



Brzina pulsnog vala u bolesnika s hipertenzivnom krizom mjerena oscilometrijskom metodom

Oscillometric Measurement of Pulse Wave Velocity in Hypertensive Crisis

 Lucija Bilinovac¹,

 Iva Kurjaković¹,

 Jurica Vuković²,

 Juraj Jug¹,

 Martina Lovrić Benčić^{1,3},

 Ingrid Prkačin^{1,2*}

¹Medicinski fakultet Sveučilišta u Zagrebu, Zagreb, Hrvatska

²Klinička bolnica Merkur, Zagreb, Hrvatska

³Medicinski fakultet Sveučilišta u Zagrebu, Klinički bolnički centar Zagreb, Zagreb, Hrvatska

¹University of Zagreb School of Medicine, Zagreb, Croatia

²University Hospital "Merkur", Zagreb, Croatia

³University of Zagreb School of Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

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SAŽETAK: Hipertenzivna se kriza definira kao vrijednost sistoličkoga tlaka višeg od 180 mmHg ili dijastoličkoga tlaka višeg od 120 mmHg te može biti prva manifestacija arterijske hipertenzije. U hipertenzivnoj su emergenciji, uz ozbiljno povišenje arterijskoga tlaka, također primjetni i dokazi da je prisutno oštećenje organa, dok u hipertenzivnoj urgenciji nema oštećenja organa. Bolesnici s hipertenzivnom krizom trebaju temeljitu kliničku procjenu kako bi se isključili sekundarni uzroci arterijske hipertenzije. Brzina pulsog vala mjera je krutosti žila, koja je izravno povezana s kardiovaskularnim rizikom i oštećenjima organa uzrokovanih hipertenzijom. Svrha je ovog istraživanja bila prikazati mjerenje krutosti žila u hitnoj službi kao neinvazivnu metodu procjene kardiovaskularnog rizika u bolesnika s hipertenzivnom urgencijom. Krutost žila izmjerena je u svih bolesnika s pomoću neinvazivne metode primjenom uređaja *Agedio B900*, koji djeluje na principu oscilometrije. Ovo je istraživanje pokazalo da su bolesnici primljeni u hitnu službu s hipertenzivnom urgencijom imali više vrijednosti brzine pulsog vala u usporedbi s referentnim rasponom i onima s rezistentnom hipertenzijom.

SUMMARY: Hypertensive crisis is defined as systolic pressure higher than 180 mmHg or diastolic pressure higher than 120 mmHg and can be the first manifestation of arterial hypertension. In a hypertensive emergency there is evidence of organ damage in addition to severe blood pressure elevation, while in hypertensive urgency there is no organ damage. Patients with hypertensive crisis require thorough clinical assessment to exclude secondary causes of arterial hypertension. 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 show the measurement of arterial stiffness in an emergency room setting as a noninvasive method of assessing cardiovascular risk in patients with hypertensive urgency. Arterial stiffness was measured for all patients with a noninvasive method using the *Agedio B900* device operating on the principle of oscillometry. This study showed that the patients presenting to the Emergency Room with hypertensive urgency had higher pulse wave velocity values when compared with the reference range and to patients with resistant hypertension. Noninvasive measurement of arterial stiffness is a novel method in the diagnostic algorithm for patients with hypertensive crisis.

KLJUČNE RIJEČI: brzina pulsog vala, hipertenzivna kriza, hipertenzivna urgencija.

KEYWORDS: pulse wave velocity, hypertensive crisis, hypertensive urgency.

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***ADDRESS FOR CORRESPONDENCE:** Ingrid Prkačin, Klinička bolnica Merkur, Ul. I. Zajca 19, HR-10000 Zagreb, Croatia. / Phone: +385-98-406-218 / E-mail: ingrid.prkacin@gmail.com

ORCID: Lucija Bilinovac, <https://orcid.org/0000-0002-0206-2884> • Iva Kurjaković, <https://orcid.org/0000-0002-6988-7303> • Jurica Vuković, <https://orcid.org/0000-0003-3727-5457> • Juraj Jug, <https://orcid.org/0000-0002-3189-1518> • Martina Lovrić Benčić, <https://orcid.org/0000-0001-8446-6120> • Ingrid Prkačin, <https://orcid.org/0000-0002-5830-7131>

