EJMI

DOI: 10.14744/ejmi.2021.76250
EJMI 2021;5(1):128–135

Research Article

The Assessment of Resistant Hypertension-Related Cardiovascular Risk

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Abstract

Objectives: The effect of resistant hypertension (RH) on cardiovascular risk has not been clarified. According to the ambulatory blood pressure monitoring (ABPM) results, cardiovascular disease outcomes are more common in patients with non-dipping pattern. We aimed to show cardiac end-organ damages in RH and non-dipping patients within the RH.

Methods: RH and regular hypertensive cases were included. Cardiovascular endpoints were determined as carotid intima-media thickness (CIMT), echocardiography parameters, and microalbuminuria. RH patients were divided into dipping and non-dipping groups according to the ABPM and the comparison of end-organ damage among themselves was performed separately.

Results: A total of 95 patients were enrolled, 61 in RH group. Significant differences were found between the RH and the regular hypertensive group in terms of CIMT and microalbuminuria (p=0.020 for the right CIMT, p=0.016 for the left CIMT, and p=0.003 for the microalbuminuria). There were no significant differences between the groups in resistant and regular hypertension (HTN) and also dipping and non-dipping groups in RH in terms of other parameters.

Conclusion: Significant differences were detected between RH and regulated HTN patients in terms of CIMT and microalbuminuria, but there was no difference between the dipping and non-dipping groups in terms of atherosclerotic burden.

Keywords: Carotid intima-media thickness, end-organ damage, hypertension, microalbuminuria, resistant hypertension

Cite This Article: *Aykan MB, Erşen M, Görmel S, Başgöz BB, Doğan T, Sağlam K. The Assessment of Resistant Hypertension-Related Cardiovascular Risk. EJMI 2021;5(1):128–135.*

Among patients receiving medical treatment to control blood pressure (BP), 12–16% have resistant hypertension (RH) according to large cohort analyses.[1,2] RH is defined as persistently uncontrolled BP (systolic BP [SBP]/diastolic BP [DBP] ≥130/80 mmHg) despite the use of at least three antihypertensive drugs at optimal doses, including a diuretic, or achieving SBP/DBP levels of below 130/80 mmHg on at least four drugs.[3] Multiple studies have shown RH as a cause of increased risk of future cardiovascular diseases (CVDs) among all patients with hypertension (HTN).[4]

The diagnosis of RH requires the exclusion of white coat effect,[4] which is best practiced by the ambulatory BP mea-

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Submitted Date: December 12, 2020 **Accepted Date:** March 02, 2021 **Available Online Date:** April 03, 2021

surement (ABPM). It is often used to detect above target BP values.[5] Besides, ABPM provides additional information about variations in BP during the day and night periods, which is known as "dipping/non-dipping" patterns.[6]

The dipping character was defined as a reduction in average SBP and DBP at night, which was ≥10%. The non-dipping pattern was also defined as <10% reduction in average SBP and DBP during the night hours (between 12:00 AM and 06:00 AM) in ABPM. No drop in BP≥ 10% or increase in reverse basically determines the non-dipping character. Similar to the positive relationship between persistently increased BP and the risk of atherosclerotic diseases, the non-dipping pattern also contributes to the occurrence of more frequent CVD outcomes in patients with HTN.[6]

In the light of the information mentioned above, we hypothesized that RH and a non-dipper pattern on ABPM might additively increase the risk of atherosclerosis and CVD. Using the carotid intima-media thickness (CIMT),[7,8] microalbuminuria,[9] and several echocardiography variables[9,10] as robust surrogate markers of atherosclerotic burden and end-organ damage, we aimed to explore whether patients with RH show a worse risk profile of future CVD events in the context of the non-dipper pattern.

Methods

Study Design and Population

We conducted this study by retrospectively reviewing the medical records of outpatients with HTN from a tertiary clinic from December 2016 through December 2017. The inclusion criteria were age ≥18 years, ABPM consistent with RH diagnosis, CIMT measured in the previous 3 months, echocardiography performed in the previous 3 months, and microalbuminuria assessed in the previous 12 months. Patients with regulated HTN based on the office BP readings were included irrespective of ABPM was performed or not. The exclusion criteria were age <18 years, pregnancy, evidence of secondary HTN, acute/chronic infectious conditions, malignancy, and medical treatment for psychiatric diseases.

