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ISSN 1607-0763 (Print); ISSN 2408-9516 (Online)
https://doi.org/10.24835/1607-0763-1224

MRI in the assessment of cerebral injury and cerebroprotective effects of renal denervation in resistant hypertension

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The purpose of this single-centre, prospective, comparative study was to evaluate the pattern and severity of the brain structural changes in patients with resistant hypertension based on MRI assessments and their changes one year after renal denervation.

Material and Methods. The study comprised 53 patients with resistant hypertension (RH), aged 52.1 ± 9.1 years, who underwent renal denervation (RDN) following the Good Clinical Practice guidelines. Patients underwent office blood pressure measurements, 24-hour blood pressure monitoring (BPM), and brain MRI scanning. Using brain MRI, the cerebrospinal fluid (CSF) system measurements, the presence and severity of periventricular white matter lesion and focal changes in the brain white matter were evaluated.

Results. Initially, patients with RH had a high incidence of the structural brain alterations: 43 (81%) patients with fine focal brain lesions, 43 (81%) patients with enlarged CSF spaces, and 48 (90%) patients with periventricular white matter lesions. After renal denervation, a significant hypotensive effect was noted. According to brain MRI, the number of patients without enlarged CSF spaces did not change significantly: 15 (25%) patients initially, and 12 (20%) patients a year later ($\chi^2 = 0.63$, p = 0.43 и $\chi^2 = 0.72$, p = 0.40). The incidence of periventricular white matter lesion did not significantly change one year after RDN; however, the incidence of fine focal brain lesions significantly decreased in 21 patients (81% to 60%, p = 0.02).

Conclusion. Thus, it has been revealed that patients with resistant hypertension are characterised by a high incidence of structural brain alterations based on MRI assessments. Bilateral renal denervation is followed by a significant decrease in the incidence of fine focal brain lesions, without a significant change in the cerebrospinal fluid volume one year after the procedure.

Keywords: MRI, brain, hypertension, renal denervation

Conflict of interest. The authors declare no conflict of interest. The study had no sponsorship.

For citation: Sukhareva A.E., Falkovskaya A.Yu., Usov V.Yu., Mordovin V.F., Manukyan M.A., Baev A.E., Solonskaya E.I., Zyubanova I.V., Maksimova A.S., Ryumshina N.I., Shelkovnikova T.A., Mochula O.V., Zavadovsky K.V. MRI in the assessment of cerebral injury and cerebroprotective effects of renal denervation in resistant hypertension. *Medical Visualization.* 2023. https://doi.org/10.24835/1607-0763-1224

Received: 22.06.2022. **Accepted for publication:** 19.12.2022. **Published online:** 28.06.2023.

Background

Hypertension is the most common disease among all cardiovascular diseases [1–3]. A protective compensatory response to increased blood pressure includes constriction of small arterioles, which prevents their rupture and equalises pulse pressure. Persistent as well as long-term transient blood pressure increase contributes to hypertrophy of the muscular walls of arterioles that results in vascular remodelling which involves increasing arterial wall thickness and decreasing lumen diameter [4]. The negative consequences of the narrowing of the cerebral arterioles lumen include a reduction in cerebral blood flow and the development of chronic cerebral ischaemia. The chronic deficiency of oxygen and nutrients induces degeneration in cerebral structures [5]. It has been recently reported that following the procedure of intravascular radiofrequency renal denervation, not only blood pressure (BP) decreases, which diminishes the damaging effect of haemodynamic load on target organs, but organ-protective effects are noted [6–9].

Histopathological studies showed that MRI-detected white matter lesions represent areas of ischaemia, gliosis, and silent infarcts, as well as areas of extracellular fluid accumulation in the brain tissue [10]. The limited anastomoses and collaterals that provide nutrition to the cortical and periventricular regions, as well as the basal ganglia of the white matter, will determine the vulnerability of these regions to haemodynamic changes that occur with a decrease in cerebral blood flow and fluctuations in systemic blood pressure.

Some case reports present the possible improvement of MR signs of structural brain alterations due to the drug therapy. It is also known that in a significant number of hypertensive patients, drug treatment is insufficient, and these patients particularly have the highest risk of cerebral complications. In recent years, endovascular methods of treatment have been successfully used to treat this group of patients, allowing to achieve a pronounced and long-lasting blood pressure reduction [11–17]. Experimental studies have revealed a fairly pronounced cerebroprotective effect of renal denervation (RDN), the pathogenesis of which is based on inhibition of the local activity of renin-angiotensin system and oxidative stress and reduction of the blood-brain barrier permeability. According to studies conducted by Japanese scientists, these effects in particular have determined the ability of RDN to prevent stroke and brain injury, as well as to increase the survival in stroke-prone spontaneously hypertensive rats [18].

