Brzina pulsnog vala kao metoda praćenja ishoda renalne denervacije

Pulse Wave Velocity as a Method of Outcome Monitoring after Renal Denervation

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SAŽETAK: Rezistentna hipertenzija definirana je nemogućnošću uspostavljanja ciljnih vrijednosti arterijskoga tlaka (AT) unatoč terapiji koja uključuje tri i više antihipertenzivnih lijekova različitih skupina (od kojih je jedan diuretik) u kombinacijama i optimalnim tolerabilnim dozama. Osim farmakološkog liječenja, bolesnike s refraktornom rezistentnom hipertenzijom upućuje se na postupak denervacije renalnog pleksusa ukoliko ne postoji zapreka. Mjerenjem krutosti žila brzinom pulsnog vala dokazan je marker povišenoga kardiovaskularnog rizika. Cilj istraživanja bio je prikazati vrijednosti mjerenja krutosti krvnih žila kao metodu praćenja ishoda denervacije renalnog pleksusa. Obuhvaćeno je 10 bolesnika koji su bili praćeni nakon denervacije renalnoga pleksusa u vremenu od jedne do četiri godine. Krutost žila mjerena je oscilometrijskim uređajem „Agedio B900". Istraživanje je pokazalo da denervacija renalnoga pleksusa, kao dodatna metoda kontrole AT-a, ima dugoročne pozitivne učinke povrh sniženja AT-a u smislu sniženja krutosti žila tijekom više godina, čime se snizuje kardiovaskularni rizik. Krutost žila mogući je novi marker praćenja ishoda denervacije renalnog pleksusa.

SUMMARY: Resistant hypertension is defined as failure to achieve target blood pressure (BP) in spite of using a minimum of 3 antihypertensive drugs of different classes, one of which must be a diuretic, at optimal tolerated doses. Device-based therapies like renal denervation are indicated in patients in whom pharmacological agents failed to control BP and patients with refractory resistant hypertension have no contraindications for the procedure. Pulse wave velocity is the measure of arterial stiffness which is directly connected to cardiovascular risk and hypertension-mediated organ damage. The aim of this study was to present measurement of arterial stiffness as a noninvasive method of assessing cardiovascular risk in patients with resistant hypertension after renal denervation. This study included 10 patients over the course of 1 to 4 years after renal denervation. Arterial stiffness was measured for patients with a noninvasive method using the Agedio B900 device operating on the principle of oscillometry. This study demonstrates that renal denervation as an additional method of controlling BP has long-term positive effects in addition to lowering BP and vascular stiffness over several years, thus lowering cardiovascular risk. Noninvasive measurement of arterial stiffness could be a novel prognostic marker of the impact of renal denervation on arterial stiffness.

KLJUČNE RIJEČI: rezistentna hipertenzija, denervacija renalnog pleksusa, krutost žila.

KEYWORDS: resistant hypertension, renal denervation, arterial stiffness.

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Arterijska hipertenzija (AH), kao glavni uzrok kardiovaskularne (KV) bolesti, jedan je od vodećih uzroka pobolijevanja i smrtnosti u svijetu[1]. S obzirom na epidemiološki trend porasta, procjenjuje se da će do 2025. godine od AH-a bolovati oko 1,56 milijardi ljudi[2]. Rezistentna hipertenzija (RAH) definirana je nemogućnošću uspostavljanja ciljnih vrijed-

As the main cause of cardiovascular (CV) disease, arterial hypertension (AH) is one of the leading causes of morbidity and mortality in the world[1]. Given its upward epidemiological trend, it is estimated that approximately 1.56 billion people will be suffering from AH by 2025[2]. Resistant arterial hypertension (RAH) is defined as the inability to achieve

