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Long-term effects of radiofrequency-based renal denervation on blood pressure and renal function by degree of renal dysfunction

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Arterial hypertension is highly prevalent in patients with chronic kidney disease (CKD)[1]. Sustained high blood pressure (BP) accelerates kidney function decline, which in turn makes hypertension difficult to treat, and renal sympathetic signalling may negatively impact kidney function and BP[1]. Renal denervation (RDN) aims to disrupt this circuit with beneficial effects on BP control and, theoretically, kidney function. Despite the strong rationale for RDN use in patients with CKD, these subjects are frequently excluded from randomised controlled trials, and the European Society of Cardiology (ESC) guidelines contraindicate RDN if the estimated glomerular filtration rate (eGFR) is below 40 mL/min/1.73 m[1,2]. As early RDN adopters, we collected data to explore the medium- to long-term effects of this therapy on BP and kidney function in subjects with various degrees of CKD.

Patients with resistant and/or uncontrolled hypertension were screened for RDN, as approved by the local institutional review board. Eligibility and enrolment were assessed by the dedicated multidisciplinary team as described previously[2]. Clinical evaluation, blood and urine tests, and abdominal imaging ruled out secondary hypertension, and preliminary medical therapy optimisation was conducted. Resistant hypertension was defined as office blood pressure (OBP) >140/90 mmHg despite at least three antihypertensive drugs, including a diuretic, at the maximum tolerated dose[1,2]. Uncontrolled hypertension was defined as BP over the target without the possibility of further therapy implementation. Ambulatory blood pressure monitoring (ABPM) for 24 hours ruled out white coat hypertension[1,2]. Kidney function was assessed through serum creatinine and eGFR (CKD Epidemiology Collaboration [CKD-EPI] equation)[3,4]. CKD was defined as an eGFR ≤60 mL/min/1.73 m[2,4]. RDN procedures were performed by trained interventional cardiologists with radiofrequency (RF) devices (unipolar Symplicity Flex catheter, later replaced by the quadripolar Spyral catheter [both Medtronic]). Ablations were bilaterally delivered, both in the main renal arteries and in suitable branches with diameters between 3 mm and 8 mm, according to the protocol[2]. High-flow hydration was provided to all patients 24 hours before and after the procedure. Contrast-induced acute kidney injury (CI-AKI) was defined by an absolute creatinine increase of >0.3 mg/dL within the 48 hours post-procedure[2].

The primary endpoints explored procedural safety and BP reduction. A) Safety: absence of major vascular complications (renal artery perforation or dissection, embolic events, major bleeding, kidney failure, stroke, myocardial infarction, any cause of death) within one month. B) BP reduction: assessed through ABPM and OBP at 12, 24, and 36 months. The secondary endpoints were kidney function in the long term and changes in antihypertensive medications.

Continuous variables are presented as mean and standard deviation (SD) and compared using paired t-tests. Categorical data are expressed as numbers and percentages, and were compared using the chi-square test.

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We included 100 patients (75% males) between 2013 and 2023. Of them, 22 patients had stage 1 CKD, 26 stage 2, 19 stage 3a, 14 stage 3b, 7 stage 4, and 12 stage 5 under renal replacement therapy (RRT)[4]. Baseline characteristics are shown in **Supplementary Table 1**.

Five patients developed CI-AKI, with subsequent recovery. Three patients developed a femoral pseudoaneurysm requiring embolisation. The eGFR showed a non-significant decrease at three years, regardless of the stage of CKD (p>0.05) **(Figure 1)**. The mean (SD) annual decline in eGFR was 1.12 (0.28) mL/min/1.73 m². Patients under RRT were excluded from the eGFR trend analysis.

A significant and sustained (up to three years) reduction of BP values was observed in all classes of CKD (p<0.05). Importantly, BP improvement allowed six patients on RRT to successfully undergo kidney transplant. Two CKD stage 4 patients (eGFR 23 mL/min/1.73 m² and 29 mL/min/1.73 m², BP reductions of 10 mmHg and 28 mmHg at 3 years) required RRT approximately two years after RDN, without AKI occurrence at the time of RDN. Similar trends in BP reduction were observed in males and females. The number of antihypertensive medications per day tended to decrease after RDN, confirming that the effect of RDN does not depend on a heavier drug burden **(Supplementary Table 2, Supplementary Table 3, Supplementary Figure 1)**.

