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Article

Renal Denervation May Benefit Aldosteronism-Related Hypertension – A Single-Center Experience

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Abstract:

Background: Renal denervation (RDN) could lower blood pressure (BP) in patients with essential hypertension. The use of an aldosterone antagonist was an independent predictor for RDN response in post-hoc analysis. This study aimed at observing the hypothesis that RDN might response more in patients with undiagnosed aldosteronism.

Method: This single-center, retrospective study enrolled the patients who underwent RDN for uncontrolled hypertension. The patients with suspected aldosteronism were identified by any following conditions prior to RDN: 1) >30 of aldosterone-renin ratio, 2) >10 mmHg of systolic BP reduction after aldosterone inhibition, or 3) slow flow on the renal angiogram. The definition of RDN responder was a patient who met either 6 mmHg of reduction in 24-hour systolic BP or 1 class of antihypertensive drug withdraw.

Result: A total of 18 patients were enrolled: 10 (55%) patients are identified as hyperaldosteronism. The baseline 24-hour systolic BP (135 ± 11.1 mm Hg vs. 143 .6 ± 19.4 mm Hg, p = 0.320) was comparable. At 3 months, the mean change in 24-hour systolic BP was numerically greater in hyperaldosteronism group (-3.4 ± 11 mm Hg vs. -11.1 ±17.1 mm Hg, p = 0.398). The proportion of RDN responder was significantly higher in this patient group [4 (50%) vs. 10 (100%), p = 0.023] at 6 months.

Conclusion: RDN was more effective in patients with suspected aldosteronism. Our findings may help to identify candidates who would benefit more in future studies.

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1. Introduction

Several prospective randomized sham-controlled trials have demonstrated that percutaneous renal denervation (RDN) lowers office and 24-hour blood pressure (BP) in patients with uncontrolled hypertension (HTN) in both the presence and absence of antihypertensive drug therapy [1–3]. This procedure provides an opportunity to achieve BP goals with lower tablet burden [4,5]. However, which

patient group benefit most from this procedure is still unclear. A post-hoc analysis of the randomized sham-controlled Symplicity HTN-3 trial indicated that the use of an aldosterone antagonist at baseline was an independent predictor of the BP response to RDN [6]. It is possible that RDN is more effective in patients with underlying hyperaldosteronism who tend to continue using an aldosterone antagonist with the effective HTN control on this patient group. The incidence of aldosterone-excess HTN, including both primary and secondary aldosteronism, may be higher than presumed clinically. Indeed, the significant antihypertensive benefit of aldosterone antagonists [7] suggests that aldosterone excess may contribute to uncontrolled HTN more commonly than indicated by standard clinical tests [8]. Therefore, we conducted this analysis to investigate the efficacy and safety of RDN in patients with uncontrol HTN and suspected aldosteronism.

2. Methods

2.1. Patient population

We reviewed consecutive patients who received catheter-based radiofrequency RDN (Symplicity Flex™ or Spyral™, Medtronic, USA) for uncontrolled HTN between September 2013 and August 2018. The institutional Review Board of MacKay Memorial Hospital approved this retrospective study (20MMHIS087e). Exclusion criteria include treatable proclaimed secondary causes, stage 5 CKD and ESRD on hemodialysis. We reviewed the patients' baseline characteristics, prescribed antihypertensive drugs, and pre-/post-procedural changes in BP via the electronic medical records of MacKay Memorial Hospital, Taipei. Most patients had office BP measurement at 0, 1, 3, and 6 months and 24-hour ambulatory BP measurement (ABPM) at 0 and 1-3 months after RDN. The medication was adjusted by the physicians' decision for clinical needs. The number of medications prescribed was recorded at 0, 1, 3, and 6 months by reviewing the electronic medical records.

2.2. Definition of suspected aldosteronism

We include the following criteria to retrospectively identify patients with suspected aldosteronism: 1) ratio of serum aldosterone concentration to plasma renin activity (ARR) > 30, 2) more than 10 mmHg of office BP reduction after administering an aldosterone antagonist, or 3) the presence of slow flow on the renal angiogram. Slow flow refers to TIMI 2 flow, which is defined as delayed or sluggish antegrade flow with complete filling of the distal territory. The details regarding which criteria fitted were shown in the Supplement.

2.3. Definition of RDN responder

A recent meta-analysis identified the mean change in 24-hour systolic BP following RDN was about 6 mmHg [9]. Therefore, RDN responders were defined by any of the following criteria: 1) 24-hour systolic BP reduction 6 mmHg, or 2) withdrawal of 1 class of antihypertensive medication. Otherwise, the patient was labeled a non-responder.