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Arterijska hipertenzija (AH) jedan je od glavnih čimbenika rizika za pobol i smrtnost u svijetu.¹ Otprilike 40 % populacije starije od 25 godina ima visok arterijski tlak (AT), što je ukupno oko milijardu ljudi, a u 1 % takvih pacijenata razvit će se hipertenzivna kriza.^{2,3}

Arterial hypertension is one of the main risk factors for morbidity and mortality worldwide.¹ Approximately 40% of the population older than 25 have high blood pressure, which accounts for around one billion people, and 1% of those patients will develop hypertensive crisis.^{2,3}

Hipertenzivna se kriza definira kao vrijednost sistoličkoga tlaka viša od 180 mmHg ili vrijednost dijastoličkoga tlaka viša od 120 mmHg. Može nastati *de novo* ili kao komplikacija postojeće primarne ili sekundarne hipertenzije. Hipertenzivna se kriza, s obzirom na prisutnost oštećenja organa, dijeli na hipertenzivnu urgenciju (HU) i hipertenzivnu emergenciju (HE). Hipertenzivna emergencija uključuje oštećenja kardiovaskularnog, renalnog i/ili cerebrovaskularnog sustava uz prisutnost povišenih vrijednosti AT-a. U hipertenzivnoj urgenciji oštećenja glavnih organa nisu potvrđena.

Točan mehanizam nastanka hipertenzivne krize nije poznat. Vjeruje se da naglo povišenje AT-a u hipertenzivnoj krizi nastaje kao posljedica naglog povišenja sistemskoga vaskularnog tlaka, što je povezano s djelovanjem humoralnih vazokonstriktora i uzrokuje intimalnu proliferaciju i fibrinoidnu nekrozu u stijenci krvne žile.³

Prema smjernicama Europskoga kardiološkog društva (ESC) Europskog društva za hipertenziju (ESH) iz 2018., krutost žila smatra se rizičnim čimbenikom za razvoj oštećenja organa uzrokovanih hipertenzijom (HMOD) s brzinom pulsog vala (BPV) >10 m/s.⁴ BPV se smatra jednim od najvažnijih kliničkih parametara za procjenu kardiovaskularnog rizika i vaskularne prilagodljivosti te za praćenje nakon liječenja. Iako većina uređaja za mjerenje BPV-a dostupnih na tržištu nudi procjenu krutosti žila u danom području (mjerenu između dviju žila), lokalno mjerenje nudi precizniju procjenu stanja arterija s obzirom na razlike u strukturama arterija. Trendovi u kardiovaskularnom praćenju upućuju na postupno napuštanje invazivnih tehnologija u korist primjene neinvazivnih metoda.⁵ Zna se da je populacija bolesnika s rezistentnom hipertenzijom visokorizična skupina u kojoj se krutost žila smatra biljekom povećanog rizika.⁶

Današnje smjernice za AH preporučuju mjerenje BPV-a kako bi se odlučilo koji će bolesnici polučiti najviše od postupka renalne denervacije. Povišen BPV je također prediktor ukupne kardiovaskularne smrtnosti, a povezuje se i sa smanjenim učinkom postupka renalne denervacije.^{7,8} Bolesnici s hipertenzivnom krizom mogu imati povišeni BPV i vaskularnu dob u usporedbi s referentnim vrijednostima, baš kao oni s rezistentnom hipertenzijom, koji su visokorizična skupina u kojima je krutost žila prepoznata kao biljeg povišenoga kardiovaskularnog rizika.⁶

Svrha je ovog istraživanja bila prikazati mjerenja brzine pulsog vala u hitnoj službi kao neinvazivne metode procjene kardiovaskularnog rizika u bolesnika s HU-om.

Bolesnici i metode

U ovo su istraživanje uključena 23 bolesnika koji su primljeni u hitnu službu Klinike za unutarnje bolesti Kliničke bolnice Merkur u Zagrebu tijekom triju uzastopnih mjeseca u 2018./2019. godini, koji su bili uključeni u istraživanje o dijagnosticanju HE-a, koje je odobrilo Etičko povjerenstvo Kliničke bolnice Merkur. Bolesnici kojima je mjerena brzina pulsog vala imali su HU. Istraživanje je uključivalo bolesnike s netom dijagnosticiranom hipertenzijom i HU-om, one s ranije dijagnosticiranom hipertenzijom i HU-om te bolesnike s rezistentnom hipertenzijom i HU-om. Nakon prijma u hitnu službu u bolesnika su provedena tri uzastopna mjerenja AT-a te im je dana oralna antihipertenzivna terapija. Većini je bolesnika dana doza od 30 ili 60 mg urapidila ili fiksna kombinacija

