Original Paper

Long-Term Outcomes of Pediatric Renovascular Hypertension

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Key Words

Renovascular hypertension • Pediatrics • Treatment • Angioplasty • Long-term outcome

Abstract

Background/Aims: Renovascular hypertension (RVHT) is an important cause of childhood hypertension. This study evaluated the clinical characteristics and outcomes of Korean children with RVHT. **Methods:** Children treated for RVHT between 2000 and 2015 at our center were retrospectively reviewed. **Results:** Forty-six children were followed for a median of 6.5 (0.66–27.23) years. Forty-five percutaneous transluminal angioplasties (PTAs) were performed in 32 children. At the last visit, clinical benefit was observed in 53.3% of children. Patients with comorbid cerebrovascular disease (CVD) showed less favorable long-term outcomes after PTA (clinical benefit in 41.7% vs. 61.1% in others) and higher restenosis rates (50% vs. 31.6% in others). Surgical procedures (bypass or nephrectomy) were performed in 8 patients. After surgery, blood pressure was normalized in 2 patients, improved in 3 patients, and unchanged in the remaining patients. Between PTA group (n=21) and medication group (n=14), percentage of atrophic kidneys became higher after follow-up period in medication group than in PTA group (60.0% vs. 26.1%, $P=0.037$). **Conclusion:** Aggressive treatment of pediatric RVHT yielded fair outcomes in our cohort. CVD comorbidity was associated with relatively poor PTA outcomes. To confirm our findings, larger cohort studies with a longer follow-up period are warranted.

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Introduction

Hypertension is relatively common, with a prevalence of up to 30% in adults older than thirty years, and is a major risk factor for cardiovascular disease. While most hypertension in adults is primary, hypertension in children and adolescents is more commonly secondary and is relatively rare, with a prevalence of 1.1-5% [1, 2]. Renovascular hypertension (RVHT) is an important cause of pediatric hypertension, accounting for 3-10% of cases [1, 3, 4]. Timely detection and management of RVHT, as a leading cause of pediatric hypertension, are critical to preventing ischemic nephropathy, chronic kidney disease (CKD) and target organ damage [5]. RVHT can be easily identified by screening for baseline plasma renin activity and Doppler ultrasonography of the kidney and can be confirmed by CT angiography and digital subtraction angiography (DSA); these assessments provide detailed data regarding the severity and extent of the disease as well as the angiographic patterns indicative of the underlying disease. RVHT occurs in various diseases, and the resulting hypoperfusion to the growing kidney leads to renal atrophy[6]. RVHT can occur in isolation as a result of fibromuscular dysplasia (FMD) of the renal arteries, as a symptom of systemic vasculitis such as Takayasu's arteritis (TA) or polyarteritis nodosa (PAN), or as an extracranial manifestation of Moyamoya disease (MMD) [7, 8]. FMD is the most prevalent cause of RVHT in Western countries; in Asia, however, TA has been reported to be a more common cause [9, 10]. RVHT treatment options include antihypertensive medication; endovascular intervention, such as percutaneous transluminal angioplasty; and surgical intervention, including revascularization surgery or unilateral nephrectomy. The choice of treatment modality should be informed by the laterality of the lesion(s), underlying conditions, and pattern of renal artery stenosis.

Several studies have assessed the effect of RVHT treatment on blood pressure (BP) control and changes in estimated glomerular filtration rate (eGFR) [3, 8, 10-13]. However, the progression in renal atrophy and the change in kidney size in RVHT have rarely been investigated [6]. As a result, the impact of treatment modalities on these parameters remains poorly understood. In Korean children in particular, a study of 16 cases was published 20 years ago [14], with no subsequent follow-up studies. Therefore, the current etiologies of RVHT in Korean children and the outcomes of RVHT according to various treatment modalities are not well known. Accordingly, the present study aimed to comprehensively investigate the clinical characteristics and outcomes of pediatric RVHT in Korean children.