2.4. Statistical Analyses

All data were analyzed using SPSS version 24.0 for Windows (IBM Corp., Chicago, IL, USA). Comparison of the baseline characteristics and blood pressure during times of follow-up between two groups were examined using the Mann-Whitney U test for continuous variables and the Fisher's exact test for categorical variables.

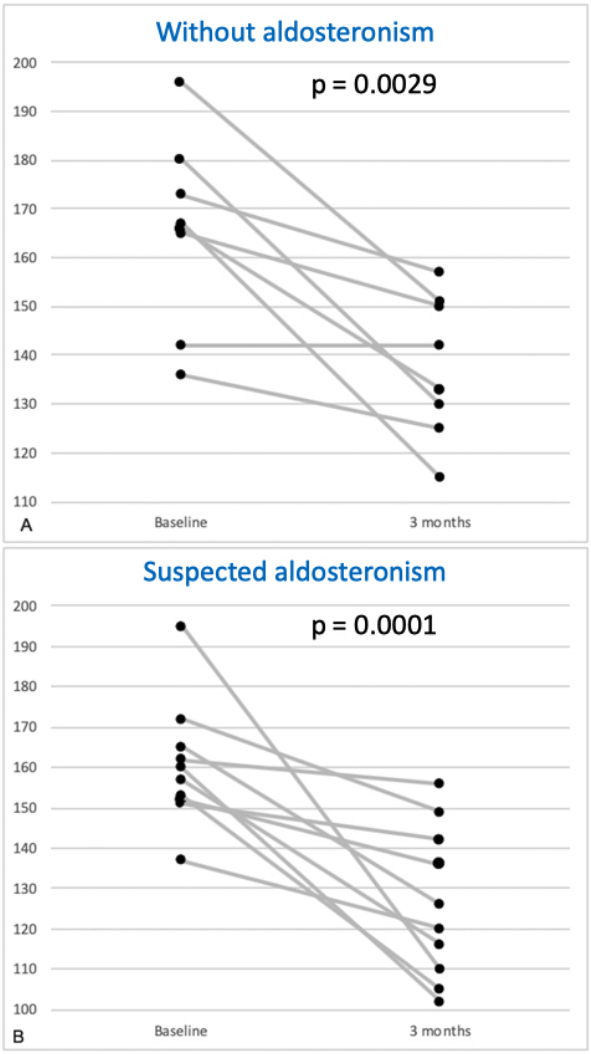

Figure 1. Office systolic blood pressure at baseline and 3 months post renal denervation. Office systolic blood pressure of each patients have been illustrated before and after renal denervation in both groups. The trend of systolic blood pressure reduction after renal denervation can be observed in both groups.

3. Results

3.1. Patient characteristics

A total of 18 patients were enrolled in the study, and 10 (55%) patients with hyperaldosteronism. Table. 1 disclosed the baseline characteristics between the groups without and with suspected aldosteronism subjects. Patient with suspected aldosteronism had a lower mean 24-hour heart rate (77.4 vs. 64.9 bpm, p = 0.002) and were less often prescribed loop diuretics or thiazide (62.5% vs. 10%, p = 0.043). Obviously, patient with suspected aldosteronism has much more MRA prescribed (0% vs. 70%, p = 0.004). The proportion of CKD (37.% vs. 80%, p = 0.145) and eGFR (65.2 ± 25.1 vs. 48.7 ± 28.5 ml/min/1.73 m2, p = 0.216) was numerically worse in suspected aldosteronism group. Spironolactone was associated with a systolic BP reduction of 11 mmHg in patients prescribed the drug.

3.2. Office and ambulatory BP

A total of 15 (83%) and 16 (88%) patients have the records of office BP and medication at 6 months and 12 months, respectively. Twelve (66%) patients had ABPM both before and after the procedure.

Table 1. Baseline characteristics.

