

# Individualised renal artery denervation improves blood pressure control in Kazakhstani patients with resistant hypertension

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## Abstract

**Background:** The prevalence of hypertension in Kazakhstan is high, and the majority of patients are not adequately controlled. Treatment with renal artery denervation (RAD) could represent a useful therapeutic option for a subset of patients in Kazakhstan with resistant hypertension.

**Aim:** To assess the impact of RAD in a cohort of patients from Kazakhstan with resistant hypertension.

**Methods:** Between March 2012 and December 2013, 63 patients underwent RAD at our tertiary care centre. Eligibility criteria were office blood pressure more than 160 mm Hg systolic (SBP) or more than 90 mm Hg diastolic (DBP) despite being treated with three or more antihypertensive medications, including a diuretic. Ambulatory blood pressure was measured at baseline and at month 12, and monitoring also included impact on insulin resistance and renal function.

**Results:** There were significant decreases of  $25 \pm 24$  mm Hg for ambulatory SBP during the daytime and of  $26 \pm 23$  mm Hg for ambulatory SBP during the nighttime ( $p < 0.0001$ ). We observed significant decreases of  $12 \pm 14$  mm Hg for ambulatory daytime DBP and of  $11 \pm 14$  mm Hg in ambulatory nighttime DBP ( $p < 0.0001$ ). A decrease in creatinine clearance was observed from  $100.2 \pm 33.6$  mL/min at baseline to  $90.2 \pm 22.8$  mL/min at month 12 ( $p < 0.001$ ). Homeostasis model assessment-insulin resistance (HOMA-IR) decreased from  $3.0 \pm 4.6$  at baseline to  $2.5 \pm 3.7$  at 12 months ( $p = 0.007$ ).

**Conclusions:** In this population RAD resulted in statistically and clinically significant blood pressure reduction at 12 months with minimal adverse events.

**Key words:** renal artery denervation, resistant hypertension, Central Asia, Kazakhstan, insulin resistance

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## INTRODUCTION

Hypertension and its associated complications affect a large number of people around the world. Currently, 26% of the world population is estimated to have hypertension [1]. Kazakhstan is a multi-ethnic country with a population of 17 million Asians and Caucasians dispersed over 2.7 million km<sup>2</sup> (6.4 persons/km<sup>2</sup>). The true prevalence of hypertension in the general population is not known; however, a recent study estimated that up to 70% of individuals 50–75 years of age in the capital city meet the standard criteria for hypertension (systolic blood pressure [SBP]  $\geq 140$  mm Hg and/or diastolic blood pressure [DBP]  $\geq 90$  mm Hg) [2].

It is estimated that 91% of patients with hypertension in a recent study in Kazakhstan were aware of their condition and 77% took antihypertensive medications [2]. However, of the patients who were receiving treatment for hypertension, only 44% had achieved adequate control [2]. This highlights the relevance of this problem in Kazakhstan and the need to identify new treatment approaches.

There have been numerous investigations of the effect of renal artery denervation in a diversity of ethnic and geographic patient groups [3–8]. These studies have utilised various technical approaches and devices. The results of SYMPLICITY HTN-3 questioned the effectiveness of this

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therapy when generally applied [9]. However, the pathophysiology of hypertension may be different across ethnic groups, and there may be some groups that respond more favourably. To our knowledge, this is the first report of the results of renal artery denervation (RAD) in patients from Central Asia with resistant hypertension. In addition, an individualised protocol was used for ablation, which was different when compared to the methods used in SYMPLICITY HTN-3.

## METHODS

This was a prospective observational study of patients who underwent RAD from March 2012 to December 2013 at our centre, and the last date of follow up was December 2014. The aim of the study was to assess the efficacy and safety of an individualised approach to renal RAD in patients in Kazakhstan.