nosti arterijskoga tlaka (AT) u bolesnika unatoč primjeni triju ili više antihipertenzivnih lijekova različitih skupina, u odgovarajućim i optimalno tolerabilnim dozama. Temeljna terapija bolesnika s RAH-om uključuje blokadu reninsko-angiotenzinsko-aldosteronskog sustava, kalcijski antagonist i diuretik s naglaskom na spironolaktonu kao četvrtim antihipertenzivnim lijekom u prethodnoj fiksnoj kombiniranoj antihipertenzivnoj terapiji – primarno kombinacija dvaju, a potom kombinacija triju antihipertenziva u jednoj tableti[3]. Lijekovi poput beta-blokatora preporučuju se kao peta linija lijekova, osim ako nisu indicirani prije s obzirom na prisutno kongestivno zatajivanje srca ili infarkt miokarda[3]. Smatra se da je prevalencija RAH-a između 10 i 20 % hipertenzivne populacije. Liječenje je RAH-a zahtjevno te, osim promjene životnih navika i optimalne farmakoterapije uz isključenje sekundarnih potencijalno liječivih uzroka, uključuje u refraktornim slučajevima dodatno liječenje. Denervacija renalnoga pleksusa ili renalna denervacija (RDN) minimalno je invazivna endovaskularna metoda selektivne ablacije aferentnih i eferentnih simpatičkih živčanih vlakana obiju bubrežnih arterija i akcesornih grana koje su promjera više od 3 mm (zbog veličine katetera)[4]. Na taj se način modulira tonus simpatičkoga živčanog sustava i snizuju vrijednosti AT-a. Svrhom liječenja smatra se smanjenje vrijednosti AT-a za 10 mmHg. Prema smjernicama za liječenje hipertenzije Europskoga kardiološkog društva (ESC; prema engl. *European Society of Cardiology*) i Europskog udruženja za hipertenziju (ESH; prema engl. *European Society of Hypertension*) iz 2018. godine, krutost žila navedena je kao rizični čimbenik u razvoju asimptomatskog oštećenja ciljnih organa u hipertenziji (HMOD; prema engl. *hypertension-mediated organ damage*), uz brzinu pulsnog vala >10 m/s (PWV; prema engl. *pulse wave velocity*)[3]. Neinvazivnim metodama mjerenja krutosti žila i brzine pulsnog vala omogućeni su evaluacija KV rizika i vaskularne prilagodljivosti te praćenje uspješnosti kontrole AT-a u skupinama bolesnika s RAH-om, kao i s hipertenzivnom krizom[5-7]. Povećana je krutost prediktor ukupne smrtnosti zbog KV-a, a povezuje se i sa smanjenim učinkom postupka RDN-a, pa se stoga preporučuje mjerenje PWV-a kako bi se odlučilo koji će bolesnici postići najviše od postupka denervacije[5].

U ovome smo radu istražili ima li RDN, kao dodatna metoda kontrole AT-a, dugoročne učinke povrh samog sniženja AT-a u smislu smanjenja krutosti žila tijekom više godina.

Bolesnici i metode

Istraživanje je uključilo 10 bolesnika s refraktornom RAH koji su nakon isključenja sekundarnih potencijalno lječivih uzroka AH-a i potvrde suradljivosti uzimanja lijekova (mjerenjem blistera), uz KMAT s vrijednostima AT-a >140/90 mmHg (prosjek 169/94 mmHg), *non-dipping* uzorkom u 50 %, i bez anatomskih zapreka za postupak RDN-a podvrgnuti postupku. Svi su u razdoblju prije odluke multidisciplinarnog tima za RDN imali u nekoliko navrata hipertenzivnu krizu, zbog čega su pregledani u hitnoj službi. Od toga su 4 bolesnice imale hipertenzivnu emergenciju (akutna bubrežna bolest, infarkt miokarda, moždani udar, edem papile), a ostali hipertenzivnu urgenciju (AT >180/120 mmHg, no bez oštećenja ciljnih organa) unatoč potvrđenom i redovitom uzimanju antihipertenzivnih lijekova (prosječan je broj iznosio šest antihipertenziva). Tijekom obrade i liječenja bolesnicima je izmjerena

