ORIGINAL ARTICLE

Hypertension Cure and Reducing Pill Burden after Adrenalectomy for Endocrine Hypertension of Adrenal Origin: A Comparative Study from an Asian and UK Cohort

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ABSTRACT

Background: The cure rate of endocrine hypertension following adrenalectomy is heterogeneous. Our aim of the study was to investigate the etiology and cure rate of endocrine hypertension between an Asian and UK cohort.

Materials and methods: This is a retrospective study of patients who underwent adrenalectomy from two tertiary centers in Singapore (cohort I) and the UK (cohort II) for endocrine hypertension. Demographic, clinical details, blood pressure data, and cure rates of hypertension were collected and analyzed.

Results: Cohort I included 115 patients (59F:56M), the mean age of 50.05 (SD 12.82), and cohort II had 128 patients (65F:63M), the mean age of 52.88 (SD 14.45) during the study period. There was a higher incidence of Conn's adenoma in cohort I, with predominantly left-sided tumors and grade I and II hypertension at presentation ($p = 0.001$). In contrast, cohort II had pheochromocytoma (PCC) as the most frequent diagnosis, right-sided tumors, and grade II and III hypertension ($p = 0.001$). Significant differences in the mean pre-op systolic and diastolic BP and choice of antihypertensive medications between the two cohorts were noted ($p = 0.001$). The hypertension cure rates were similar (70 vs 69%) between the two cohorts. In patients where no cure was achieved, adrenalectomy resulted in a decrease in the pill burden (decreased number of classes and standard dose) in both the cohorts ($p = 0.03$). The complications rates and overall mortality were comparable between the cohorts.

Conclusion: The etiology of adrenal hypertension is different between the East and the West. Adrenalectomy cured hypertension in the majority of the patient and reduced pill burden where no cure for hypertension was achieved.

Keywords: Adrenal, Adrenalectomy, Aldosterone-producing adenoma, Cushing's adenoma, Hypertension, Pheochromocytoma.

World Journal of Endocrine Surgery (2021): 10.5005/jp-journals-10002-1314

INTRODUCTION

Arterial hypertension is the condition where there is a non-physiological persistent elevation of systemic blood pressure defined as a resting systolic BP (SBP) $\geq$140 mm Hg or diastolic BP (DBP) $\geq$90 mm Hg. The condition is a major cardiovascular risk factor for stroke, ischemic heart disease, and heart failure.[1] It is estimated that roughly 10% of the global population has essential hypertension which has no identifiable cause. The prevalence of hypertension for adults aged between 30 years and 69 years was 26% for men and 21% for women in Singapore, compared with 31% among men and 26% among women in the UK, based on National Health Statistics. On the other hand, the prevalence of secondary hypertension was thought to be around 5% but more recent studies have shown the prevalence to be closer to 20%,[2] especially in younger patients with hypertension.[3] The most common causes of secondary hypertension are renovascular disease and endocrine conditions.[4]

Presentation with hypertension is common in many endocrine conditions due to hormonal imbalances associated with the gland of origin. Three endocrine conditions commonly presenting with hypertension include primary aldosteronism (PA), conditions causing glucocorticoid excess (Cushing's syndrome), and pheochromocytoma-paraganglioma syndromes (PCC/PGL). Adrenalectomy is the standard treatment for patients with

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endocrine hypertension and offers the patient a realistic chance of cure.[5–8] It is not uncommon to see residual hypertension in patients treated for endocrine hypertension, due to the fact that some component of essential hypertension exists in these patients, especially in the elderly.

The prevalence of PA is estimated to be about 30% in hypertensive patients.[9] The prevalence of PA increases with the grade of hypertension, seen in about 2% of those with grade I hypertension and up to 20% of patients with resistant hypertension.[9,10] Similarly, in patients with endogenous Cushing's syndrome, hypertension is seen in up to 80% of adults and 60% of children but maybe even as high as 95% in ectopic ACTH secretion.[11–13] The third adrenal condition causing hypertension is a PCC-PGL, wherein patients may have paroxysmal hypertension but a third present with persistent hypertension.[14] The response of hypertension to adrenal surgery varies with the underlying condition and other parameters such as gender and duration of hypertension.[15,16] It should be mentioned that adrenalectomy for Cushing's syndrome is not to cure hypertension through a good proportion of patients present with hypertension, unlike PA and PCC/PPGL.