However, it should be noted that the data on cerebroprotective effects of RDN available for the current date are sporadic and, as a rule, they are based on the results of experimental studies [19–21]. Clinical trials addressed to this problem are limited to the study which revealed a reduction of structural signs of hypertensive encephalopathy 6 months after renal denervation [22]. The obtained results are promising for further research in this regard, but have certain limitations, since longer-term outcomes of the intervention were not analysed in this study.

Therefore, **the purpose of this work** was to evaluate the protective effects related to the state of the brain based on MRI against the dynamic progressive decrease in blood pressure after renal denervation in patients with resistant hypertension.

Materials and Methods

The study was performed following the principles of Good Clinical Practice and the guidelines of the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee of the Cardiology Research Institute, Tomsk National Research Medical Centre. All study subjects signed an informed consent form prior to the study start. According to the legislation of the Russian Federation, all information is kept strictly confidential. In this prospective, single-centre, comparative study, all study subjects (n = 53) were diagnosed with resistant hypertension based on persistent high blood pressure readings with continuous use of three or more antihypertensive drugs, one of which is a diuretic. Patients were instructed not to change their combination of antihypertensive agents. All patients underwent transcatheter bilateral renal denervation, the average number of radiofrequency ablations applied to each side was 13 ± 1.8 applications. There were no undesirable side effects directly related to renal denervation in any of the patients treated with RDN. To assess the state of the brain as a target organ in hypertension, all patients underwent brain MRI at admission (before RDN), six months after RDN, and one year after the procedure. All patients were examined by a neurologist. There was no neurological deficit in the patients.

The study was performed using a high-field magnetic resonance tomograph with a field strength of 1.5 Tesla. Each patient underwent MRI in the axial, sagittal, and coronal projections, using T1, T2, T2 FLAIR, and DWI sequences. However, in our opinion, T1, T2, T2 FLAIR sequences are the most informative modes for achieving the stated objectives. To obtain T1- and T2-weighted images, a spin-echo pulse sequence was used. For T1-weighted images performed in the axial and sagittal planes, the following parameters were used: TR = 450 ms, TE = 15 ms, angle α = 70°. T2-weighted images were

Table 1. Dynamics of changes in blood pressure indicators after renal denervation

Parameters	At baseline	24 weeks after RDN n = 48	p	48 weeks after RDN n=41	p
Average 24h SBP, mm Hg	160.84 ± 19.38	147.92 ± 18.42	<0.01	145.00 ± 15.54	<0.01
Average 24h DBP, mm Hg	97.38 ± 15.50	89.02 ± 14.72	<0.01	86.78 ± 11.96	<0.01
Day-night SBP index, %	6.74 ± 6.75	5.84 ± 7.91	0.849	7.45 ± 7.28	0.304
Day-night DBP index, %	10.94 ± 7.87	10.20 ± 8.49	0.745	12.36 ± 8.75	0.237
SBP load, %	88.35 ± 13.40	70.08 ± 24.92	<0.01	68.72 ± 25.94	<0.01
DBP load, %	70.82 ± 27.56	54.82 ± 29.93	<0.01	49.91 ± 31.95	<0.01

Note. SBP – systolic blood pressure; DBP – diastolic blood pressure.

acquired with the following parameters: TR = 6,000 ms, TE = 117 ms and were taken in the axial plane. The slice thickness amounted to 4 mm. In all cases, the protocol for brain MRI was unchanged.

When analysing brain tomograms, the volume of CSF and the presence of dyscirculatory foci, lacunar infarcts, and periventricular white matter lesions were assessed.

Post-processing of images and measurements were carried out using eFilm Workstation v.3.4 (MergeHealthcare, 2010) and 3D Slicer v.4.9.0. The outline of the CSF spaces was automatic, according to the specified range of the MR signal intensity corresponding to the CSF, and, if necessary, an adjustment was made. After that, the volume (cm3) of all selected voxels was calculated. Fazekas visual scale was used to assess the severity and prevalence of periventricular white matter lesions.

Focal lesions of the white matter were defined as dotted areas no less than 3 mm, hyperintense on T2-weighted images and without a decrease in the MR signal intensity on T1-weighted images. The localisation of dyscirculatory foci was assessed in the following regions of the brain: I, the subcortical region (cerebellum, subcortical white matter, and cerebral cortex); II, the basal ganglia (basal ganglia, internal capsule, and thalamus); III, the brainstem (medulla oblongata, pons, and cerebral peduncles).

