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

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.

KEYWORDS: resistant hypertension, denervation, arterial stiffness.

SAŽETAK: Rezistentna hipertenzija definirana je nemogućnošću uspostavljanja ciljnih vrijednosti arterijskog 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 pulsog vala dokazan je markeri povišenoga kardiovaskularnog rizika. Cilj istraživanja bio je prikazati vrijednosti mjerjenja krutosti krvnih žila kao metodu praćenja ishoda denervacije ishoda renalnog pleksusa. Ovučavaeno je 10 bolesnika koji su bili praćeni nakon denervacije renalnog pleksusa u vremenu od jedne do četiri godine. Krutost žila mjerena je oscilometrijskim uređajem „Agedio B900”. Istraživanje je pokazalo da denervacija renalnog pleksusa, kao dodatna metoda kontrola AT-a, ima dugoročne pozitivne učinke povrh sniženja AT-a u smislu sniženja krutosti žila tijekom više godina, čime se snižuje kardiovaskularni rizik. Krutost žila mogući je novi marker praćenja ishoda denervacije renalnog pleksusa.

KEYWORDS: rezistentna hipertenzija, denervacija renalnog pleksusa, krutost žila.

CITATION: Cardiol Croat. 2020;15(11-12):306-11. | https://doi.org/10.15836/ccar2020.306

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TO CITE THIS ARTICLE: Kurjaković I, Jug J, Lovrić Benčić M, Vuković J, Prkačin I. Pulse Wave Velocity as a Method of Outcome Monitoring after Renal Denervation. Cardiol Croat. 2020;15(11-12):306-11. | https://doi.org/10.15836/ccar2020.306

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2020.306

Atherosclerotic vascular disease (AVD) is one of the leading causes of morbidity and mortality in the world1. Given its upward epidemiological trend, it is estimated that approximately 1.56 billion people will be suffering from AH by 20252. Resistant arterial hypertension (RAH) is defined as the inability to achieve...
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 anatomske zapreke za postupak RDN-a podvrgnuti postupku. Svi su u razdoblju prije odluke multidisciplinarnog tima za RDN poznati hipertenzivni uzroci i potrebu za nadogradnjom lječenja. U postupku za RDN-a, s lijevom ili desnim hipertenzijom, hipertenzivni uzroci, na osnovu koje je RDN teško vodljiv, su uključeni u postupak za RDN-a. 

Kroz postupak za RDN-a, bolesnici su dobili optimalno lječenje, uključujući medicinu i rehabilitaciju, te smanjenje vrijednosti AP-a. Uzmemo u obzir i opterećenje ciljnih organa, a uključujući i hipertenzivne bolesti, te smanjenje vrijednosti PWV-a kako bi se odlučilo koji će bolesnici postići najviše od učinkom postupka RDN-a, pa se stoga preporučuje mjerenje ukupne smrtnosti zbog KV-a, a povezuje se i sa smanjenim kongestivno zatajivanje srca ili infarkt miokarda, osim ako nisu indicirani prije s obzirom na prisutno Lijekovi poput beta-blokatora preporučuju se kao peta linija 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 pulsog vala >10 m/s (PWV; prema engl. pulse wave velocity). Neinovativnim metodama mjerenja krušnosti žila i brzine pulsog 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 krvom. 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 dervenacije.

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

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 (CNPAP) 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 anti-hypertensive medication. 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.
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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 broj uporabljenih lekov za lječenje AT-a bio je 6 (min. 4, maks. 8). Tri su bolesnika bila dijabetičara (1 muškarac). Sve izmjerene vrijednosti (sustolički BAT, diastolički BAT, sistolički CAT, diastolički CAT, 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 nije smanjivao kako bi se objektivirao učinak samog postupka RDN.