Age, gender, height, weight, smoking status, comorbid diseases, medications, and laboratory results in the previous 3 months at the time of admission were retrieved from the medical records. Body mass index (BMI) was calculated as the body weight divided by height square. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault equation.[11] Hemoglobin A1c (HbA1c) values were evaluated only in the diabetic group. The local ethics committee approved the study protocol (Nr. 17-17/15).

Definition of RH, Regulated HTN, and non-Dipper Pattern

The diagnosis of RH required that the patient had mean SBP readings ≥ 130 mmHg or DBP ≥80 mmHg in ABPM despite the use of at least three antihypertensive drugs at optimal doses, including a diuretic, or individuals achieving SBP/DBP levels of below 130/80 mmHg using four medications, as recommended by the 2017 American College of Cardiology and American Heart Association HTN Guidelines.[3] The diagnosis of regulated HTN required that the patient had mean SBP readings <130 mmHg or DBP readings <80 mmHg with the use of three or fewer antihypertensive drugs. The dipping character was defined as a reduction in average SBP and DBP at night, which was ≥10%. The non-dipping pattern was also defined as <10% reduction in average SBP and DBP during the night hours (between 12:00 AM and 06:00 AM) in ABPM. No drop in BP≥ 10% or increase in reverse basically determines the non-dipping character.[6]

Markers of Atherosclerosis and End-Organ Damage

CIMT is measured using a standardized approach in the clinic of radiology. CIMT was measured by B-mode ultrasonography method using a Siemens Acuson S3000 ultrasound device and an 18 MHz linear transducer. Measurements were made with the patients in the supine position and the neck turned to the opposite side. CIMT measurement was measured 1 cm away from the bifurcation point of the right and left common carotid artery as standard.[8] In this measurement, the right and left main CIMT averages were recorded after being calculated using the existing software (Syngo Arterial Health Package). In this study, the arithmetic mean of the right and left CIMT was taken separately. Although the upper limit of regular range changes by age, CIMT measurements above 0.9 mm are almost always considered as abnormal.[12]

Transthoracic echocardiography is routinely performed in the clinic of cardiology. While performing echocardiography, recommendations of the American Echocardiography Association were taken as basis.[13] In this clinic, Philips IE33 6.0 (Andover, MA, USA) echocardiography device equipped with a 2.5 MHz transducer was used. M mode, two-dimensional, and Doppler echocardiography methods were used during echocardiography measurements. We recorded the following echocardiography parameters; left ventricular ejection fraction (LVEF), left atrial volume index (LAVI), interventricular septum thickness (IVSD), and left ventricular relaxation dysfunction (LVRD).

Microalbuminuria was accepted positive if albumin-to-creatinine ratio in a random spot urine collection was ≥30 mg/g.[14]

Statistical Analysis

We presented descriptive statistics as a percentage of the total. We examined the uniformity of continuous variables to a normal distribution using the Kolmogorov–Smirnov test. Normally distributed continuous data expressed as mean±standard deviation and data that are not normally distributed expressed as median (interquartile range). We tested the differences between the RH and regulated HTN groups and dippers and non-dippers RH groups either by Chi-square test, Student's t-test, or Mann–Whitney U-test according to the distribution and type of variables. We accepted $p<0.05$ as statistically significant. We performed statistical analyses using SPSS 22.0 software (SPSS Inc., Chicago, Illinois).

Results

The overall sample included 95 subjects, 61 patients in the RH group and 34 patients in the regulated HTN group. The two group were similar for age but there were significantly more women in the regulated HTN group (68.9% vs. 91.2%, p=0.010). Table 1 shows the clinical and laboratory characteristics of the two groups. Smoking, mean BMI, obesity, diabetes mellitus (DM), and chronic kidney disease, estimated GFR, and lipid parameters showed no difference, while fasting plasma glucose and mean HbA1c were significantly higher in the RH group (Table 1).