Statistical data analysis was performed using Statistica 10.0 software. In the statistical description of the study results for quantitative characteristics, the median and quartiles (Me (Q1; Q3) were calculated, as according to the Shapiro-Wilk test (W), the distribution in the samples is non-normal. Qualitative and ordinal variables are presented as absolute and relative frequencies [n (%)]. Comparison of characteristics in the before-after study was carried out using the following criteria: quantitative and ordinal variables – the Wilcoxon test (Z); qualitative variables – McNemar's Chi-square test (χ^2NM).

Differences were considered significant at a significance level (p) less than 0.05.

Results

The study included 53 patients with RH who underwent renal denervation. The mean age of the patients was 52.1 ± 9.1 years.

After RDN procedure, there was a significant decrease in blood pressure based on 24-hour blood pressure monitoring (Table 1).

Initially, patients with RH had a high incidence of the structural brain alterations: 43 (81%) patients with fine focal brain lesions, 43 (81%) patients with enlarged CSF spaces, and 48 (90%) patients with periventricular oedema, 10 (20%) patients with lacunar infarcts, 10 (20%) patients with acute cerebrovascular accident.

Enlarged CSF spaces were graded 0–II as follows: grade 0 – no disturbances; grade I – enlargement (increase in volume) of the lateral cerebral ventricles or external subarachnoid spaces; grade II – enlargement (increase in volume) of the lateral cerebral ventricles and external subarachnoid spaces.

When evaluating the state of the brain after RDN, the proportion of patients without enlarged CSF spaces did not change significantly: 25% initially, 20% a year later (χ^2 = 0.63 p = 0.43). The proportion of patients with grade I enlarged CSF spaces after 6 months insignificantly decreased from baseline 50% to 45% (χ^2 = 0.50, p = 0.49) and significantly increased after 12 months from 50% to 64% (χ^2 = 4.00, p = 0.046) due to lowering the proportion of patients without enlarged CSF spaces and patients with grade II enlarged CSF spaces to 16% (χ^2 = 1.56, p = 0.21) with baseline 25%. Changes pattern of the CSF spaces volume after radiofrequency denervation of the renal arteries is presented in Table 2.

The incidence of periventricular white matter lesions did not significantly change one year after the procedure as shown in Table 3.

However, the incidence of fine focal brain lesions significantly decreased (81 to 60%, p = 0.02).

The number and size of fine focal brain lesions significantly decreased one year following RDN (Table 4 and Figure 1).

Figure 2 shows a clinical example of a decrease in the number of fine focal brain lesions after RDN.

Table 2. Changes in the severity of cerebrospinal fluid dynamics according to the MRI of the brain after renal denervation, expressed in% of the number of participants

Severity of CSF disorders	Before RDN	6 months after RDN	p	12 months after RDN	p
No disorders	25	30	0.72	20 (60)	0.02
Grade I	50	45	0.22	64 (0)	0.25
Grade II	25	25	0.60	16 (5)	0.38

Table 3. Changes in the incidence of periventricular edema before renal denervation and 24, 48 weeks after the procedure

Grades of periventricular white matter lesion	Before RDN, %	Through (6 months) 24 weeks after RDN, %	p	Through 12 months (48 weeks) after RDN, %	p
0	10	7	0.31	4	0.08
1	50	50	1.00	48	0.78
2	20	25	0.40	28	0.19
3	20	18	0.71	20	0.72

Table 4. Changes in the incidence of fine focal brain injuries 48 weeks after the procedure

After RDN	n	p
0 – no changes	29	0,02
1 – increase in number or size of the foci	3	0,25
2 – decrease in number or size of the foci	21	0,38
Total number of subjects	53	

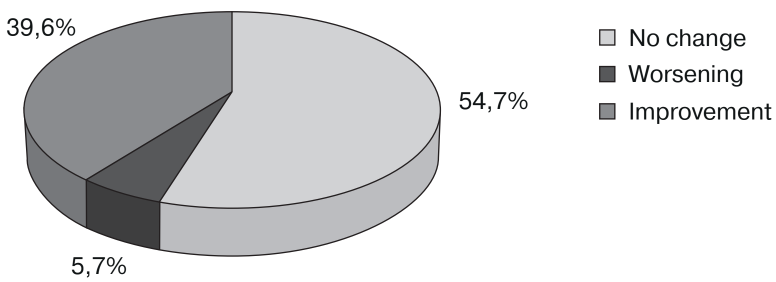

Fig. 1. Changes in the MRI pivture after the application of RFA.
An MRI-detected decrease in the number and/or size of foci was considered as an improvement. An MRI-detected increase in the number and/or size of foci was considered as a worsening. Under the improvement of the condition, an MRI picture was taken, in which a decrease in the number and / or size of foci was noted. Under the deterioration of the condition, an MRI picture was taken, in which an increase in the number and / or size of foci was noted.