Hypertensive crisis is defined by systolic blood pressure values over 180 mmHg or diastolic blood pressure values higher than 120 mmHg. It can develop *de novo* or as a complication of existing primary or secondary arterial hypertension. Hypertensive crisis can be divided into hypertensive urgency (HU) and hypertensive emergency (HE) regarding target organ damage. Hypertensive emergency includes damage to the cardiovascular, renal, and/or cerebrovascular system in addition to high blood pressure values. In hypertensive urgency, end organ damage is not present.

The exact mechanism of hypertensive crisis is unknown. It is believed that the sudden elevation in blood pressure in hypertensive crisis comes from a sudden increase of systemic vascular pressure, which is connected to the action of humoral vasoconstrictors leading to intimal proliferation and fibrinoid necrosis of the blood vessel wall.³

According to the ESC (European Society of Cardiology) and ESH (European Society of Hypertension) guidelines from 2018, arterial stiffness is recognized as a risk factor for development of hypertension-mediated organ damage (HMOD) with a pulse wave velocity (PWV) >10 m/s.⁴ PWV is considered one of the most important clinical parameters for evaluation of cardiovascular risk and vascular adaptability and for follow up after the treatment. Although most commercially available PWV measuring devices offer regional estimates of arterial stiffness (measured between two vessels), local measurement offers a more precise evaluation of the condition of the arteries considering the difference between structure of the arteries. The trend in cardiovascular monitoring is shifting from invasive technologies towards noninvasive ones.⁵ The population of patients with resistant hypertension is known to be a high-risk group in which arterial stiffness is recognized as a marker of increased risk.⁶

Today's hypertension guidelines suggest PWV measurement in order to determine the best candidates for renal denervation procedures. Pulse wave velocity is a predictor of total cardiovascular mortality, which associates PWV with diminished response on renal denervation procedure.^{7,8} Increased PWV was found in elderly patients with isolated systolic hypertension and diabetes mellitus.⁷ Patients with hypertensive crisis could have increased PWV and vascular age compared with the reference values, just like the population of patients with resistant hypertension, who are known to be a high-risk group in which arterial stiffness is recognized as a marker of increased cardiovascular risk.⁶

The aim of this study was to evaluate the measurement of pulse wave velocity in the emergency room as a noninvasive method of assessing cardiovascular risk in patients with hypertensive urgency.

Patients and Methods

This study included 23 patients who presented to the emergency room of the Clinic for Internal Diseases of the University Hospital "Merkur" in Zagreb over the course of 3 consecutive months in 2018/2019, who were included in a study of diagnosing hypertensive emergency approved by the Ethics Committee of the University Hospital "Merkur". Patients whose pulse wave velocity was measured had hypertensive urgency. The study included patients with newly diagnosed hypertension and HU, patients with earlier diagnosed hy-

oralnih antihipertenziva (ACE inhibitor + blokator kalcijevih kanala). Nakon što se bolesnike informiralo o sudjelovanju u istraživanju te su dali informirani pristanak, izmjerena im je brzina pulsno vala.

Za mjerenje brzine pulsno vala korišten je uređaj *Agedio B900 Pulse Wave Analysis System* (Njemačka). Taj uređaj radi na principu oscilometrije. Uključuje manšetu koja dolazi u tri različite veličine – kao mala, srednja i velika, ovisno o veličini nadlaktice koja se prethodno izmjeri, zatim sami mjerni uređaj te *Apple iPad* s programom koji prikazuje rezultate. Uređaj omogućuje istodobno mjerenje brahijalnog tlaka i krutosti žila u jednom postupku. Krutost žila kvantificira se kao BPV i izražava u m/s.⁹ Zdravstveni djelatnik u uređaj unosi i dodatne podatke kao što su bolesnikova dob, spol, tjelesna težina i visina. Nakon mjerenja uređaj ispostavlja dva izvješća, jedno za bolesnike s procjenom vaskularne dobi, i jedno za liječnika koje izvještava o hemodinamskim čimbenicima: centralni krvni tlak, tlak pulsa, prosječni arterijski tlak te augmentacijski indeks.⁹

Aritmetička sredina i standardna devijacija služe za prikaz podataka normalne distribucije, a srednja vrijednost za ostale podatke. Podatci su analizirani s pomoću parametrijskih i neparametrijskih testova (Studentov t-test, Mann-Whitneyev U-test). Korelacija se određivala izračunavanjem Pearsonova koeficijenta korelacije. Za statističku je analizu uporabljen program MS Excel.