Materials and Methods

Children who were treated for RVHT or renal artery stenosis (RAS) at Seoul National University Children's Hospital (SNUCH), a tertiary referral hospital in Korea, between January 2000 and April 2015 were retrospectively reviewed. The diagnosis of RVHT or RAS was made by DSA or intraoperative findings. We collected data, including gender, age at diagnosis, BP upon referral to our center, etiology, location of involved lesion, treatment modality (PTA, surgery, or medication), serum creatinine, kidney size, urine protein or albumin/creatinine, and left ventricular mass (LVM), both at the time of diagnosis and during the disease course. We also documented information regarding the intracranial vessels when available and defined cerebrovascular disease (CVD) co-morbidity as presence of angiographic evidence of cerebrovascular abnormalities such as narrowing and aneurysmal dilatation; most of the patients with CVD co-morbidity had Moyamoya disease or syndrome, family history of CVD, or neurologic symptom of seizure. Estimated GFR was calculated using the Schwartz formula for children younger than 18 years, and the Cockcroft-Gault equation was used for older patients.

BP was categorized as normal or stage I or II hypertension using the previously described parameters, specifically, the 95th percentile for normal BP vs. hypertension and the 99th percentile plus 5 mmHg to distinguish between stage I vs. II, based on the published reference values for the height and BP profiles of Korean children [15]. The LVM-for-height z score was used to assess left ventricular hypertrophy, and

the children with an LV mass above the 95th percentile for height (z score >1.64) were classified as having LVH [16]. We used reference data for kidney size in healthy Korean children of the same age to determine atrophy [17-19]; kidneys smaller than two standard deviations (SD) below the average value (z score < -2) were considered atrophic. Proteinuria was defined as a urine protein-to-creatinine ratio greater than 0.2 mg/mg or a urine microalbumin-to-creatinine ratio greater than 30 mcg/mg.

RVHT etiologies were diagnosed as follows. TA was diagnosed if there were typical angiographic abnormalities of narrowing or occlusion of the entire aorta and/or its primary branches, or large arteries in the proximal upper or lower extremities in addition to RAS, as according to known diagnostic criteria of TA [20, 21]. A diagnosis of FMD was made in patients who had no evidence of other vasculitis and had a “string of beads” appearance or focal lesions in the middle or distal segments of the renal artery on angiographic images [9, 10, 22]. Using well-known diagnostic criteria, patients whose cerebral angiography showed stenosis or occlusion at the terminal portion of the internal carotid artery (ICA) and/or at the proximal portion of the anterior cerebral arteries (ACAs) and/or the middle cerebral artery (MCA), as well as abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase, were categorized as having MMD [23]. Mid-aortic syndrome (MAS) was diagnosed if luminal narrowing of the abdominal aorta was accompanied by stenosis of the major branches in the abdomen. When no evidence for a secondary cause for the aortic narrowing was identified, idiopathic MAS was diagnosed [24].

Outcomes were assessed in terms of the degree of BP control, change in eGFR, and change in kidney size. The degree of BP control was determined using the criteria proposed by Ellis et al. [25] as follows: 1) cured, defined as normal BP with no antihypertensive treatment; 2) improved BP with the same or reduced treatment; 3) no change in BP despite angiographic success; or 4) technical failure (i.e., unable to pass a balloon catheter or unable to dilate the vessel with a balloon). We sub-categorized patients with “improved BP” into group (A), including patients with normal BP, and group (B), including patients with stage I hypertension. Of these categories, “cured” and “improved BP” were combined into a category referred to as “clinical benefit”.

The results were reported in terms of the median, range, mean, standard deviation and proportion. Finally, *t*-tests and χ^2 tests were used to compare the PTA and medication groups as appropriate.

