Testiranje autonomnoga živčanog sustava u bolesnika s kardiovaskularnim bolestima: od istraživanja do kliničke primjene

Autonomic Nervous System Testing in Cardiovascular Patients: From Research to Clinical Application

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SAŽETAK: Autonomni živčani sustav (ANS) ima ključnu ulogu u kardiovaskularnoj (KV) regulaciji kroz dinamičku interakciju svojih simpatičkih i parasimpatičkih dijelova. Disregulacija autonomne ravnoteže sve se više prepoznaje kao važan patofiziološki doprinos širokom rasponu KV poremećaja. Različite neinvazivne metode, poput varijabilnosti srčanog ritma, oporavka srčanog ritma, osjetljivosti barorefleksa, praćenja arterijskoga tlaka i testiranja nagibnim stolom, pokazale su znatnu dijagnostičku i prognostičku vrijednost u procjeni autonomne funkcije, dok komplementarni postupci poput testa aktivnoga stajanja, Valsalvina manevra i testa dubokog disanja mogu ponuditi dodatan uvid u autonomnu kontrolu, ali su i dalje nedovoljno iskorišteni u rutinskoj praksi. Unatoč rastućim dokazima koji podržavaju njihovu kliničku relevantnost, šira klinička primjena testiranja ANS-a ostaje ograničena metodološkom heterogenošću, nedostatkom jedinstvenih standarda i nedovoljnim konsenzusom o interpretaciji i kliničkim putevima odlučivanja. Ovaj članak pruža integrirani pregled uobičajeno primjenjivanih modaliteta testiranja ANS-a, sažimajući njihovu fiziološku osnovu i procjenjujući njihovu kliničku primjenjivost u kardiologiji. Osim tehnološkog napretka, uspostavljanje jedinstvenih međunarodnih smjernica, standardiziranih protokola i okvira za interpretaciju temeljenih na konsenzusu bit će ključno za osiguranje dosljednosti, poboljšanje usporedivosti između istraživanja i olakšavanje integracije testiranja ANS-a u rutinsku kardiološku praksu. Zahvaljujući takvim zajedničkim naporima procjena ANS-a ima potencijal da se razvije od istraživačkog instrumenta do komponente personalizirane KV medicine.

KLJUČNE RIJEČI: autonomni živčani sustav, kardiovaskularne bolesti, autonomna disfunkcija, stratifikacija rizika, klinička dijagnostika.

SUMMARY: The autonomic nervous system (ANS) plays a pivotal role in cardiovascular (CV) regulation through the dynamic interplay of its sympathetic and parasympathetic divisions. Dysregulation of autonomic balance is increasingly recognized as an important pathophysiological contributor to a broad range of CV disorders. A variety of non-invasive methods, such as heart rate variability, heart rate recovery, baroreflex sensitivity, blood pressure monitoring, and tilt-table testing, have demonstrated substantial diagnostic and prognostic value in assessing autonomic function across CV disorders, while complementary procedures such as the active standing test, Valsalva maneuver, and deep-breathing test may offer additional insight on autonomic control but remain underutilized in routine cardiology. Despite growing evidence supporting their clinical relevance, the broader clinical adoption of ANS testing remains limited by methodological heterogeneity, absence of unified standards, and insufficient consensus on interpretation and clinical decision pathways. This article provides an integrated overview of commonly used ANS testing modalities, summarizing their physiological basis and evaluating their clinical applicability in cardiology. In addition to technological advances, establishing unified international guidelines, standardized protocols, and consensus-based interpretation frameworks will be crucial to ensure consistency, improve comparability between studies, and facilitate the integration of ANS testing into routine cardiological practice. Through such collaborative efforts, ANS assessment has the potential to evolve from a research instrument into a component of personalized CV medicine.

KEYWORDS: autonomic nervous system, cardiovascular diseases, autonomic dysfunction, risk stratification, clinical diagnostics.

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Uvod

Dinamična interakcija između mozga i srca, posredovana prije svega autonomnim živčanim sustavom (ANS), pruža bitan uvid u kardiovaskularnu (KV) regulaciju i cjelokupno fiziološko funkcioniranje KV sustava. ANS, koji se sastoji od simpatičke i parasimpatičke grane, ima središnju ulogu u regulaciji otkucaja srca (HR), vaskularnog tonusa i kontraktilnosti miokarda.[1] Kontinuiranom modulacijom ovih funkcija ANS održava KV homeostazu kao odgovor na unutarnje i vanjske podražaje. Autonomna regulacija srca uključuje složene refleksne mehanizme, uključujući baroreceptorske i kardiopulmonalne reflekse, kao i izravnu inervaciju srca vagalnim i simpatičkim vlaknima.[2,3]

Poremećaj ove osjetljive ravnoteže često je karakteriziran prekomjernom simpatičkom aktivacijom i/ili parasimpatičkim povlačenjem te je impliciran u patogenezi različitih KV bolesti,[4] uključujući arterijsku hipertenziju (HTN),[5] zatajivanje srca (HF),[6] aritmije[7] i ishemijsku bolest srca (CAD).[8] Autonomna disfunkcija ne samo da pridonosi nastanku i napredovanju bolesti nego je povezana i s nepovoljnim kliničkim ishodima, uključujući povećan morbiditet i mortalitet.[9] Kao takva, procjena autonomne funkcije ima znatnu kliničku važnost za rano otkrivanje, stratifikaciju rizika, terapijsko odlučivanje i za prognostičku evaluaciju u KV medicini.[9,10] Unatoč prepoznatoj važnosti, standardizirano autonomno testiranje ostaje nedovoljno iskorišteno u rutinskoj kardiološkoj praksi, uglavnom zbog ograničene svijesti, neadekvatne edukacije i ograničene dostupnosti infrastrukture za testiranje i validiranih protokola.

Za procjenu funkcije ANS-a dostupan je niz neinvazivnih testova, uključujući varijabilnost otkucaja srca (HRV), osjetljivost barorefleksa (BRS), odgovore arterijskoga tlaka (BP) na fiziološke podražaje i testiranje nagibnim stolom.[10] Napredne metode poput mikroneurografije i aktivnosti simpatičkoga živčanog sustava kože pružaju izravne ili surogatne mjere simpatičkog odljeva, dok kardiovagalni i simpatički refleksni testovi (npr. duboko disanje, Valsalvin manevar) ostaju ključni za funkcionalnu procjenu. Novi indeksi poput kapaciteta ubrzanja i usporivanja HR-a, kao i komplementarne vaskularne mjere kao što su brzina pulsnog vala i krutost arterija, nude dodatne uvide u autonomnu regulaciju, posebno u supkliničkoj ili ranoj fazi disfunkcije.[10-12] Ovi dijagnostički alati mogu pomoći kliničarima u otkrivanju suptilnih oblika disautonomije, praćenju učinkovitosti terapijskih intervencija i poboljšanju individualiziranog liječenja.[12]

Svrha je ovoga članka pružiti sveobuhvatan pregled testiranja ANS-a, s posebnim naglaskom na njegovu primjenu u kardiologiji. Predstavit ćemo fiziološke temelje, metodološke principe, kliničku korisnost i interpretativne okvire svakog testa. Sintezom trenutačnoga znanja i isticanjem potencijala spomenutih alata, svrha nam je potaknuti njihovu širu integraciju u KV dijagnostiku i skrb.

Pregled metoda testiranja autonomne funkcije

U ovom odjeljku predočujemo glavne testove autonomne funkcije koji su opsežno proučavani posljednjih godina. Svaki će test biti razmotren s obzirom na svoju fiziološku osnovu, kliničku primjenjivost i relevantnost za procjenu KV-a.

VARIJABILNOST SRČANOG RITMA

Varijabilnost srčanog ritma odnosi se na fiziološki fenomen varijacije u vremenskim intervalima između uzastopnih otkucaja srca, obično mjereno kao vrijeme između uzastopnih

Introduction

The dynamic interplay between the brain and the heart, mediated primarily through the autonomic nervous system (ANS), provides essential insights into cardiovascular (CV) regulation and overall physiological functioning of the vascular system. The ANS, comprising the sympathetic and parasympathetic branches, plays a central role in regulating heart rate (HR), vascular tone, and myocardial contractility.[1] Through continuous modulation of these functions, the ANS maintains CV homeostasis in response to both internal and external stimuli. Cardiac autonomic regulation involves complex reflex mechanisms, including baroreceptor and cardiopulmonary reflexes, as well as direct innervation of the heart by vagal and sympathetic fibers.[2,3]

Disruption of this delicate balance is often characterized by excessive sympathetic activation and/or parasympathetic withdrawal and has been implicated in the pathogenesis of various CV diseases,[4] including hypertension (HTN),[5] heart failure (HF),[6] arrhythmias,[7] and ischemic heart disease.[8] Autonomic dysfunction not only contributes to disease onset and progression but is also associated with adverse clinical outcomes, including increased morbidity and mortality.[9] As such, the assessment of autonomic function holds substantial clinical relevance for early detection, risk stratification, therapeutic decision-making, and prognostic evaluation in CV medicine.[9,10] Despite its widely-recognized importance, standardized autonomic testing remains underutilized in routine cardiology practice, largely due to limited awareness, inadequate training among clinicians, and constrained availability of testing infrastructure and validated protocols.

A variety of non-invasive tests are available for the assessment of ANS function, including heart rate variability (HRV), baroreflex sensitivity (BRS), blood pressure (BP) responses to physiological stimuli, and tilt-table testing.[10] Advanced methods such as microneurography and skin sympathetic nerve activity provide direct or surrogate measures of sympathetic outflow, while cardiovagal and sympathetic reflex tests (e.g., deep breathing, Valsalva maneuver) remain essential for functional evaluation. Novel indices such as HR acceleration and deceleration capacity, as well as complementary vascular measures such as pulse wave velocity and arterial stiffness, offer additional insights into autonomic regulation, particularly for subclinical or early-stage dysfunction.[10-12] These diagnostic tools can help clinicians detect subtle forms of dysautonomia, monitor the efficacy of therapeutic interventions, and improve individualized patient management.[12]

The aim of this article is to provide a comprehensive overview of ANS testing, with a particular focus on its application in cardiology. We will present the physiological foundations, methodological principles, clinical utility, and interpretative frameworks of each test. By synthesizing current knowledge and emphasizing the potential of these tools, we aim to encourage their broader integration into CV diagnostics and patient care.

Overview of autonomic function testing methods

In this section, we present the principal autonomic function tests that have been extensively studied in recent years. Each test will be discussed in terms of its physiological basis, clinical applicability, and relevance to CV assessment.

HEART RATE VARIABILITY

Heart rate variability (HRV) refers to the physiological phenomenon of variation in the time intervals between consecutive

R-valova (RR intervala) na elektrokardiogramu (EKG).[13] Ta varijabilnost ne odražava patološku nepravilnost, nego fiziološku prilagodljivost srca promjenjivim unutarnjim i vanjskim uvjetima te se smatra ključnim neinvazivnim markerom funkcije ANS-a.[13,14] HRV proizlazi iz kontinuirane i dinamičke interakcije između simpatičkog i parasimpatičkog dijela ANS-a u regulaciji aktivnosti sinoatrijalnoga čvora (SNA). Viši HRV općenito upućuje na veći vagalni (parasimpatički) utjecaj i bolju KV prilagodljivost, dok je smanjeni HRV često povezan s autonomnom disfunkcijom, povećanom simpatičkom dominacijom i povećanim rizikom od neželjenih KV ishoda.[15] Kao takav, HRV pruža vrijedan uvid u ravnotežu autonomne kontrole, odaziv na stres, kapacitet oporavka i ukupnog KV zdravlja. U KV patologiji neravnoteža između simpatičke i parasimpatičke aktivnosti može pridonijeti progresiji bolesti i lošim kliničkim ishodima.[15,16] Stoga analiza HRV-a služi ne samo kao dijagnostički alat već i kao prognostički marker u različitim srčanim stanjima.[16]

Kvantitativna procjena HRV-a olakšava se naprednim, validiranim softverskim platformama sposobnima za izdvajanje sveobuhvatnog raspona HRV indeksa iz EKG zapisa (**slika 1**).[17] Ovi se parametri mogu izvesti iz različitih vrsta EKG podaheartbeats, typically measured as the time between successive R-waves (RR intervals) on an electrocardiogram (ECG).[13] This variability does not reflect pathological irregularity but rather the heart's physiological adaptability to changing internal and external conditions and is considered a key non-invasive marker of ANS function.[13,14] HRV arises from the continuous and dynamic interaction between the sympathetic and parasympathetic divisions of the ANS in regulating sinoatrial node activity (SNA). Higher HRV generally indicates greater vagal (parasympathetic) influence and better CV adaptability, whereas reduced HRV is often associated with autonomic dysfunction, increased sympathetic dominance, and heightened risk of adverse CV outcomes.[15] As such, HRV provides valuable insight into the balance of autonomic control, stress reactivity, recovery capacity, and overall CV health. In CV pathology, an imbalance between sympathetic and parasympathetic activity may contribute to disease progression and poor clinical outcomes.[15,16] Therefore, HRV analysis serves not only as a diagnostic tool but also as a prognostic marker in various cardiac conditions.[16]

The quantitative assessment of HRV is facilitated through advanced, validated software platforms capable of extracting a comprehensive range of HRV indices from ECG recordings

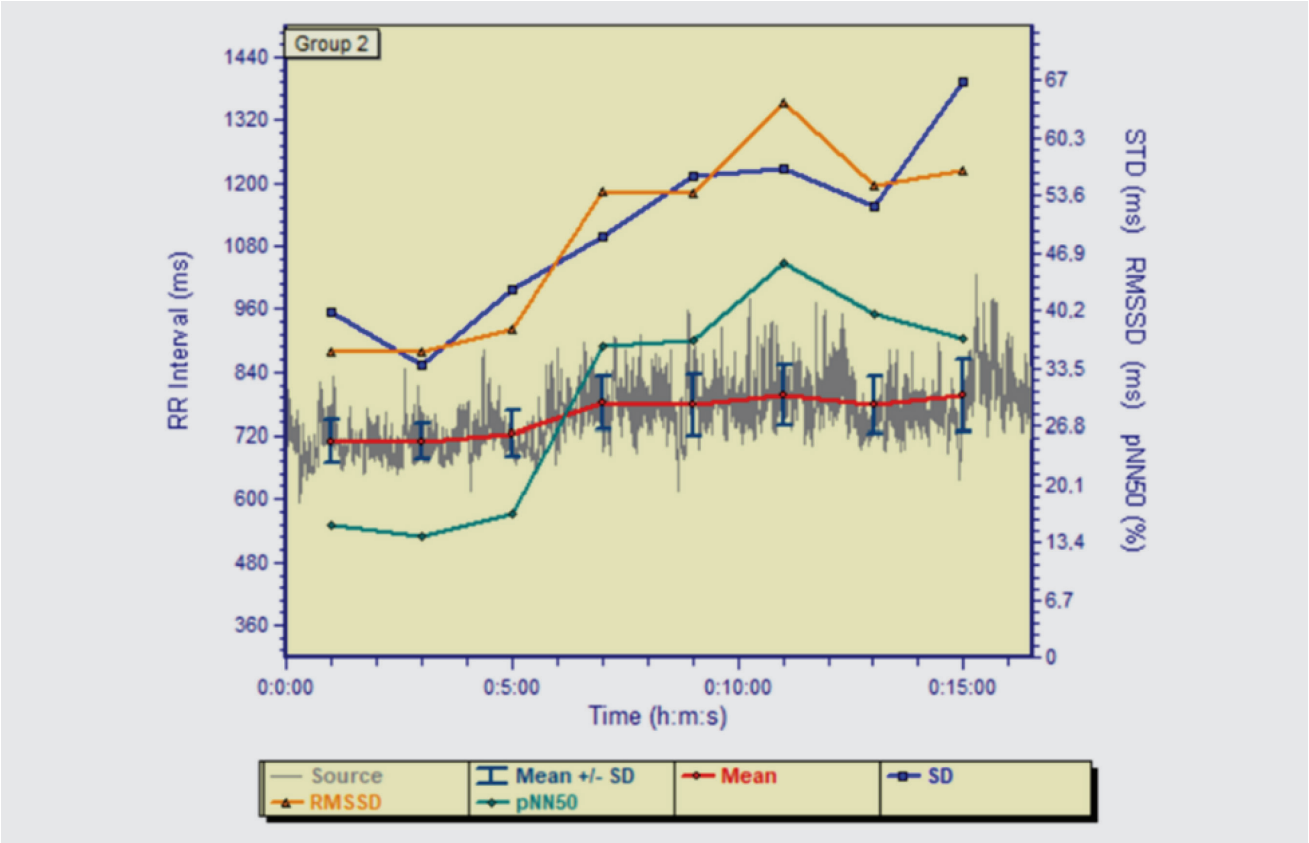

FIGURE 1. Heart rate variability analysis derived from electrocardiogram recording.