Rezultati

Prosječna je dob bolesnika bila $64,0 \pm 10,76$ godine. Žene su činile 61,87 % bolesnika (14 bolesnica), a 39,13 % bili su muškarci (9 bolesnika). Žene su bile starije od muškaraca ($\bar{Z} 67,00 \pm 10,52$ godina, $M 59,33 \pm 9,92$ godine, $p = 0,05$).

Najčešći klinički znakovi i simptomi u bolesnika bili su glavobolja (30 %), epistaksa (18 %), bol u prsnoj koži (17 %), zaduha (15 %), psihomotorni nemir (10 %), srčane aritmije (6 %) i parestezije (4 %).

Prosječni brahijalni sistolički tlak bio je $190,87 \pm 9,61$ mmHg, to jest viši od 180 mmHg, što je jedan od kriterija za hipertenzivnu krizu. Prosječni brahijalni dijastolički tlak bio je $108,91 \pm 16,23$ mmHg. Prosječni centralni sistolički tlak bio je $155,34 \pm 19,61$ mmHg, a prosječni centralni dijastolički tlak bio je $102,86 \pm 17,14$ mmHg (**tablica 1**).

Vrijednosti BPV-a bile su više od referentnih vrijednosti za tu dob u svih bolesnika, s prosječnom vrijednosti od $10,71 \pm 1,96$ m/s. Studentov t-test pokazao je statistički značajnu razliku između vrijednosti BPV-a izmjerenih u muškaraca i u žena ($M 9,85 \pm 1,78$, $\bar{Z} 11,26 \pm 1,94$; $p = 0,05$). Ostale izmjerene vrijednosti nisu bile statistički značajno različite. Srednja vrijednost povećane vaskularne dobi u usporedbi s biološkom dobi bolesnika bila je $7,91 \pm 2,27$ godina. Vrijednosti BPV-a bile su u pozitivnoj korelaciji s dobi ($r = 0,9461$, $p < 0,0001$). Središnji sistolički tlak bio je u slaboj pozitivnoj korelaciji s BPV-om ($r = 0,4659$, $p = 0,025$). Ostale uspoređivane varijable nisu bile u statistički značajnim korelacijama.

Rasprava

Primarni čimbenik koji utječe na krutost žila jest starenje, što potvrđuju i rezultati ovog istraživanja. Razlike u BPV-u između muškaraca i žena mogu se stoga objasniti starijom dobi

pertension and HU, and patients with resistant hypertension and HU. After being admitted to the emergency room, three consecutive measurements of blood pressure were performed for all patients and oral antihypertensive therapy was given. Most patients were given 30 or 60 mg of urapidil or a fixed combination of oral antihypertensives (ACE inhibitor + calcium channel blocker). After the patients were informed about participating in a clinical study and gave their informed consent, pulse wave velocity was measured.

The device used for measuring pulse wave velocity was the *Agedio B900 Pulse Wave Analysis System* (Germany). The device works on the principle of oscillometry. It includes a cuff, which comes in three different sizes – small, medium, and large, depending on the size of the arm which is measured in advance, the measuring device itself, and an *Apple iPad* with a software that shows the results. It allows for brachial blood pressure and arterial stiffness to be measured in a single procedure. Arterial stiffness is quantified as PWV and expressed in m/s.⁹ The clinician inputs additional patient data such as age, sex, body weight, and height into the device. After the measurement the device produces two reports, one for the patient, containing the estimated vascular age, and one for the clinician, with hemodynamic parameters: central blood pressure, pulse pressure, mean arterial pressure, and augmentation index.⁹

Arithmetic mean and standard deviation were used to present the data which followed normal distribution, and median value was used for the rest. The data were analyzed using parametric and nonparametric tests (Student's t-test, Mann-Whitney U test). Pearson's correlation coefficient was calculated to determine correlation. The program used for statistical analysis was MS Excel.