Results

Initial presentations

During the study period, a total of 46 patients (male:female, 24:22) were diagnosed with RVHT at our institution. The median age at diagnosis was 7.5 (range 0.17-21) years, and the median follow-up duration was 6.5 (range 0.66-27.23) years. The initial BP upon referral was stage I hypertension in 6 patients, stage II hypertension in 37 patients, and normal BP on antihypertensive medication in 3 patients. One-third (15 of 46) of the patients had bilateral disease. In two-thirds of the patients, stenosis was limited to the main trunk, while the remaining patients exhibited stenosis with more extensive involvement. FMD and MMD comprised more than half of the causes of RAS, followed by TA (17.4%) and others (Table 1, Figure 1). At presentation, renal function impairment, assessed as an eGFR <60 ml/min/1.73 m², was observed in 4 patients with acute kidney injury due to malignant hypertension and cardiomyopathy. Ten (16.4%) of the affected kidneys were smaller than -2 SD of the kidney sizes of healthy Korean children. Proteinuria was observed in 12 patients (26%), 9 of whom were severely hypertensive (greater than stage 2 hypertension), one of whom had AKI, and the other two of whom had normal to stage 1 hypertension while on more than three antihypertensive agents.

Treatment of RVHT

Angioplasty. Upon diagnosis of RAS, PTA was attempted when feasible, and 32 patients underwent a total of 45 procedures (two procedures in 8 cases and three or four procedures in one case each). Six patients underwent bilateral PTA. Four of these patients underwent a bilateral procedure during their first PTA, while the other 2 patients underwent two

consecutive procedures for each artery. At our institution, PTA in children is limited to balloon dilatation only. Stent insertion is not considered because the patients are growing children who will need larger-sized vessels in the future. Furthermore, the restenosis rate has been reported to be significantly higher in the stent insertion group than in the balloon dilatation group [13].

When short-term (3 months), mid-term (1 year), and long-term (>1 year, at the last visit) outcomes were assessed (data not shown), more than half of the patients (60%) were found to have experienced a short-term clinical benefit ("improved BP" in 14, "cured" in 1 among the 25 patients whose BP data was available) after the first PTA,

while PTA was considered a technical failure in 3 patients. Technical failure occurred in 2 of 11 cases (18%) with isolated main renal artery involvement, and the other one case with technical failure was the only patient in whom angioplasty of the involved segmental artery had been attempted among the six cases with segmental or intrarenal artery involvement.

Table 1. Demographic data of the forty-six patients with RVHT

Parameter	Patient cohort (n=46 children)
Sex, n(%)	
Male	24 (52.2)
Female	22 (47.8)
Age at presentation (years)	0.17-21 (median 7.5)
Initial BP, n(%)	
Stage I hypertension	6 (13.0)
Stage II hypertension	37 (80.4)
eGFR at presentation (ml/min/1.73 m ²)	91.4 ± 29.6
Proteinuria, n(%)	12 (26)
Size of affected kidney at presentation (z score)	-0.88 ± 2.09
Etiology, n(%)	
Fibromuscular dysplasia	14 (30.4)
Moyamoya disease	10 (21.7)
Takayasu's arteritis	8 (17.4)
Mid-aortic syndrome	2 (4.3)
Neurofibromatosis, type 1	2 (4.3)
Alagille syndrome	1 (2.2)
Vasculopathy with STAT1 mutation	1 (2.2)
Vascular anomaly	1 (2.2)
Tumor compression	1 (2.2)
Unknown	6 (13)
Follow-up period (years)	0.66-27.23 (median 6.5)
Renal artery stenosis, n(%)	
Laterality	
Unilateral	31 (67.4)
Bilateral	15 (32.6)
Stenosis pattern	
Main trunk only	29 (63.0)
Segmental or intrarenal artery	6 (13.0)
Mixed	11 (23.9)

Fig. 1. Etiological distribution of patient cohort.

Fig. 2. Treatment modalities chosen for pediatric patients with renovascular hypertension. *One patient who underwent angioplasty after contralateral nephrectomy was included in the surgery group. †These two patients underwent another PTA for contralateral RAS (not described in this figure).