The figure presents a comprehensive analysis of heart rate variability based on a short-term electrocardiogram recording. Displayed on the left side of the graph is the tachogram, illustrating the temporal sequence of RR intervals, which reflect beat-to-beat fluctuations in heart rate. This visual representation enables qualitative assessment of autonomic modulation. The right side of the figure demonstrates the time-domain analysis of RR intervals, including key HRV parameters: standard deviation of normal-to-normal intervals (SDNN), root mean square of successive differences (RMSSD), and the percentage of successive RR intervals that differ by more than 50 ms (pNN50). These indices are widely used markers of parasympathetic activity and overall autonomic nervous system balance. The analysis was conducted using the *aHRV Analysis* software platform, developed by Nevrokard (Nevrokard, Izola, Slovenia). This specialized software provides validated algorithms for the extraction, processing, and quantification of HRV metrics from ECG data, ensuring high analytical accuracy and reproducibility. The tool is designed to support both clinical and research applications in the evaluation of cardiac autonomic regulation.

taka, uključujući kratkotrajne snimke (obično u trajanju od 5 minuta),[17] kontinuirano 24-satnog snimanje EKG-a,[18,19] kao i EKG segmente dobivene tijekom ili u fazi oporavka nakon standardiziranih protokola testiranja opterećenjem.[20] Među dostupnim modalitetima 24-satno snimanje EKG-a ostaje klinički najinformativniji pristup procjeni HRV-a zbog svoje superiorne prediktivne valjanosti u stratifikaciji KV rizika i sposobnosti da podrži sveobuhvatne analize, uključujući vremensku domenu, frekvencijsku domenu i nelinearne metrike.[19,21]

U bolesnika s HF-om 24-satni i kratkotrajni HRV zapisi pokazali su prognostičku vrijednost, no dugoročni zapisi pružaju jasniju diferencijaciju među NYHA funkcionalnim klasama.[21] Osim toga, mjere HRV-a izvedene iz 24-satnih zapisa znatno koreliraju s BRS metrikama u istraživanjima zdravih ispitanika, pokazujući da dugoročni HRV obuhvaća autonomna regulatorna obilježja koja dopunjuju izravnu BRS procjenu.[22] Ključno je da se HRV parametri mogu izvući iz standardnih EKG podataka, čime se olakšava njihova integracija u rutinske kliničke tijekove rada i omogućuje longitudinalno praćenje. Ovi indeksi nude kvantitativne markere autonomne ravnoteže i srčane autonomne regulacije u stvarnim fiziološkim uvjetima. Najčešće procjenjivani HRV parametri sažeti su u **tablici 1**.[13,23]

Što se tiče kliničke interpretacije i prognostičke relevantnosti HRV-a u KV bolesnika, važni dokazi podupiru HRV kao klinički koristan, neinvazivan biomarker disfunkcije ANS-a u širokom spektru stanja, uključujući infarkt miokarda (IM), HF, aritmije i iznenadnu srčanu smrt (SCD). To posebno podupiru opsežni sustavni pregledi i metaanalize, koji pružaju postojane dokaze o povezanosti između smanjenog HRV-a i

(**Figure 1**).[17] These parameters can be derived from various types of ECG data, including short-term recordings (typically 5 minutes in duration),[17] continuous 24-hour Holter monitoring,[18,19] as well as ECG segments obtained during or in the recovery phase after standardized exercise testing protocols.[20] Among available modalities, 24-hour Holter ECG recording remains the most diagnostically robust and clinically informative approach to HRV assessment, owing to its superior predictive validity in CV risk stratification and its capacity to support comprehensive analyses, including the time-domain, frequency-domain, and non-linear metrics.[19,21]

For example, 24-hour and short-term HRV recordings have both shown prognostic value in patients with HF, but long-term Holter recordings provide clearer differentiation among NYHA functional classes.[21] Additionally, HRV measurements derived from 24-hour recordings correlate significantly with BRS metrics in studies of healthy subjects, demonstrating that long-term HRV captures autonomic regulatory features that complement direct BRS assessment.[22] Crucially, HRV parameters can be extracted from standard ECG data, thereby facilitating their integration into routine clinical workflows and enabling longitudinal patient monitoring. These indices provide quantitative markers of autonomic balance and cardiac autonomic regulation under real-world physiological conditions. The most commonly assessed HRV parameters are summarized in **Table 1**.[13,23]

Regarding clinical interpretation and prognostic relevance of HRV in cardiac patients, substantial evidence supports HRV as a clinically useful, non-invasive biomarker of ANS dysfunction across a broad spectrum of CV conditions, including myocardial infarction (MI), HF, arrhythmias, and sudden cardiac death (SCD).

TABLE 1. Key heart rate variability parameters and their physiological significance.[13,23]

Parameter (Unit)	Domain	Definition and physiological interpretation
SDNN (ms)	Time-domain	Standard deviation of all normal-to-normal (NN) intervals; represents overall HRV and reflects total autonomic influence
RMSSD (ms)	Time-domain	Root mean square of successive NN interval differences; reflects short-term HRV and is a robust index of parasympathetic (vagal) activity
pNN50 (%)	Time-domain	Percentage of successive NN intervals differing by more than 50 ms; indicates the degree of parasympathetic (vagal) heart rate modulation
LF (ms^2 or nu)	Frequency-domain	Low-frequency power (0.04-0.15 Hz); reflects a mix of sympathetic and parasympathetic influences, associated with baroreflex activity and blood pressure regulation
HF (ms^2 or nu)	Frequency-domain	High-frequency power (0.15-0.40 Hz); primarily represents parasympathetic (vagal) activity and is linked to respiratory sinus arrhythmia
LF/HF ratio	Frequency-domain	Ratio of low- to high-frequency power; used as an index of sympathovagal balance, as higher ratios suggest sympathetic predominance, whereas lower ratios reflect vagal dominance
SD1 (ms)	Non-linear (Poincaré)	Standard deviation of instantaneous beat-to-beat variability (short axis of the Poincaré plot); reflects short-term HRV and parasympathetic activity
SD2 (ms)	Non-linear (Poincaré)	Standard deviation of continuous long-term variability (long axis of the Poincaré plot); represents total HRV influenced by both branches of the autonomic nervous system
Approximate entropy (ApEn)	Non-linear	Quantifies the complexity and predictability of NN interval dynamics; lower values indicate reduced signal complexity and potential autonomic dysfunction

povećanog rizika od smrtnosti.[24] Novije opservacijske i mehanističke studije dodatno sugeriraju da analiza HRV-a može olakšati ranu identifikaciju autonomne disregulacije, poboljšano fenotipiziranje hipertenzivnih bolesnika i praćenje terapijskog odgovora, posebno kod podtipova karakteriziranih pojačanom simpatičkom aktivnošću.[25] Iako su ovi nalazi uglavnom izvedeni iz presječnih i kohortnih dizajna, oni nude klinički relevantne uvide u autonomne obrasce kod različitih hipertenzivnih sindroma.

U bolesnika nakon IM-a prospektivna kohortna istraživanja koja se koriste standardiziranim kratkotrajnim snimanjima EKG-a pokazala su da su znatno smanjeni parametri HRV-a – posebno niski SDNN i povišeni omjer LF/HF – povezani s povećanim rizikom od aritmijskih događaja i nepovoljnih ishoda, čak i u bolesnika s očuvanom ejekcijskom frakcijom.[26] Nedavna kohortna istraživanja u jednom centru pokazuju da su viši parasimpatički markeri (RSMSSD i HF komponente) i niži omjer LF/HF neovisno povezani sa smanjenim rizikom od fibrilacije atrija (AF) nakon kateterske ablacije. Ovi nalazi sugeriraju da parametri HRV-a mogu imati neovisnu prognostičku vrijednost, dopunjujući konvencionalne dijagnostičke alate i alate za stratifikaciju rizika u kliničkoj kardiologiji.[27]

Unatoč dobro utvrđenoj prognostičkoj relevantnosti, dijagnostička korisnost od HRV-a kao samostalnog parametra ostaje ograničena zbog njegove osjetljivosti na brojne zbunjujuće čimbenike. To uključuje dob, cirkadijalne ritmove, tjelesnu kondiciju, metabolički status, farmakološku terapiju (kao što su beta-blokatori, ACE inhibitori), respiratorne obrasce i psihološka ili emocionalna stanja, a sve to može znatno utjecati na mjerenja HRV-a i smanjiti njihovu interpretabilnost. Stoga, iako je smanjeni HRV osjetljiv marker autonomne disregulacije, nedostaje mu specifičnost za bolest. Njegova se dijagnostička vrijednost najbolje ostvaruje kada se interpretira u kontekstu dodatnih kliničkih, biokemijskih i slikovnih podataka.[28] S terapijskoga gledišta, analiza HRV-a nudi neinvazivan način praćenja učinaka liječenja i procjene odgovora bolesnika na intervencije usmjerene na autonomnu regulaciju.[28,29] Te intervencije uključuju farmakološko liječenje (kao što su beta-blokatori, ivabradin), kardiološku rehabilitaciju temeljenu na vježbama, stimulaciju vagusnog živca, tehnike *biofeedbacka* i promjene načina života poput treninga svjesnosti i smanjenja stresa.[29] Poboljšanja HRV-a dosljedno su povezana s boljim kliničkim ishodima i smanjenom smrtnošću, posebno u bolesnika s HF-om. Nadalje, integracija HRV-a u postojeće okvire stratifikacije rizika, zajedno s utvrđenim biomarkerima poput troponina i modernim tehnikama snimanja, može poboljšati rano prepoznavanje bolesnika s visokim rizikom i podržati personalizirano terapijsko donošenje odluka.[30]

OPORAVAK SRČANOG RITMA

Oporavak srčanog ritma (HRR) klinički je relevantan, neinvazivan marker funkcije ANS-a, koji posebno odražava dinamičku reaktivaciju parasimpatičkog (vagalnog) tonusa nakon prestanka vježbanja. Definira se kao brzina kojom HR opada od vrhunca vježbanja do određene vremenske točke tijekom faze oporavka. Fiziološki se smatra da HRR odražava međudjelovanje između neposredne vagalne reaktivacije i postupnoga simpatičkog povlačenja, prije svega posredovanog mehanizmima barorefleksa i modulacijom SNA-a.[31] Čini se da se HRR sastoji od dviju različitih faza: početnoga brzog pada HR-a unutar prve minute nakon vježbanja, pre-

This is strongly supported by large-scale systematic reviews and meta-analyses, which provide robust evidence for the association between reduced HRV and increased mortality risk in both healthy individuals and patient populations.[24] More recent observational and mechanistic studies further suggest that HRV analysis may facilitate early identification of autonomic dysregulation, improved phenotyping of patient with hypertension, and monitoring of therapeutic response, especially in hypertensive subtypes characterized by heightened sympathetic activity.[25] While these findings are largely derived from cross-sectional and cohort-based designs, they provide clinically relevant insights into autonomic patterns across different hypertensive syndromes.

In patients recovering from MI, prospective cohort studies using standardized short-term Holter recordings have demonstrated that markedly reduced HRV parameters – particularly low SDNN and elevated LF/HF ratio – are associated with an increased risk of arrhythmic events and adverse cardiac outcomes, even in patients with preserved ejection fraction.[26] Recent single-center cohort studies indicate that higher parasympathetic markers (RSMSSD and HF components) and a lower LF/HF ratio are independently associated with a reduced risk of atrial fibrillation (AF) following catheter ablation. These findings suggest that HRV parameters may hold independent prognostic value, complementing conventional diagnostic and risk stratification tools in clinical cardiology.[27]

Despite its well-established prognostic relevance, the diagnostic utility of HRV as a standalone parameter remains limited due to its susceptibility to numerous confounding factors. These include age, circadian rhythms, physical conditioning, metabolic status, pharmacological therapy (such as β-blockers, ACE inhibitors), respiratory patterns, and psychological or emotional states, all of which can significantly influence HRV measurements and reduce their interpretability. Therefore, although reduced HRV represents a sensitive marker of autonomic dysregulation, it lacks disease specificity. Its diagnostic value is best realized when interpreted in the context of additional clinical, biochemical, and imaging data.[28] From a therapeutic perspective, HRV analysis offers a non-invasive means of monitoring treatment effects and evaluating patient response to interventions targeting autonomic regulation.[28,29] These interventions include pharmacological therapies (such as β-blockers, ivabradine), exercise-based cardiac rehabilitation, vagus nerve stimulation, biofeedback techniques, and lifestyle modifications such as mindfulness training and stress reduction.[29] Improvements in HRV have been consistently associated with better clinical outcomes and reduced mortality, particularly in patients with HF undergoing different rehabilitation programs. Furthermore, the integration of HRV into existing risk stratification frameworks, together with established biomarkers such as troponin and modern imaging techniques, may enhance early recognition of high-risk patients and support personalized therapeutic decision-making.[30]