target arterial pressure (AP) values in patients despite the application of three or more antihypertensive drugs of different classes in adequate and optimally tolerated doses. The basic treatment for patients with RAH includes renin-angiotensin-aldosterone system inhibitors, calcium antagonists, and diuretics, with an emphasis on spironolactone as the fourth antihypertensive drug in the previous fixed combination antihypertensive therapy – primarily a combination of two, and subsequently a combination of three antihypertensives in a single pill[3]. Medications such as beta-blockers are recommended as fifth-line drugs, unless they have been already indicated by congestive heart failure or myocardial infarction[3]. It is believed that the prevalence of RAH is between 10 and 20% of the hypertensive population. Treatment for RAH is challenging, requiring lifestyle changes and optimal pharmacotherapy with exclusion of other potentially treatable causes as well as additional treatment in refractory cases. Denervation of the renal plexus or renal denervation (RDN) is a minimally invasive endovascular method of selective ablation of afferent and efferent sympathetic nerves of both renal arteries and accessory branches with a radius above 3 mm (due to catheter size)[4]. This modulates the tonus of the sympathetic nervous system and reduces AP values. The goal of the treatment is reducing AP values by 10 mmHg. According to the 2018 guidelines for the treatment of hypertension from the European Society of Cardiology and European Society of Hypertension, arterial stiffness is listed as a risk factor in the development of asymptomatic hypertension-mediated organ damage, with >10 m/s pulse wave velocity (PWV)[3]. Noninvasive measurement of arterial stiffness and PWV allows the evaluation of CV risk and vascular elasticity as well as monitoring the effectiveness of AP control in patient groups with RAH and hypertensive crisis[5-7]. Elevated stiffness is a predictor of total CV mortality and is associated with reduced effectiveness of RDN, so measurement of PWV is recommended to determine which patients will receive the most benefit from a denervation procedure[5].

In this article, we examine whether RDN, as an additional method of AP control, has long-term effects in addition to AP reduction itself in the form of reduction of arterial stiffness over several years.

Patients and Methods

The study included 10 patients with refractory RAH who underwent RDN after secondary potentially treatable AH causes were excluded, medication adherence was confirmed (using blister packs), and if continuous noninvasive arterial pressure (CNAP) AP values were >140/90 mmHg (average 169/94 mmHg), non-dipping in 50%, and there were no anatomical barriers to a RDN procedure. Before the multidisciplinary RDN team reached their decision, all of the patients had multiple hypertensive crises for which they were examined by emergency services. Four female patients were classified as having a hypertensive emergency (acute renal disease, myocardial infarction, stroke, papillary edema) and the rest as hypertensive urgency (AT >180/120 mmHg but with no target organ damage) despite confirmed adherence to taking antihypertensive medication (the average number was six hypertensives). During processing and treatment, the patients' arterial stiffness was measured (on multiple occasions) and they agreed to participation in a clinical study and signed in-

krutost krvnih žila (nekoliko puta) te su pristali na sudjelovanje u kliničkom istraživanju i potpisali informirani pristanak. Bolesnici su svrstani u dvije skupine. U prvoj su skupini višemjesečno (do 12 mjeseci) praćeni ishodi postupka RDN i ona je uključila šest bolesnika (kojima su prije postupka izmjerene vrijednosti brahijalnoga arterijskoga tlaka (BAT), centralnoga arterijskog tlaka (CAT) i PWV-a te su mjerenja ponovljena poslije mjesec dana, te šest i dvanaest mjeseci nakon zahvata. U drugoj su skupini dugoročno (više godina) praćeni ishodi postupka RDN i ona je obuhvatila četiri bolesnice s izmjerenim vrijednostima BAT-a, CAT-a i PWV-a dvije, tri i četiri godine nakon zahvata (oscilometrijskim aparatom koristimo se od sredine 2017. godine, pa stoga podatci za dio bolesnika kojima je RDN učinjen prije 2017. godine nisu dostupni). Krutost žila mjerena je uređajem *Agedio B900 Pulse Wave Analysis System* (Njemačka) koji provodi neinvazivno mjerenje oscilometrijskom metodom[8]. U jednom mjerenju uređaj istodobno daje podatak o krutosti žila (PWV u m/s, prilagođeno prema dobnim skupinama) i CAT-u[8]. Uređaj se sastoji od orukvice za nadlakticu (od triju različitih veličina u ovom su istraživanju rabljene najveće orukvice oznake L – large, a prema izmjerenom obujmu nadlaktice), mjernog uređaja i iPada na kojem se očitavaju rezultati[8]. Mjerenje traje nekoliko minuta te daje dva detaljna izvještaja, jedan za bolesnika i jedan za liječnika. U bolesnikovu se izvješću nalazi podatak o krutosti krvnih žila te usporedba s referentnim vrijednostima prema dobi (čime se povećava bolesnikova suradljivost bolesnika jer aktivno sudjeluje u daljnjem kreiranju postupanja), dok se u liječničkome izvješću nalaze hemodinamski parametri, vrijednosti CAT, srednjeg arterijskog tlaka te tlaka pulsa[8]. Podatci uzeti za istraživanje uključivali su i praćenje bubrežne funkcije koja je procijenjena glomerularnom filtracijom (eGFR) te su analizirani parametrijskim i neparametrijskim testovima (Studentov t-test, Mann-Whitneyev U-test, ANOVA). Za utvrđivanje povezanosti izračunan je Spearmanov koeficijent korelacije. Program uporabljen za statističku analizu podataka jest Statistica v.10,0.