Patients are referred to our centre from local and regional hospitals and clinics after multiple attempts to lower blood pressure (BP) are unsuccessful (more than 160 mm Hg SBP or more than 90 mm Hg DBP). Patients are then reassessed at our centre and treated pharmacologically. If patients still remain resistant after one month, they are considered for RAD. To be eligible for this study cohort, patients must have had office BP more than 160 mm Hg systolic or more than 90 mm Hg diastolic despite being treated with three or more antihypertensive medications from different pharmacologic classes, including a diuretic. Patients must have been using the maximal tolerated doses with no changes for a minimum of two weeks before screening. For determination of baseline BP, three office measurements were performed at a single visit, with the patient in a sitting position, and an average was calculated. To be included in this study, patients must have been  $\geq 18$  years of age and informed consent been given. The study was reviewed and approved through a local ethics committee according to the principles in the Declaration of Helsinki.

Patients were excluded if there were secondary causes of hypertension (e.g. significant stenosis of the renal artery), renal insufficiency (glomerular filtration rate [GFR]  $< 45$  mL/min), pregnancy, type 1 diabetes, or bilateral femoral or iliac artery occlusion.

Ambulatory BP change from baseline to month 12 was the primary endpoint in our study. Other parameters included office BP, glucose levels during oral glucose tolerance test for patients with body mass index (BMI)  $> 30$  kg/m<sup>2</sup>, insulin in blood in type 2 diabetics, echocardiography, calculated insulin sensitivity (homeostasis model assessment-insulin resistance [HOMA-IR]), 24-h electrocardiogram, home BP measurements by patient, creatinine, and fasting blood glucose. During the period of study, antihypertensive dose changes were made in response to BP; however, medication substitutions were not permitted unless they were needed due to adverse drug reactions or intolerance. We measured ambulatory

blood pressure using a BPlab device, and measurements were taken three times per hour between 8 a.m. and 10 p.m., and twice per hour at night. Measurements were taken from the arm in which the BP was the highest. Patients were defined as responders if they had more than 10 mm Hg decrease in office SBP.

## Procedure

Patients were premedicated with IM diazepam. Local anaesthetic was administered and a 6-French sheath was introduced into the right femoral artery. Heparin 80 IU/kg was given as an intravenous bolus with a target activated clotting time  $> 250$  s. Angiography with a pigtail catheter was performed to visualise the renal arteries. A renal guiding catheter was used to deliver the ablation catheter (Symplcity, Ardian, Medtronic). Two operators performed the procedures.

Bilateral treatment of the renal arteries was performed where renal artery diameter was  $\geq 2.5$  mm. If the diameter of the renal artery was greater than 5 mm, six or more ablations were performed using an ablation catheter. Four or five ablations were performed if the renal artery was less than 4 or 5 mm in diameter [10]. Ablation was performed on all existing accessory arteries when the diameter was greater than 2.5 mm. Where there was non-significant stenosis of the renal artery, ablation was performed in the areas where there were no lesions. The range of temperatures of the tip of the catheter in the renal arteries was 46–65°C. Approximately 8 W of energy was used per treatment point. A series of 2-min energy deliveries were accomplished along each artery. Control angiography was used in each patient to exclude post-procedural complications.

## Statistical analysis

Descriptive analysis was performed by presenting the mean  $\pm$  standard deviation (SD) for continuous data and proportions for categorical data. Ambulatory BP was the primary outcome of interest and means at baseline and 12 months were compared using a two-sample t-test. Statistical analyses were performed using SPSS Statistics version 22.

## RESULTS

A total of 63 patients met eligibility criteria and underwent RAD. The majority of these patients had Kazakh ethnicity (67%). Ninety-two per cent of patients were overweight ( $\geq 25$  kg/m<sup>2</sup>), and two-thirds of patients were obese ( $\geq 30$  kg/m<sup>2</sup>). The median number of antihypertensives was four, and the most common diuretic used was spironolactone. The baseline characteristics are listed in Table 1.