Results

Average age of patients was 64.0 ± 10.76 years. 61.87% were women (14 patients) and 39.13% were men (9 patients). Female patients were older than male patients ($F 67.00 \pm 10.52$ years, $M 59.33 \pm 9.92$ years, $p = 0.05$).

The most common signs and symptoms the patients presented with were headache (30%), epistaxis (18%), chest pain (17%), dyspnea (15%), psychomotor agitation (10%), cardiac arrhythmias (6%), and paresthesia (4%).

Average brachial systolic blood pressure was 190.87 ± 9.61 mmHg, i.e. higher than 180 mmHg, which is a criterion for hypertensive crisis. Average brachial diastolic pressure was 108.91 ± 16.23 mmHg. Average central systolic blood pressure was 155.34 ± 19.61 mmHg, and average central diastolic blood pressure was 102.86 ± 17.14 mmHg (**Table 1**).

Values of PWV were higher than reference values for their age in all patients, averaging at 10.71 ± 1.96 m/s. Student's t-test showed a statistically significant difference between PWV measured in men and women ($M 9.85 \pm 1.78$, $F 11.26 \pm 1.94$; $p = 0.05$). Other values that were measured did not show statistically significant difference. The median value of increased vascular age compared with biological age of patients was 7.91 ± 2.27 years. PWV values show positive correlation with age ($r = 0.9461$, $p < 0.0001$). Central systolic blood pressure showed a weak positive correlation with PWV ($r = 0.4659$, $p = 0.025$). Other compared variables showed no statistically significant correlation.

TABLE 1. Blood pressure and pulse wave velocity values in patients with hypertensive crisis.

N	Age (years)	BBP sys. mmHg	BBP dias. mmHg	CBP sys. mmHg	CBP dias. mmHg	PWV (m/s)	Vascular age	Sex
1	61	182	74	134	77	9.6	9	M
2	56	182	95	159	101	9.4	9	M
3	58	195	105	153	110	9.3	9	M
4	68	200	120	154	108	11.0	9	M
5	48	180	130	153	122	8.1	9	M
6	53	212	130	140	112	8.5	8	M
7	48	192	136	156	122	8.2	9	M
8	63	180	90	152	80	10.3	9	F
9	73	186	92	156	94	11.9	9	F
10	82	203	96	181	102	15.0	9	F
11	75	180	100	146	100	11.8	9	F
12	77	180	100	130	67	12.4	9	F
13	69	190	100	141	85	10.7	8	F
14	53	190	110	114	81	7.3	0	F
15	61	201	115	120	94	10.0	3	F
16	66	212	121	188	128	12.1	9	F
17	77	185	129	160	104	12.9	9	F
18	51	197	126	179	127	9.6	7	F
19	63	187	110	169	113	10.9	8	M
20	76	188	108	166	111	12.9	9	F
21	66	192	86	185	91	11.8	8	F
22	49	185	122	167	126	8.9	5	F
23	79	191	110	170	111	13.7	9	M

BBP – brachial blood pressure, CBP- central blood pressure, sys. - systolic, dias. – diastolic.

u kojoj se u žena pojavljuje HU. Prosječne vrijednosti BPV-a izmjerene u ovom pilot istraživanju bile su više od 10 m/s, što je granična vrijednost za HMOD.⁴ BPV kao takav biljeg je povećanog kardiovaskularnog rizika te se može primijeniti kako bi se bolesnike podijelilo u skupine ovisno o terapiji koju trebaju, bilo da je to monoterapija, kombinacija fiksne doze ili trostruka antihipertenzivna terapija. Budući da je dio pacijenata uključen u ovo istraživanje imao HU kao prvu manifestaciju AH-a bez prethodne dijagnoze AH, mjerenje BPV-a kao varijable koja se mijenja tijekom duljeg razdoblja omogućuje procjenu kardiovaskularnoga stanja u takvih bolesnika. Bolesnici s HU-om te oni s HE-om imaju povišen rizik od nove epizode nekontroliranog povišenja AT-a u prvih šest mjeseci nakon pojave tih stanja.¹⁰ Stoga je nužno takve bolesnike pratiti i optimirati njihovu antihipertenzivnu terapiju. Mjerenje BPV-a dodatni je parametar u takvom praćenju jer na taj parametar može utjecati dugoročna kontrola AT-a. Bolesnici u ovom istraživanju imali su mnogo višu prosječnu vrijednost BPV-a