Rezultati

Prva skupina bolesnika (višemjesečno praćenje)

U istraživanje je uključeno ukupno šest bolesnika (2 muškarca i 4 žene) prosječne dobi 58,33 godine (raspon 50 – 65 godina). Medijan broja uporabljenih lijekova za liječenje AT-a bio je 6 (min. 4, maks. 8). Tri su bolesnika bila dijabetičari (1 muškarac). Sve izmjerene vrijednosti (sistolički BAT, dijastolički BAT, CAT u sistoli i dijastoli, PWV, starost žila) pokazuju niže vrijednosti u svim kontrolama nakon razdoblja praćenja tijekom 12 mjeseci (osim frekvencije srca i broja lijekova), kao što je prikazano u **tablici 1**. Broj se lijekova u prvih šest mjeseci ne smanjuje kako bi se objektivirao učinak samog postupka RDN.

Prosječna vrijednost CAT-a u sistoli prije RDN iznosila je 159 mmHg, a u naknadnim se mjerenjima vrijednost smanjuje kako slijedi: 129 mmHg (1 mj., p <0,001), 134,17 mmHg (6 mj., p <0,0001) te 125,66 mmHg (12 mj., p = <0,0001). Prosječna vrijednost CAT-a u dijastoli prije RDN-a iznosila je 104 mmHg te u naknadnim mjerenjima pokazuje sniženje kako slijedi: 89,33 mmHg (1 mj., p = 0,03), 93,83 mmHg (6 mj., p = 0,04) te 88,17 mmHg (12 mj., p = 0,02). Prosječna vrijednost PWV-a prije RDN iznosila je 9,80 m/s te pokazuje niže vrijednosti u idućim mjeformed consent. Patients were divided into two groups. The first group included multiple months (up to 12) of RDN outcome monitoring and comprised six patients who underwent measurement of brachial arterial pressure (BAT), central arterial pressure (CAT), and PWV at baseline and one, six, and twelve months after the procedure. The second patient group represented long-term (over multiple years) outcome monitoring for RDN and comprised four patients with BAT, CAT, and PWV values measured two, three, and four years after the procedure (an oscillometric device has only been in use since 2017, so some data for patients on whom RDN was performed before 2017 are not available). Arterial stiffness was measured using the Agedio B900 Pulse Wave Analysis System (Germany) that uses a noninvasive oscillometric method[8]. In a single measurement, the device simultaneous provides data on arterial stiffness (PWV in m/s, adjusted according to age group) and CAT[8]. The device consists of an upper-arm cuff (of the 3 available sizes, this study used the largest cuffs marked L for large, based on the measurement of the patients' upper arms), a measurement device, and an iPad that displays the results[8]. Measurement lasts several minutes and the device provides two detailed reports, one for the patient and one for the physician. The patient's report shows patient data on arterial stiffness and a comparison with reference values according to age (which increases patient compliance because they actively participate in creating the next steps of their treatment), whereas the physician's report presents hemodynamic parameters, the CAT value, mean arterial pressure, and pulse pressure[8]. Data used in the present study also included renal function monitoring which was assessed based on estimated glomerular filtration rate (eGFR); data were analyzed using parametric and nonparametric tests (Students t test, Mann-Whitney U test, ANOVA). Spearman rank-order correlation coefficient was calculated to determine associations between variables. The Statistica v.10.0 program was used for statistical data analysis.