Characteristic	Without aldosteronism (n = 8)	Suspected aldosteronism (n=10)	P
Age (y)	56.0 ± 13.7	63.6 ± 15.8	0.300
Men	75%	50%	0.367
Blood pressure			
Office SBP (mmHg)	165.6 ± 19.3	159.5 ± 14.9	0.458
Office DBP (mmHg)	82.1 ± 18.6	85.2 ± 12.1	0.677
Mean 24-hour SBP (mmHg)*	135.0 ± 11.1	143.6 ± 19.4	0.320
Mean 24-hour DBP (mmHg)*	73.4 ± 13.6	75.4 ± 11.0	0.764
Mean 24-hour HR (beat per min)*	77.4 ± 6.5	64.9 ± 6.3	0.002
Comorbidity			
eGFR (mL/min/1.73 m2)	65.2 ± 25.1	48.7 ± 28.5	0.216
Chronic Kidney Disease	37.5%	80%	0.145
Diabetes	75%	50%	0.367
Previous stroke	25%	30%	1.000
Coronary artery disease	12.5%	30%	0.588
Atrial fibrillation	0%	10%	1.000
Obstructive sleep apnea	0%	10%	1.000
Renal artery atherosclerosis	0%	30%	0.216
Medication			
Number of medication class	3.9 ± 1.4	4.6 ± 1.1	0.239
ACEi or ARB	37.5%	80%	0.145
Calcium-channel blocker	100%	100%	
Beta blocker	87.5%	70%	0.588
Alpha blocker	62.5%	50%	0.664
Central alpha2 agonist	0%	10%	1.000
Aldosterone antagonist	0%	70%	0.004
Loop diuretics or thiazide	62.5%	10%	0.043
Direct-acting vasodilator	37.5%	70%	0.342
Vasoactive hormone			
Renin activity (ng/mL/hr) †	7.9 ± 12.7	7.8 ± 12.6	0.988
Aldosterone (ng/dL) †	10.1 ± 7.4	27.9 ± 21.4	0.143
Aldosterone-to-renin ratio (ARR)	7.6 ± 6.8	80.9 ± 136.5	0.320
ARR >30	0%	60%	

* There are 7 patients in group without aldosteronism and 8 patients in suspected hyperaldosteronism group had ABPM measurement data.
† There are 4 patients in group without hyperaldosteronism and 8 patients in suspected aldosteronism group had been checked for renin activity and aldosterone.
SBP, systolic blood pressure, DBP, diastolic blood pressure, HR, heart rate, eGFR, estimated Glomerular filtration rate, ACEi, Angiotensin-converting enzyme inhibitor, ARB, angiotensin receptor blockers.

All ABPM were performed during the first to third month post RDN. On average, office systolic BP was 165.6 ± 19.3 mmHg in the group without suspected aldosteronism and 159.5 ± 14.9 mmHg in suspected aldosteronism group (p = 0.458) at baseline. At 3 months post RDN, mean office systolic BP was 142.6 ± 11.5 mmHg vs. 121.4 ± 17.9 mmHg (p = 0.039), respectively. In the group without suspected aldosteronism, the average reduction in office systolic BP was numerically greater (-27.0 ± 21.9 mmHg vs -10.5 ± 6.0 mmHg, p = 0.096) but not statistically significant at 1 month. However, the difference became smaller at 3 months, with a reverse trend (-28.8 ± 20.7 mmHg vs. -38.7 ± 25.8 mmHg, p = 0.484) between two groups (Table 2). At 6 months post RDN, all the differences were attenuated, perhaps due to drug withdraw in many patients. The office systolic BP at baseline and 3 months was illustrated in Figure. 1. Mean 24-hour systolic BP at baseline was 135 ± 11.1 mmHg vs. 143.6 ± 19.4 mmHg (p = 0.32), respectively. At 1-3 months post RDN, the 24-hour systolic BP both decreased to 130.8 ± 15.7 mmHg vs. 132.6 ± 13.6 mmHg (p = 0.838), respectively. Numerically, the decline in 24-hour systolic BP was greater in suspected aldosteronism group (-3.4 ± 11.0 mmHg vs. -11.1 ± 17.1, p =0.398) (Table. 2).

Table 2. Office and 24-hour systolic blood pressure at times of follow-up

	Office SBP (mmHg)				24-hour SBP (mmHg)	
	Baseline*	1 month†	3 months‡	6 months§	Baseline†	1–3 months?
Without aldosteronism	65.6±19.3	142.9±21.5	142.6±11.5	151.0±22.8	135.0±11.1	130.8±15.7
Suspect aldosteronism	159.5±14.9	144.1±7.7	121.4±17.9	137.5±18.5	143.6±19.4	132.6±13.6
P	0.458	0.887	0.039	0.293	0.320	0.838
		Δ 1 month†	Δ 3 months‡	Δ 6 months§		Δ 1–3 months?
Without aldosteronism		-27.0±21.9	-28.8±20.7	-20.5±27.3		-3.4±11.0
Suspect aldosteronism		-10.5±6.0	-38.7±25.8	-25.7±25.4		-11.1±17.1
P		0.096	0.484	0.748		0.398