We hypothesize that the incidence of adrenal conditions causing hypertension varies with geography and therefore the cure rate of adrenalectomy to treat hypertension should differ as well. Our study aimed to compare the outcomes of cure following adrenalectomy for endocrine hypertension between an Asian and UK cohort.

MATERIALS AND METHODS

The study is a retrospective analysis of patients who underwent adrenalectomy for endocrine hypertension in two tertiary centers, one from the East (cohort I: National University Hospital, Singapore) and the West (cohort II: Royal Victoria Hospital, Belfast). The study period for the cohort from Singapore was between 2001 and 2018 ($n = 128$) and for the UK cohort the study period was 2009 to 2018 ($n = 135$). Data for the period 2001 to 2008 in the UK cohort were very limited and hence not used in the analysis. The demographic details collected were age, gender, race, and clinicopathological parameters collected were diagnosis, nature of surgery (laparoscopic vs open), grade of hypertension, class, and a number of pre- and postoperative blood pressure medications, the cure rate of hypertension and mortality. Exclusion criteria were patients who were normotensive at presentation (13 from cohort I and 7 from cohort II). Institutional Board Review approval was obtained for the study from both the centers.

Diagnosis of the Endocrine Conditions

Standard diagnostic tests were used at both centers to confirm the diagnosis of the underlying adrenal condition. For PA, saline loading tests were performed to confirm autonomous aldosterone secretion in those with elevated plasma aldosterone levels or with elevated plasma aldosterone/plasma renin activity (PRA) ratio (ARR) >50 ng/100 mL/ng/mL/h with suppressed PRA values <0.7 ng/mL/h. All PA patients underwent lateralization studies with adrenal vein sampling before adrenalectomy. The diagnosis of adrenal Cushing's was made following a non-suppressible cortisol level with 1 mg overnight dexamethasone suppression test, along with elevated 24-hour urinary cortisol levels and a suppressed ACTH. Elevation of 24-hour urinary metanephrines performed on two separate occasions along with localization scans with computed tomography (CT) or magnetic resonance imaging (MRI)

was used for diagnosis of PCC/PGL. In patients with PCC/PGL where there was a suspicion of metastasis I[123] MIBG scan was used in the UK and DOTA-PET (due to non-availability of I[123]) in Singapore.

Définitions

As the definition of the grade of hypertension, we used the most current Guidelines for the management of Hypertension of the European Society of Cardiology and the European Society of Hypertension (ESC/ESH Task Force for the Management of Arterial Hypertension).[17] Elevated BP (blood pressure) is considered as an office SBP at least 140 mm Hg and/or DBP at least 90 mm Hg, which is equivalent to a 24-h average blood pressure monitoring (ABPM) average of at least 130/80 mm Hg, or a home blood pressure monitoring (HBPM) average at least 135/85 mm Hg.(23).

The cure was classified as normalization of blood pressure after surgical therapy, and normalization of biochemical parameters, which included serum potassium and ARR, serum cortisol, and 24-hour urinary metanephrines for PCC/PPGL. Complete cure is defined as the state where the SBP and/or DBP normalized without any antihypertensive medications for a period of 1 year; Partial cure–where patients were normotensive following surgery and there was a reduction in the number of classes of antihypertensives or reductions in the dose of the antihypertensives. All patients were followed for a minimum of a period of 2 years following surgery.

Classes of Antihypertensives

The preferred drugs used in the treatment of hypertension include calcium channel blockers (CCB), beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), diuretics, and alpha-blockers (AB's). The various drugs under each category and the standard doses used in the treatment of hypertension are shown in Table 1. The nature of the antihypertensives used depends on the underlying etiology of endocrine hypertension.

Surgery

All patients underwent surgery under general anesthesia after optimization of their blood pressures with antihypertensives described above. Most patients underwent laparoscopic surgery (anterior or posterior approach) for benign disease and those that were suspicious for malignant or deemed as large size unsuitable for laparoscopic surgery underwent open adrenalectomy.

Statistical Analysis

Categorical data are shown as rates and proportions, compared with the X^2 test, whereas continuous data were evaluated using the t-test, and the rest as means ($\pm$standard deviation). Analysis of variance was used to compare the variables among the two cohorts. Changes in paired values (data before and after treatment) were analyzed using the paired t-test. Factors found to be significant on univariate analysis for cure were evaluated by multivariate analysis using the Cox proportional hazards regression model. p values <0.05 were considered to be statistically significant.