Results for the primary efficacy endpoint (change in ambulatory BP after one year) are presented in Figure 1 and are based on data for 92% of patients. There were statistically significant decreases in SBP and DBP over 12 months for both nighttime and daytime measurements ( $p < 0.0001$ ). There

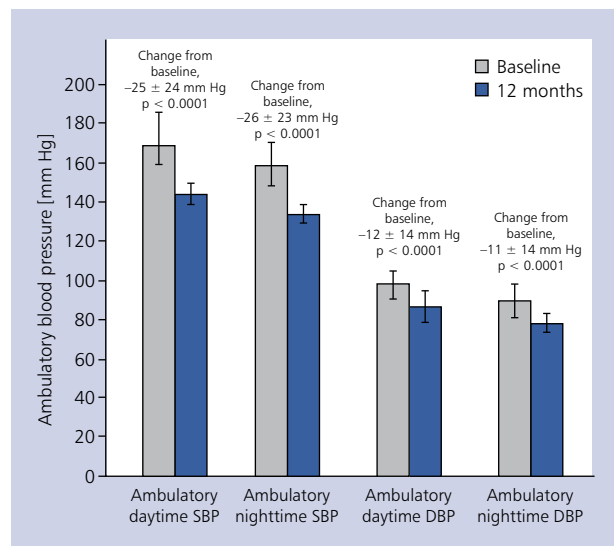
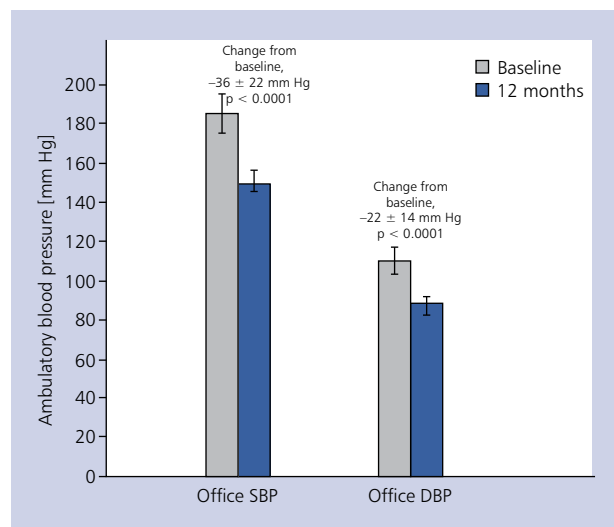
**Table 1.** Baseline characteristics of patients receiving renal artery denervation

Total number of patients	63
Age [years]	54.4 ± 9.4 (33–72)
Gender, male	35 (56%)
Ethnicity:	
Kazakh	42 (67%)
European	21 (33%)
Body mass index [kg/m <sup>2</sup> ]	30.8 ± 4.4
Medical history:	
Family history of hypertension*	29 (46%)
Coronary artery disease	9 (14%)
Hypercholesterolemia*	16 (26%)
Prior stroke	18 (29%)
Diabetes mellitus type 2	20 (32%)
Insulin resistance	6 (9%)
Estimated GFR [mL/min]	100.2 ± 33.6 (41–165)**
Oral glucose tolerance test [mmol/L]†	6.8 ± 2.5
Fasting blood glucose [mmol/L]	6.2 ± 2.3
HOMA-IR	3.0 ± 4.6
Office SBP [mm Hg]	186 ± 21
Office DBP [mm Hg]	111 ± 14
Ambulatory SBP daytime [mm Hg]	168 ± 22
Ambulatory DBP daytime [mm Hg]	98 ± 15
Ambulatory SBP nighttime [mm Hg]	159 ± 22
Ambulatory DBP nighttime [mm Hg]	89 ± 16
Median number of antihypertensive medications (interquartile range)	4 (4–5)
Non-significant stenosis	12 (19%)
Accessory renal artery present	7 (11%)

