The Importance of the Smoothness Index in Managing Hypertension

**SAŽETAK:** Prosječni arterijski tlak (AT) mjeren u liječničkoj ordinaciji zlatni je standard za dijagnosticiranje i liječenje arterijske hipertenzije. Međutim, AT se tijekom dana mijenja pa izmjerena vrijednost ne odražava uvijek stvarni tlak. Stoga je također važno mjeriti i varijabilnost AT-a, koja je povezana s većom učestalosću kardiovascularnih događaja, smrti i oštećenja ciljnih organa. Liječenje mora biti usmjeren ne samo na smanjenje 24-satnog prosječnog AT-a nego i na normalizaciju varijabilnosti AT-a tijekom dana i noći. Utvrđeno je da smanjenje prosječnog AT-a uzrokuje proporcionalno smanjenje njegove varijabilnosti, pa zbog toga za kontrolu hipertenzije može biti korisna primjena dugodjelujućih lijekova. Metoda 24-satnoga kontinuiranoga mjerenja arterijskog tlaka nudi nekoliko prednosti, poput pružanja informacija o maksimalnom učinku i trajanju učinka lijekova protiv hipertenzije, kao i omogućivanja izračuna indeksa omjera prosječne promjene AT-a i njegove standardne devijacije. Indeks omjera prosječne promjene AT-a i njegove standardne devijacije bio je viši za kombinirane lijekove i lijekove u većim dozama. Za lijekove s višim indeksom omjera prosječne promjene AT-a i njegove standardne devijacije dokazano je da su superiorini u pružanju kardiovascularne zaštite i u prevenciji oštećenja ciljnih organa.

**SUMMARY:** Average clinic blood pressure (BP) is the gold standard for the diagnosis and treatment of hypertension. However, BP fluctuates throughout the day and the measurement does not always reflect the actual BP. Therefore it is also important to measure BP variability, which has been associated with an increased frequency of cardiovascular events, death, and target organ damage. Treatment has to be directed not only towards reducing the 24-hour BP average but also towards normalizing the variability of BP during the day and at night. It has been found that reduction in average BP leads to a proportional reduction in its variability, which is why the use of long-acting medications may be beneficial in controlling hypertension. A 24-hour BP reading offers several advantages, such as providing information on the maximum effect and duration of effect of hypertension medication and enabling calculation of the smoothness index. A meta-analysis of studies demonstrated different effects and smoothness indices among hypertension medications. The smoothness index was higher for combined medications and medications at higher doses. Medications with a higher smoothness index have been shown to be superior in providing cardiovascular protection and preventing target organ damage.

**KLJUČNE RIJEČI:** varijabilnost arterijskoga tlaka, 24-satno kontinuirano mjerenje arterijskog tlaka, indeks omjera prosječne promjene arterijskoga tlaka i njegove standardne devijacije, kardiovaskularna zaštita.

**KEYWORDS:** blood pressure variability, 24-hour blood pressure measurement, smoothness index, cardiovascular protection.

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**ADDRESS FOR CORRESPONDENCE:** Rok Accetto, Ob pristanu 5, SLO-1000 Ljubljana, Slovenia. / Phone: +386-31-684-799 / E-mail: rok@accetto.eu

**ORCID:** Rok Accetto, https://orcid.org/0000-0001-9417-7904

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Convencional mjereno vrijednosti arterijskoga tlaka (AT) u ambulanti još se uvijek primjenjuje kao zlatni standard za probir, dijagnosticiranje i liječenje arterijske hipertenzije. Međutim, AT nije statična vrijednost, nego se mijenja iz otkucaja u otkucaj, ovisi o circadian rhythm, and can have significant variability throughout the day and night. It has been shown that reducing average BP leads to a proportional reduction in its variability, which is why the use of long-acting medications may be beneficial in controlling hypertension. A 24-hour BP reading offers several advantages, such as providing information on the maximum effect and duration of effect of hypertension medication and enabling calculation of the smoothness index. A meta-analysis of studies demonstrated different effects and smoothness indices among hypertension medications. The smoothness index was higher for combined medications and medications at higher doses. Medications with a higher smoothness index have been shown to be superior in providing cardiovascular protection and preventing target organ damage.