RESULTS

There were 115 patients (59F:56M) in cohort I and 128 patients (65F:63M) in cohort II during the study period as shown in Table 2. The mean age was comparable in the two cohorts [cohort I vs II: 50.05 (SD; 12.82) vs 52.88 (SD; 14.45)]. There was a significant difference in the race of patients recruited in the two centers whereby all patients were Caucasians from cohort II while in cohort I the Chinese ethnicity prevailed (74%) ($p = 0.001$).

Table 1: Standard doses and the classes of antihypertensives used in the treatment of endocrine hypertension

Calcium channel blockers	mg	Beta-blockers	mg
Amlodipine (norvasc)	5	Atenolol	50
Nifedipine (adalat)	30	Bisoprolol	5
Verapamil	180	Carvedilol	25
Diltiazem	180	Metoprolol tartrate (IMM)	100
Felodipine (Plendil)	5	Propanolol	80
		Labetalol	200
AR antagonists	mg	Timolol	10
Losartan	50		
Valsartan	80	Vasodilators, alphaB	
Irbesartan	150	Prazosin	1
Candesartan	8	Terazosin	1
Telmisartan	40	Phenoxybenzamine	20
		Hydralazine	100
ACE Inhibitors	mg		
Captopril	12.5	Diuretics	mg
Enalapril	5	Frusemide (lasix)	40
Lisinopril	10	Spironolactone (aldactone)	25
Quinapril	10	Hydrochlorothiazide	25
Fosinopril	40	Amiloride	5
Cilazapril	2.5	Indapamide (thiazide)	1.25
Benazepril	10	Bumetanide (burinex)	0.5
Perindopril	2	Metolazone	2.5
		Torsemide	20

The causes of endocrine hypertension were significantly different in the two cohorts ($p = 0.001$). In cohort I, surgery was performed for Conn's (67%) followed by PCC/PGL (19%) and Cushing's syndrome (14%). In cohort II, most operations were performed for PCC/PGL (67%), Conn's (19%), and Cushing's syndrome (14%). The majority of the cases in both the cohorts were performed laparoscopically (87 vs 82%), using an anterior or posterior approach. Open procedures were slightly higher in cohort II (15 vs 10% in cohort I) and conversion rates were similar in both the cohorts (I vs II: 2.6 vs 3.1%). Pathology was most common on the left side in cohort I (69/115; 60%) whereas more common on the right side in cohort II (69/128; 54%) ($p = 0.001$). Bilateral surgery was more commonly observed in the cohort II compared to cohort I (17 vs 5%).

In terms of hypertension, patients from cohort I had grade I and II hypertension whereas cohort II had more grade II and III hypertensions ($p = 0.001$) preoperatively. Following surgery, both cohorts had a similar response in their hypertension control with the majority in the normal or grade I blood pressure range (95 vs 92%: $p = $ NS). The mean pre-op and postoperative SBP and DBP were different in the two cohorts ($p = 0.001$) and are shown in Table 3 and Figure 1. In cohort II, the most commonly used class of drug was alpha-blockers whereas in cohort I calcium channel blocker was the most commonly used class of drug, and this correlates with the predominant pathology being treated at each center.

The overall cure of hypertension was similar in the two cohorts (SG vs UK: 70 vs 69%) ($p = 0.77$) and there was no significant difference in cure rate between the various pathologies [Conn's (74:63%) ($p = 0.30$) vs PCC/PPGL (73:69%) ($p = 0.46$) and Cushing's (50:78%) ($p = 0.09$)] treated. There was no significant change in the

Table 2: Clinicopathological parameters of the two cohorts

Parameters		Cohort I cohort (East) (n = 115)	Cohort II cohort (West) (n = 128)	p value
Age	Mean (SD)	50.05 (12.82)	52.88 (14.45)	0.28
Gender	Female	59	65	0.93
	Male	56	63	
Race	Chinese	85	0	0.001
	Malay	12	0	
	India	3	0	
	Caucasian	15	128	
Diagnosis	Conn's	77	24	0.001
	Cushing's	16	18	
	PCC	22	86	
Surgery	Laparoscopic	100	105	0.35
	Open	12	19	
	Lap converted to open	3	4	
Size of tumor (in cm) (mean)	Conn's	1.6	1.8	0.46
	Cushing's	4.5	3.5	
	PCC	5.1	4.4	
Side of surgery	Right	69	69	0.001
	Left	40	37	
	Bilateral	6	22	
Grade of hypertension (pre-op)	Grade I	76	20	0.001
	Grade II	23	55	
	Grade III	16	53	