HEART RATE RECOVERY

Heart rate recovery (HRR) is a clinically relevant, non-invasive marker of ANS function, particularly with regard to the dynamic reactivation of parasympathetic (vagal) tone following exercise cessation. It is defined as the rate at which HR declines from peak exertion to a specific time point during the recovery phase. Physiologically, HRR is thought to reflect the interplay between immediate vagal reactivation and gradual sympathetic withdrawal, primarily mediated via baroreflex

težno potaknuta parasimpatičkom reaktivacijom, nakon čega slijedi sporiji, progresivni pad, pod utjecajem kontinuirane parasimpatičke aktivnosti i progresivnoga simpatičkog povlačenja. Ovaj bifazni obrazac omogućuje HRR-u da obuhvati i akutne i trajne aspekte autonomnog oporavka.[31,32] Najčešće iskorištavana i klinički validirana vremenska točka jest HRR izmjeren 1 minutu nakon vježbanja, gdje se smanjenje od ≤12 otkucaja u minuti općenito smatra abnormalnim. Ovaj je prag povezan s povećanim rizikom od nepovoljnih KV ishoda i široko je prihvaćen u kliničkim i istraživačkim okruženjima.[33,34] Međutim, normativne vrijednosti mogu varirati ovisno o dobi, spolu, kao i o razini KV kondicije, farmakološkom liječenju i komorbiditetima. Važno je napomenuti da liječene osobe obično pokazuju vrijednosti HRR-a koje prelaze 20 – 30 otkucaja u minuti 1 minutu nakon vježbanja. Stoga interpretaciju HRR-a treba kontekstualizirati uporabom referentnih raspona specifičnih za populaciju i stanje kad god je to moguće.[35] HRR se može pouzdano procijeniti samo nakon standardiziranog testiranja opterećenjem, koje se obično provodi na pokretnoj traci ili na ergometrijskom biciklu s jasno definiranom točkom završetka vježbanja. Takvo testiranje vježbanjem također omogućuje procjenu odgovora HR-a na vježbanje, što je važan pokazatelj KV funkcije i autonomne regulacije (**slika 2**), a obično uključuje praćenje BP-a. Produljena mjerenja pulsa 2, 3 ili 5 minuta nakon vježbanja mogu pružiti dodatni uvid u autonomnu disonanciju, u slučaju kašnjenja u parasimpatičkoj reaktivaciji.[35,36]

mechanisms and modulation of SNA.[31] HRR appears to consist of two distinct phases: initial rapid decline in HR within the first minute after exertion, predominantly driven by parasympathetic reactivation, followed by a slower, progressive decline, influenced by continued parasympathetic activity and progressive sympathetic withdrawal. This biphasic pattern enables HRR to capture both acute and sustained aspects of autonomic recovery.[31,32] The most commonly used and clinically validated time point is HRR measured at 1 minute after exertion, where a decrease of ≤12 beats per minute is generally considered abnormal. This threshold has been associated with an increased risk of adverse CV outcomes and is widely accepted in clinical and research settings.[33,34] However, normative values may vary depending on age, sex, and CV fitness level, as well as pharmacological treatment and comorbid conditions. Notably, trained individuals typically exhibit HRR values exceeding 20-30 beats per minute at 1 minute after exertion. Therefore, HRR interpretation should be contextualized using population- and condition-specific reference ranges whenever possible.[35] HRR may only be reliably assessed after standardized exercise testing, typically conducted using a treadmill or cycle ergometer with a clearly defined point of exercise termination. Such exercise testing also allows for the evaluation of HR response to exertion, which is an important indicator of CV function and autonomic regulation (**Figure 2**), and commonly includes BP monitoring. Extended measurements of HR at 2, 3, or 5 minutes after exertion may

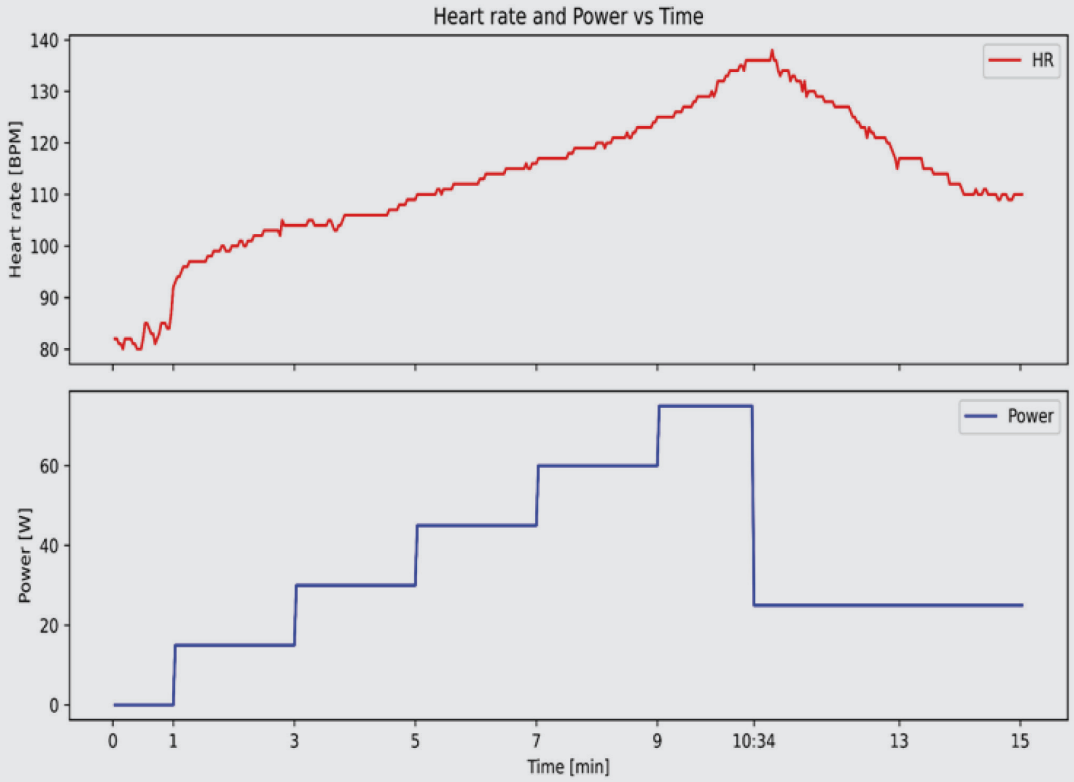

FIGURE 2. Monitoring heart rate (HR) response during and after exercise on a cycle ergometer.

The exercise begins after the first minute at an initial workload of 15 W, with incremental increases of 15 W every 2 minutes. The highest workload achieved was 75 W, corresponding to approximately 85% of the patient's age-predicted maximal heart rate. The recording was obtained from a 60-year-old patient undergoing treatment for arterial hypertension.

S prognostičkoga stajališta HRR je pokazao umjerenu osjetljivost i specifičnost u predviđanju ukupne smrtnosti, SCD-a i incidencije CAD-a, posebno kada se primjenjuje u kombinaciji s drugim kliničkim pokazateljima.[35-37] Vjeruje se da oštećeni HRR odražava trajnu simpatičku aktivaciju i/ili otupljenu parasimpatičku reaktivaciju, a oboje su poznati čimbenici koji pridonose nepovoljnim KV događajima. Nedostatak adekvatnoga vagalnog tonusa nakon vježbanja uklanja ključni antiaritmični pufer, povećavajući rizik od ventrikularnih aritmija, oštećene koronarne perfuzije i SCD, što sve pridonosi lošoj prognozi.[38,39] Na primjer, među ispitanicima s dokumentiranom BKS-om, velika metaanaliza koja je obuhvatila više od 2400 sudionika pokazala je da je oslabljeni HRR 1 minutu nakon vježbanja (pragovi u rasponu od ≤12 do ≤21 otkucaja u minuti) bio snažan prediktivni pokazatelj ukupne smrtnosti, s omjerom združenog rizika od oko 5,8. Ovi nalazi ističu prognostičku važnost čak i suptilnih oštećenja u autonomnom oporavku nakon vježbanja.[40] Novija velika prospektivna istraživanja dodatno su pojačala i poboljšala prognostičku relevantnost HRR-a u različitim populacijama. Nedavna prospektivna kohortna studija obuhvatila je gotovo 10 000 odraslih osoba podvrgnutih standardiziranom testiranju bicikl-ergometrom te je pokazala da je smanjeni HRR u 1 minuti, definiran kao vrijednost niža od 5. percentile neovisno povezan s povećanim rizikom od ukupnom smrtnosti (omjer rizika približno 1,70). Važno je napomenuti da je ova povezanost ostala snažna čak i u osoba s očuvanim kapacitetom za vježbanje, ističući HRR kao osjetljiv marker ranoga autonomnog oštećenja u populacijama za koje se tradicionalno smatra da imaju niži KV rizik.[41]

Treba naglasiti da HRR nije samostalni dijagnostički alat, nego prognostički biomarker koji dobiva kliničku vrijednost kada se interpretira unutar sveobuhvatne procjene autonomne funkcije. Smanjeni HRR dosljedno je povezan s nepovoljnim kliničkim ishodima, uključujući HTN, progresiju CAD-a i veću učestalost KV događaja kod srčanog zastoja, što je pokazano u višestrukim opservacijskim istraživanjima i kliničkim pregledima.[36,42,43] Ovakve osobe obično pokazuju odgođeni autonomni oporavak nakon napora, karakteriziran oslabljenom parasimpatičkom reaktivacijom i održivom simpatičkom aktivnošću, za razliku od zdravih osoba i sportaša treniranih izdržljivošću, koji pokazuju brzu i učinkovitu vagalnu reaktivaciju (**slika 3**). S obzirom na njegovu prognostičku relevantnost i jednostavnost procjene, nekoliko autora zagovara rutinsko uključivanje procjene HRR-a u protokole kliničkog testiranja vježbanjem.[42,44]

S terapijske perspektive, HRR služi kao osjetljivi pokazatelj autonomnog oporavka i kardiorespiratorne izdržljivosti, koristan za praćenje učinkovitosti liječenja KV bolesti. Dokazi iz većih istraživanja dosljedno povezuju poboljšanja HRR-a s povoljnijim kliničkim ishodima, uključujući smanjene stope hospitalizacije i nižu smrtnost. Nasuprot tomu, neke ranije intervencijske studije koje su izvijestile o poboljšanjima HRR-a nakon kardiološke rehabilitacije provedene su u relativno malim kohortama jednog centra s uzastopnim uključivanjem bolesnika, što zahtijeva oprezno tumačenje zbog ograničene vanjske valjanosti dobivenih nalaza.[45] Ipak, u različitim dizajnima studija pokazalo se da kardiološka rehabilitacija temeljena na tjelovježbi poboljšava HRR, a u kombinaciji s kombiniranim treningom i terapijom beta-blokatorima daje veće koristi od samog farmakološkog liječenja.[46] Iako su te studije pružile važne podatke za dokaz koncepta, ograničena

provide further insight into autonomic dissonance in case of a delay in parasympathetic reactivation.[35,36]

From a prognostic standpoint, HRR has demonstrated moderate sensitivity and specificity in predicting all-cause mortality, SCD, and incident coronary artery disease (CAD), particularly when used in combination with other clinical indicators.[35-37] Impaired HRR is believed to reflect sustained sympathetic activation and/or blunted parasympathetic reactivation, both of which are known contributors to adverse CV events. The lack of adequate vagal tone after exertion removes a key antiarrhythmic buffer, increasing the risk of ventricular arrhythmias, impaired coronary perfusion, and SCD, all of which contribute to poor prognosis.[38,39] For example, among patients with documented CAD, a robust meta-analysis encompassing more than 2,400 participants demonstrated that attenuated HRR at 1 minute after exertion (thresholds ranging from ≤12 to ≤21 beats per minute) was strongly predictive of all-cause mortality, with a pooled hazard ratio of around 5.8. These findings highlight the prognostic importance of even subtle impairments in autonomic recovery after exertion.[40] More recent large-scale prospective studies have further reinforced and refined the prognostic relevance of HRR across diverse populations. In particular, a 2024-2025 prospective cohort study including nearly 10,000 adults undergoing standardized cycle ergometer testing demonstrated that a blunted 1-minute HRR, defined as a value below the 5th percentile, was independently associated with an increased risk of all-cause mortality (hazard ratio approximately 1.70). Notably, this association remained robust even in individuals with preserved exercise capacity, highlighting HRR as a sensitive marker of early autonomic impairment in populations traditionally considered to be at lower CV risk.[41]

It should be emphasized that HRR is not a standalone diagnostic tool but rather a prognostic biomarker that gains clinical value when interpreted within a comprehensive assessment of autonomic function. Reduced HRR has been consistently associated with adverse clinical outcomes, including HTN, progression of CAD, and higher incidence of CV events in HF, as demonstrated across multiple observational studies and clinical reviews.[36,42,43] These individuals typically exhibit delayed autonomic recovery after exertion, characterized by attenuated parasympathetic reactivation and sustained sympathetic activity, in contrast to healthy individuals and endurance-trained athletes, who demonstrate rapid and efficient vagal reactivation (**Figure 3**). Given its prognostic relevance and simplicity of assessment, several authors advocate for the routine incorporation of HRR assessment into clinical exercise testing protocols.[42,44]

From a therapeutic perspective, HRR serves as a sensitive indicator of autonomic recovery and cardiorespiratory fitness, useful for monitoring treatment efficacy in CV disease. Evidence from larger observational cohorts and more methodologically robust studies consistently links improvements in HRR with more favorable clinical outcomes, including reduced hospitalization rates and lower mortality. In contrast, some earlier interventional studies reporting improvements in HRR following cardiac rehabilitation were conducted in relatively small, single-center cohorts with consecutive patient enrollment, which warrants cautious interpretation due to the limited external validity of these findings.[45] Nonetheless, exercise-based cardiac rehabilitation has been shown to improve HRR across different study designs, with combined exercise training and β-blocker therapy yielding greater

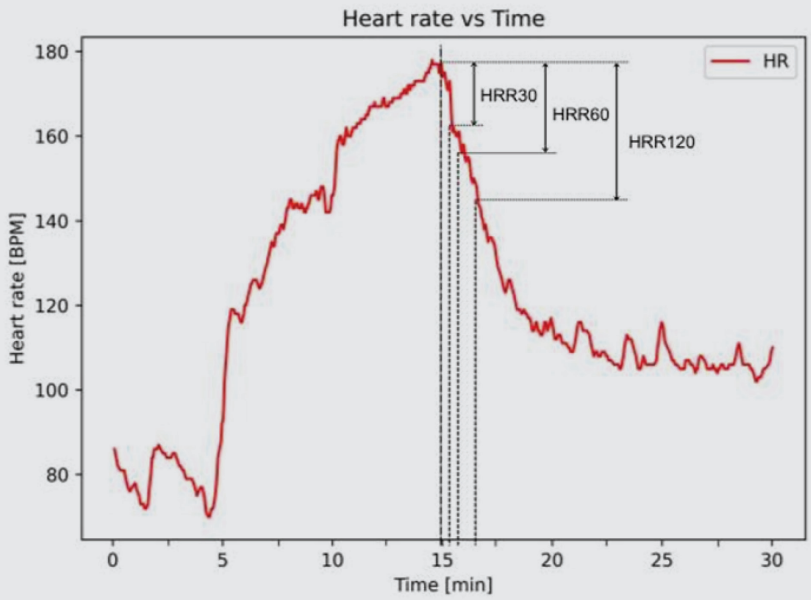

FIGURE 3. Heart rate recovery (HRR) after exercise cessation.

During the first 5 minutes, the subject was at rest. This was followed by 5 minutes of exertion at 40% of maximal oxygen uptake (VO_2max), which was subsequently increased to 60% VO_2max, and finally up to 80% VO_2max. The subject reached 85% of age-predicted maximal heart rate by the 15th minute. The data shown are from a healthy 23-year-old individual. HRR30 – heart rate decline at 30 seconds after exertion; HRR60 – heart rate decline at 1 minute after exertion; HRR120 – heart rate decline at 2 minutes after exertion.

veličina uzorka i dizajn studije mogu ograničiti generalizaciju nalaza.