* 8 patients in group without aldosteronism and 10 patients in suspected aldosteronism group had measurement data.
† 7 patients in group without aldosteronism and 8 patients in suspected aldosteronism group had measurement data.
‡ 5 patients in group without aldosteronism and 8 patients in suspected aldosteronism group had measurement data.
§ 4 patients in group without aldosteronism and 8 patients in suspected aldosteronism group had measurement data.
? 5 patients in group without aldosteronism and 7 patients in suspected aldosteronism group had measurement data.
SBP = systolic blood pressure

3.3. Response to renal denervation

The percentage of drug classes in use by the group is depicted in Figure. 2 ; the proportion of patients prescribed at least four classes of drug decreased from 39% to 23% within three months and to 11% at 6 months (Figure. 2). Compared to the control group, the number of drug classes continued to decrease till 6 months in suspected aldosteronism group (Figure. 2). Fourteen (78%) patients responded to the RDN procedure in sixth month. The response rate was numerically higher in suspected aldosteronism group [50% (n = 4) vs. 90% (n = 9), p = 0.118] at 3 months; and further higher at 6 months [50% (n=4) vs. 100% (n = 10), p = 0.023]. In general, 11 patients (61%) had response to RDN in the first month. The proportion and timeline of response in two groups are depicted in Figure. 3.

4. Discussion

Due to the massive size of the global uncontrolled HTN population, identification of the sub-population most likely to respond to renal denervation remains a critical unmet need for therapy optimization. Currently, RDN is mainly performed in patients with resistant hypertension [10]. The causes of resistant hypertension are usually multifactorial; therefore, purely essential resistant hypertension without any secondary cause is uncommon in clinical practice [11]. Some potential predictors of RDN response have been identified [12,13]. Post-hoc analysis of the Symplicity HTN-3 study indicated that patients who received aldosterone antagonists had a better RDN BP response. Although the underlying mechanism is unclear, one hypothesis is that patients with hyperaldosteronism have an over-activated renin-angiotensin-aldosterone system (RAAS) responding well to aldosterone antagonists and renal denervation might have additive effect on pre-existing neurohormonal blockade in patients with extremely activated RAAS [14]. Hyperaldosteronism includes both primary and secondary aldosteronism. The precise etiology and prevalence of secondary aldosteronism remain poorly understood because few studies focus on this complex phenomenon. Compared to the well-established criteria for primary aldosteronism, the secondary type depends

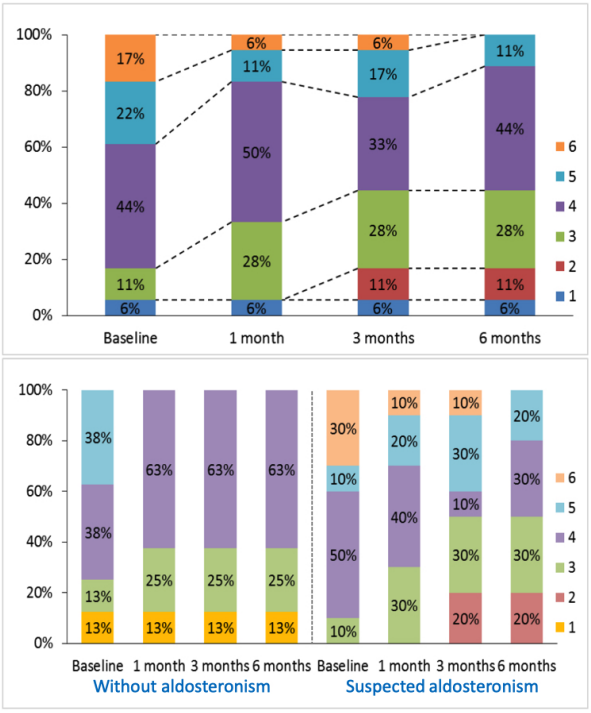

Figure 2. Percentage of drug class number distribution. Upper panel showed the percentage of drug classes in use of overall patients at baseline and at 1, 3, 6 months. The percentage of patients taking less than four classes of drug increase from 17% to 45%. The percentage of drug classes in use by groups is depicted at the lower panel, which showed the percentage of patients taking less than four classes of drug increase more significantly in suspected aldosteronism group.