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Conventional blood pressure (BP) measurement in an outpatient clinic is still used as the gold standard for screening, diagnosing, and treating hypertension. However, BP is not static and changes from heartbeat to heartbeat, depending on the circadian rhythm, and can have significant variability throughout the day and night. It has been shown that reducing average BP leads to a proportional reduction in its variability, which is why the use of long-acting medications may be beneficial in controlling hypertension. A 24-hour BP reading offers several advantages, such as providing information on the maximum effect and duration of effect of hypertension medication and enabling calculation of the smoothness index. A meta-analysis of studies demonstrated different effects and smoothness indices among hypertension medications. The smoothness index was higher for combined medications and medications at higher doses. Medications with a higher smoothness index have been shown to be superior in providing cardiovascular protection and preventing target organ damage.
kadijalnom ritmu, a na njega utječu i razna stanja, uključujući poremećaje disanja tijekom noći. Pojedinačno očitanje AT-a stoga nije dovoljno za adekvatnu procjenu rizika od kardiovascularnog morbiditeta i mortaliteta povezanih s visokim vrijednostima AT-a. Također je važno mjeriti varijabilnost AT-a. Ona je, uključujući veću cirkadijalnu varijaciju AT-a, povezana na svom učestalošću kardiovascularnih događanja, smrti i oštećenja ciljnih organa. Dok su hipertenzija uzrokovana takožvim učinkom bile kute i obrnuti fenomen maskirane hipertenzije dobro poznati, kratkoročna varijabilnost AT-a, uključujući noćnu hipertenziju, jutarnji nagor posat AT-a i jutarnja hipertenzija dobele su manje pozornosti.1

Budući da je oštećenje ciljnih organa pri hipertenziji znatno povezano i s 24-satnim prosjekom AT-a i s njegovom varijabilnošću, liječenje mora biti usmjeren ne samo na smanjenje vrijednosti 24-satnoga prosječnog AT-a nego i na normalizaciju njegove varijabilnosti tijekom dana i noći. Zbog toga se djelotvornost lijekova protiv hipertenzije sve više procjenjuje na temelju 24-satnoga kontinuiranog mjerenja arterijskog tlaka (KMAT).

Nedavna ispitivanja u bolesniku s hipertenzijom pokazala su da su procjena i kvantifikacija varijabilnosti AT-a važni prognostički pokazatelji.2,3 Veća varijabilnost AT-a neovisno je povezana s povećanjem rizika od oštećenja ciljnih organa te kardiovascularnog morbiditeta i mortaliteta.4,5 Najnovije europske smjernice za liječenje arterijske hipertenzije predlažu da se više pozornosti posveti dosljednosti kontrole AT-a. Osim odgovarajućeg smanjenja prosječne vrijednosti AT-a, i kontrola njegovih varijabilnosti pridonosi optimalnoj kardiovascularnoj zaštiti u bolesnika s hipertenzijom.6 Varijabilnost AT-a procjenjuje se i računa na temelju 24-satnog KMAT-a.

Očitanja AT-a tijekom samopraćenja te mjerenja u ambulanti provedena u duljim intervalima rabe se za procjenu dugoročne varijabilnosti AT-a.6 Neka su istraživanja pokazala da je vrijednost AT-a u izravnoj korelaciji s AT-om te da je, posljedično tomu, općenito veća u hipertenzivnih nego u normotenzivnih osoba. Također je utvrđeno da smanjenje prosječnog AT-a dovodi do odnosnog smanjenja njegove varijabilnosti, pa zbog toga u njegovoj kontroli može biti korisna primjena dugodjevljivih lijekova.6,8

Metoda 24-satnog KMAT-a donosi nekoliko prednosti, kao što su informacije o maksimalnom učinku i trajanju učinka lijekova protiv hipertenzije i mogućnost izrčavanja indeksa omjera promjene AT-a-ja i njegove standardne devijacije.