Više istraživanja dodatno podupire osjetljivost HRR-a na terapijsku modulaciju. Kontrolirane fiziološke studije koje ispituju učinke farmakoloških sredstava za snizivanje HR-a, poput beta-blokatora i ivabradina, kao i stimulacije vagalnog živca, pokazale su povoljne promjene u indeksima autonomnog oporavka, uključujući HRR.[47]

Konačno, dokazi iz opservacijskih i rehabilitacijskih kohorti, uključujući ranije, ali metodološki ispravne longitudinalne studije, sugeriraju da je strukturirani trening vježbanjem dosljedno povezan s poboljšanjima HRR-a tijekom vremena.[48] Iako neke od tih studija prethode suvremenim rehabilitacijskim protokolima, njihovi nalazi ostaju relevantni i podržavaju ulogu HRR-a kao dinamičkog markera terapijskog odgovora.

AMBULATNO I KUĆNO PRAĆENJE ARTERIJSKOGA TLAKA

Precizna procjena BP-a ključna je i za dijagnozu i za učinkovito liječenje HTN-a.[49] Iako se mjerenja BP-a u ordinaciji još uvijek široko primjenjuju u rutinskim kliničkim okruženjima, njihova pouzdanost može biti ugrožena čimbenicima poput efekta „bijelog ogrtača" ili maskirane hipertenzije.[50] Kako bi se prevladala ta ograničenja, praćenje BP-a izvan kliničkog okruženja, poput kućnog praćenja (HBPM) i 24-satno mjerenje arterijskog tlaka (ABPM), može pružiti dosljednije i klinički važnije informacije. ABPM, koji kontinuirano bilježi BP tijekom 24-satnog razdoblja tijekom tipične dnevne rutine i sna, nudi vrijedne podatke o cirkadijalnim fluktuacijama BP-a i

benefits than pharmacological treatment alone.[46] While these studies provided important proof-of-concept data, their limited sample size and study design may constrain the generalizability of the findings.

Additional studies further supports the responsiveness of HRR to therapeutic modulation. Controlled physiological studies examining the effects of pharmacological heart rate-lowering agents, such as β-blockers and ivabradine, as well as vagal nerve stimulation, have demonstrated favorable shifts in autonomic recovery indices, including HRR.[47]

Finally, evidence from observational and rehabilitative cohorts, including earlier but methodologically sound longitudinal studies, suggests that structured exercise training is consistently associated with improvements in HRR over time.[48] Although some of these studies predate contemporary rehabilitation protocols, their findings remain relevant and support the role of HRR as a dynamic marker of therapeutic response.

AMBULATORY AND HOME BLOOD PRESSURE MONITORING

Precise evaluation of BP is crucial for both the diagnosis and effective management of HTN.[49] Although in-office BP measurements are still widely used in routine clinical settings, their reliability can be compromised by factors such as the white coat effect or masked HTN.[50] To overcome these limitations, BP monitoring outside the clinical environment, such as home blood pressure monitoring (HBPM) and 24-hour ambulatory blood pressure monitoring (ABPM), may provide more consistent and clinically meaningful information. ABPM, which continuously records BP throughout a 24-hour period during a patient's typi-

funkcionalnom statusu ANS-a.[51,52] ABPM se izvodi s pomoću prijenosnog uređaja koji se nosi na nadlaktici i koji se automatski napuhuje u unaprijed određenim intervalima, a može se provoditi u zdravstvenoj ustanovi ili kod kuće tijekom normalnih svakodnevnih aktivnosti.[52] Ova metoda omogućuje mjerenje BP-a s obzirom na dnevno-noćni ritam i njegove varijacije, pružajući potpuniju sliku povišenja vrijednosti BP-a (**slika 4**). U kontekstu autonomne disfunkcije, mjerenja HR-a u kombinaciji s vrijednostima BP-a mogu pružiti daljnji uvid u autonomnu funkciju, posebno kada se dopune dodatnom analizom parametara HRV-a. Također je važno uzeti u obzir obrasce kretanja vrijednosti BP-a tijekom različitog doba dana. Specifični obrasci, poput normalnoga noćnog pada, odsutnosti pada (nepadanja), obrnutog pada (obrazac uspona) i abnormalnih jutarnjih skokova BP-a, prepoznati su pokazatelji funkcije ANS-a. Ti obrasci odražavaju ravnotežu i interakciju između simpatičke i parasimpatičke aktivnosti.[53]

Osobe koje nemaju normalan noćni pad BP-a (tzv. *non-dippers*) često pokazuju pojačanu noćnu simpatičku aktivnost praćenu smanjenim vagalnim tonusom. Ovu povezanost prije svega podržavaju podatci iz velikih, dobro karakteriziranih kohortnih studija, poput *African-PREDICT*, koja je pokazala da su obrasci *non-dippers* i ublaženi jutarnji porast

cal daily routine and sleep, offers valuable data on circadian BP fluctuations and the functional status of the ANS.[51,52] ABPM is performed using a portable device worn on the patient's arm, which automatically inflates at preset intervals, and can be conducted either in a clinical setting or at home during normal daily activities.[52] This method allows for the measurement of BP in relation to the day-night rhythm and its variation, providing a more complete picture of BP elevation and the specific times of day when it occurs (**Figure 4**). In the context of autonomic dysfunction, HR measurements combined with BP values can provide further insights into autonomic function, especially when supplemented by additional analysis of HRV parameters, as previously discussed. It is also important to consider BP patterns during different times of the day. Specific patterns, such as normal nocturnal dipping, absence of dipping (non-dipping), reverse dipping (riser pattern), and abnormal morning BP surges are recognized indicators of ANS function. These patterns reflect the balance and interaction between sympathetic and parasympathetic activity.[53]

Clinically, individuals who lack the normal nocturnal fall in BP (non-dippers), often exhibit heightened nocturnal sympathetic activity accompanied by diminished vagal tone. This association has been supported primarily by data from large,

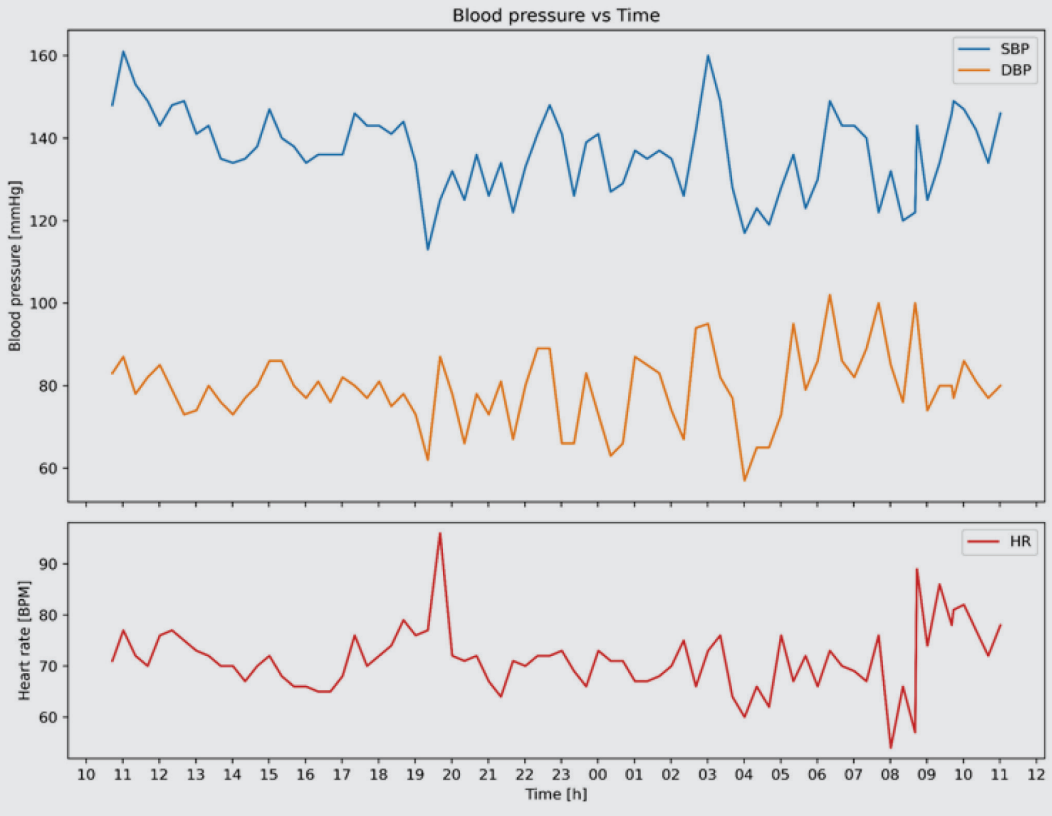

FIGURE 4. 24-hour ambulatory blood pressure monitoring.

The image displays a 24-hour automatic blood pressure recording, starting at 10:43 and ending at 11:01 the following day. The analysis was performed using the rectangular waveform matching method. Statistical analysis of the full recording and the day-night periods incorporates the weighting of measurement intervals. Sleeping and waking periods were manually defined (sleep: 21:00 to 06:00). The recording was obtained from a 42-year-old female patient with hypertension. Monitoring was technically successful (100%). Average blood pressure: 137/79 mmHg; daytime: 139/81 mmHg; nighttime: 133/77 mmHg. Mild nocturnal dip (4% systolic / 5% diastolic). Systolic blood pressure (SBP) was above target, while diastolic blood pressure (DBP) was within normal limits. Pulse pressure was elevated (57 mmHg). Heart rate: 71 bpm (day: 73, night: 69; 5% nocturnal dip). Morning blood pressure surge: 17/28 mmHg; Heart rate increase: 5 bpm.

BP-a povezani sa smanjenim BRS-om i nižim HRV-om, što su oba markera disfunkcije ANS-a.[54] Daljnji uvid u odnos između cirkadijalne varijacije BP-a i autonomne regulacije pružaju populacijske opservacijske studije uporabom ABPM-a. Na primjer, istraživanje *HI-JAMP* pokazalo je da se odgovor BP-a na dnevnu tjelesnu aktivnost (također poznata kao aktisenzitivnost) razlikuje među fenotipovima padanja, uključujući obrasce bez padanja, ekstremnog padanja i obrnutog padanja, što odražava heterogenost u autonomnoj modulaciji.[55] Osim svoje utvrđene uloge u dijagnozi HTN-a, 24-satni ABPM može pružiti klinički korisne, neinvazivne uvide u autonomnu funkciju, posebno kada se integrira s drugim autonomnim indeksima. To je posebno relevantno u stanjima kao što su dijabetes, opstruktivna apneja u snu i HF, gdje neravnoteža ANS-a često pridonosi progresiji bolesti i KV riziku.[56] Stoga se može zaključiti da bi ABPM trebao biti šire primjenjivan u kliničkoj praksi, ne samo kao dijagnostički standard za HTN već i kao dodatni alat za procjenu funkcije ANS-a kod različitih srčanih, metaboličkih i neuroregulatornih poremećaja.[57] To također može imati važne prognostičke implikacije, jer autonomna neravnoteža pridonosi oštećenju organa, aritmogenezi i lošim KV ishodima.[52,58]

Što se tiče liječenja HTN-a, HBPM je vrijedan za dugoročno praćenje i poticanje pridržavanja. Međutim, ne obuhvaća noćni BP ili cirkadijalnu varijabilnost, što ograničava njegovu korisnost u procjeni funkcije ANS-a.[59] Nasuprot tomu, ABPM ima središnju ulogu u procjeni učinkovitosti antihipertenzivne terapije pružajući kontinuirane 24-satne podatke, uključujući profile noćnog BP-a i kratkoročnu varijabilnost. To omogućuje identifikaciju neadekvatnogga noćnog snizivanja BP-a, individualno optimiranje vremena primjene i kombinacije antihipertenzivnih lijekova.[60] ABPM je posebno koristan u upravljanju stanjima povezanim s povećanim KV rizikom i koja zahtijevaju strogu kontrolu BP-a, poput kronične bolesti bubrega,[61] hipertrofije lijeve klijetke,[62] i HF-a.[63] Kada se primjenjuje uz alate kao što su EKG, analiza HRV-a ili testiranje opterećenjem, ABPM poboljšava ukupnu procjenu funkcije ANS-a.[64] Ukratko, ABPM pruža značajnu kliničku vrijednost i u liječenju HTN-a i u procjeni funkcije ANS-a, podržavajući individualiziraniji i patofiziološki pristup liječenju. Uz mjerenja u mirovanju i pokretima, pretjerani odgovor arterijskog tlaka na vježbanje (EBPR) pruža dinamičku procjenu vaskularne i autonomne reaktivnosti pod fiziološkim stresom. EBPR, karakteriziran abnormalno strmim porastom sistoličkoga tlaka tijekom stupnjevanog vježbanja, odražava pretjeranu simpatičku aktivaciju, oštećeno barorefleksno puferiranje i povećanu arterijsku krutost.[65] Iako nije dio standardnog praćenja BP-a, integriranje nalaza EBPR s podatcima ABPM-a ili HRV-a nudi komplementaran uvid u autonomno hemodinamičko povezivanje i rani KV rizik.[66] Osobe koje pokazuju EBPR često pokazuju promijenjene noćne profile BP-a ili obrasce bez pada na ABPM-u, što naglašava zajedničke autonomne puteve koji leže u osnovi regulacije BP-a tijekom vježbanja i cirkadijalne regulacije BP-a.[66,67]

OSJETLJIVOST BAROREFLEKSA

Osjetljivost barorefleksa označuje sposobnost ANS-a da modulira HR kao odgovor na akutne promjene BP-a, čime pridonosi kratkoročnoj KV stabilnosti. Odražava funkcionalni integritet barorefleksnog luka, posebno osjetljivost baroreceptora smještenih u karotidnom sinusu i aortalnom luku, koji detektiraju fluktuacije BP-a i pokreću odgovarajuće auto-

well-characterized cohort studies, such as the African Prospective study on the Early Detection and Identification of Cardiovascular disease and Hypertension (African-PREDICT), which demonstrated that non-dipping BP patterns and blunted morning BP surges are associated with reduced BRS and lower HRV, both markers of ANS dysfunction.[54] Further insight into the relationship between circadian BP variation and autonomic regulation has been provided by population-based observational studies using ABPM. For example, the Hypertension and Ambulatory Blood Pressure Monitoring Project in Japan (HI-JAMP) study showed that BP responsiveness to daily physical activity (also known as actisensitivity) differs across dipping phenotypes, including non-dipping, extreme dipping, and reverse dipping patterns, reflecting heterogeneity in autonomic modulation.[55] In addition to its established role in the diagnosis of HTN, 24-hour ABPM may provide clinically useful, non-invasive insights into autonomic function, especially when integrated with other autonomic indices. This is particularly relevant in conditions such as diabetes, obstructive sleep apnea, and HF, where ANS imbalance frequently contributes to disease progression and CV risk.[56] Therefore, it can be concluded that ABPM should be more broadly implemented in clinical practice, not only as a diagnostic standard for HTN, but also as a supplementary tool for evaluating ANS function in various cardiometabolic and neuroregulatory disorders.[57] This may also have important prognostic implications, as autonomic imbalance contributes to end-organ damage, arrhythmogenesis, and poor CV outcomes.[52,58]

