In patients with coronary disease or heart failure, a decrease in nocturnal secretion of melatonin or its metabolite 6-sulfatoxymelatonin (aMT6S), excreted via urine, was observed (30,31). On the isolated rat hearts, melatonin had a protective effect on myocardial ischemia-reperfusion damage and reduced necrosis and the size of the infarct zone (32). For the first time in the human population a study by Reiter and al. from 2011 showed that the size of the infarct zone and the ejection fraction of the left ventricle in patients with myocardial infarction with ST segment elevation have a circadian dependence. In their study, the greatest myocardial damage was recorded one hour after the onset of ischemia and five hours after reperfusion (33). Research by Mahmoud et al showed that the highest incidence of stent thrombosis was recorded in the early morning hours (34). It is interesting that clock shifting for one hour during summer time is light saving time is associated with transient increase in the incidence of acute myocardial infarction in the spring as the consequence of sleep deprivation and poorer sleep quality, while for the winter time data are controversial (35). In a prospective randomized study, Domínguez-Rodríguez et al. showed that intravenous administration of melatonin in patients with STEMI treated by primary percutaneous coronary intervention correlated with a reduction in mortality and rehospitalization due to heart failure in a two-year follow-up period. The effect of melatonin was reflected in the attenuation of matrix metalloproteinase-9, a key enzyme involved in myocardial remodeling due to acute myocardial infarction (36). A study published in Lancet in 2018 showed the importance of chronobiology in cardiac surgery. Perioperative myocardial injury due to aortic valve replacement was significantly lower in patients operated in the afternoon, compared to surgeries performed in the morning.

This could be due to circadian expression of the myocardial gene with the nuclear receptor Rev-Erbα, which is the highest in the morning. Cardioprotection would be made possible by the eventual pharmacological application of Rev-Erbα receptor antagonists (37).

Circadian distribution of cardiovascular events in patients with breathing disorders during sleep

Patients with heart failure with reduced ejection fraction (HFrEF) often have breathing disorders during sleep as a comorbidity, such as obstructive (OSA) and central sleep apnea (CSA). Disruption of the circadian rhythm is associated with disturbed sleep due to various breathing disorders, with the consequent imbalance of autonomic, hemodynamic, humoral and vascular regulation (38). It has been observed that sudden cardiac death occurs most often during sleep, in the period from midnight to six in the morning, in contrast to general population, where the incidence is the highest in the morning, after waking up (39). This is supported by the findings of Bitter et al, who showed that in patients with OSA and HFrEF activations of the implantable cardioverter defibrillator (ICD) due to ventricular tachycardia were registered most often during the night, from 00:00 am to 05:59 am, while in patients with CSA activations occur at any time of the day or night (40). Obstructive apnea is known to occur only during sleep, while Cheyne Stokes breathing, as a central respiratory disorder, can also occur during wakefulness (41). Episodes of apnea lead to hypoxemia, hypercapnia, increased sympathetic tone, increased intrathoracic pressure and cardiac arrhythmias (38). Therefore, a careful, multidisciplinary evaluation of these vulnerable patient groups is needed.

Conclusion

Although numerous studies have shown the impact of circadian rhythm changes on the cardiovascular system, it should be emphasized that most of them were conducted on the healthy subjects. Therefore, potential studies of circadian rhythm should be performed on people suffering from cardiovascular diseases. It is known that cardiovascular drugs are used at the certain time of the day, in order to achieve maximum effects and while minimizing side effects. Future studies would provide detailed clarification of the circadian system role in cardiovascular complications in humans, as well as a better understanding and development of chronotherapy, with possible implementation not only in medical treatment, which can be implemented not only in medical treatment, but also in elective cardiovascular interventions, with adaptation to the biological rhythm of the individual patient.

There is no conflict of interest.

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