Markers of Atherosclerosis and End-Organ Damage

As shown in Table 2, median microalbuminuria (mg) was

Table 1. Characteristics of patients with RH and regulated hypertension

	RH (n=61)	Regulated hypertension (n=34)	P
Age (mean±SD)	63.6±10.96	62.85±7.85	0.725
≥65 years, n (%)	31 (50.8)	14 (41.2)	0.360
Female gender, n (%)	42 (68.9)	31 (91.2)	<0.001
Smoker, n (%)	12 (19.7)	3 (8.8)	0.160
BMI (kg/m2±SD)	32.09±5.02	30.48±4.87	0.136
Obesity, n (%)	41 (67.2)	21 (61.8)	0.593
DM, n (%)	34 (55.7)	15 (44.1)	0.270
Chronic kidney disease, n (%)	21 (35)	7 (21.2)	0.160
FBG (mmHg±SD)	153.68±72.34	115.64±36.98	0.020
HbA1c (%±SD)	8.19±2.37	6.38±0.82	0.011
GFR (mL/min±SD)	64.85±16.42	69.39±14.89	0.179
LDL (mg/dL±SD)	119.87±34.41	131.00±39.84	0.219
HDL (mg/dL±SD)	46.19±10.64	50.66±10.85	0.069
Triglyceride (mg/dL±SD)	153.00±145.00	178±147.50	0.781
Total cholesterol (mg/dL±SD)	203.10±44.06	217.33±39.50	0.143
SBP (mmHg±SD)	142.08±14.36	121.17±5.64	<0.001
DBP (mmHg±SD)	87.78±9.11	73.3±4.39	<0.001

SD: Standard deviation; DM: Diabetes mellitus; BMI: Body mass index; Obesity: Patients with a BMI over 25 are accepted as obese; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; GFR: Glomerular filtration rate; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Significant P values are in bold. RH: Resistant hypertension, HbA1c: Hemoglobin A1c.

Table 2. Microalbuminuria, echocardiography findings, and CIMT values in the groups of RH and regulated hypertension patients

	RH (n=61)	Regulated hypertension (n=34)	P
Microalbumin, median (IQR) (mg/L)	13.78 (58.09)	8.88 (8.39)	0.003
CIMT, right (mm)	0.73±0.22	0.64±0.17	0.020
CIMT, left (mm)	0.76±0.29	0.65±0.20	0.016
LVEF (%)	67.92±4.92	69.72±5.44	0.143
LAVI (mm)	20.87±6.58	17.86±4.91	0.051
LVRD (grade)	0.80±0.40	0.93±0.25	0.117
IVSD (mm)	12.07±2.01	12.58±6.06	0.661

LVEF: Left ventricular ejection fraction; LAVI: Left atrial volume index; IVSD: Interventricular septum thickness; LVRD: Left ventricular relaxation dysfunction; CIMT: Carotid intima-media thickness; RH: Resistant hypertension; IQR: Interquartile range.

significantly higher in the RH group. Likewise, CIMT (mm) calculated on both sides was significantly higher in the RH group. There were no significant differences between the two groups in terms of echocardiography findings LVEF, LAVI, LVRD, and IVSD.

Patients with RH with Non-Dipper Pattern Versus Dipper Pattern on ABPM

Most of the patients with RH were non-dippers on ABPM. There were no statistically significant differences in age, gender, and comorbid diseases between the group of non-dippers with RH (n=43, 61.5%) and dippers (n=18, 29.5%) (Table 3). As expected, the use of diuretics, calcium channel blockers, and beta-blockers was significantly higher in the group of RH (Table 5). As they are prescribed as the first-line drugs in most cases, the frequency of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) use was similar in the two groups. The average number of antihypertensives in the group of RH was also significantly higher (3.58 vs. 2.67) (p=0.010).

Non-dippers had significantly higher mean FBG and HbA1c than the non-dippers (Table 2). Other blood tests were not different.

The level of microalbuminuria (mg), CIMT (mm), and echocardiographic findings LVEF, LAVI, LVRD, and IVSD was not different in the groups of non-dippers and dippers (Table 4).