Contd…

Contd…

Parameters		Cohort I cohort (East) (n = 115)	Cohort II cohort (West) (n = 128)	p value
Grade of hypertension (postoperative)	Normal	93	88	0.51
	Grade I	9	29	
	Grade II	13	10	
	Grade III	0	1	
Classes of medications	CCB	96	46	0.001
	BB	58	53	0.15
	AB	44	95	0.001
	Diuretics	35	23	0.02
	ACEI	40	29	0.03
Cure of hypertension	Yes	81 (70%)	88 (69%)	0.77
All-cause mortality		10 (9%)	10 (7%)	0.67

CCB, calcium channel blocker; BB, beta-blocker; AB, alpha-blocker; ACEI, acetylcholine esterase inhibitors; PCC, pheochromocytoma

Table 3: The mean preoperative and postoperative systolic and diastolic blood pressures between the two cohorts (*p* = 0.001)

	Cohort I (n = 115)				Cohort II (n = 128)			
	SBP Pre	SBP Post	DBP Pre	DBP Post	SBP Pre	SBP Post	DBP Pre	DBP Post
Conn's	154.37	122.28	90.7	78.14	174.08	134.06	97.2	82.66
PCC	156.81	113.03	82.77	77.9	173.27	133.46	96.7	78.34
Cushing's	160.79	103.76	98.72	84.02	160.64	127.00	92.00	79.64

SBP; systolic blood pressure, DBP; diastolic blood pressure; PCC, pheochromocytoma
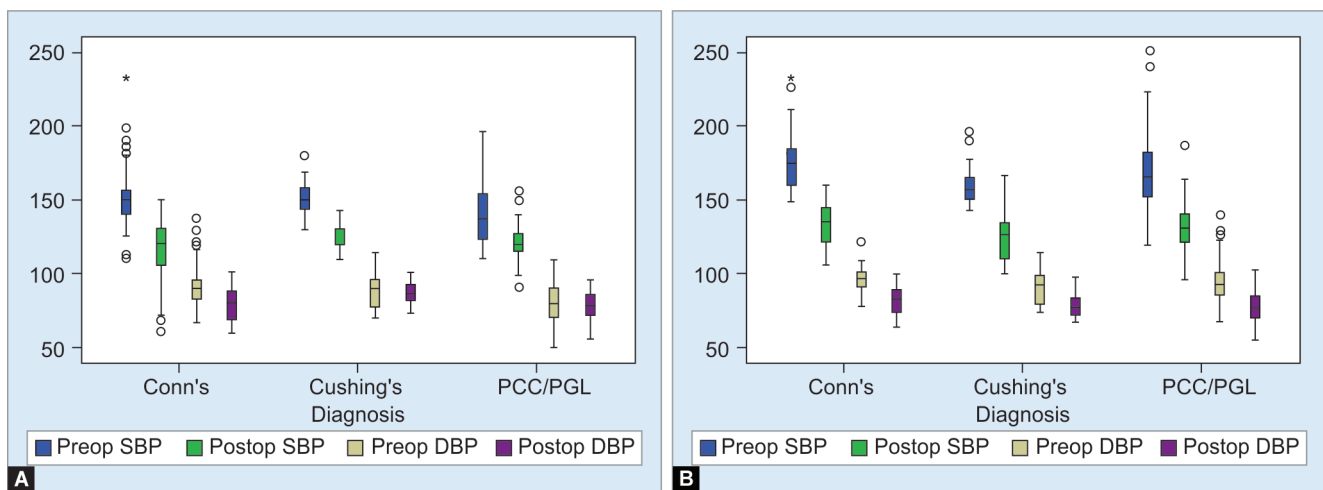

Figs 1A and B: The differences in preoperative (preop) and postoperative (postop) systolic and diastolic blood pressures in the two cohorts are based on the etiology

drop of SBP (32 vs 38%) (*p* = 0.07) and DBP (10 vs 16%) (*p* = 0.06) between the two cohorts. The number of patients from the two cohorts who had a reduction in the class of drugs and reduction in standard dose is shown in Figure 2.