Results

First patents group (months-long monitoring)

This group included a total of 6 patients (2 men and 4 women) with an average age of 58.33 (range 50-65 years of age). The median number of drugs being taken for AT was 6 (min. 4, max. 8). Three patients had diabetes (one man). All measured values (systolic BAT, diastolic BAT, systolic and diastolic CAT, PWV, arterial age) were lower at all controls after the follow-up, over a period of 12 months (other than heart frequency and number of medications), as shown in **Table 1**. The number of medications was not reduced in the first 6 months to objectivize the effect of the RDN procedure.

The average systolic CAT value before RDN was 159 mmHg, whereas the values were lower in all the subsequent measurements as follows: 129.00 mmHg (1 month, p<0.001), 134.17 mmHg (6 months, p<0.0001), and 125.66 (12 months, p<0,0001). The average diastolic CAT value before RDN was 104 mmHg, which was lowered in subsequent measurements as follows: 89.33 mmHg (1 month, p=0.03), 93.83 mmHg (6 months, p=0.04), and 88.17 mmHg (12 months, p=0.02). Average arterial age before RDN was 9 years above the average for the age of the patients, whereas subsequent measurements showed a reduction as follows: 4.00 years (1 month, p<0.01), 5.67 years

TABLE 1. Blood pressure and pulse wave velocity values in the first group of patients.

Variables	0 m	1 m	p	6 m	p	12 m	p
BBP sys	**172.83**	137.50	0.0003	149.33	0.0026	138.67	0.0015
BBP dias	**102.17**	87.17	0.0311	92.00	0.0461	86.00	0.0261
CBP sys	**159.00**	129.00	0.0001	134.17	0.0001	125.66	0.0002
CBP dias	**104.00**	89.33	0.0355	93.83	0.0485	88.17	0.0244
PWV (m/s)	**9.80**	8.85	0.0439	8.70	0.0249	8.53	0.0248
Age of vessels/year	**9.00**	4.00	0.0035	5.67	0.0058	4.67	0.0042
HR (/min)	**84.67**	72.67	0.3155	69.83	0.1946	70.67	0.2109
Medication number	**6.33**	6.33	1	6.33	1	5.83	0.6041
Creatinine (μmol/L)	**115.33**	112.87	0.8233	98.23	0.5884	94.83	0.4048
eGFR (ml/min/1.73m^2)	**56.61**	58.24	0.7865	65.66	0.5133	68.75	0.3562

BBP – brachial blood pressure; CBP- central blood pressure; sys – systolic; dias – diastolic; PWV– pulse wave velocity; HR-heart rate; m-month; eGFR – estimated glomerular filtration rate.

renjima kako slijedi: 8,85 m/s (1 mj., p = 0,04), 8,70 m/s (6 mj., p = 0,03) te 8,53 m/s (12 mj., p = 0,02). Prosječna starost žila prije RDN-a bila je 9 godina više nego prosjek za dob, a u naknadnim je mjerenjima pokazivala pad vrijednosti kako slijedi: 4 god. (1 mj., p <0,01), 5,67 god. (6 mj., p <0,005) te 4,67 god. (12 mj., p <0,005). Vrijednost PWV-a može se uspoređivati međusobno jer su svi bolesnici u približno jednakoj dobnoj skupini (50 – 65 godina). Razlika je u vrijednostima PWV-a evidentna i u skupini dijabetičara i nedijabetičara vrijednosti se smanjuju (dugoročni p = 0,093). Iako statistički neznačajno, tijekom 12 mjeseci prati se postupno poboljšanje bubrežne funkcije (eGFR 56,61 *vs.* 68,75 mL/min/1,73m^2 nakon 12 mj., p = 0,35).