Data are presented as number (percentage) or mean ± standard deviation; DBP — diastolic blood pressure; GFR — glomerular filtration rate; HOMA-IR — homeostasis model assessment-insulin resistance; SBP — systolic blood pressure; \*In patients where these data were available; \*\*Three patients were included who had significant risk factors and GFR between 41 and 45 mL/min/m<sup>2</sup> (e.g. history of multiple stroke: n = 2; stage III arterial hypertension: n = 3); †Performed in patients with body mass index ≥ 30 kg/m<sup>2</sup> (n = 40)

was a decrease of 25 ± 24 mm Hg for ambulatory SBP during the daytime and a decrease of 26 ± 24 mm Hg for ambulatory SBP during the nighttime. Similarly, we observed a decrease of 12 ± 14 mm Hg for ambulatory DBP daytime and a decrease in ambulatory DBP nighttime of 12 ± 14 mm Hg.

Decreases in office BP were also observed, and the results were more marked than in ambulatory BP changes. There was a decrease of 36 ± 22 mm Hg in office SBP and a decrease of 22 ± 14 mm Hg in office DBP measurements (Fig. 2).

**Figure 1.** Ambulatory blood pressure at baseline and 12 months, by daytime and nighttime; DBP — diastolic blood pressure; SBP — systolic blood pressure**Figure 2.** Office blood pressure at baseline and 12 months; DBP — diastolic blood pressure; SBP — systolic blood pressure

Non-significant spasm of the renal artery was observed after the procedure in 11 (17%) patients. Most patients reported experiencing mild pain after the procedure. One patient experienced a mild haematoma at the access site area after the procedure. There were no significant procedure-related complications in any of the patients. Mean creatinine ± SD rose from 90.7 ± 38.4 mmol/L at baseline to 100.0 ± 43.3 mmol/L at 12 months (p = 0.051). There was a corresponding decrease in creatinine clearance from 100.2 ± 33.6 mL/min to 90.2 ± 22.8 mL/min (p < 0.001).

**Table 2.** Systolic (SBP) and diastolic (DBP) office blood pressure, by ethnicity

Ethnic Group	Office SBP [mm Hg]		Office DBP [mm Hg]	
	Baseline	12 months	Baseline	12 months
European (n = 19)	184 ± 19	151 ± 10	108 ± 13	88 ± 8
Kazakh (n = 39)	187 ± 21	150 ± 14	111 ± 14	89 ± 8

Note: data in this table are based upon patients who had complete data available. Data are presented as mean ± standard deviation

Twenty (32%) patients had type 2 diabetes mellitus and all patients had adequate control of blood sugar throughout the 12-month observation period. Six patients had a positive oral glucose tolerance test (OGTT) at baseline. There was no statistically significant change in mean OGTT between baseline and month 12 ( $6.7 \pm 2.5$  vs.  $6.1 \pm 1.9$ ;  $p = 0.25$ ). The insulin sensitivity as measured by HOMA-IR decreased from a mean ± SD —  $3.0 \pm 4.6$  at baseline to  $2.5 \pm 3.7$  at 12 months ( $p = 0.007$ ).

A reduction in 24-h pulse pressure was observed between baseline and 12 months ( $71.2 \pm 16.0$  vs.  $51.9 \pm 9.6$ ;  $p < 0.0001$ ). The median number of antihypertensive medications decreased from four at baseline to three at month 12. In a post-hoc subgroup analysis, patients were defined as responders if they had more than 10 mm Hg decrease in office SBP. Based on this definition, eight (13%) patients were non-responders after one year. We observed a decrease in the median number of antihypertensive medications from four to three in non-responders and from five to three in responders.

Post-hoc subgroup analyses were performed for office BP by ethnic group (Table 2). We observed similar mean decreases from baseline for the Kazakh patients compared to the European patients in systolic and diastolic office blood pressure measurements.