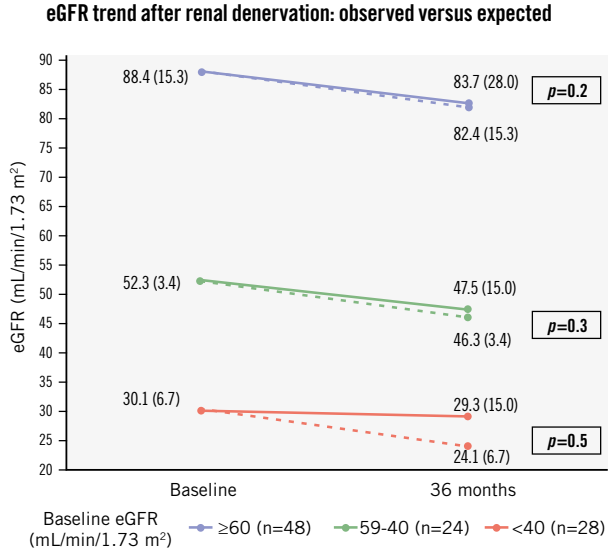

Figure 1. *Trend of kidney function after renal denervation at three years of follow-up. Values of eGFR are expressed as mean (SD). The continuous lines represent the mean (SD) observed eGFR at follow-up, for each group we considered (eGFR ≥60, 59-40, <40 mL/min/1.73 m²). Dashed lines represent the expected mean (SD) eGFR, considering an estimated physiological mean reduction of 2 mL/min/1.73 m²/year for patients with hypertensive nephropathy. The observed mild eGFR decline was lower than expected in each subgroup. Even though statistically non-significant (p>0.05), this may suggest a possible slowing-down effect on the progression of kidney dysfunction, related to a reduction of blood pressure values and a decrease in the excessive adrenergic activation that typically characterise patients with CKD. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate SD: standard deviation*

This study adds reassuring data to the clinically relevant and frequently debated question regarding RDN therapy in patients with reduced GFR. Our main findings are as follows: 1) RF-RDN is safe and effective in selected hypertensive patients regardless of the presence and degree of kidney dysfunction. 2) RDN may slow down kidney function decline over time, which can prove especially beneficial among patients with established CKD. 3) Despite the lack of a control arm, the observed eGFR decline at 3 years was lower than expected (2 mL/min/1.73 m²/year). Randomised studies should be considered to assess whether blood pressure lowering with RDN can be renoprotective in low-GFR hypertensive subjects. Our data aligned with the Global Simplicity Registry[5].

We acknowledge several limitations: the data are derived from a single-centre experience; detailed follow-up data for medical therapies are not available for all patients; and data on other parameters, such as cystatin-c or albuminuria and urine albumin/creatinine ratio, were available only in a minority of subjects and were not considered.

In conclusion, RF-RDN can be safe and effective in selected patients with CKD, with long-term benefits that extend beyond BP reduction. A slowing down of kidney function decline in any degree of pre-existing kidney disease emerged from our experience. If larger studies support our findings, guidelines should reconsider the restrictions on performing RDN in patients with CKD.

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Conflict of interest statement

F. Ribichini declares consulting fees and payments of honoraria from Medtronic. G. Gambaro declares payment of honoraria from Medtronic. The other authors have no relevant conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Baseline characteristics of patients undergoing renal denervation.

Supplementary Table 2. Blood pressure trend after renal denervation, assessed by means of ambulatory blood pressure measurements.

Supplementary Table 3. Office blood pressure trend at follow-up in males and females with baseline eGFR ≥40 and <40 mL/min/1.73 m^2.

Supplementary Figure 1. Drug burden (number of antihypertensive medications/day) at baseline and at three years of follow-up in all RDN patients.

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Supplementary data

Supplementary Table 1. Baseline characteristics of patients undergoing renal denervation.