Of the 34 patients who were not cured of cohort I, 25 (74%) had a reduction in the number of classes of drugs and 5 (14%) had a reduction in the standard dose of the prescribed medications. In cohort II, 34 (85%) had a reduction in the number of classes of drugs and 5 (13%) had a reduction in the standard dose of the prescribed medications. The association of reduction in a class of antihypertensives and cure between the two cohorts is shown (*p* = 0.03). An increase in antihypertensive class was required in 4 (12%) patients from cohort I and 1 (0.7%) patient from cohort II to maintain hypertension. None of the parameters like age, gender,

number of antihypertensive agents and duration were predictors of persistence of HT.

In terms of complications, three patients from cohort I and four patients from cohort II required conversion from laparoscopic to open procedure. The reasons for conversion in cohort I were bleeding in one patient and CBD injury in another due to dense adhesions from previous abdominal surgery requiring a choledochojujenostomy. The third patient sustained a ureteric injury during a posterior retroperitoneal approach due to distorted anatomy from previous laparoscopic anterior resection. In cohort II, conversions to open procedure were for bleeding. All-cause mortality within 30 days of surgery in both the cohorts was similar and was due to cardiovascular accidents (stroke and myocardial infarction).
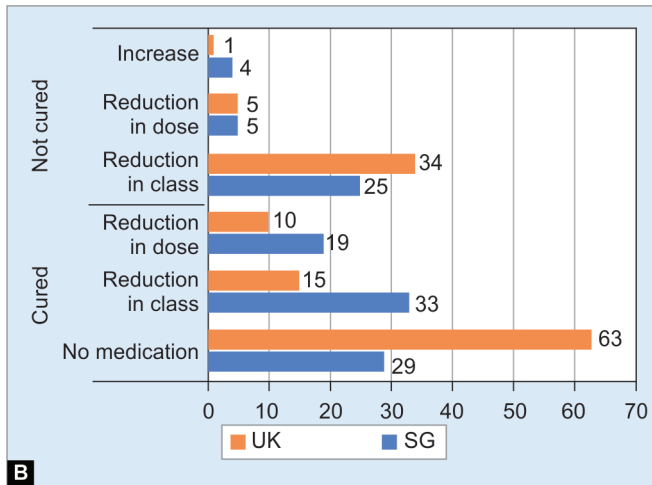
Fig. 2: Outcomes of cure in the two cohorts highlighting a reduction in dose and class in medications

Discussion

The study is the first comparative study between the East and West in terms of outcomes of endocrine hypertension and the findings are as follows: different etiology of hypertension with a higher rate of Conn's in the East and PCC/PPGL in the west, more left-sided tumors in the East compared to right-sided tumors in the West, grade I and II hypertension in the East compared to grade II and III hypertension in the West, significant differences in the mean pre-op SBP and DBP and choice of antihypertensive medications between the two cohorts. The cure rates, improved blood pressure control, complications from surgery, and overall mortality were similar between the cohorts.

One of the interesting findings of the study is the difference in etiology between the two cohorts in that the predominant cause of endocrine hypertension was Conn's adenoma in Asia and PCC/PPGL in the UK. An earlier study from Singapore showed the prevalence of PA to be around 5% of adults with hypertension, but the actual figures could be closer to 8%.[18] The prevalence of PA increased from 5.6 cases per year in the early '90s to 12.6 per year in the later years due to improved screening.[19] A similar study from Japan showed the prevalence of endocrine hypertension to be around 9% with a significant proportion of the cases attributed to PA.[20]

In a cross-sectional study from the UK published recently, the prevalence of PA in newly diagnosed, never treated hypertension was found to be around 3%;[21] slightly lower compared to other published studies from Europe with prevalence rates of about 5–8%.[22,23] There is a difference in healthcare expenditure between the two countries with Singapore currently spending about 4.4% and the UK about 9.6% of the GDP on healthcare based on the 2017 statistics published by the World Health Organization,[24] this does not explain the difference in the higher prevalence of PA in Asia. The differences between the prevalence rates of PA between the two cohorts could be attributed to possibly increased screening in Asia, early referral to specialist clinics for further investigations[25] and underdiagnosis in UK.[26]