## DISCUSSION

The SYMPLICITY HTN-1 trial stimulated scientific interest in RAD, and subsequent studies sought to test the hypotheses generated by the earlier trials [5, 11]. Uncontrolled and controlled studies that followed, including SYMPLICITY HTN-2 and studies performed in Norway, the Czech Republic, and Poland, suggested that renal artery denervation may result in significant BP lowering in resistant patients, but the results were not uniformly positive [12–17]. In the wake of the findings of the SYMPLICITY HTN-3 study there has been much written attempting to explain the lack of efficacy of RAD [9, 18]. In addition to the possibility that renal denervation does not work, hypotheses have been put forward suggesting various factors that could influence the effectiveness of this procedure [18, 19]. These have included operator experience, identification of an appropriate patient population, type of catheter used for the procedure, accessory artery ablation, ablation of arteries with non-significant stenosis, and degree of ablation. The majority of the patients in our study

were Kazakh, and to our knowledge this is the first report of RAD in this Asian ethnic group.

A strength of our study is that prior to enrolling patients, each operator (MA, AG) had experience performing the procedure at least 20 times. During the study, the two operators performed approximately the same number of procedures. Ambulatory BP measurements were done for all patients, which should have minimised the white coat phenomenon. In addition, we sought to estimate the impact of RAD on daytime and nocturnal BP separately. The reason for this was so that we could observe the balance of sympathetic and parasympathetic activity and also because nighttime BP has been shown to be a stronger predictor of adverse cardiovascular events [20, 21]. The criteria we used to determine the number of ablations resulted in a higher number of ablation points compared to some recent studies [22–24]. Our approach of treating accessory arteries and arteries with non-significant stenosis may have increased the likelihood of achieving more effective ablation.

More than half of our patients had obesity ( $BMI > 30 \text{ kg/m}^2$ ). OGTT in obese patients was performed, but we did not observe any change in OGTT results. This is in contrast to other studies that have shown a decrease in oral glucose tolerance after RAD [25]. There are unresolved questions regarding the impact of RAD on kidney function. We observed an increase in creatinine and a decrease in mean estimated GFR over one year. A mono-electrode was used for all procedures and at least five ablations were administered. This required us to use more contrast dye compared with a multi-electrode device. This is one possible explanation for the observed decrease in renal function.

Several post-hoc analyses of the data were performed based on patient response status. We were interested to learn whether the response status was impacted by the number of antihypertensive medications. We observed a similar trend in both the responder group and the non-responder group, with both groups showing a decrease in median number of antihypertensive medications from baseline to one year. Therefore, the decrease observed in BP is probably not due to a change in the antihypertensive agents. A post-hoc analysis of BP changes by ethnic group found similar decreases in SBP and DBP in Europeans compared to Kazakhs (Table 2). However, we do not consider the results of this analysis as definitive because the subgroups were small, and it is difficult to clearly identify

ethnicity because of the multi-ethnic background of many Central Asian patients.

We observed statistically significant and clinically meaningful reductions in ambulatory and office BP measurements one year after the procedure was performed. Our observations are consistent with some of the other non-controlled studies that have been performed [6, 8]. A recent analysis of the Global SYMPPLICITY Registry in South Korea suggested that some Asian populations may have a greater response to RAD, compared to Caucasian patients [26]. The effect size we observed in BP reduction was similar to that observed in the Asian patients in their study. However, further clinical research using rigorous trial design are required in order to understand whether renal denervation has any role in the treatment of resistant hypertension [27]. There is a need for future research with newly designed devices because these may improve the efficacy of renal denervation [28].

### Limitations of the study

Our study has some limitations. The most important one is that there was no control group, and therefore placebo effect cannot be ruled out and adjustments for regression to the mean cannot be performed. Secondly, it is not known if there were any changes in compliance to antihypertensive medication or lifestyle (e.g. diet or exercise, smoking habits) during the follow-up, which could have impacted the results after one year. Thirdly, we attempted to perform Doppler of the renal arteries the day following the procedure, but some of the images were not interpretable because of the high rate of obesity in our patient group.