Učinak antihipertenzivnog lijeka mjeri se tako da se izračuna omjer između smanjenja AT-a nego neposredno prije sljedeće doze (najniža vrijednost) i AT-a kad je učinak lijeka najjači, što je obično između 2 i 8 sati nakon uzimanja lijeka (vrhna vrijednost). Međutim, omjer najniže vrhne vrijednosti ne smatra se optimalnim pokazateljem jer postoje brojni čimbenici koji mogu utjecati na rezultat, poput nepravilne distribucije izmjerenih vrijednosti AT-a, visoke raspršenosti rezultata, beznačajno visokih ili niskih vrijednosti AT-a ili ograničene reproducirivosti. Omjer najniže i vrhne vrijednosti uzima u obzir dva kratka segmenta 24-satnog profila AT-a. Zbog toga je vrlo vjerojatno da može odražavati spontane fluktuacije AT-a, a ne stvarni učinak liječenja. To se u velikoj mjeri može izbjeći primjenom indeksa omjera prosječne promjene AT-a i njegove standardne devijacije (slika 1). Taj indeks u obzir uzi- ma standardne devijacije (odstupanja) prosječnog AT-a svaki sat vremena i prosječni 24-satni AT. Viši indeks označuje stabilniji antihipertenzivni učinak.
Metaanalysis of studies investigating the effect of medications on the smoothness index, published as early as in 2010, clearly demonstrated differences between the effects of some hypertension medications. The meta-analysis included 5188 study participants of which 65% were male. There were 2033 patients (39%) who received monotherapy with telmisartan 80 mg, 712 received ramipril 10 mg, 206 amlodipine 5 mg, 50 losartan 50 mg, 197 valsartan 80 mg and 430 valsartan 160 mg, 140 telmisartan 40 mg, and 1260 patients received combinations of losartan or telmisartan or valsartan with hydrochlorothiazide. The placebo group consisted of 160 participants. The smoothness index has been shown to be higher for systolic BP as compared with diastolic BP. The meta-analysis showed that telmisartan and amlodipine have similar smoothness indices, which are higher than those of losartan, valsartan, and ramipril. Among monotherapies, losartan had the lowest smoothness index. It was followed by ramipril, valsartan, telmisartan 80 mg and amlodipine 5 mg, of which the last two showed comparable smoothness indices that were the highest among other antihypertensive medications (Figure 2).

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**FIGURE 1. Calculation of smoothness index.**

![Figure 1](https://doi.org/10.1097/HJR.0b013e32833e1150)

**FIGURE 2. The smoothness index of different antihypertensive medications. Adapted from: J Hypertens. 2010 Nov;28(11):2177-83.**

*P < 0.05; †P < 0.01; ‡P < 0.001; §P < 0.0001 vs. telmisartan 80 mg

A5 – amlodipine 5 mg, DBP – diastolic blood pressure, L50 – losartan 50 mg, R10 – ramipril 10 mg, SBP – systolic blood pressure, T40 – telmisartan 40 mg, T80 – telmisartan 80 mg, V80 – valsartan 80 mg, V160 – valsartan 160 mg

**SI** = average of 24-hourly ΔBP/SD$_{ΔBP}$

**SI** = smoothness index

BP = blood pressure

SD$_{ΔBP}$ = standard deviation of the average of the hourly mean ambulatory blood pressure reductions over 24 hours

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Indeks omjera prosječne promjene AT-a i njegove standar
dne devijacije bio je viši za kombinirane lijekove koji su sadržavali hidroklorotiazid nego za monoterapije i placebo.

Randomizirano, kontrolirano, 4 x 4 faktorijsko ispitivanje objavljeno 2014. godine, istraživalo je učinak kombinacije telmisartana i amlodipina na indeksa omjera prosječne promjene AT-a i njegove standardne devijacije i uključilo je 1461 dijabetes

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The smoothness index was higher for combined medica
tions containing hydrochlorothiazide as compared with mon
otherapy and placebo.

A randomized, controlled, 4 x 4 factorial design study pub
dished in 2014 investigating the effect of a combination of tel

misartan and amlodipine on the smoothness index included 1461 study participants which received telmisartan (20, 40, or 80 mg) in combination with amlodipine (2.5, 5, or 10 mg). The study demonstrated for the first time the dose-dependency of the smoothness index and the magnitude of the effect that can be expected from treatment with a combination of two long-acting agents. Improvements of the smoothness index were significantly greater with combinations than with either monotherapy. The smoothness index achieved with the highest-dose combination (telmisartan 80 mg/amlodipine 10 mg) was about twice that achieved with amlodipine monotherapy. This correlated with the effects on 24-hour average ambula
tory BP in the study.11

The smoothness index is clinically relevant. It correlates with regression of left ventricular hypertrophy during hyper
tension therapy and is an independent indicator of changes in carotid artery wall thickness during therapy. Medications with a higher smoothness index have been shown to be su
perior in providing cardiovascular protection and preventing target organ damage.