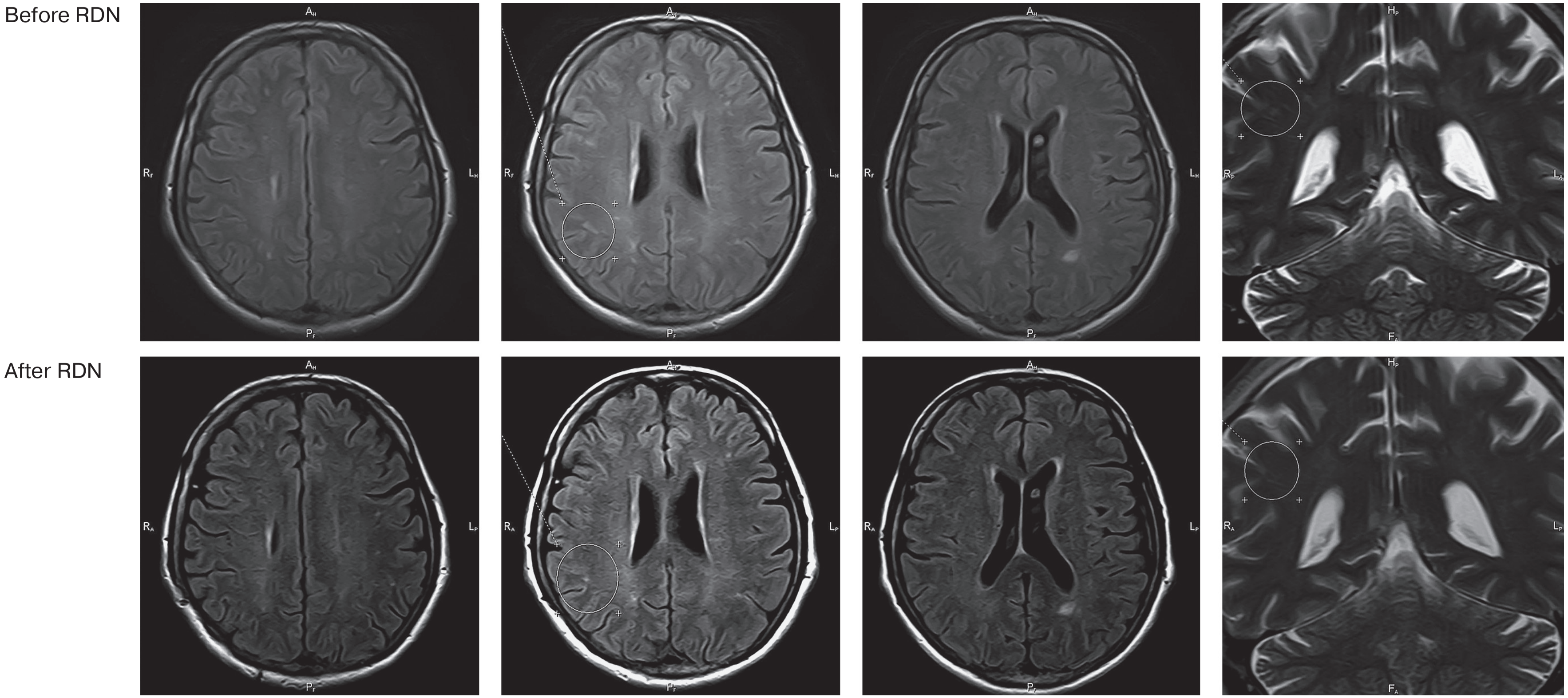

Fig. 2. Patient T., female, 55 years old, diagnosed with grade II resistant RH. Baseline 24-hour blood pressure was 148/77 mm Hg. MRI was performed using T2-FLAIR sequence in the axial plane and T2 sequence in the coronal plane. The top row shows the MRI scans obtained before the RDN. Focal changes due to dyscirculatory disorders are visualised in the semioval centre, the radiant crown, and the frontal and occipital forceps of the radiation of the corpus calossum.

The bottom row shows the tomography results obtained 48 weeks after RDN, accompanied by a decrease in 24-hour blood pressure by 21/10 mm Hg (up to the level of 127/67 mm Hg). One lesion localised in the occipital sections of the radiant crown has decreased in size. Indicated by a circle.