In terms of HTN treatment, HBPM is valuable for long-term follow-up and promoting patient adherence. However, it does not capture nocturnal BP or circadian variability, thereby limiting its utility in assessing ANS function.[59] In contrast, ABPM plays a central role in evaluating the effectiveness of antihypertensive therapy by providing continuous 24-hour data, including nighttime BP profiles and short-term variability. This allows clinicians to identify inadequate nocturnal dipping, optimize medication timing and combinations, and better individualize antihypertensive regimens.[60] ABPM is particularly beneficial in managing conditions associated with increased CV risk and requiring strict BP control, such as chronic kidney disease,[61] left ventricular hypertrophy,[62] and HF.[63] When used alongside tools such as ECG, HRV analysis, or exercise stress testing, ABPM enhances the overall assessment of ANS function.[64] In summary, ABPM provides substantial clinical value in both HTN management and the evaluation of ANS function, supporting a more individualized and pathophysiology-based approach to care. In addition to resting and ambulatory measurements, exaggerated blood pressure response to exercise (EBPR) provides a dynamic assessment of vascular and autonomic reactivity under physiological stress. EBPR, characterized by an abnormally steep rise in systolic BP during graded exercise, reflects excessive sympathetic activation, impaired baroreflex buffering, and increased arterial stiffness.[65] Although it is not part of standard BP monitoring, integrating EBPR findings with ABPM or HRV data offers complementary insights into autonomic-hemodynamic coupling and early CV risk.[66] Individuals exhibiting EBPR often demonstrate altered nocturnal BP profiles or non-dipping patterns on ABPM, underscoring the shared autonomic pathways underlying both exercise and circadian BP regulation.[66,67]

BAROREFLEX SENSITIVITY

Baroreflex sensitivity denotes the ability of the ANS to modulate HR in response to acute changes in BP, thereby contributing to short-term CV stability. It reflects the functional integrity of the baroreflex arc, particularly the sensitivity of baroreceptors lo-

nomne prilagodbe.[68] Procjena BRS-a može se provesti farmakološkim ili nefarmakološkim pristupima. Farmakološka metoda obično uključuje intravensku primjenu vazoaktivnih tvari, poput fenilefrina, kako bi se izazvale prolazne promjene BP-a, uz istodobno mjerenje refleksnih HR odgovora.[69] Nefarmakološke procjene uključuju standardizirane manevre i analitičke tehnike, poput Valsalvina manevra, primjene usisavanja ili tlaka u vratnoj komori za stimulaciju baroreceptora i spontane sekvencijske analize.[69,70] Potonja metoda identificira prirodno nastale sekvence promjena sistoličkog tlaka i RR intervala, omogućujući neinvazivnu i kontinuiranu procjenu pojačanja barorefleksa u uvjetima mirovanja.[71] Podatci se obično analiziraju linearnom regresijom (nagib RR intervala s obzirom na sistolički tlak) ili spektralnom analizom u frekvencijskoj domeni, kvantificirajući koherenciju između oscilacija BP-a i HR-a (**slika 5**). Novije metode uključuju analizu prijenosne funkcije i pristupe temeljene na modelima za poboljšanu rezoluciju.[72]

Nedavna istraživanja ističu rastuću kliničku relevantnost BRS-a kao neinvazivnog markera funkcije ANS-a i snažnoga prognostičkog pokazatelja kod KV bolesti.[72,73] Giannoni *i sur.* (2022.) upozoravaju na to da BRS neovisno predviđa nepovoljne ishode u bolesnika s kroničnim HF-om, uz osjetljivost kemorefleksa. Bolesnici s oštećenim BRS-om pokazali su mno-

cated in the carotid sinus and aortic arch, which detect fluctuations in arterial pressure and trigger appropriate autonomic adjustments.[68] Assessment of BRS can be performed through pharmacological or non-pharmacological approaches. The pharmacological method typically involves intravenous administration of vasoactive substances such as phenylephrine to provoke transient changes in BP, with concurrent measurement of the resulting reflexive HR responses.[69] Non-pharmacological assessments include standardized maneuvers and analytical techniques, such as the Valsalva maneuver, application of neck chamber suction or pressure to stimulate baroreceptors, and spontaneous sequence analysis.[69,70] The latter method identifies naturally occurring sequences of systolic BP and RR interval changes on a beat-to-beat basis, allowing for non-invasive and continuous estimation of baroreflex gain under resting conditions.[71] Data are typically analyzed using linear regression (slope of RR interval vs. systolic BP) or spectral analysis in the frequency domain, quantifying the coherence between BP and HR oscillations (**Figure 5**). Newer methods include transfer function analysis and model-based approaches for improved resolution.[72]

Recent research highlights the growing clinical relevance of BRS as a non-invasive marker of ANS function and a powerful prognostic indicator in CV disease.[72,73] Giannoni et al.

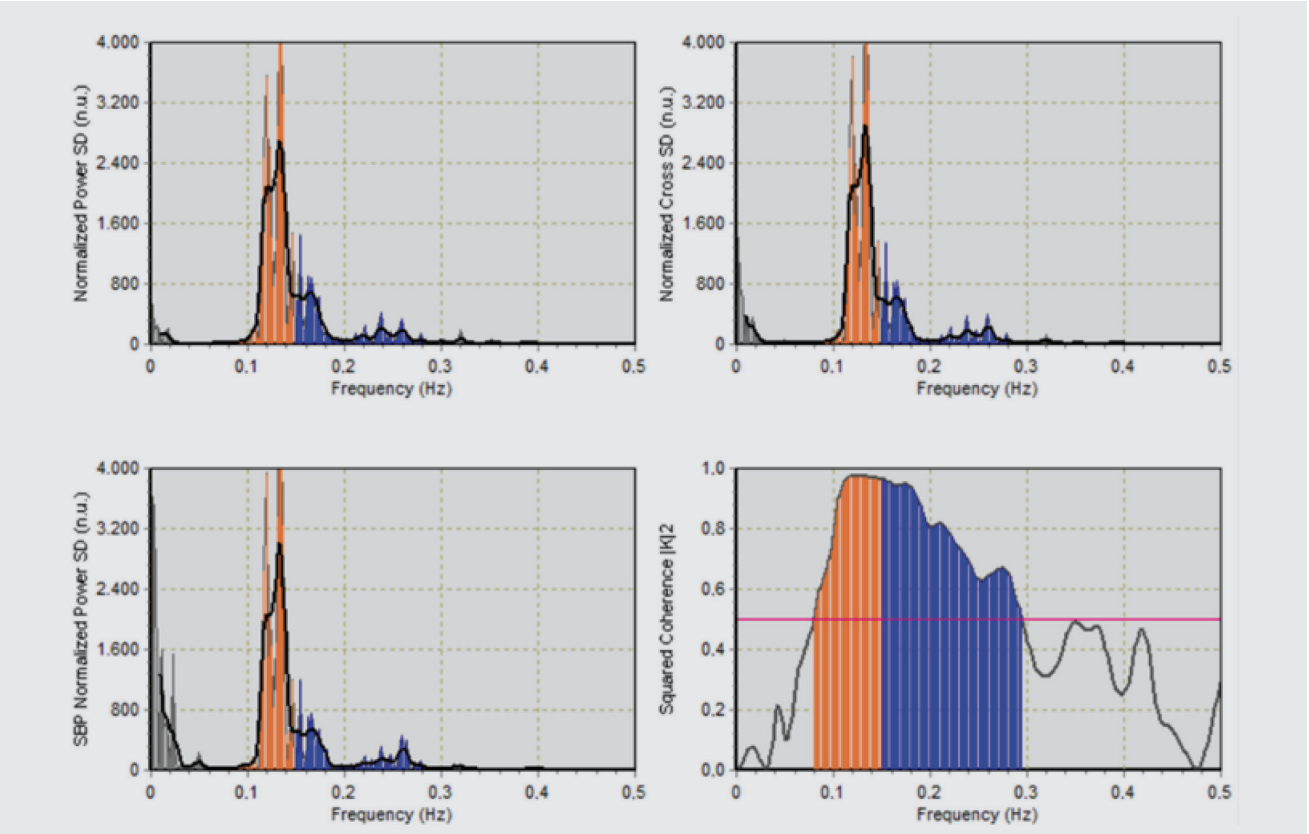

FIGURE 5. Spectral analysis of baroreflex sensitivity.

This figure illustrates the spectral analysis of baroreflex sensitivity (BRS), showing the power spectra of RR intervals and blood pressure, along with the calculated cross-spectrum and coherence function. The degree of coherence between heart rate and blood pressure oscillations in the low-frequency range is quantified, providing an index of baroreflex coupling. The analysis was performed using the *BRS Analysis* software (Nevrokard, Izola, Slovenia), which offers validated algorithms for both spectral and sequence-based BRS assessment. The software integrates simultaneous electrocardiography and blood pressure recordings, enabling accurate and reproducible evaluation of cardiac autonomic regulation in both clinical and research settings.

go veće stope smrtnosti od KV bolesti i hospitalizacije, što podupire njegovu potencijalnu korisnost u stratifikaciji rizika i kliničkom liječenju. Iako je ova studija metodološki postojana, važno je napomenuti da nalazi izvedeni iz specijaliziranih populacija s HF-om mogu zahtijevati opreznu generalizaciju na šire skupine bolesnika.[74] Zhou *i sur.* (2023.), koristeći se podatcima temeljenima na populaciji iz Maastrichtske studije, pokazali su inverznu vezu između BRS-a i sistoličkog tlaka te varijabilnosti tlaka. Ovi nalazi upućuju na to da smanjeni BRS pridonosi oštećenoj KV regulaciji i može biti uključen u rane patofiziološke procese koji dovode do HTN-a.[75] Ovi nalazi naglašavaju da BRS služi ne samo kao marker autonomne funkcije već i kao potencijalna meta preventivnih strategija.

BRS je također povezan s ortostatskom hipotenzijom (OH), stanjem karakteriziranim pretjeranim padom BP-a pri ustajanju, često zbog neadekvatne autonomne kompenzacije. U nedavnom opservacijskom istraživanju *Klop i sur.* (2025.) pokazali su da BRS opada s godinama i znatno je smanjen u osoba koje pokazuju OH. Ovo je smanjenje povezano s oštećenom KV adaptacijom i smanjenom cerebralnom oksigenacijom tijekom promjene položaja (posturalnog prijelaza). Iako istraživanje pruža vrijedan mehanistički uvid, njezin presječni dizajn zahtijeva oprezno tumačenje u pogledu uzročnosti. Ipak, ovi podatci naglašavaju potencijalnu kliničku vrijednost procjene BRS-a u identificiranju osoba s povećanim rizikom od komplikacija povezanih s OH-om.[76]

Nadovezujući se na prognostičku relevantnost BRS-a kod kroničnog HF-a, nedavna terapijska istraživanja istražila su modulaciju autonomnog tonusa kao potencijalnu intervenciju.[74,77] Gentile *i sur.* (2024.) pregledali su novu ulogu stimulacije n. vagusa u bolesnika s HF-om, ističući da oštećeni BRS odražava smanjenu parasimpatičku (vagalnu) aktivnost i pretjerani simpatički pogon, koji su ključni doprinosi progresiji bolesti. Povećanjem aktivnosti vagalnoga eferentnog živca, stimulacija vagusnog živca može poboljšati BRS, smanjiti rizik od aritmija i pozitivno utjecati na srčanu funkciju i remodeliranje. Ove studije podupiru koncept da BRS nije samo biomarker autonomne disfunkcije već i potencijalno modificirajući parametar s terapijskim implikacijama.[77]

Sveukupno, BRS je klinički vrijedan, neinvazivan marker autonomne regulacije, koji nudi visoku specifičnost i dobru osjetljivost za otkrivanje autonomne disfunkcije, posebno u osoba s HF-om. U kombinaciji s komplementarnim autonomnim testovima poput HRV-a i dubokog disanja, BRS pridonosi sveobuhvatnoj procjeni autonomne funkcije.[78,79]

TESTIRANJE NAGIBNIM STOLOM

Testiranje nagibnim stolom (TTT) standardizirani je, neinvazivni dijagnostički postupak koji se rabi za procjenu ANS-a, posebno u kontekstu neobjašnjive sinkope, ortostatske intolerancije i autonomne disfunkcije.[80] Procjenjuje KV odgovor na kontrolirane posturalne promjene, obično iz ležećeg u uspravni položaj, simulirajući tako ortostatski stres pod nadziranim uvjetima.[80,81] U kliničkoj praksi postupak uključuje pričvršćivanje osobe na motorizirani stol koji ga pasivno naginje iz ležećeg položaja pod kutom između 15° i 75°, obično ga održavajući 20 do 45 minuta. Kontinuirano EKG praćenje i neinvazivno praćenje BP-a primjenjuju se za bilježenje odgovora HR i BP-a tijekom cijelog testa (**slika 6**).[81,82] U nekim protokolima farmakološka provokacija s agensima poput nitroglicerina može se iskoristiti za povećanje dijagnostičkog prinosa, posebno kada početni pasivni nagib daje nejasne rezultate.[82]

(2022) found that BRS, alongside chemoreflex sensitivity, independently predicted adverse outcomes in patients with chronic HF. Patients with impaired BRS exhibited significantly higher rates of CV mortality and hospitalization, supporting its potential utility in risk stratification and clinical management. While this study was methodologically robust, it is important to note that the findings were derived from specialized HF populations and may require cautious generalization to broader patient groups.[74] Zhou et al. (2023) used population-based data from the Maastricht Study and demonstrated an inverse relationship between BRS and both systolic BP and BP variability. These findings suggest that reduced BRS contributes to impaired CV regulation and may be involved in the early pathophysiological processes leading to HTN.[75] These findings emphasize that BRS serves not only as a marker of autonomic function but also as a potential target for preventive strategies.