After the short-term success of PTA in 35 arteries of 29 patients, 14 arteries of 12 patients (40%) developed restenosis in a median of 17.1 (1.4-63.5) months (Figure 2). Eight patients (10 arteries) underwent further PTA, two others underwent nephrectomy or bypass surgery, and the remaining 2 were medically managed. Repeat PTA in 2 arteries of 2 patients among the 8 patients who underwent further PTA failed technically, while 5 of the other 6 patients experienced restenosis. Two patients eventually required bypass surgery, and another two patients lost kidney function of the involved site. Of the 12 patients with restenosis of the renal artery, 7 (FMD n=3, MMD n=4) had RAS combined with CVD, and the other patients had FMD without CVD (n=2), RAS of unknown cause, idiopathic MAS or neurofibromatosis type 1 (NF1). Interestingly, none of the TA patients (n=8) experienced restenosis. CVD comorbidity was common in the restenosis group. When comparing RAS with CVD to RAS without CVD, the presence of CVD was associated with a higher restenosis rate (50% vs. 31.6%).

The long-term outcome of patients (except for two who were lost within 1 year) was “cured” in 4 patients and “improved BP” in 12 patients, resulting in a total of 16 patients (53.3%) who experienced clinical benefit from PTA. Among these 16 patients, 7 (43.8%) had main renal artery involvement without other vasculopathies. Of the 9 patients with a “BP unchanged” outcome, 6 had accompanying CVD. Patients with CVD comorbidity had less favorable long-term outcomes after treatment, with clinical benefit achieved in only 41.7%, while 61.1% of the patients without CVD experienced a clinical benefit. Stratified by RVHT etiology, 70% of the 10 FMD patients (cured in 3, improved in 4) and all five TA patients (cured in 1, improved in 4) experienced long-term clinical benefit, while only one-third

(cured in none, improved in 3) of the nine MMD patients received clinical benefit from PTA.

Surgery. Surgical treatments were applied in a total of 8 patients, including six who were also treated with PTA. The etiologies were MMD in two patients, FMD in two patients, and NF1, MAS, Alagille syndrome, and tumor compression in one patient each; five of the patients had bilateral involvement. Aorto-renal bypass using an autologous graft (i.e., great saphenous vein) was performed in four patients when PTA had failed to improve RAS, while five patients underwent unilateral nephrectomy for atrophied kidneys (one underwent both procedures for each kidney).

Regarding the final outcome, 2 patients were cured, 3 patients showed improved BP (group A), and the remaining 3 patients exhibited no clinical benefit. Of the 3 patients who experienced no clinical benefit, one patient with unilateral RAS had impaired renal function (eGFR 30.1 ml/min/1.73 m²) with proteinuria at the time of diagnosis. Nephrectomy of the already atrophied kidney did not halt the progression of the patient's CKD. This patient also had CVD resembling MMD, and both CVD and CKD likely contributed to the poor outcome. The other two patients had contralateral RAS that was managed with PTA, although only one patient obtained clinical benefit after the procedure. At the last visit, two of the 8 surgically treated patients showed decreased eGFR of less than 60 (54 and 54) ml/min/1.73 m²; these patients already had impaired renal function at diagnosis (58 and 30 ml/min/1.73 m²) and diminished preoperative eGFR (66 and 64 ml/min/1.73 m²).

Overall outcome

At the last follow-up, most of the patients (86%) had normal or improved BP on three or fewer antihypertensive drugs, and 8 patients (18.6%) required no antihypertensives. The choice of medications varied from angiotensin converting enzymes (ACEs) inhibitors/angiotensin receptor blockers (ARBs) to diuretics, but calcium channel blockers (CCBs) were generally chosen as the first-line treatment. ACEs inhibitors or ARBs were chosen with careful monitoring of renal function when CCBs were not efficacious enough to control BP. When echocardiography was performed (n=30), the LVM-for-height z score was 0.45±1.60, and LVH (z score > 1.64) was observed in 7 cases (23.3%).