Prosječna vrijednost CAT-a u sistoli prije RDN iznosila je 159 mmHg, a u naknadnim se mjerjenjima vrijednost smanjuje kako slijedi: 129 mmHg (1 mj., p = 0,001), 134,17 mmHg (6 mj., p = 0,0000) te 125,66 mmHg (12 mj., p = 0,0000). Prosječna vrijednost CAT-a u dijastoli prije RDN-a iznosila je 104 mmHg te u naknadnim mjerjenjima pokazuje niži nivo slijedi: 93,83 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-ja iznosila je 308 m/s te prosječne vrijednosti u iducim mje-
U tabeli je prikazan pritisak i vrelu lijevog vjetra u prvoj skupini pacijenata.

| Varijable | 0 m | 1 m | p | 6 m | p | 12 m | p |
|-----------|-----|-----|---|-----|---|------|---|
| 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 |
| Medication number | 6.33 | 6.33 | 0.5 | 6.33 | 0.5 | 5.83 | 0.6041 |
| Creatinine (µmol/L) | 115.33 | 112.87 | 0.8233 | 98.23 | 0.5884 | 94.83 | 0.4048 |
| eGFR (ml/min/1.73m²) | 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.

**Druga skupina bolesnika (višegodišnje praćenje)**

Četiri bolesnika iz drugih skupina bile su žene prosječnog dobi 61,75 godina (raspon 50–70 godina), a 50 % njih bolje od šećernice. S obzirom na to da je riječ o bolesnicima slične godine, mogu se uspoređivati podaci u smislu praćenja dugoročnog ishoda RDN-a (podataka prije RDN-a nema).

**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, and in subsequent measurements as follows: 9.22 m/s after 3 years (p=0.9669), and 9.32 m/s after 4 years (p=0.5469). The average arterial age 2 years after RDN was older 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...
Rasprava

Denervacija renalnog pleksusa (RDN) kao dodatna metoda liječenja RAH-a postupak je koji je posljednjih godina izazvao brojne kontrovezne. 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 mjenjanje 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. 5 Samo istraživanje zaslužuje niz zamjerki koje su primarno vezane za postupak isporučuje radiofrekventne energije (koji se u istraživanju razlikovalo od jedne „abli- rane“ točke do više njih). Nakon tog istraživanja sama je metoda RDN poboljšana tako da je usavršen kateter koji je spiralna oblika te jednim dodiru izravno 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 „abliiranih“ točaka). 6 U pruhodnim smjernicama ESH-a iz 2018. godine, a zbog nedostatka randomiziranih istraživanja RDN nije preporučen kao regularna dodatna metoda kontrole AT-a u bolesnika s reflektornom rezistentnom hipertenzijom. 7 Nedavno objavljeni rezultati Global SYMPLICITY Registra iz 2019. godine na 1742 bolesnika koji su praćeni tijekom 3 godine nakon RDN-a dokazala su sigurnost i učinkovitost postupka uz znatno snižene vrijednosti brahijalnoga tlaka koje pokazuju trend stabilnosti uz očuvanu brahijalnu funkciju. 8 Dodatna istraživanja, a nakon izdavanja zadnjih ESH smjernica (u lipnju 2018. godine) potvrdila su učinkovitost i sigurnost RDN-a, a to ne samo u bolesnika s RAH-om nego i u ostalim skupinama hipertona. 9

Povišena brzina pulsnog vala dokazan je biljeg povišenog KV rizika u bolesnika na antihipertenzivnoj terapiji, posebice u onih s RAH-om. 10 Krutost žila je neovisni čimbenik koji je povezan direktno s endotelsonom disfunkcijom i razvojem prekliničke arterioskleroze. 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 interventionalizam. 12 U svim istraživanjima krovišta s RDN-a uzrokovana je sefaloderma radiofrekventnom energijom s povećanjem intimalne i mediale mase žila te povećanjem stijenke arterija. 13

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. 5 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 RN depends on the number of ablation points). 6 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. 7 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. 8 Additional studies after the publication of the latest 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 hypertensive patients. 9

Increased pulse wave velocity has been shown to be a marker of elevated CV risk in patients receiving antihypertensive therapy, especially those with RAH. Arterial stiffness is an independent marker which is directly proportional to endothelial dysfunction and development of pre-clinical atherosclerosis. 10 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. 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 pogorsanja bubrežne funkcije koja je cijelo vrijeme bila stabilna i u poboljšanju, iako statistički nije utvrđena značajna razlika.

Fremda 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 organs 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 komorbidite i KV smrtnost u dugoročnom ishodu nakon postupka RDN-a.

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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