Discussion

The primary factor affecting the stiffness of the arterial wall is aging, which was also confirmed by the results of this study. Difference in pulse wave velocity between men and women in this study can therefore be explained by the higher age at which women present with hypertensive urgency. Average values of PWV measured in this pilot study were higher than 10 m/s, which is a borderline value for HMOD.⁴ The PWV itself is a marker of increased cardiovascular risk and can be used to divide patients into groups based on the therapy they need, whether that be monotherapy, fixed combination therapy, or triple therapy for hypertension. Since a part of the patients included in this study presented with HU as a first manifestation of AH without an earlier diagnosis of AH, measuring PWV as a parameter which changes over a longer period allows for the assessment of cardiovascular status for these patients. Patients with hypertensive urgency as well as those with hypertensive emergency have an increased risk for an

od onih s rezistentnom hipertenzijom iz drugog istraživanja provedena u Kliničkoj bolnici Merkur. Prosječne vrijednosti BPV-a u bolesnika s rezistentnom hipertenzijom bile su 8,84 m/s. Isti je mjerni uređaj uporabljen i u toj studiji, što omogućuje izravnu usporedbu.⁶ Ti su rezultati u skladu s hipotezom da je brzina porasta AT-a važnija od trajanja AT-a glede nastanka vaskularnih oštećenja.^{10,11} Nakon mjerenja vrijednosti AT-a bolesnicima su propisani oralni antihipertenzivi te im je izmjerena BPV. BPV se mora mjeriti unutar 24 sata od zbrinjavanja AT-a i uspostavljanja dijagnoze hipertenzivne krize. Iz podataka je razvidno da je vrijednost BPV-a povišena usprkos terapiji. Ipak, ta metoda mjerenja krutosti žila još uvijek nije prvi izbor u hitnim slučajevima jer traje dulje od klasičnoga mjerenja AT-a.¹² Daljnji bi razvoj tehnologije mogao dovesti do poboljšanja na tom polju, čime bi neinvazivno mjerenje BPV-a postalo široko rasprostranjeno u hitnim službama, uz standardno mjerenje AT-a.

Zaključak

Bolesnici primljeni u hitnu službu s HU-om imaju povišene vrijednosti BPV-a u usporedbi s referentnim vrijednostima i u usporedbi s onima s rezistentnom hipertenzijom. Iako HU ne implicira oštećenje ciljnih organa, takvi su bolesnici izloženi većemu kardiovaskularnom riziku, koji je izravno povezan s BPV-om. Potrebna su daljnja istraživanja o dugoročnoj prediktivnoj vrijednosti BPV-a mjerenoj tijekom hipertenzivne krize.

other episode of uncontrolled blood pressure elevation in the six months following presentation.¹⁰ Regular follow-up and optimizing their antihypertensive therapy is therefore necessary in these patients. Measuring PWV is an additional parameter in such follow-up because it can be affected by long-term control of blood pressure. The patients in this study had a significantly higher mean value of PWV than the patients with resistant hypertension included in another study conducted at the University Hospital "Merkur". Mean values of PWV in patients with resistant hypertension were 8.84 m/s. The same measuring device was used in that study, allowing for a direct comparison.⁶ This finding is in accordance with the hypothesis that the speed at which blood pressure rises is more important than the duration of hypertension for the occurrence of vascular injury.^{10,11} After measuring office blood pressure, patients were given oral antihypertensives and their PWV was measured. It is necessary to measure PWV within 24 hours from blood pressure measurement to establish the diagnosis of hypertensive crisis. From the data it was visible that PWV remained elevated despite therapy. However, the method of measuring arterial stiffness is still not the first choice in an emergency since it takes more time than the classical blood pressure measurement.¹² Further advancements in technology can lead to improvement in this area, making the noninvasive measuring of PWV a widespread test in emergency room, together with blood pressure measurement.

Conclusion

Patients presenting to the emergency room with hypertensive urgency have elevated values of PWV compared with reference values and compared with patients with resistant hypertension. Although hypertensive urgency does not imply target organ damage, patients have increased cardiovascular risk, which is directly connected to PWV. Additional research is required on the long-term predictive value of PWV measured during hypertensive crisis.

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