Of the 58 involved kidneys in 43 patients, 21 kidneys (36.2%) were smaller than -2 SD below the size of kidneys of healthy Korean children. However, eGFR was within the normal range in most of the patients. Three patients (7.0%) had CKD with an eGFR less than 60 ml/min/1.73 m², including the two described above. The other patient had unilateral RAS from idiopathic MAS with an initial eGFR of 85.8 ml/min/1.73 m² and was managed with PTA followed by medication; 4 years later, the patient's eGFR decreased to 50-60 ml/min/1.73 m². Proteinuria was found in only 3 (7.0%) patients. The eGFR at the last visit was 53.7, 66.8, and 71.1 ml/min/1.73 m² in these patients; two of these patients had already had impaired renal function at their initial presentation (eGFR 30.1, 46.3 ml/min/1.73 m²), and the other was a patient who underwent a third PTA for restenosis accompanied by stage 2 hypertension 2 months before the last visit.

Angioplasty versus medication only

Excluding the 8 patients who were treated with surgery and the 3 patients who were lost before the 1-year follow-up, the remaining patients were grouped according to their primary treatment modality: PTA group (n=21 treated with PTA without failure) and medication group (n=14). Medication group included the patients for whom PTA was not indicated because of their multifocal or diffuse stenosis of renal artery or already shrunken non-functioning kidney, and those in whom PTA or surgery had failed. A comparison of these groups is presented in Table 2. Age, sex, follow-up duration, initial and final eGFR, final BP, and number of antihypertensive medications at the last visit were not significantly different between the two groups. As expected, the renal artery involvement pattern differed, with segmental or intrarenal artery involvement more prevalent in the medication group (medication vs. PTA, 75.0% vs. 21.9%, p=0.003) and main renal artery involvement more

Table 2. Final outcomes of the PTA group vs. the medication group

	Total (n=43)	PTA group (n=21)	Medication group (n=14)	P
Age at diagnosis (years)	7.82±4.49	8.31±4.87	7.50±3.96	0.608
Follow-up period (years)	8.62±6.12	7.82±6.45	10.56±5.64	0.2
Sex (M:F)	24:22	11:10	6:8	0.581
Etiology (FMD:MMD:TA:Others)	12:10:8:13	8:6:5:2	2:2:3:7	0.051
Final systolic BP (mmHg)	123.54±13.99	124.19±14.76	121.43±14.02	0.584
Final diastolic BP (mmHg)	70.78±15.12	73.43±16.89	70.86±10.92	0.619
Initial eGFR (ml/min/1.73 m ²)	91.41±29.57	99.68±28.60	86.99±30.46	0.224
Final eGFR (ml/min/1.73 m ²)	91.96±21.81	94.06±25.57	90.73±13.80	0.661
CKD (eGFR <60 ml/min/1.73 m ²) (n,%)	3 (7.0)	1 (4.8)	0 (0)	
Initial kidney size (z score)	-0.88±2.09	0.05±1.32	-1.36±2.06	0.019
Final kidney size (z score)	-1.57±3.07	-0.74±2.61	-2.73±2.74	0.030
Initially atrophic kidneys (n, %)*	10 (19.6)	2 (9.5)	4 (26.7)	0.210
Atrophic kidneys at last follow-up (n, %)*	21 (37.5)	6 (26.1)	9 (60)	0.037
Final LV mass-for-height z score	0.45±1.60	0.70±1.86	0.20±1.34	0.498
LVH (n, %)	7 (23.3)	5 (35.7% of 14)	1 (11.1% of 9)	0.340
Proteinuria at last follow-up (n, %)	3 (7.0)	2 (9.5)	0 (0.0)	
Final No. of Drugs	1.63±1.18	1.48±1.12	1.50±0.94	0.948

*The denominator in each group is the total number of affected kidneys. In the PTA group, the denominator is the total number of operated kidneys. We excluded unavailable data; Initial vs. Final; in 'Total', n=51 vs. n=56; in 'PTA group', n=21 vs. n=23; in 'Medication group', n=15 vs. n=15.

common in the PTA group. At the time of diagnosis, 4 of the 15 involved kidneys (26.7%) were smaller than -2 SD below the size of the reference kidneys for Korean children in the medication group, and this number increased to 9 (60%) after mean follow-up of 10.56 years. In the PTA group, 2 kidneys (9.5%) were atrophic at diagnosis, and 6 (26.1%) were atrophic at the last follow-up (Figure 3). The difference in the proportion of atrophic kidneys between the two groups was statistically significant at the last visit. Moreover, in the PTA group, two patients who initially exhibited kidney asymmetry had symmetric kidneys by the time of the last follow-up.