on a diagnosis of exclusion and is perhaps associated with multiple underlying cardiovascular risk factors. Therefore, secondary aldosteronism in those with difficult-to-control hypertension may be quite common in daily practice. The common etiologies of secondary aldosteronism include renal parenchymal disease and impaired renal perfusion secondary to systemic disorders. Slow flow on renal angiogram without treatable stenosis might be the feature of this mechanism causing hyperaldosteronism related HTN. The impact of slow renal flow on BP control should be cautiously investigated in future studies because this is a common phenomenon on angiogram in the stenotic renal artery post angioplasty. The disappointing outcome on BP lowering by endovascular angioplasty alone in previous study possible imply unresolved underlying hyperaldosteronism [15]. To include the complex clinical presentation of hyperaldosteronism described above, we developed three criteria to identify hyperaldosteronism in our patients. In this retrospective study, the hormone level was checked with or without HTN medication, which may affect the absolute value of aldosterone and renin. Therefore, we used ratio of aldosterone to renin to screen the patient with excessive aldosterone. Impairment of renal perfusion is the main cause of secondary aldosterone; thus, slow-flow on renal angiography is one of the criteria. Office BP decreased more than 10mmHg after using spironolactone at least one month is another criterion. Hyperaldosteronism status was suggested when a patient has a significant BP response to aldosterone inhibition. Our study demonstrated that RDN was associated with a greater BP response in patient with suspected aldosteronism. Despite higher baseline 24-hour heart rate in the control group predicting better RDN response [16], the patients in suspected aldosteronism group showed comparable BP effects at 1 month and more delayed responders from 3 to 6 months. These findings might reveal that a possible patient population had continuous BP decline for months as reported in previous randomized control trials [1]. Decreased spillover of norepinephrine could happen soon after RDN, but the process to modulate RAAS could last much longer. Notably, the recent SPYRAL HTN ON-MED trial also showed an apparent time effect of gradually decreasing

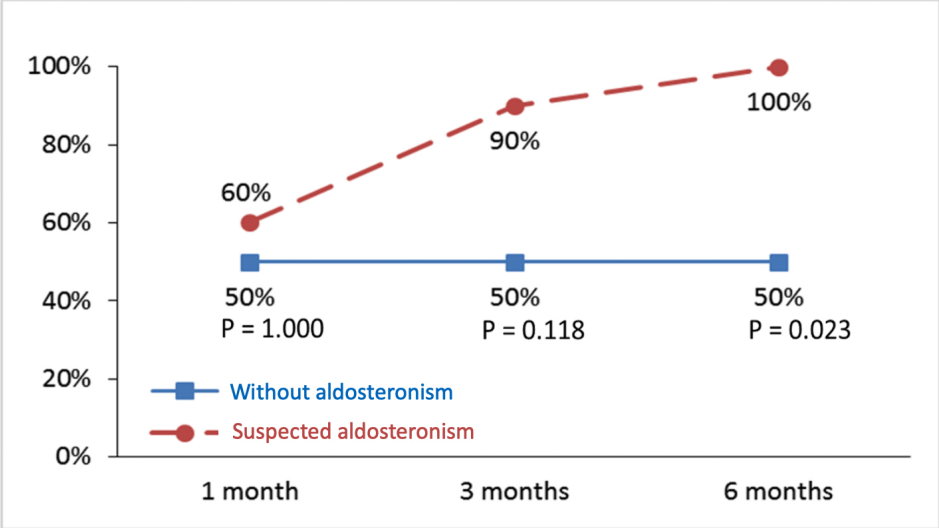

Figure 3. Response rate to renal denervation (RDN) by groups. The change in proportion of responders in both groups during 6 months after RDN. 50% of patients in group without aldosteronism group responded to RDN at 1 month after procedure. 60% of patients in suspected aldosteronism group responded to RDN at 1 month after procedure. Response rate increase to 90% and 100% at respectively 3 months and 6 months after procedure.

systolic BP in the RDN treated group compared to the sham control group [1]. However, the present 24-hour BP measurements at 1-3 months also seem to indicate that RDN could help to lower BP immediately within 1 to 3 months in the majority of RDN recipients. Several indices have been suggested to identify RDN responders including high baseline BP [17], lower arterial stiffness [18], and impaired baroreceptor sensitivity (19). A post-hoc sub-analysis of the SPYRAL HTN OFF-MED trial suggested that higher ambulatory basal heart rate was associated with greater BP response to RDN [2]. Our analysis report that hyperaldosteronism could be an important marker of RDN response. Three criteria to defined this patient group may be helpful in clinical practice. This retrospective post-hoc analysis has important limitations, including the relatively small sample size. Some patients had missing data on ABPM measurement, office BP or renin/aldosterone during the study period. We also assumed the presence of occult hyperaldosteronism based on an operational definition. However, despite these limitations, we did observe a clear difference in RDN response rate between groups.

5. Conclusion

In conclusion, we observed a superior 24-hour systolic BP response rate following RDN in the group with suspected hyperaldosteronism. Our experience indicates the need to test the hypothesis that aldosteronism-related hypertension may response to RDN.

Conflicts of Interest:
The authors declare no conflict of interest.

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