BRS has also been associated with orthostatic hypotension (OH), a condition characterized by an excessive drop in BP upon standing, often due to inadequate autonomic compensation. In a recent observational study, Klop et al. showed that BRS declines with age and is markedly reduced in individuals exhibiting OH. This reduction was linked to impaired CV adaptation and attenuated cerebral oxygenation during postural transitions. While the study provides valuable mechanistic insight, its cross-sectional design warrants cautious interpretation regarding causality. Nevertheless, these data underscore the potential clinical value of BRS assessment in identifying patients at elevated risk of OH-related complications.[76]

Building on the prognostic relevance of BRS in chronic HF, recent therapeutic research has explored modulation of autonomic tone as a potential intervention.[74,77] Gentile et al. (2024) reviewed the emerging role of vagus nerve stimulation in patients with HF, highlighting that impaired BRS reflects reduced parasympathetic (vagal) activity and excessive sympathetic drive, both key contributors to disease progression. By enhancing vagal efferent activity, vagus nerve stimulation may improve BRS, reduce arrhythmic risk, and positively influence cardiac function and remodeling. These studies support the hypothesis that BRS is not only a biomarker of autonomic dysfunction but also a potentially modifiable parameter with therapeutic implications.[77]

Overall, BRS is a clinically valuable, non-invasive marker of autonomic regulation, offering high specificity and good sensitivity for detecting autonomic dysfunction, particularly in populations with HF. When combined with complementary autonomic tests such as HRV and deep breathing, BRS contributes to a comprehensive evaluation of autonomic function.[78,79]

TILT-TABLE TESTING

Tilt-table testing (TTT) is a standardized, non-invasive diagnostic procedure used to evaluate the ANS, particularly in the context of unexplained syncope, orthostatic intolerance, and autonomic dysfunction.[80] It assesses the CV response to controlled postural changes, typically from a supine to an upright position, thereby simulating orthostatic stress under monitored conditions.[80,81] In clinical practice, the procedure involves securing the patient to a motorized table that passively tilts them from a horizontal (supine) position to an angle between 15° and 75°, typically maintained for 20 to 45 minutes. Continuous ECG and non-invasive BP monitoring are used to record HR and BP responses throughout the test (**Figure 6**).[81,82] In some protocols, pharmacological provocation with agents such as nitroglycerin may be employed to increase diagnostic yield, especially when initial passive tilt yields inconclusive results.[82]

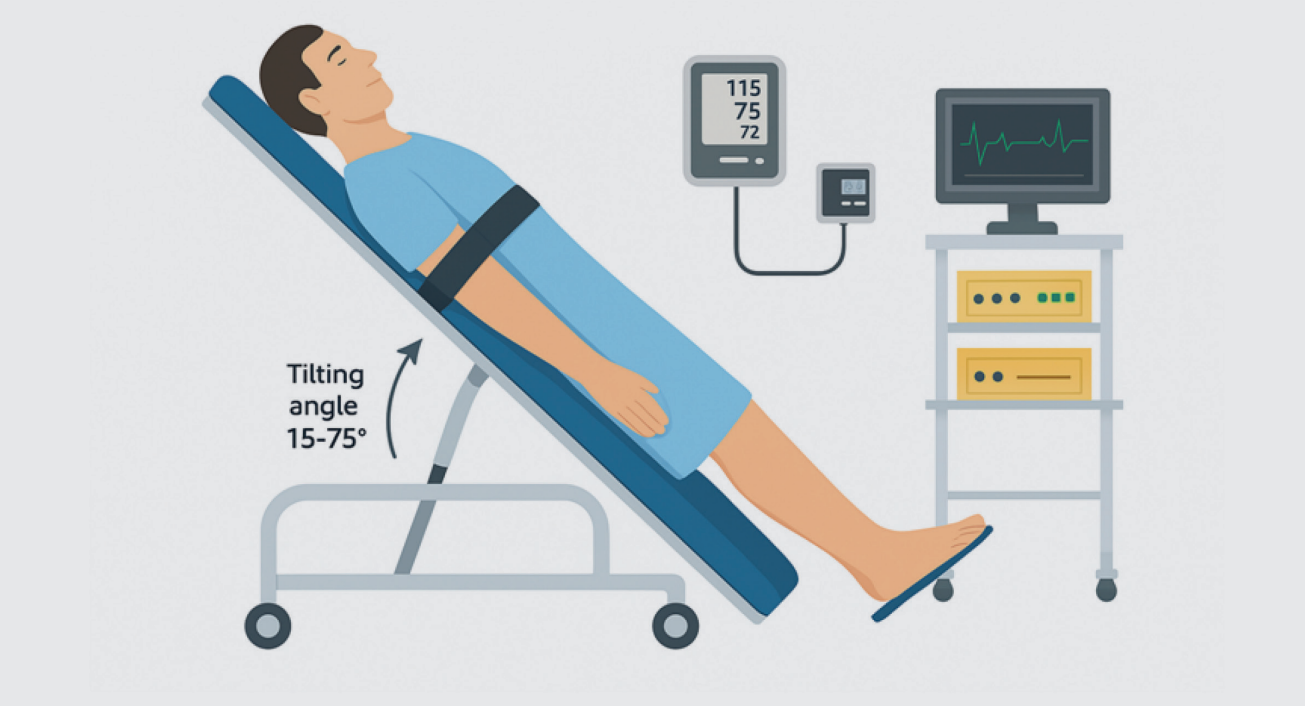

FIGURE 6. Tilt-table testing.
Schematic representation of the tilt-table test showing a patient secured on an adjustable motorized table that can be tilted to various angles, with continuous noninvasive monitoring of blood pressure, heart rate, and electrocardiographic activity to assess autonomic cardiovascular responses to postural changes.

Primarna dijagnostička vrijednost TTT-a leži u njegovoj sposobnosti reprodukcije simptoma i otkrivanja abnormalnih autonomnih odgovora, posebno u procjeni vazovagalne sinkope, sindroma posturalne ortostatske tahikardije i ortostatske intolerancije.[81-83] Pomaže u razlikovanju refleksno posredovane sinkope od drugih uzroka prolaznog gubitka svijesti, poput aritmija, CAD-a ili strukturne bolesti srca, što možda nije vidljivo rutinskim testiranjem.[84,85] TTT je formalno uveden u kliničku praksu potkraj 80-ih godina prošloga stoljeća i od tada je postao dobro uspostavljena dijagnostička metoda u procjeni sinkope i autonomne disfunkcije.[86] Njegova dijagnostička osjetljivost kreće se od 60 % do 85 %, dok specifičnost varira između 90 % i 95 %, ovisno o bolesnicima i protokolu. Iako negativni rezultat ovog testa definitivno ne isključuje refleksnu sinkopu, pozitivan rezultat pruža snažnu dijagnostičku podršku, posebno kada je reprodukcija simptoma popraćena karakterističnim hemodinamskim promjenama.[86-88] Dok se lažno pozitivni rezultati mogu pojaviti u zdravih pojedinaca, osobe s anamnezom refleksne sinkope obično pokazuju kraće vrijeme do sinkope i izraženiji, trajniji pad BP-a. Lažno negativni rezultati zabilježeni su u do 30 % oboljelih. U takvim slučajevima, produljeno praćenje EKG-a može kasnije otkriti kardioinhibitorni mehanizam.[89]

Testiranje nagibom stola omogućuje procjenu OH-a u kontroliranim uvjetima primjenom trajnog ortostatskoga stresa uz kontinuirano praćenje BP-a i HR-a.[90] Može otkriti patološko smanjenje sistoličkog i/ili dijastoličkog tlaka koje zadovoljava dijagnostičke kriterije (≥20/10 mmHg), čak i u osoba s nejasnim ortostatskim mjerenjima uz krevet. To ga čini posebno korisnim za identificiranje neurogenog OH-a, razlikovanje od drugih uzroka ortostatske intolerancije i otkrivanje odgođe-

The primary diagnostic value of TTT lies in its ability to reproduce symptoms and detect abnormal autonomic responses, particularly in the evaluation of neurally mediated syncope (vasovagal syncope), postural orthostatic tachycardia syndrome, and orthostatic intolerance.[81-83] It helps distinguish between reflex-mediated syncope from other causes of transient loss of consciousness, such as arrhythmias, CAD, or structural heart disease, which may not be evident in routine testing.[84,85] TTT was formally introduced into clinical practice in the late 1980s and has since become a well-established diagnostic modality in the evaluation of syncope and autonomic dysfunction.[86] Its diagnostic sensitivity ranges from 60% to 85%, while specificity varies between 90% and 95%, depending on the patient population and the protocol employed. Although a negative tilt-table test does not definitively exclude reflex syncope, a positive test provides strong diagnostic support, particularly when symptom reproduction is accompanied by characteristic hemodynamic changes.[86-88] While false positives may occur in healthy individuals, patients with a history of reflex syncope typically present a shorter time to syncope and a more pronounced, sustained drop in BP. False negatives have been reported in up to 30% of cases. In such cases, prolonged ECG monitoring may subsequently uncover a cardioinhibitory mechanism.[89]

Tilt-table testing enables the assessment of OH under controlled conditions by applying sustained orthostatic stress while continuously monitoring beat-to-beat BP and HR.[90] It can reveal a pathological decrease in systolic and/or diastolic BP that meets diagnostic criteria (≥20/10 mmHg), even in patients with inconclusive bedside orthostatic measurements. This makes it especially useful for identifying neurogenic OH, distinguishing it from other causes of orthostatic intoler-

nih oblika koji se manifestiraju tek nakon duljeg uspravnog držanja.[91] Testiranje nagibom posebno je indicirano u slučajevima kada simptomi poput vrtoglavice, presinkope ili neobjašnjivih padova sugeriraju ortostatski mehanizam, ali konvencionalni testovi stajanja nisu dijagnostički, kao i kod osoba koje ne mogu izvesti aktivno testiranje stajanja zbog krhkosti ili ograničene pokretljivosti.[92] Tada se TTT preporučuje s drugim testovima autonomne funkcije, uključujući procjenu BRS-a, analizu HRV-a, Valsalvin manevar i testove dubokog disanja, kako bi se formirao sveobuhvatan autonomni profil. Kada se interpretira zajedno s kliničkom anamnezom i rezultatima drugih testova, nudi vrijedne uvide u autonomnu regulaciju KV funkcije i podržava točnu dijagnozu, stratifikaciju rizika i odluke o liječenju.[92-94]

Alternativne i nove metode za procjenu funkcije autonomnoga živčanog sustava

Iako su mnoge od tih metoda izvorno razvijene ili prije svega primijenjene u neurologiji, endokrinologiji ili istraživačkim okruženjima, njihova sposobnost kvantificiranja autonomne regulacije KV funkcije čini ih posebno relevantnima u kardiologiji. Te, dodatne metode mogu se kombinirati s osnovnim testovima autonomne funkcije, kao što su HRV, BRS ili TTT kako bi se pružili komplementarni uvidi u regulaciju HR-a, varijabilnost BP-a i autonomnu ravnotežu (**tablica 2**). Takvi parametri su kritično uključeni u patofiziologiju i procjenu rizika od različitih stanja, uključujući sinkopu, aritmije, HF i ishode nakon IM-a.[95,96]

ance, and for detecting delayed forms that manifest only after prolonged upright posture.[91] Tilt testing is particularly indicated in cases where symptoms such as dizziness, presyncope, or unexplained falls suggest an orthostatic mechanism, but conventional standing tests are non-diagnostic, as well as in patients unable to perform active stand testing due to frailty or mobility limitations.[92] In such contexts, TTT is recommended in conjunction with other autonomic function tests, including BRS assessment, HRV analysis, the Valsalva maneuver, and deep breathing tests in order to form a comprehensive autonomic profile. When interpreted in conjunction with clinical history and other test results, it offers valuable insights on the autonomic regulation of CV function and supports accurate diagnosis, risk stratification, and management decisions.[92-94]

Alternative and emerging methods for assessing autonomic nervous system function

Although many of these methods were originally developed or primarily applied in neurology, endocrinology, or research settings, their ability to quantify autonomic regulation of CV function makes them particularly relevant in cardiology. These additional methods can be combined with core autonomic function tests, such as HRV, BRS, or tilt-table testing to provide complementary insights into HR regulation, BP variability, and autonomic balance (**Table 2**). Such parameters are significantly involved in the pathophysiology and risk assessment of various cardiac conditions, including syncope, arrhythmias, HF, and post-MI outcomes.[95,96]

TABLE 2. Summary of alternative methods for autonomic nervous system assessment.[97-119]

Method	Description	Primary purpose	Current use in cardiology
Deep breathing test	Monitors HRV during controlled breathing cycles	Evaluation of parasympathetic (vagal) function and respiratory sinus arrhythmia	Occasionally used in clinical autonomic assessment
Valsalva maneuver	Assesses changes in BP and HR during forced expiration against a closed airway	Evaluation of baroreflex sensitivity within the autonomic reflex arc	Sometimes used for autonomic testing and baroreflex evaluation
Active stand test	Monitors BP and HR responses upon moving from supine to standing position	Detection of orthostatic hypotension and assessment of baroreflex function	Commonly underused in routine clinical practice
Acceleration / Deceleration capacity	Quantifies the heart's ability to accelerate or decelerate during sinus rhythm	Sensitive marker of overall ANS function and cardiovascular prognosis	Primarily used in research and emerging clinical studies
Microneurography	Records sympathetic nerve activity using intraneural microelectrodes	Direct measure of muscle sympathetic nerve activity	Used exclusively in research settings due to its invasiveness
Sympathetic skin response	Measures changes in skin potential evoked by stimuli	Evaluation of sudomotor (sympathetic) pathway integrity	Rarely used in cardiology; more common in neurological testing
Skin conductance response	Tracks variations in skin conductance during physiological arousal	Assessment of sympathetic sudomotor activity and emotional reactivity	Experimental; primarily used in psychophysiological research

Abbreviations: BP – blood pressure; HR – heart rate; HRV – heart rate variability

TEST DUBOKOG DISANJA

Test dubokog disanja jednostavna je, neinvazivna klinička metoda za procjenu kardiovagalne (parasimpatičke) funkcije. Tijekom postupka osoba izvodi duboko, tempirano disanje fiksnom brzinom (obično 5 do 6 udisaja u minuti), dok kontinuirano EKG praćenje bilježi varijabilnost HR-a. To omogućuje procjenu respiratorne sinusne aritmije, fiziološke fluktuacije srčanog ritma između udisaja i izdisaja. Ključna je dijagnostička metrika razlika između maksimalnog i minimalnog srčanog ritma unutar svakoga respiratornog ciklusa (ili omjera izdisaja/udisaja, omjer E/I), izračunata tijekom nekoliko respiratornih ciklusa i često usrednjena tijekom šest uzastopnih udisaja.[97] Neki znanstvenici naglašavaju da je HRV tijekom dubokog disanja vrlo osjetljiv marker vagalne modulacije, što omogućuje rano otkrivanje parasimpatičke disfunkcije čak i prije nego što postanu očiti klinički znakovi autonomnog oštećenja.[98] Han i Zhang (2025.) predložili su novu metriku povezivanja HR-a i disanja koja nudi vrhunsku osjetljivost za otkrivanje promjena u autonomnoj ravnoteži izvan konvencionalnih mjera HRV-a. Njihovi nalazi podupiru kliničku korisnost ovog pristupa kao neinvazivnog alata za procjenu autonomne funkcije.[99]

VALSALVIN MANEVAR

Valsalvin je manevar dobro utvrđena, neinvazivna metoda za procjenu autonomne funkcije, posebno integriteta baroreflekse kontrole i kardiovagalnog tonusa.[100] Izazivanjem prisilnog izdisaja uz zatvoreni dišni put, ovaj manevar izaziva karakteristične promjene HR-a i BP-a u četiri fiziološke faze.[100,101] Valsalvin omjer, definiran kao omjer vršnog ritma srca tijekom naprezanja i najnižeg ritma tijekom oporavka, ključni je indeks parasimpatičke funkcije, dok prateći odgovori BP-a pružaju uvid u simpatičku vazomotornu kontrolu.[102] Njegovu kliničku relevantnost u kardiologiji pokazali su Felker *i sur.* (2006.), koji su ga predstavili kao novu, neinvazivnu metodu za procjenu tlaka punjenja srca kod HF-a.[103] Iako je njegova kardiološka primjena od tada dobila ograničenu pozornost u istraživanjima, Park *i sur.* (2023.) nedavno su naglasili njegovu vrijednost u identificiranju kasno nastale odgođene ortostatske intolerancije, suptilne, ali klinički značajne manifestacije autonomne disfunkcije.[104] Valsalvin manevar može se rutinski izvoditi uz druge testove autonomne funkcije, kao što su HRV, BRS, duboko disanje i testiranje nagibnim stolom, kako bi se omogućila sveobuhvatna procjena regulacije ANS-a u kardiologiji.[102,105]