Discussion

In this study, we compared adult RH patients with regulated HTN patients and also compared dipper and non-dipper RH patients in terms of cardiac end-organ damages and atherosclerotic burden. We found that both CIMT and microalbuminuria, which are valuable predictors for determining the elevated risk of CVD, were significantly higher among RH patients. In contrast, we did not find any difference in echocardiographic parameters. Besides, no difference in CIMT, microalbuminuria, and echocardiographic parameters was observed between dipper and non-dipper RH patients.

The results of the present study are considered interesting as we were able to demonstrate an increased burden of end-organ damage or atherosclerosis in subjects with RH

Table 3. Characteristics of patients with dipper and non-dipper resistant hypertensive patients

	Non-dippers (n=43)	Dippers (n=18)	P
Age (mean±SD)	65.37±9.15	59.38±13.78	0.051
≥65 years, n (%)	23 (53.5)	8 (44.4)	0.510
Female gender, n (%)	30 (69.8)	12 (66.7)	0.810
Smoker, n (%)	9 (20.9)	3 (16.7)	0.700
BMI (kg/m2±SD)	31.78±4.84	32.81±5.50	0.327
Obesity, n (%)	27 (62.8)	14 (77.8)	0.255
DM, n (%)	27 (62.8)	7 (38.9)	0.080
Chronic kidney disease, n (%)	18 (41.9)	3 (16.7)	0.051
FBG (mmHg±SD)	168.71±78.57	118.61±37.58	0.003
HbA1c (%±SD)	8.59±2.43	6.88±1.67	0.047
GFR (mL/min±SD)	63.35±15.64	70.33±15.54	0.088
LDL (mg/dL±SD)	122.20±35.93	114.41±30.84	0.413
HDL (mg/dL±SD)	47.82±11.16	42.35±8.38	0.046
Triglyceride (mg/dL±SD)	150.00±119.00	198.00±97.00	0.448
Total cholesterol (mg/dL±SD)	206.67±46.03	194.70±39.05	0.323
SBP (mmHg±SD)	141.8±14.68	142.61±13.98	0.955
DBP (mmHg±SD)	87.53±9.92	88.38±7.04	0.825
ABPM daytime SBP (mmHg±SD)	136.13±16.68	138.22±12.54	0.596
ABPM daytime DBP (mmHg±SD)	79.65±8.67	81±11.28	0.654
ABPM night – SBP (mmHg±SD)	134.37±17.41	116.5±11.66	<0.001
ABPM night – DBP (mmHg±SD)	77.51±11.79	67.16±8.7	0.004
ABPM day SBP (mmHg±SD)	135.51±16.27	131.38±12.83	0.299
ABPM day DBP (mmHg±SD)	78.90±8.18	76.44±9.01	0.326

SD: Standard deviation; DM: Diabetes mellitus; BMI: Body mass index; Obesity: Patients with a BMI over 25 are accepted as obese; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ABPM: Ambulatory blood pressure measurement; FBG: Fasting blood glucose; GFR: Glomerular filtration rate; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Significant P values are in bold; HbA1c: Hemoglobin A1c.

Table 4. Microalbuminuria levels, echocardiography findings, and CIMT values in the groups of dippers and non-dippers

	Non-dippers (n=43)	Dippers (n=18)	P
Microalbumin, median (IQR) (mg/L)	15.51 (114.20)	12.90 (22.55)	0.080
CIMT, right (mm)	0.74±0.22	0.71±0.23	0.604
CIMT, left (mm)	0.78±0.33	0.71±0.17	0.285
LVEF (%)	68.17±4.86	67.31±4.72	0.514
LAVI (mm)	20.76±7.24	21.12±4.78	0.393
LVRD (grade)	0.87±0.33	0.62±0.50	0.039
IVSD (mm)	12.35±2.18	11.37±1.36	0.115

LVEF: Left ventricular ejection fraction; LAVI: Left atrial volume index; IVSD: Interventricular septum thickness; LVRD: Left ventricular relaxation dysfunction; CIMT: Carotid intima-media thickness; IQR: Interquartile range.