The epidemiological data pertaining to the incidence of PCC/PPGL are sparse. A nationwide Dutch study showed the incidence of PCC to be rising over the last 2–3 decades, mostly due to improved imaging.[27] In patients with hypertension, the prevalence of PCC

is estimated to be in the West 0.1–0.6%,[28] and in Asia prevalence is low, around 2 per 100,000 population.[29] The study from the US using the Health Care Utilization Project Nationwide Inpatient Sample (HCUP-NIS) for a period of 5 years showed the incidence of hormone active tumors including PCC to be significantly higher in Caucasians in comparison to Asians and Blacks.[30] Over 70% of the patients presented with hypertension in the series.

The National Audit data published by the British Association of Endocrine and Thyroid Surgeons in 2017 showed that over 30% of the adrenalectomy performed was for PCC compared to 18% for Conn's and Cushing's adenoma.[31] The results presented in our study show a similar pattern with the UK cohort consisting of Caucasians only showing a higher incidence of PCC/PPGL compared to the Asian cohort. The incidence of germline mutations such as VHL, MEN 2, and NF-1 associated with PCC is low in Asia due to lack of acceptance for genetic screening by the patients[32,33] and non-referral to genetic services.[34] In our study, there were only 6 patients with germline mutations (MEN2a and MEN2b) from the Asian cohort in comparison to 22 germline mutations (MEN2a, MEN2b, SDH, VHL, and NF) in the Western cohort.

There was a difference in the laterality of the tumors between the two cohorts with right-sided lesions seen more in the UK compared to the left-sided lesions in Asia. Looking at individual pathologies, Conn's adenoma was predominantly seen on left in Asia, with no laterality in the other two pathologies. Many studies pertaining to adrenalectomy for Conn's syndrome showed a predominance of left-sided lesions.[6,35–37] In the UK, PCC/PPGL and Cushing's adenoma was more predominantly seen on the right. The differences in laterality are more likely due to selection bias.

The overall preoperative BP appeared to be lower in Singapore when compared to the UK and this may be due to the more stringent screening for secondary hypertension and earlier detection of secondary causes of hypertension. Evidence suggests that PA increases with the grade of hypertension, with higher grades seen in resistant hypertension. Similarly, high grades of BP are seen in PCC, with over 60% presenting with sustained hypertension and 30% with a paroxysmal disease, and about a third presenting with hypertensive crisis. Differences seen in the grade of hypertension and the mean pre- and postoperative BP (systolic and diastolic) between the two cohorts are more due to the underlying predominant pathology in each. The above also explains the difference in the choice of antihypertensive medications in the two cohorts prescribed for the underlying conditions.

Despite the differences in the etiology of hypertension in the two cohorts, the cure rates were similar and are consistent with published series.[35,38–42] A significant proportion of patients had normalization of BP through the reduction in the number of antihypertensive agents or in the standard dosages of the medications. Studies have shown that risk factors associated with persistent hypertension include advanced age,[43,44] duration of hypertension,[41,44,45] male gender,[45] and family history of hypertension.[46,47] There were no significant predictors of the persistence of HT in this study.

The reasons for persistent hypertension despite the removal of the trigger could be the coexistence of primary hypertension and the damage inflicted to the vascular endothelium and the kidneys.[48] Recently, gene expression studies on patients with persistent hypertension following adrenalectomy showed a few genes associated with biological pathways related to hypertension to be over- or under-expressed.[42] Response of endocrine hypertension

to adrenalectomy therefore can be heterogeneous similar to that reported in this study. Rossi et al. showed that vascular media-to-lumen ratio and media width were greater in patients with persistent hypertension due to the breakdown in some of the protective reflex mechanisms to control the blood pressure.[49]

To summarize, there is a difference in the incidence of adrenal conditions leading to hypertension between the East and the West. The outcomes of intervention in the form of hypertensive cure and complications are excellent in expert centers irrespective of the underlying adrenal cause. However, a small proportion of patients will not have their hypertension cured due to vascular remodeling and coexistent essential hypertension. Perhaps early diagnosis and treatment will mitigate the end-organ damage and vascular endothelial changes associated with long-standing endocrine hypertension.

The paper was accepted as a poster presentation for the European Association of Endocrine Surgeons 2020 Meeting in Greece.

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