Results and discussion

Currently, all issues concerning the safety of RDN as a relatively studied invasive method for the treatment of resistant hypertension are settled, and the interests of most researchers have shifted to the efficacy of this procedure. It should be noted that a sufficient number of studies has proven its safety for the kidneys and renal blood flow [23], and five sham-controlled studies convincingly demonstrated the superiority of RDN in terms of lowering blood pressure to the sham procedure. But transferring RDN method into practice requires the accumulation of data on its efficacy and organ-protective effects.

When analysing the initial MRI image of the brain in patients with RH, we found that the vast majority of patients had fine focal lesions, enlarged CSF spaces and periventricular white matter lesions, which may reflect the representative MRI pattern of cerebral alterations. After RDN, there was no decrease in the incidence of periventricular white matter lesions and enlargement of CSF spaces, which may indicate the poor reversibility of these alterations. At the same time, the cerebroprotective effect of RDN manifested itself mainly as a decrease in incidence of fine focal lesions. In our opinion, this effect is better accounted for the potential dependence of these foci on the state of microcirculation. It is well-known, as blood pressure chronically increases, brain cells experience oxygen deprivation. Under anaerobic conditions, the cell seeks to fulfil the energy deficit by activating the processes of glycolysis. As a result, the production of lactate and carbon dioxide occurs, which in turn increases the permeability of the vascular wall. On MRI, these changes in the brain are presented as foci of enhancement on T2-weighted images due to the increased water content. With normalization of blood pressure and reduction of oxidative stress, the brain tissue oxygenation improves, which reduces the permeability of the vascular wall. Furthermore, the reduced sympathetic vasoconstriction and improved microcirculation may have additional value. On MRI images, it manifests itself as a decrease in the foci size of fine focal lesions or their disappearance on T2-weighted images.

The mechanisms of the cerebroprotective properties of renal denervation currently include a decrease in the local activity of the renin-angiotensin system and oxidative stress in the brain, suppression of damage to the blood-brain barrier, as well as reduction of brain inflammation. According to Japanese scientists, these effects in particular were associated with the ability of RDN to prevent stroke and brain injury, as well as to increase the survival in stroke-prone spontaneously hypertensive rats [24]. In another experimental work, rats with renovascular hypertension in the brain also demonstrated a decrease in oxidative stress following the renal denervation procedure [25]. Moreover, it is the reduction of cerebral oxidative stress that the authors attributed to the key mechanisms of the antihypertensive effect of renal denervation [26, 27].

The obvious value of this study is a relatively large number of patients after renal denervation and an assessment of alterations of brain MRI parameters after the procedure. There are very few studies addressed to this problem and given the rising global interest in new methods of treating hypertension (including invasive ones), it is these methods that need active accumulation of data on the safety and efficacy of the procedure. However, this study has a number of limitations: it is a single-arm, prospective, single-centre study with an assessment of the dynamics of changes before and after renal denervation without a sham control group. Therefore, the data obtained should be confirmed by further studies in comparison with the sham control group, as well as with pharmacotherapy.

Conclusions

According to the received data, patients with resistant hypertension are characterised by a high incidence of structural brain alterations based on MRI assessments. The representative MRI pattern of cerebral alterations in patients with RH includes the high incidence of periventricular white matter lesions, enlarged CSF spaces, and fine focal lesions. A year after bilateral renal denervation with a significant antihypertensive effect, there is a decrease in the incidence of fine focal brain lesions, without a significant change in the incidence of periventricular white matter lesions and enlarged CSF spaces.

The data obtained need to be confirmed in controlled and more numerous studies.

Authors' participation

Sukhareva A.E. – conceptualization, methodology, investigation–brain MRI scanning, formal analysis, literature review, writing–original draft.

Falkovskaya A.Yu. – conceptualization, methodology, investigation–clinical data selection & interaction with patients, literature review, formal analysis, writing–review & editing.

Mordovin V.F. – conceptualization, methodology, writing–review.

Usov V.Yu. – conceptualization, consultation regarding planning stage and study findings interpretation, writing–editing.

Manukyan M.A. – investigation–clinical data selection, interaction with patients, formal analysis.

Baev A.E. – investigation–renal denervation procedure.

Solonskaya E.I. – investigation, formal analysis.
Zyubanova I.V. – investigation, formal analysis.
Maksimova A.S. – formal analysis.
Ryumshina N.I. – formal analysis.
Shelkovnikova T.A. – formal analysis.
Mochula O.V. – literature review.
Zavadovsky K.V. – investigation–clinical and instrumental data acquisition; writing–review &editing.

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