	Total n=100	**eGFR ≥60 mL/min/1.73m^2 n=48**	**eGFR 40-59 mL/min/1.73m^2 n=24**	**eGFR <40 mL/min/1.73m^2 n=28**	***p* value**
Age (years)	60.4±14.0	59.8±12.7	64.5±14.0	59.8±15.8	0.1
Male sex	75 (75)	32 (66.6)	17 (70.8)	26 (92.8)	**0.03**
BMI (kg/m^2)	29.4±5.4	29.4±5.7	30.3±5.1	28.8±5.3	0.08
Cardiovascular risk factors					
Hypertension	100 (100)	48 (100)	24 (100)	28 (100)	1
Diabetes mellitus	44 (44)	14 (29.1)	13 (54.1)	17 (60.7)	**0.01**
Smoking	13 (13)	7 (14.5)	5 (20.8)	1 (3.5)	0.1
Dyslipidaemia	67 (67)	36 (75)	13 (54.1)	18 (64.2)	0.1
Past medical history					
CAD	31 (31)	16 (33.3)	8 (33.3)	7 (25)	0.7
Previous TIA/stroke	13 (13)	4 (8.3)	6 (12.5)	3 (10.7)	0.1
PAD	33 (33)	11 (22.9)	9 (37.5)	13 (46.4)	0.09
COPD	15 (15)	9 (18.7)	1 (4.1)	5 (17.8)	0.23
OSAS	10 (10)	6 (12.5)	2 (8.3)	2 (7.1)	0.7
Baseline kidney function					
Creatinine (mg/dL)	2.4±3.4	0.87±0.16	1.42±0.28	5.23±4.62	**<0.01**
eGFR (mL/min/1.73m^2)	61.0±31.9	81.9±15.1	51.5±4.9	20.8±12.8	**<0.01**
Baseline blood pressure					
Systolic 24-h ABPM (mmHg)	156.4±18.4	155.2±18.2	157.0±22.7	158.1±14.3	0.1
Diastolic 24-h ABPM (mmHg)	84.8±13.2	83.0±13.4	82.1±12.6	86.1± 14.8	0.3
Systolic OBP (mmHg)	152.1±23.9	151.0±20.8	149.7±30.4	156.3±22.6	0.3
Diastolic OBP (mmHg)	80.4±11.6	80.6±11.0	74.8±9.8	85.0±14.1	**0.02**
Antihypertensive medications					
N. medications/day	4.9±1.1	4.6±1.2	5.1±1.1	5.2±1.2	**0.01**
Procedural details					
Contrast medium amount (mL)	70.6±17.0	71.5±20.1	89.0±44.6	71.8±26.1	**<0.01**
Unipolar Symplicity Flex™ catheter	7 (7)	0 (0)	2 (8.3)	5 (17.8)	**0.01**
Quadripolar Symplicity Spyral™ catheter	93 (93)	48 (100)	22 (91.6)	23 (82.2)	**0.01**
Total number of ablations	39.4±11.1	38.1±8.7	37.0±11.1	34.7±11.5	0.19
Major complications	0 (0)	0 (0)	0 (0)	0 (0)	-
Minor complications	4 (4)	1 (2)	0 (0)	3 (10.7)	0.09
CI-AKI	3 (3)	0 (0)	1 (4.1)	2 (7.1)	0.19

Continuous variables are expressed as mean±SD; categorical variables are expressed as n (%).

ABPM: ambulatory blood pressure measurements; BMI: body mass index; CAD: coronary artery disease; CI-AKI: contrast-induced acute kidney injury; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LV: left ventricle; OBP: office blood pressure; OSAS: obstructive sleep apnea syndrome; PAD: peripheral artery disease; TIA: transient ischemic attack.

Supplementary Table 2. Blood pressure trend after renal denervation, assessed by means of ambulatory blood pressure measurements.

BP values refer to the 24-hours mean (SD) systolic and diastolic values.

ABPM - All patients							
	Baseline n=100	**12 months n=65**	***p* value**	**24 months n=43**	***p* value**	**36 months n=27**	***p* value**
SBP (mmHg)	155.8±17.7	139.1±15.6	**0.007**	143.3±18.5	**0.01**	140.5±16.2	**0.01**
Δ		-16.4±20.7		-11.4±19.6		-22.2±22.3	
DBP (mmHg)	84.8±13.3	77.7±11.5	**0.004**	78.7±11.3	**0.02**	76.9±9.9	**0.005**
Δ		-6.9±14.3		-5.6±13.5		-7.8±13.4	

ABPM: ambulatory blood pressure measurements; DBP: diastolic blood pressure; SBP: systolic blood pressure.

ABPM - eGFR≥60 ml/min/1.73 m^2							
	Baseline n=37	**12 months n=36**	***p* value**	**24 months n=18**	***p* value**	**36 months n=12**	***p* value**
SBP (mmHg)	155.2±18.3	138.4±20.0	**0.005**	134.8±25.2	**0.01**	137.8±17.0	**0.01**
Δ		-16.9±20.7		-15.4±23.9		-20.7±22.1	
DBP (mmHg)	83.0±13.5	78.8±15.2	**0.029**	78.4±10.9	**0.003**	72.8±7.7	**0.007**
Δ		-4.2±11.6		-6.4±7.9		-9.6±10.2	

ABPM: ambulatory blood pressure measurements; DBP: diastolic blood pressure; SBP: systolic blood pressure.