### CONCLUSIONS

This is the first report on RAD in Kazakhstani patients with resistant hypertension. We observed statistically and clinically meaningful decreases in BP over a one-year period in this population, with minimal adverse effects. Ablation of accessory renal arteries and arteries with non-significant stenosis may be important for mediating BP reductions when using RAD.

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**Conflict of interest:** none declared

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Zachęcamy wszystkich zainteresowanych miażdżycą, hipercholesterolemią, leczeniem dyslipidemii do uczestnictwa w tym wydarzeniu. Nad znakomitym programem merytorycznym kongresu czuwają sławy europejskiej lipidologii — profesorowie: Alberico Catapano, Michal Vrablik, Jan Boren.



Więcej informacji — pod adresem: [www.eas2017.com](http://www.eas2017.com) lub u Ambasadora 85. Kongresu EAS w Polsce — prof. dra hab. n. med. Krzysztofa J. Filipiaka, Redaktora Naczelnego „Kardiologii Polskiej”

# Poprawa kontroli ciśnienia tętniczego po denerwacji tętnic nerkowych u chorych z nadciśnieniem tętniczym opornym zamieszkałych w Kazachstanie

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## Streszczenie

**Wstęp:** Częstość występowania nadciśnienia tętniczego w Kazachstanie jest wysoka, a u większości chorych kontrola ciśnienia tętniczego jest niewystarczająca. Denerwacja tętnic nerkowych może być przydatną metodą leczenia u chorych z nadciśnieniem tętniczym opornym.

**Cel:** Badanie przeprowadzono w celu oceny wpływu denerwacji tętnic nerkowych w grupie chorych z nadciśnieniem tętniczym opornym zamieszkałych w Kazachstanie.

**Metody:** W okresie od marca 2012 r. do grudnia 2013 r. w ośrodku medycznym trzeciego stopnia referencyjności u 63 chorych wykonano zabieg denerwacji tętnic nerkowych. Kryteria włączenia obejmowały wynik gabinetowego pomiaru ciśnienia tętniczego wynoszący ponad 160 mm Hg dla ciśnienia skurczowego lub ponad 90 mm Hg dla ciśnienia rozkurczowego, mimo stosowania 3 lub więcej leków przeciwnadciśnieniowych, w tym diuretyku. Całodobowy automatyczny pomiar ciśnienia tętniczego wykonano na początku badania i po 12 miesiącach. Monitorowano także wpływ na insulinooporność oraz czynność nerek.

**Wyniki:** Całodobowy pomiar ciśnienia tętniczego wykazał istotne obniżenie dziennych ( $o 25 \pm 24$  mm Hg) i nocnych ( $o 26 \pm 23$  mm Hg) wartości ciśnienia skurczowego ( $p < 0,0001$ ). Stwierdzono również istotne obniżenie dziennych ( $o 12 \pm 14$  mm Hg) i nocnych ( $o 11 \pm 14$  mm Hg) wartości ciśnienia rozkurczowego ( $p < 0,0001$ ). Zaobserwowano zmniejszenie klirensu kreatyniny — ze  $100,2 \pm 33,6$  ml/min na początku badania do  $90,2 \pm 22,8$  ml/min po 12 miesiącach ( $p < 0,001$ ). Insulinooporność oceniona za pomocą modelu homeostazy (wskaźnik HOMA-IR) zmniejszyła się z  $3,0 \pm 4,6$  na początku badania do  $2,5 \pm 3,7$  po 12 miesiącach ( $p = 0,007$ ).

**Wnioski:** W badanej populacji denerwacja tętnic nerkowych spowodowała statystycznie i klinicznie istotne obniżenie ciśnienia tętniczego w okresie 12 miesięcy przy znikomej liczbie zdarzeń niepożądanych.

**Słowa kluczowe:** denerwacja tętnic nerkowych, nadciśnienie tętnicze oporne, Azja Środkowa, Kazachstan, insulinooporność  
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