Druga skupina bolesnika (višegodišnje praćenje)

Četiri bolesnika iz druge skupine bile su žene prosječne dobi 61,75 godina (raspon 50 – 70 godina), a 50 % njih boluje od šećerne bolesti. S obzirom na to da je riječ o bolesnicama slične dobi i istog spola, mogu se uspoređivati podatci u smislu praćenja dugoročnog ishoda RDN-a (podataka prije RDN-a nema). Prosječna vrijednost CAT-a u sistoli 2 godine nakon RDN-a iznosila je 129 mmHg te dalje kako slijedi: nakon 3 godine 133,25 mmHg (p = 0,6437) te nakon 4 godine 120,75 mmHg (p = 0,0538). Prosječna vrijednost CAT-a u dijastoli 2 godine nakon RDN-a bila je 85,26 mmHg te dalje kako slijedi: nakon 3 godine 91,25 mmHg (p = 0,3515) te nakon 4 godine 79,75 mmHg (p = 0,1187). Prosječna vrijednost PWV-a 2 godine nakon RDN-a bila je 9,92 m/s; nakon 3 godine 9,87 m/s (p=0,9669) te nakon 4 godine 9,32 m/s (p = 0,5469). Prosječna starost žila 2 godine nakon RDN bila je 5,5 godina viša nego referentna vrijednosti za dob te u sljedećim mjerenjima kako slijedi: nakon tri godine starost žila iznosi 6 god. (p = 0,8089), a nakon četiri godine praćenja starost je 4 god. (p = 0,1536). Svaka se godina praćenja uspoređivala s prethodnom. Neparametrijskim testom za varijable dobivene su vrijednosti Spearmanova koeficijenta za povezanost promjena centralnog sistoličkog i dijastoličkog tlaka s promjenama PWV-a. Vrijednosti su sljedeće: CAT u sistoli *vs.* PWV-u: r = 0,7043, p <0,001, CAT u dijastoli *vs.* PWV-u:

(6 months, p<0.005), and 4.67 years (12 months, p<0.005). PWV values can be compared between patients since they were all in a similar age group (50-65 years of age). The difference in PWV values was evident, and there was a reduction in both diabetic and nondiabetic patients (long-term p=0.093). Although not statistically significant, there was a gradual improvement in renal function over the 12 months (eGFR 56.61 vs 68.75 mL/min/1.73m^2 after 12 months, p=0.35).

Second patient group (years-long monitoring)

The four patients in the second group were women with an average age of 61.75 years (range 50-70 years of age), half of which had diabetes. Given that the patients were of similar age and the same sex, data can be compared regarding the long-term outcomes for RDN (no data available from before the RDN procedure). The average systolic CAT value 2 years after RDN was 259 mmHg and in subsequent measurements as follows: 133.25 mmHg after 3 years (p=0.6437) and 120.75 mmHg after 4 years (p=0.0538). The average diastolic CAT value 2 years after RDN was 85.25 mmHg and in subsequent measurements as follows: 91.25 mmHg after 3 years (p=0.3515) and 79.75 mmHg after 4 years (p=0.1187). The average PWV value 2 years after RDN was 9.92 m/s; 9.87 m/s after 3 years (p=0.9669); and 9.32 m/s after 4 years (p=0.5469). Average arterial age 2 years after RDN was 5.5 years higher than the reference value for the patient age, and changed over subsequent measurements as follows: after 3 years arterial age was 6 years (6=0.8089), and 4 years after RDN the average arterial age was 4 years higher compared with reference values (p=0.1536). Every year of follow-up was compared with the previous one. Variables were analyzed with a nonparametric test to determine Spearman coefficient values for the association between changes in systolic and diastolic pressure and changes in PWV. The values were as follows: systolic CAT vs PWV: r=0.7043, p<0.001; diastolic CAT vs PWV: r=0.4406, p<0.05; systolic CAT vs diastolic CAT: 0.5592, p<0.01. Over several years of monitoring renal function at baseline and before

r = 0,4406, p <0,05, CAT u sistoli *vs.* CAT-u u dijastoli: 0,5592, p <0,01 Tijekom višegodišnjeg praćenja bubrežne funkcije na početku praćenja, a prije RDN-a, srednja je vrijednost iznosila eGFR 60,61 *vs.* 64,85 mL/min/1,73m^2 nakon 4 godine od RDN postupka.