Table 5. The antihypertensive drugs information

	RH (n=61)	Regulated hypertension (n=34)	P
Diuretics, n (%)	61 (100)	28 (82.4)	0.002
ACEI, n (%)	21 (34.4)	14 (41.2)	0.510
ARB, n (%)	40 (65.6)	20 (58.8)	0.510
Calcium channel blockers, n (%)	46 (75.4)	18 (52.9)	0.020
Beta-blockers, n (%)	36 (59)	11 (32.4)	0.010
Alpha-blockers, n (%)	7 (11.5)	-	-
Number of drugs (mean)	3.58	2.67	0.010

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; RH: Resistant hypertension.

compared to regulated HTN. In general, the non-dipping pattern has repeatedly been linked to a higher risk of earlier end-organ damage and worse cardiovascular outcomes.

In our study, we could not find worse cardiovascular endpoints in patients with non-dipping patterns. The primary reason for this may be the evaluation of circadian BP variability only in the RH group. On the other hand, in the RH group, the drugs used in large numbers may reduce the changes that lead to poor endpoints in addition to taking control of BP. However, it is not known how long the subjects have RH. In cases with a non-dipping pattern, the time required for poor endpoints to occur may not yet have passed.

We think our study fits the general HTN sample in the society. Because, we determined that nearly half of the RH patients was 65 years and older in our study. Gijo'n-Conde et al. reported that 78.1% of the whole group consisted of individuals aged 60 and over.[15]

Microalbuminuria is considered to be a well-known marker for subclinical organ damage. It has been previously reported that the presence of microalbuminuria is more frequent in patients with RH than in those with regulated HTN group.[16] Furthermore, we found that the incidence of microalbuminuria is significantly higher in the RH group compared to the regulated HTN group (p=0.003). In a study conducted by Oliveras et al., a higher nighttime SBP correlated with microalbuminuria.[17] Although we found the level of microalbuminuria higher in non-dipper patients than in dipper patients, we remained a little far from statistical significance (p=0.08). Spot urine microalbumin value was used in our study. The gold standard method for detecting microalbuminuria is the 24 h urine collection method. We think that due to this test difference, no difference was found in the non-dipping group with RH in our study. On the other hand, the microalbuminuria-related differences between groups may be related to the DM age of the patients. From retrospective records, we could not obtain data on patients' DM ages.

Several studies revealed that fatal and non-fatal coronary and cerebral events are associated with increased CIMT,[18,19] which is a surrogate marker of atherosclerosis. Atherosclerotic burden and cardiac end-organ damage among RH and regulated HTN patients are well studied,[15,20] and CIMT found to be significantly elevated among RH patients.[21] Similarly, in our study, we found that CIMT of RH patients is considerably higher than CIMT of regulated HTN patients (p=0.02 for the right CIMT; p=0.016 for the left CIMT). However, we did not notice such a difference in CIMT between dipper and non-dipper RH patients. A meta-analysis consisting of 3753 normotensives, untreated, and treated HTN

patients propounded a positive correlation between non-dipping patterns and CIMT.[22] Furthermore, Ozdemir et al. found CIMT higher in the non-dipping group of patients with HTN.[23] However, the authors did not separately examine the RH group. We could not notice any literature focused on the assessment of CIMT among dipper and non-dipper RH patients. We think that this is due to the fact that dipping and non-dipping patterns form a special group within the RH in our study.

A meta-analysis published in 2010 reported that ongoing non-dipping status in HTN might be associated with poor cardiac outcomes, though conflicting studies have also been reported.[24] Cuspidi et al. reported that there was no significant difference in subclinical organ damage assessed by echocardiography according to dipping and non-dipping status in patients with increased nighttime BP.[25] We did not find any significant difference between groups in terms of transthoracic echocardiography study results. Increased LAVI is an indicator of impaired left ventricular diastolic properties. This condition has been reported as one of the indicators of poor cardiac end-organ damages, especially in hypertensive patients. In our study, we noticed that LAVI tends to make a difference, although not statistically significant, in RH patients (p=0.051).[24] In this sense, although the literature information is not clear, we can state that our findings are partially consistent with the novel.