TEST AKTIVNOG STAJANJA (ORTOSTATSKO MJERENJE ARTERIJSKOG TLAKA)

Ortostatsko mjerenje BP-a pruža jednostavan, neinvazivan način procjene autonomne KV regulacije i sposobnosti ANS-a da očuva hemodinamsku stabilnost tijekom posturalnog prijelaza. Nakon najmanje 5 minuta odmora u ležećem položaju osoba odmah ustaje i kontinuirano se bilježe HR i BP tijekom 3 do 10 minuta, prema odgovarajućem protokolu ili smjernicama.[106] Međutim, u rutinskoj kliničkoj praksi rijetko se provodi kontinuirano praćenje. Umjesto toga, uobičajeno se primjenjuje standardizirani protokol uz krevet koji se koristi povremenim oscilometrijskim mjerenjima BP-a provedenima u definiranim intervalima nakon ustajanja, kako preporučuju trenutačne smjernice. Iako ovaj pristup nudi nižu vremensku rezoluciju i osjetljivost u usporedbi s metodama od otkucaja

DEEP BREATHING TEST

The deep breathing test is a simple, noninvasive clinical method for evaluating cardiovagal (parasympathetic) function. During the procedure, the patient performs deep, paced breathing at a fixed rate (typically 5 to 6 breaths per minute), while continuous ECG monitoring captures the heart's beat-to-beat variability. This allows for assessment of respiratory sinus arrhythmia, the physiological fluctuation in HR between inspiration and expiration. The key diagnostic metric is the difference between the maximal and minimal HR within each respiratory cycle (or the expiratory/inspiratory ratio, E/I ratio), computed over several respiratory cycles and often averaged across six consecutive breaths.[97] Some scientists emphasize that HRV during deep breathing is a highly sensitive marker of vagal modulation, providing early detection of parasympathetic dysfunction even before overt clinical signs of autonomic impairment become apparent.[98] Han and Zhang (2025) proposed a novel heartbeat-respiration coupling metric that offers superior sensitivity for detecting shifts in autonomic balance beyond conventional HRV measures. Their findings support the clinical utility of this approach as a non-invasive tool for evaluating autonomic function in clinical cardiology.[99]

VALSALVA MANEUVER

The Valsalva maneuver is a well-established, non-invasive method for assessing autonomic function, particularly the integrity of baroreflex control and cardiovagal tone.[100] By inducing forced expiration against a closed airway, this maneuver provokes characteristic changes in HR and BP across four physiological phases.[100,101] The Valsalva ratio, defined as the ratio of peak HR during strain to the lowest HR during recovery, is a key index of parasympathetic function, whereas accompanying BP responses provide insight into sympathetic vasomotor control.[102] Its clinical relevance in cardiology was demonstrated by Felker et al. (2006), who introduced it as a novel, non-invasive method for assessing cardiac filling pressures in HF.[103] Although its cardiological application has since received limited attention in research, Park et al. (2023) more recently underscored its value in identifying late-onset delayed orthostatic intolerance, a subtle yet clinically significant manifestation of autonomic dysfunction.[104] The Valsalva maneuver can be routinely performed alongside other autonomic function tests, such as HRV, BRS, deep breathing, and tilt-table testing, in order to enable a comprehensive assessment of ANS regulation in cardiology.[102,105]

ACTIVE STAND TEST (ORTHOSTATIC BLOOD PRESSURE MEASUREMENT)

The orthostatic (active standing) test provides a simple, non-invasive means of evaluating autonomic CV regulation and the capacity of the ANS to preserve hemodynamic stability during postural transition. After at least 5 minutes of supine rest, the patient promptly stands, and continuous beat-to-beat measurements of HR and BP are recorded over 3 to 10 minutes, according to the respective protocol or guideline.[106] However, continuous beat-to-beat monitoring is rarely performed in routine clinical practice. Instead, a standardized bedside protocol using intermittent oscillometric BP measurements performed at defined intervals after standing is commonly applied, as recommended by current guidelines. Although this approach offers lower temporal resolution and sensitiv-

do otkucaja, ostaje izvediviji i široko primjenjiv u svakodnevnoj kliničkoj praksi.[107] Ovaj se test prije svega primjenjuje za identifikaciju autonomnih disfunkcija poput OH-a.[107,108] U kardiologiji je posebno relevantan za otkrivanje oštećenja baroreflekса ili simpatičkog zatajivanja koji pridonose sinkopi, vrtoglavici, padovima ili drugim ortostatskim simptomima. Suprotno tomu, ortostatska hipertenzija, definirana kao pretjerano povećanje sistoličkog tlaka pri ustajanju, također je privukla pozornost kao potencijalni marker simpatičke hiperaktivnosti i povećanog KV rizika.[109] Osim dijagnostičke klasifikacije, Gronwald i *sur.* (2024.) istaknuli su njezinu dodatnu vrijednost u procjeni HRV-a pod ortostatskim stresom, nudeći uvid u parasimpatičku reaktivnost i dinamiku oporavka.[110] Unatoč svojoj praktičnosti, ortostatski test ima znatna ograničenja u otkrivanju određenih oblika autonomne disfunkcije. Kirbiš *i sur.* (2013.) istaknuli su da test aktivnog stajanja može propustiti odgođene ili suptilne autonomne odgovore, koji se pouzdanije otkrivaju testiranjem nagibnim stolom ili 24-satnim ABPM-om. Ograničenja također uključuju smanjenu ponovljivost zbog individualne varijabilnosti, mišićne aktivnosti i respiratornog utjecaja, kao i praktično ograničenje u osoba s krhkošću ili smanjenom pokretljivošću.[111] Iako mu nedostaje standardizacija i kontrolirani gravitacijski podražaj pasivnoga nagibnog testa, ortostatski test ostaje vrijedna komponenta sveobuhvatne autonomne procjene, posebno kada se interpretira zajedno s komplementarnim mjerama kao što su HRV, BRS, Valsalvin manevar i nalazi TTT-a.[107,108,112]

KAPACITET UBRZANJA I USPORIVANJA OTKUCAJA SRCA

Napredna HRV analiza primjenom fazno ispravljenog usrednjavanja signala daje kapacitet ubrzanja (AC) i kapacitet usporivanja (DC), koji odražavaju simpatičku i parasimpatičku modulaciju HR-a. Iako se prije svega primjenjuju u istraživanjima, ove metrike pojavljuju se kao osjetljivi markeri autonomne neravnoteže. DC je, posebno, pokazao prognostičku vrijednost u bolesnika s HF-om, predviđajući i aritmičku i ukupnu smrtnost.[113] U novije vrijeme, AC i DC također su povezani s cirkadijalnim obrascima BP-a kod esencijalne hipertenzije, što ističe njihovu potencijalnu važnost u široj KV regulaciji.[114]

MIKRONEUROGRAFIJA

Mikroneurografija je invazivna tehnika koja omogućuje izravno snimanje aktivnosti simpatičkog živca u ljudi umetanjem mikroelektrode u periferni živac, obično peronealni živac. Pruža mjerenja simpatičke aktivnosti mišićnog živca u stvarnom vremenu, nudeći jedinstven uvid u funkciju ANS-a.[115] U kardiologiji se mikroneurografija uporabljuje za istraživanje simpatičke prekomjerne aktivnosti u stanjima kao što su HF, HTN i aritmije. Omogućuje preciznu procjenu simpatičkog odljeva, dopunjujući neizravne mjere poput HRV-a. Iako je tehnički zahtjevna i ograničena na specijalizirane istraživačke centre, njezin potencijal u otkrivanju autonomne disfunkcije kod CSV bolesti mogao bi biti značajan. Buduća istraživanja, zajedno s neinvazivnim markerima aktivnosti ANS-a, mogla bi poboljšati naše razumijevanje autonomnih doprinosa KV riziku.[116]

SIMPATIČKI KOŽNI ODGOVOR

Simpatički kožni odgovor (SSR) mjeri promjene u električnom potencijalu kože izazvane aktivacijom znojnih žlijezda, što odražava sudomotornu simpatičku aktivnost. Kao neinvazivan i lako primjenjiv test, SSR se prije svega rabi za procjenu

ity compared to beat-to-beat methods, it remains more feasible and widely applicable in everyday clinical settings.[107] This test is primarily used to identify autonomic dysfunctions such as OH.[107,108] In cardiology, it is particularly relevant for uncovering baroreflex impairment or sympathetic failure contributing to syncope, dizziness, falls, or other orthostatic symptoms. Conversely, orthostatic hypertension, defined as an excessive increase in systolic BP upon standing, has also gained attention as a potential marker of sympathetic overactivity and increased CV risk.[109] Beyond the diagnostic classification, Gronwald et al. (2024) have highlighted the additional value of active stand tests in assessing HRV under orthostatic stress, providing insight into parasympathetic reactivity and recovery dynamics.[110] Despite its practicality, the orthostatic test has notable limitations in detecting certain forms of autonomic dysfunction. Kirbiš et al. (2013) pointed out that the active stand test may miss delayed or subtle autonomic responses, which are more reliably detected with tilt-table testing or 24-hour ABPM. Limitations also include reduced reproducibility due to individual variability, muscle activity, and respiratory influence, as well as a practical constraint in patients with frailty or impaired mobility.[111] Although it lacks the standardization and controlled gravitational stimulus of passive tilt testing, the orthostatic test remains a valuable component of comprehensive autonomic evaluation, particularly when interpreted in conjunction with complementary measures such as HRV, BRS, Valsalva maneuver, and TTT findings.[107,108,112]

HEART RATE ACCELERATION AND DECELERATION CAPACITY

Advanced HRV analysis using phase-rectified signal averaging yields acceleration capacity (AC) and deceleration capacity (DC), which reflect sympathetic and parasympathetic HR modulation, respectively. Although primarily used in research, these metrics are emerging as sensitive markers of autonomic imbalance. DC, in particular, has shown prognostic value in patients with HF, predicting both arrhythmic and all-cause mortality.[113] More recently, AC and DC have also been associated with circadian patterns of BP in essential HTN, highlighting their potential relevance in broader CV regulation.[114]

MICRONEUROGRAPHY

Microneurography is an invasive technique that enables direct recording of sympathetic nerve activity in humans by inserting a microelectrode into a peripheral nerve, typically the peroneal nerve. It provides real-time measurements of muscle sympathetic nerve activity, providing unique insights into ANS function.[115] In cardiology, microneurography has been used to investigate sympathetic overactivity in conditions such as HF, HTN, and arrhythmias. It allows precise assessment of sympathetic outflow, complementing indirect measures such as HRV. Although technically demanding and limited to specialized research centers, its potential in detecting autonomic dysfunction in CSV disease could be significant. Future research combined with noninvasive markers of ANS activity could enhance our understanding of autonomic contributions to CV risk.[116]

SYMPATHETIC SKIN RESPONSE

The sympathetic skin response (SSR) measures changes in electrical potential on the surface of the skin triggered by sweat gland activation, reflecting sudomotor sympathetic activity. As a noninvasive and easily applicable test, SSR is primarily used

autonomnih neuropatija malih vlakana.[117] U kardiologiji SSR može pomoći u identificiranju suptilne autonomne disfunkcije koja se ne otkriva standardnim testovima KV refleksa. Istraživanje je pokazalo abnormalne nalaze SSR-a u osoba s perifernom arterijskom bolešću, što upućuje na promijenjenu simpatičku funkciju. Slične su promjene zabilježene kod HF-a i sinkope.[118] Iako je još uvijek uglavnom istraživački alat, SSR bi mogao podržati autonomno profiliranje kod KV bolesti kada se primjenjuje uz druge procjene.

ODGOVOR KOŽNE VODLJIVOSTI

Odgovor kožne vodljivosti (SCR) neinvazivna je mjera sudomotorne simpatičke aktivnosti, koja odražava autonomnu funkciju malih vlakana. U kardiologiji može pomoći u otkrivanju autonomne disfunkcije u stanjima kao što su HF, sinkopa ili dijabetička neuropatija.[119] Uporaba i ponovljivost SCR-a čine ga korisnim komplementarnim alatom, iako je potrebna daljnja validacija.

Klinička korisnost i primjena testiranja autonomnoga živčanog sustava u svakodnevnoj praksi

Uključivanje procjene ANS-a u procjenu KV bolesti nudi značajnu dijagnostičku i prognostičku vrijednost. Neinvazivni modaliteti poput HRV-a, HRR-a, BRS-a, TTT-a i ABPM-a pružaju komplementarne uvide u autonomnu regulaciju i KV rizik (**tablica 3**). Prve formalne preporuke za analizu HRV-a izdala je sredinom 90-ih godina 20. st. Radna skupina Europskog društva za kardiologiju i Sjevernoameričko društvo za elektrostimulaciju i elektrofiziologiju, uspostavljajući standardizirane metrike za mjerenja vremenske i frekvencijske domene. Od tada su metodološki napredak, digitalna analiti-

to assess small-fiber autonomic neuropathies.[117] In cardiology, SSR may help identify subtle autonomic dysfunction not detected by standard CV reflex tests. Studies have demonstrated abnormal SSR findings in patients with peripheral arterial occlusive disease, indicating altered sympathetic function. Similar changes have been reported in cardiac conditions such as HF and syncope.[118] Although still mainly a research tool, SSR could support autonomic profiling in CV disease when used alongside other assessments.

SKIN CONDUCTANCE RESPONSE

Skin conductance response (SCR) is a noninvasive measure of sudomotor sympathetic activity, reflecting small-fiber autonomic function. In cardiology, it may aid in detecting autonomic dysfunction in conditions such as HF, syncope, or diabetic neuropathy.[119] The efficacy and reproducibility of SCR make it a useful complementary diagnostic tool, though further validation in CV populations is needed.