Rasprava

Denervacija renalnog pleksusa (RDN) kao dodatna metoda liječenja RAH-a postupak je koji je posljednjih godina izazvao brojne kontroverze. Prvotna istraživanja SYMPLICITY HNT-1 i HNT-2 pokazala su da je RDN sigurna i učinkovita metoda sniženja vrijednosti AT-a mjerenih u ordinaciji za 27/17 mmHg nakon 12 mjeseci i 32/12 mmHg nakon 6 mjeseci (zamjerka je istraživanjima što nije praćeno kontinuirano mjerenje tijekom 24 sata /KMAT/).[4] Istraživanje SYMPLICITY HNT-3 studije tijekom 2014. godine koje je pratilo učinak RDN-a KMAT-om izazvao je dvojbe jer nije dokazao sniženje vrijednosti AT-a za 10 i više mmHg.[4] Samo istraživanje zaslužuje niz zamjerki koje su primarno vezane za postupak isporuke radiofrekventne energije (koji se u istraživanju razlikovao od jedne „abliranе" točke do više njih). Nakon tog istraživanja sama je metoda RDN poboljšana tako je usavršen kateter koji je spiralna oblika te jednim dodirom isporučuje radiofrekventnu energiju na endoluminalnom dijelu renalne arterije ne samo na jednoj (kao u SYMPLICITY HNT-3) nego istodobno na četirima dodirnim točkama (uspjeh postupka RDN ovisi o broju „abliranih" točaka).[4] U prethodnim smjernicama ESH-a iz 2018. godine, a zbog nedostatka randomiziranih istraživanja RDN nije preporučen kao regularna dodatna metoda kontrole AT-a u bolesnika s refraktornom rezistentnom hipertenzijom.[5] Nedavno objavljeni rezultati Global SYMPLICITY Registra iz 2019. godine na 1742 bolesnika koji su praćeni tijekom 3 godine nakon RDN-a dokazali su sigurnost i učinkovitost postupka uz znatno snižene vrijednosti brahijalnoga tlaka koje pokazuju trend stabilnosti uz očuvanu bubrežnu funkciju.[9] Dodatna istraživanja, a nakon izdavanja zadnjih ESH smjernica (u lipnju 2018. godine) potvrdila su učinkovitost i sigurnost RDN-a, i to ne samo u bolesnika s RAH-om nego i u ostalim skupinama hipertoničara.[10]

Povišena brzina pulsnog vala dokazan je biljeg povišenog KV rizika u bolesnika na antihipertenzivnoj terapiji, posebice u onih s RAH-om.[6] Krutost žila je neovisni čimbenik koji je povezan direktno s endotelnom disfunkcijom i razvojem preklinične ateroskleroze.[11] U odabiru bolesnika za RDN preporučuje se odrediti krutost žila mjerenjem PWV-a, koji je prediktor ukupne i KV smrtnosti, povezujući ga ako je povišen (mjereno invazivnim metodama) sa slabijim odgovorom na postupak RDN-a.[5] U ovome smo istraživanju neinvazivnom oscilometrijskom metodom prikazali smanjenje vrijednosti PWV-a nakon RDN-a (prva skupina), no nema dostupnih dugoročnih rezultata o djelovanju na komorbiditete te kardiovaskularnu smrtnost, tj. zaključci se mogu izvući posredno. U drugoj se skupini prati povoljan dugoročni ishod u bolesnica nakon RDN-a kroz razdoblje do četiri godine. Vrijednost „p" između kontrolnih mjerenja tlakova te PWV-a većinom je neznačajna, što pokazuje dugotrajnu uspješnost RDN-a u liječenju RAH-a, te opovrgava čestu pretpostavku da RDN ima „rok trajanja" te da vrijednosti tlaka počinju ponovno biti slabije regulirane nakon otprilike 12 mjeseci. Analiza povezanosti promjena centralnoga sistoličkog i dijastoličkog tlaka s promjenama PWV-a pokazuje višu povezanost sa sistoličkim

RDN, the mean value was eGFR 60.61 vs 64.85 mL/min/1.73m^2 four years after the RDN procedure.