When all groups were evaluated, there was no significant difference in the presence of obesity. Irvin et al. reported obesity as 60.5% in the RH group and 56.3% in the regulated HTN group. They found no statistically significant difference between the two groups.[20] There was no significant difference in the frequency of DM between our groups. Irvin et al. reported that the frequency of DM in the RH group was 53.5%.[20] DM is supposed to be a risk factor for impaired BP control, non-dipping pattern, and RH.[26] However, the presence of DM is known to be a risk factor for HTN above all. There is a balanced distribution of DM presence in our study group.

When the laboratory data of FBG were examined, a statistically significant difference was found between the RH and the regulated HTN groups, against RH patients (p=0.02). Furthermore, such a distinction was observed against non-dipping patients compared to dippers (p=0.003). Like FBG, HbA1c levels were significantly higher among RH patients than those of regulated HTN patients (p=0.011). This significant difference was observed against the non-dipping group among the RH patients (p=0.047). As mentioned previously, there was no significant difference in the presence of DM between groups. We believe that patients in the RH group have poor diabetic control. We think that DM control has an important place in BP regulation as well as the presence of DM. There was no significant difference between the groups in terms of lipid parameters.

Diuretics were the most commonly used drugs in this study, especially in the RH group. By definition of RH, it is not surprising that diuretics are the most frequently used drug in this group. The total rate of ACEI or ARB use was 100% in the RH group. Irvin et al. reported that the overall rate of ACEI or ARB use in the RH group was 79.1%.[20] In the RH group, diuretics, calcium channel blockers, and beta-blockers were used significantly more than the regulated HTN group. Irvin et al. reported the use of beta-blockers in the same group as 62.8%; the rate of calcium channel blocker use as 76.7%.[20] When we compared the use of drugs according to the dipping and non-dipping status, we did not find a class of drugs that were particularly protective of the non-dipping situation. In the literature, Irvin et al. reported that diuretics as a class of protective drugs from non-dipping status in the whole group with high BP.[20] Following current guidelines, we could not identify a class of drugs that would be protective of non-dipping status and that we could recommend it first. In our opinion, RH patients have been using these drugs for a long time. Although these drugs are not successful in controlling BP, they may have reduced the development of end-organ damage.

The mean number of medications used in the RH group was found to be 3.58. Gijo'n-Conde et al. reported this number as 3.44 in their study.[15] According to our findings, the rate of patients taking four or more drugs in the RH group was 52.4%. Therefore, although at least three drugs are mentioned in the definition of RH, most of the patients need four or more drugs. The mean number of medications used by patients in the regulated HTN group was 2.67.

The regulated HTN group was included in the study as the group that met the BP target. It is meaningful that the number of drugs needed in this group is higher than the two drugs. In the SPRINT study, which recently compared the intensive versus the standard approach in BP regulation and made a prominent impact, the number of antihypertensive medications required to achieve SBP <120 mmHg was reported as 2.8 drugs.[27]

This study has several limitations. First, the assurance of the certainty of the records is limited due to its retrospective nature. Retrospective studies may include bias related to the ability to keep records. Second, the small number of patients may be particularly important in terms of end-organ markers without significant difference. Third, the study is in cross-sectional design. Therefore, the results cannot be assumed to be causal.

Conclusion

According to the current study, there is a significant difference between the RH and regulated HTN groups in terms of CIMT and microalbuminuria. However, there was no difference in terms of GFR and echocardiography parameters in the same groups. The differences in end-organ damage between RH and regulated HTN groups generally do not disappear with lowering the BP target to lower limits. There is no difference in terms of poor endpoints of CVD among dipping/non-dipping patients evaluated in the RH group.

Disclosures

Ethics Committee Approval: T.C. Health Sciences University Non Interventional Clinical Researches Ethics Committee Decision No: 17/17-15 Date: 19 December 2017.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.A., K.S.; Design – M.A., B.B., K.S.; Supervision – K.S.; Materials – M.A., M.E., S.G.; Data collection &/or processing – M.A., M.E., S.G.; Analysis and/or interpretation – M.A., B.B., K.S.; Literature search – M.A., B.B., M.E., S.G.; Writing – M.A., B.B.; Critical review – M.A., B.B,K.S.

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