Clinical utility and implementation of autonomic nervous system testing in everyday practice

The inclusion of ANS evaluation in CV assessment offers considerable diagnostic and prognostic value. Non-invasive modalities such as HRV, HRR, BRS, TTT, and ABPM each provide complementary insights into autonomic regulation and CV risk (**Table 3**). The first formal recommendations for HRV analysis were issued in the mid-1990s by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, establishing standardized metrics for time- and frequency-domain measures. Since then, methodological advancements, digital analytics,

TABLE 3. Summary of main autonomic nervous system tests and their clinical and diagnostic value in cardiovascular conditions.[13-94]

Test	Clinical value	Sensitivity / Specificity	Cardiovascular diseases where autonomic testing provides diagnostic and prognostic insight
HRV	Diagnostic and prognostic marker of autonomic tone and cardiac control variability; useful for risk stratification and early detection of ANS dysfunction	High Se for autonomic impairment; Moderate Sp depending on analysis method.	HF; IHD; arrhythmias; DAN; HTN
HRR	Prognostic indicator of post-exercise vagal reactivation and autonomic balance; predictor of mortality and exercise tolerance	High Sp and moderate Se for mortality prediction	IHD; HF; SCD risk; exercise intolerance
ABPM	Diagnostic and therapeutic tool assessing BP variability, circadian rhythm (dipping), and orthostatic BP response; supports treatment optimization	High Se and Sp for BP dysregulation	HTN; OH; masked HTN; nocturnal HTN
BRS	Combined diagnostic and prognostic assessment of baroreceptor reflex arc integrity and autonomic control	Moderate-high Se and high Sp, technique-dependent	HF; IHD; syncope arrhythmias; autonomic neuropathies
Tilt-Table Test	Diagnostic test for syncope, orthostatic intolerance, and autonomic instability; prognostic value when combined with hemodynamic or reflex parameters	Moderate-high Se and high Sp for autonomic instability and syncope differentiation	VVS; OH; POTS

Abbreviations: ANS – autonomic nervous system; **ABPM** – ambulatory blood pressure monitoring; **BP** – blood pressure; **BRS** – baroreflex sensitivity; **DAN** – diabetic autonomic neuropathy; **HF** – heart failure; **HRR** – heart rate recovery; **HRV** – heart rate variability; **HTN** – hypertension; **IHD** – ischemic heart disease; **OH** – orthostatic hypotension; **POTS** – postural orthostatic tachycardia syndrome; **SCD** – sudden cardiac death; **Se** – sensitivity; **Sp** – specificity; **VVS** – vasovagal syncope

ka i širenje kliničkih dokaza poboljšali interpretaciju HRV-a i proširili njezinu relevantnost u KV i sistemskim bolestima.[120] Unatoč tom napretku, HRV i drugi markeri povezani s ANS-om još nisu potpuno integrirani u suvremene europske ili američke kliničke smjernice.

Izjava o konsenzusu Cheshirea *i sur.* iz 2021., koju je podržalo Američko autonomno društvo i druga stručna tijela, naglasila je hitnu potrebu za standardizacijom i konsenzusom u testiranju ANS-a. Preporučila je da autonomna evaluacija uključuje kombinaciju validiranih mjera koje se odnose na kardiovagalne, adrenergičke i sudomotorne domene, interpretirane u širemu kliničkom kontekstu, a ne kao izoliranu dijagnostiku. Dokument je dodatno istaknuo važnost metodološkog usklađivanja, uspostavljanja normativnih referentnih podataka i stručnog nadzora kako bi se osigurala točnost i usporedivost među institucijama. Uspostavljanje takvih okvira temeljenih na konsenzusu, ključan je korak prema integraciji testiranja ANS-a u rutinsku kardiološku praksu.[121] U skladu s tim preporukama, Verdugo i Matamala (2021.) primijetili su da je, unatoč dugogodišnjoj kliničkoj uporabi autonomnih testova, njihova široka primjena ograničena nedostatkom standardiziranih postupaka i kriterija za interpretaciju. Naglasili su da uvođenje međunarodno dogovorenih standarda sada pruža koherentan okvir za provođenje i tumačenje autonomnog testiranja, čime se poboljšava dijagnostička pouzdanost, usporedivost među centrima i klinička primjenjivost. Autori se zalažu za sustavnu integraciju standardiziranih autonomnih procjena u procjenu KV bolesti kako bi se poboljšali dijagnostička preciznost, terapijsko vođenje i dosljednost istraživanja.[122]

Ažuriranje kliničke neurokardiologije iz 2024. godine koje su proveli Ajijola **i** *sur.* (2025.) ističe da je disfunkcija ANS-a patofiziološka osnova mnogih KV bolesti, uključujući aritmije, HF i postinfarktne sindrome. Autori naglašavaju da napredak u neuroanatomiji, neurofiziologiji i neuromodulaciji sve više oblikuje KV terapiju, postupno prebacujući fokus sa simptomatskog liječenja prema ciljanoj modulaciji neuronske kontrole. Autonomno testiranje i neuromodulatorne strategije smatraju se obećavajućim alatima za profinjenu stratifikaciju rizika i individualiziranu terapiju, iako se njihova klinička primjena još uvijek razvija. Rad poziva na razvoj standardiziranih biomarkera, poboljšanih senzorskih tehnologija i sustava zatvorene petlje koji povezuju procjenu ANS-a s terapijom. Konačno, naglašava važnost interdisciplinarne suradnje kako bi se uspostavili jedinstveni okviri za integraciju autonomne procjene i neuromodulatornog liječenja u glavnu kliničku praksu.[123] Osiguravanje preciznosti i točnosti ostaje temeljno u autonomnom testiranju, kako je naglasio Odjel za politiku Američkog udruženja za neuromuskularnu i elektrodijagnostičku medicinu, koji je uspostavio temeljna načela za standardiziranu izvedbu, sigurnost pacijenata i pouzdanu interpretaciju.[124] Brzim širenjem digitalnih zdravstvenih tehnologija i nosivih sustava za praćenje, autonomne mjere, posebno HRV, sada se mogu besprijekorno integrirati, poboljšavajući rano otkrivanje autonomne disfunkcije i omogućujući longitudinalno praćenje terapijske učinkovitosti.[125]

Ograničenja

Treba priznati nekoliko ograničenja ovog članka. Prvo, budući da je riječ o narativnoj sintezi, a ne o sustavnom pregledu ili metaanalizi, odabir studija može biti podložan pristranosti,

and expanding clinical evidence have refined HRV interpretation and broadened its relevance across CV and systemic diseases.[120] Despite this progress, HRV and other ANS-related markers have yet to be fully integrated into contemporary European or American clinical guidelines.

The 2021 consensus statement by Cheshire et al., endorsed by the American Autonomic Society and other expert bodies, underscored the pressing need for standardization and consensus in ANS testing. It recommended that autonomic evaluation incorporate a combination of validated measures addressing cardiovagal, adrenergic, and sudomotor domains, interpreted within the broader clinical context rather than as isolated diagnostics. The document further highlighted the importance of methodological harmonization, establishment of normative reference data, and expert oversight to ensure accuracy and comparability across institutions. Establishing such consensus-based frameworks represents a crucial step toward integrating ANS testing into routine cardiological practice.[121] In line with these recommendations, Verdugo and Matamala (2021) observed that, despite the long-standing clinical use of autonomic tests, their widespread implementation has been limited by the lack of standardized procedures and interpretative criteria. They emphasized that the introduction of internationally accepted standards now provides a coherent framework for performing and interpreting autonomic testing, thereby improving diagnostic reliability, cross-center comparability, and clinical applicability. The authors advocate for the systematic integration of standardized autonomic assessments into CV evaluation to enhance diagnostic precision, therapeutic guidance, and research consistency.[122]

The 2024 update on Clinical Neurocardiology by Ajijola et al. (2025) highlights that ANS dysfunction represents a fundamental pathophysiological basis of many CV diseases, including arrhythmias, HF, and post-infarction syndromes. The authors emphasize that advances in neuroanatomy, neurophysiology, and neuromodulation are increasingly shaping CV therapeutics, gradually shifting focus from symptomatic management towards targeted modulation of neural control. Autonomic testing and neuromodulatory strategies are viewed as promising tools for refined risk stratification and individualized therapy, although their clinical translation is still evolving. The paper calls for the development of standardized biomarkers, improved sensor technologies, and closed-loop systems linking ANS assessment with therapy. Finally, it stresses the importance of interdisciplinary collaboration to establish unified frameworks for integrating autonomic assessment and neuromodulatory treatment into mainstream clinical practice.[123] Ensuring precision and accuracy remains fundamental in autonomic testing, as emphasized by the Policy Department of the American Association of Neuromuscular and Electrodiagnostic Medicine, which established core principles for standardized performance, patient safety, and reliable interpretation.[124] With the rapid expansion of digital health technologies and wearable monitoring systems, autonomic measures, particularly HRV, can now be seamlessly integrated into clinical workflows, enhancing early detection of autonomic dysfunction and enabling longitudinal monitoring of therapeutic efficacy.[125]

Limitations

Several limitations of this article should be acknowledged. First, as a narrative synthesis rather than a systematic review or meta-analysis, the selection of studies may be subject to

što potencijalno ograničava reproducibilnost. Drugo, pregledana literatura pokazuje znatnu heterogenost u dizajnu studije, metodološkoj strogosti, populacijama, protokolima testiranja ANS-a, metodama prikupljanja podataka, analitičkim pristupima i kliničkim krajnjim točkama. Ova varijabilnost obuhvaća male opservacijske studije, intervencijska ispitivanja u jednom centru, velike prospektivne kohorte i mehanističke ili eksperimentalne studije, što komplicira izravne usporedbe i ograničava mogućnost donošenja konačnih zaključaka u vezi s kliničkim pragovima ili standardiziranim primjenama. Treće, iako mnoge studije pružaju vrijedne fiziološke i prognostičke uvide u autonomne markere poput HRV-a, HRR-a, mjera izvedenih iz ABPM-a i BRS-a, ukupna snaga dokaza je heterogena. Veće, studije i metaanalize općenito podržavaju kliničku korisnost ovih markera, dok nalaze iz manjih intervencijskih studija u jednom centru ili studija u ranoj fazi treba tumačiti s oprezom zbog ograničene generalizacije. Osim toga, nekoliko se studija usredotočuje na surogatne krajnje točke, a ne na tvrde KV ishode, što može utjecati na translacijsku relevantnost nekih nalaza. Konačno, brzi tehnološki napredak i razvoj analitičkih tehnika u procjeni ANS-a mogu ograničiti generalizaciju starijih studija tijekom vremena. Uzevši sve u obzir, iako konvergencija nalaza u različitim populacijama podržava kliničku relevantnost autonomnih markera za stratifikaciju rizika, prognostičku procjenu i praćenje terapijskih intervencija, čitatelji bi trebali uzeti u obzir dizajn studije, metodološku kvalitetu i karakteristike populacije pri tumačenju rezultata i njihove primjene u kliničkoj praksi. Buduća bi istraživanja trebala težiti standardiziranim protokolima, većim multicentričnim studijama i klinički značajnim krajnjim točkama kako bi se ojačala translacijska vrijednost testiranja ANS-a.

Zaključak

Rano prepoznavanje autonomne disfunkcije omogućuje ciljane intervencije, poput optimizacije farmakoterapije, promjene načina života ili kardiološke rehabilitacije, što može smanjiti rizik od aritmija, poboljšati kontrolu BP-a i poboljšati kliničke ishode. Uključivanje mjera ANS-a u rutinsku kardiološku praksu može podržati sveobuhvatniji i integrativniji pristup KV skrbi, premošćujući funkcionalnu i strukturnu procjenu. Testiranje autonomne funkcije nudi jedinstvene fiziološke uvide koji se ne mogu dobiti konvencionalnim hemodinamskim ili slikovnim metodama, pružajući funkcionalnu dimenziju koja dopunjuje strukturnu dijagnostiku i pomaže u personaliziranom liječenju. Dokazi koji podupiru ove primjene obuhvaćaju širok raspon dizajna studija, od malih opservacijskih kohorti do velikih prospektivnih studija i preporuka temeljenih na konsenzusu. Iako mnoge studije pružaju uvide u HRV, HRR, BRS i druge autonomne markere, ukupna snaga dokaza ostaje heterogena. Varijacije u metodološkoj kvaliteti, veličini uzorka, dizajnu studije, populacijama i ishodima ograničavaju dosljednost među studijama i treba ih uzeti u obzir pri tumačenju kliničkih implikacija. Metaanalize i veće kohortne studije općenito pružaju najpouzdanije podatke, dok nalazi iz manjih ili studija s jednim centrom zahtijevaju oprezno tumačenje. Unatoč tim ograničenjima, konvergentni smjer dokaza u različitim populacijama podržava kliničku relevantnost autonomnih markera za stratifikaciju rizika, prognostičku procjenu i praćenje terapijskih intervencija. Šira primjena u kliničkoj praksi zahtijevat će standardizirane

bias, potentially limiting reproducibility. Second, the reviewed literature exhibits substantial heterogeneity in study design, methodological rigor, patient populations, ANS testing protocols, data acquisition methods, analytical approaches, and clinical endpoints. This variability spans small observational studies, single-center interventional trials, large prospective cohorts, and mechanistic or experimental studies, which complicates direct comparisons and constrains the ability to draw definitive conclusions regarding clinical thresholds or standardized applications. Third, while many studies provide valuable physiological and prognostic insights into autonomic markers such as HRV, HRR, ABPM-derived measures, and BRS, the overall strength of the evidence is heterogeneous. Larger studies and meta-analyses generally support the clinical utility of these markers, whereas findings from smaller, single-center, or early-phase interventional studies should be interpreted with caution due to limited generalizability. Additionally, several studies focus on surrogate endpoints rather than hard CV outcomes, which may affect the translational relevance of some findings. Finally, rapid technological advances and evolving analytical techniques in ANS assessment may limit the generalizability of older studies over time. Taken together, although the convergence of findings across diverse populations supports the clinical relevance of autonomic markers for risk stratification, prognostic assessment, and monitoring of therapeutic interventions, readers should consider study design, methodological quality, and population characteristics when interpreting results and applying them to clinical practice. Future research should aim towards standardized protocols, larger multicenter studies, and clinically meaningful endpoints to strengthen the translational value of ANS testing.

Conclusion

Early recognition of autonomic dysfunction enables targeted interventions, such as optimization of pharmacotherapy, lifestyle modification, or cardiac rehabilitation, which may reduce arrhythmic risk, improve BP control, and enhance clinical outcomes. Incorporating ANS measures into routine cardiology practice can support a more comprehensive and integrative approach to CV care, bridging functional and structural assessment. Autonomic function testing offers unique physiological insights that cannot be captured by conventional hemodynamic or imaging methods, providing a functional dimension that complements structural diagnostics and aids in personalized, patient-centered management. The evidence supporting these applications spans a wide range of study designs, from small observational cohorts to large prospective studies and consensus-based recommendations. While many studies provide robust insights on HRV, HRR, BRS, and other autonomic markers, the overall strength of evidence remains heterogeneous. Variations in methodological quality, sample size, study design, patient populations, and outcome measures limit consistency across studies and should be considered when interpreting clinical implications. Meta-analyses and larger cohort studies generally provide the most reliable data, whereas findings from smaller or single-center studies warrant cautious interpretation. Despite these limitations, the convergent direction of evidence across diverse populations supports the clinical relevance of autonomic markers for risk stratification, prognostic assessment,

protokole, stručnu poduku i međunarodno usklađene smjernice za optimizaciju izvedbe testova, interpretacije rezultata i integracije u KV skrb. Buduća bi istraživanja trebala dati prioritet većim, multicentričnim studijama s klinički značajnim krajnjim točkama kako bi se ojačala translacijska vrijednost testiranja ANS-a i dodatno utvrdila njegova uloga u modernoj kardiologiji.

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and monitoring of therapeutic interventions. Broader implementation in clinical practice will require standardized protocols, professional training, and internationally harmonized guidelines to optimize test performance, result interpretation, and integration into CV care. Future research should prioritize larger, multicenter studies with clinically meaningful endpoints to strengthen the translational value of ANS testing and further establish its role in modern cardiology.

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