ABPM - eGFR 59-40 ml/min/1.73 m^2							
	Baseline n=24	**12 months n=20**	***p* value**	**24 months n=14**	***p* value**	**36 months n=7**	***p* value**
SBP (mmHg)	157.0±22.7	147.5±13.6	0.1	147.9±17.4	0.08	140.8±15.5	**0.03**
Δ		-9.5±5.5		-9.1±6.6		-16.2±7.5	
DBP (mmHg)	82.2±12.7	78.3±12.1	0.1	76.3±10.5	**0.02**	71.8±10.7	**0.04**
Δ		-3.4±3.7		-5.9±4.1		-10.4±4.8	

ABPM: ambulatory blood pressure measurements; DBP: diastolic blood pressure; SBP: systolic blood pressure.

ABPM - eGFR <40 ml/min/1.73 m^2							
	Baseline n=28	**12 months n=16**	***p* value**	**24 months n=13**	***p* value**	**36 months n=9**	***p* value**
SBP (mmHg)	158.2±14.3	141.3 ±18.1	**0.007**	140.9±14.8	**0.002**	142.3±13.3	**0.03**
Δ		-16.2±24.2		-16.3±19.2		-13.6±10.0	

DBP (mmHg)	86.2± 14.9	80.3 ± 11.8	**0.03**	81.4± 13.1	**0.049**	80.2± 11.5	**0.01**
Δ		-5.8±12.3		-4.7±10.9		-6.0±11.0	

ABPM: ambulatory blood pressure measurements; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Supplementary Table 3. Office blood pressure trend at follow-up in males and females with baseline eGFR ≥40 and <40 mL/min/1.73 m^2.

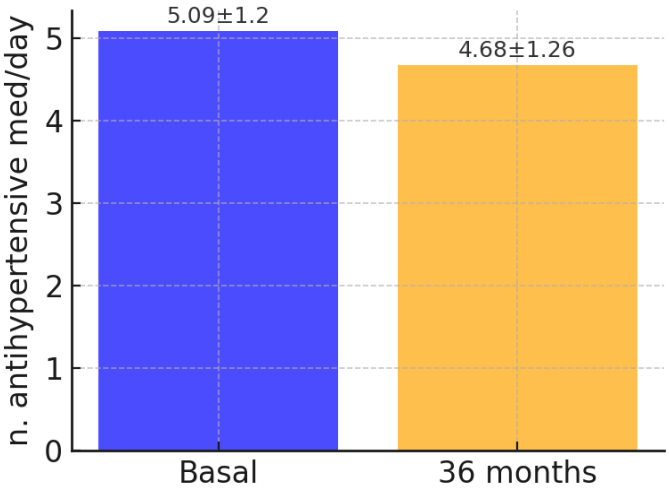
Male population was more represented than females in our cohort of patients (75%). Analysis was based on the comparison of OBP measurements at baseline and at 24 months after renal denervation, and on a dichotomic classification between patients with baseline eGFR≥40 and <40 ml/min/1.73 m^2 to augment the statistical significance, since the relative lack of data at follow-up.

	Men – eGFR ≥ 40 ml/min/1.73 m^2			**Women – eGFR ≥ 40 ml/min/1.73 m^2**		
OBP	**Baseline n=47**	**36 months n=12**	***p* value**	**Baseline n=19**	**36 months n=7**	***p* value**
SBP (mmHg)	153.4±18.2	137.1±13.4	**0.007**	155.3±23.6	132.2±16.1	**0.03**
Δ		-16.3±19.4			-23.1±18.2	
DBP (mmHg)	84.2±10.7	78.6±8.2	**0.03**	77.8±11.2	69.3±8.2	**0.01**
Δ		-5.6±9.7			-8.5±10.9	

DBP: Diastolic Blood pressure; eGFR: Estimated Glomerular Filtration Rate; OBP: Office Blood Pressure; SBP: Systolic Blood Pressure.

	Men – eGFR < 40 ml/min/1.73 m^2			**Women – eGFR < 40 ml/min/1.73 m^2**		
OBP	**Baseline n=28**	**24 months n=11**	***p* value**	**Baseline n=6**	**24 months n=4**	***p* value**
SBP (mmHg)	159.2±13.4	140.4±16.0	**0.02**	173.5±9.4	145.5± 8.5	**0.02**
Δ		-18.8±21.9			-24.0±1.0	
DBP (mmHg)	89.9±17.4	81.7±13.4	0.1	92.2±17.3	69.5±5.5	0.09
Δ		-8.2±16.2			-7.0±1.0	

DBP: Diastolic Blood pressure; eGFR: Estimated Glomerular Filtration Rate; OBP: Office Blood Pressure; SBP: Systolic Blood Pressure.



Supplementary Figure 1. Drug burden (number of antihypertensive medications/day) at baseline and at three years of follow-up in all RDN patients.

Although not statistically significant (p=0.4), the trend towards a reduction of medical therapy suggests that the observed pressure reduction after RDN is not related to drug changes.