Discussion

As an additional method of treatment for RAH, renal plexus denervation (RDN) is a procedure that has caused numerous controversies in recent years. Initially, the SYMPLICITY HNT-1 and HNT-2 showed that RDN was a safe and effective method of reducing office AP values by 27/17 mmHg after 12 months and 32/12 mmHg after 6 months (a weakness of the study was that 24 h ambulatory blood pressure monitoring (ABPM) was not used)[4]. However, the SYMPLICITY HNT-3 study that followed the effect of RND using ABPM caused some doubts because a rection in AP values of 10 or more mmHg was not demonstrated[4]. The study itself received a number of criticisms that were primarily associated with the radiofrequency energy delivery procedure (which varied in the study between one or more ablated points). After that study, the RDN method was improved by perfecting the catheter, which is of a spiral shape and relivers radiofrequency energy to the endoluminal part of the renal artery in a single touch, not just at one point (as in SYMPLICITY HNT-3) but at 4 points of contact (the success of RDN depends on the number of ablation points)[4]. Due to the lack of randomized studies, the previous 2018 ESH guidelines did not recommend RDN as a regular additional method of AP control in patients with refractory resistant arterial hypertension[5]. Recently published results of the Global SYMPLICITY Registry from 2019 that includes 1742 patients monitored for 3 years after RDN demonstrated the safety and effectiveness of the procedure with significantly reduced brachial pressure values, which indicate a trend towards stability with preserved renal function[9]. Additional studies after the publication of the lastest ESH guidelines (in June 2018) have confirmed the effectiveness and safety of RDN not only in patients with RAH but also in other groups of hypertonic patients[10].

Increased pulse wave velocity has been shown to be a marker of elevated CV risk in patients receiving antihypertensive therapy, especially those with RAH[6]. Arterial stiffness is an independent marker which is directly proportional to endothelial dysfunction and development of pre-clinical atherosclerosis[11]. In choosing patients for RDN, it is recommended to determine arterial stiffness by measuring PWV, which is a predictor of total and CV mortality and if elevated (measured by invasive methods) is associated with poorer response to RDN[5]. In this study, we found a reduction in PWV values after RND measured using a noninvasive oscillometric method (first group), but no data is available on long-term outcomes regarding comorbidity and cardiovascular mortality, i.e. conclusions can be made only indirectly. In the second group in the present study, we observed beneficial long-term outcomes over a period of four years in patients who underwent RDN. The "p" value between follow-up AP pressure measurements and PWV values was mostly not statistically significant, which indicates the long-term efficacy of RDN in treating RAH and contradicts the common assumption that RDN has a "best before date" and that pressure once again starts being poorly regulated after approximately 12 months. Analysis of the association between changes in central systolic and diastolic pressure and changes in PWV found a stronger association with systolic (r=0.7043) than diastolic AP (r=0.4406). During the course of both the months-long and the year-long RDN outcome monitoring, no deterioration of renal

(r = 0,7043) nego dijastoličkim AT-om (r = 0,4406). Tijekom višemjesečnog, kao i višegodišnjeg praćenja ishoda RDN-a na bubrežnu funkciju nije došlo do pogoršanja bubrežne funkcije koja je cijelo vrijeme bila stabilna i u poboljšanju, iako statistički nije utvrđena značajna razlika.

Premda je u ovome istraživanju riječ o malom broju bolesnika, dobiveni su podatci poprilično značajni te zahtijevaju daljnja istraživanja na većem uzorku uz praćenje dugotrajnih učinaka postupka RDN-a na usporavanje oštećenja ciljnih organa i ukupnu smrtnost.

Zaključak

Pozitivni učinci RDN-a pokazuju dugoročno stabilne vrijednosti AT-a tijekom razdoblja praćenja do 4 godine. Brzina pulsnog vala dokazan je marker povišenog KV rizika te obećavajući prediktor postupka, kao i marker praćenja ishoda RDN-a. Potrebna su dodatna istraživanja s većim brojem ispitanika u svrhu određivanja važnosti sniženja vrijednosti PWV-a na komorbiditete i KV smrtnost u dugoročnom ishodu nakon postupka RDN-a.

function was observed and it remained stable throughout or even improved, although not statistically significantly.

Although this study included only a small number of patients, the data that has been obtained is significant and indicate the need for further research on larger samples with monitoring of long-term effects of RDN on slowing down target organ damage and total mortality.

Conclusion

The positive effects of RDN were found to include long-term AP stability in the monitoring period that lasted up to 4 years. Pulse wave velocity is an established marker of elevated CV risk and a promising predictor for the procedure as well as an RDN outcome marker. Further studies with a larger number of participants are needed to determine the significance of PWV reduction regarding comorbidities and CV mortality after a RDN procedure.

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