The eGFR was not significantly different between the initial and final datasets in both groups; similarly, the LVM-for-height z score and prevalence of LVH were not significantly different.

Discussion

In this study, the long-term outcome of RVHT in a pediatric nephrology unit of a tertiary hospital was assessed. A total of 46 patients have been managed in this millennium at our center and were reviewed in this study. The patients demonstrated various clinical courses and underwent a variety of treatment modalities, with fair final outcomes after a median of 6.5 years. While RVHT is a well-known cause of secondary hypertension in childhood, at the time of referral, many of the affected kidneys were already smaller than normal, implying a delayed diagnosis. In this study, we assessed changes in the size of the affected kidneys over time according to the treatment modality; this approach differentiates our study from previous reports on pediatric RVHT [3, 10, 11, 13, 26-28]. Indeed, kidney sizes decreased in some patients over time. As expected, those who were managed with PTA without technical failure had better outcomes in terms of kidney size than those who relied on medication, while some of the affected kidneys became atrophic regardless of treatment (Figure 3, Table 2).

While previous studies reported that TA was more prevalent than FMD as underlying conditions in Asia [9, 10], FMD (30.4%) and MMD (21.7%) were more common than TA

Fig. 3. Initial versus final eGFR and kidney size z score in each group were plotted a. Initial and final eGFRs of the PTA group. The follow-up period of the PTA group was a median of 5.2 years. b. Initial and final eGFRs of the medication group. The follow-up period of the medication group was a median of 8.3 years. c. Initial and final kidney size z scores of the PTA group. d. Initial and final kidney size z scores of the medication group. In all graphs, the differences between the initial and final values were not statistically significant.

(17.4%) in our study population. The low prevalence of TA in our study may be due to the relatively low incidence of tuberculosis (TB) in Korea compared with in regions reporting a high prevalence of TA [8, 29]; however, it is still too early to confirm this hypothesis, as our study population was not sufficiently large. In addition, TA is not clearly differentiated from FMD solely by angiographic findings [9, 22]. In contrast, MMD was more common in our study, possibly because MMD is highly prevalent in East Asia, Korea and Japan, as published by our center 20 years ago [14]. While RAS associated with MMD primarily involves the proximal renal artery [7, 30], it is difficult to differentiate MMD from FMD based on angiographic pattern. Therefore, some of the FMD patients or those with proximal RAS of unknown origin in this study may develop MMD in the future and may be re-classified later as having MMD. If this occurs, the prevalence of MMD as the cause of disease may increase further in this Korean population.

Adult patients mainly rely on pharmacologic treatment because most cases (90%) of RAS in adulthood are caused by atherosclerosis, in which case, medication can both reduce cardiovascular disease risk and provide optimal control of BP. More recently, PTA or surgical management has been recommended only in selected cases [31-33]. However, in children, who have a longer life expectancy, management of RVHT involves not only BP control but also preservation of kidney function [5]. Therefore, surgical revascularization and PTA have been applied when feasible for decades to preserve the affected kidneys. In our institution, after detection of RAS on imaging studies, when the affected kidneys are viable, PTA has been utilized as the first-line management strategy, rather than relying on pharmacologic measures for an extended period of time [14]. As a result, assessment of PTA by comparing the number of medications used before and after the procedure was not appropriate for the present study. Long-term clinical benefit was achieved in 53.3% of our PTA patients, and

this rate is consistent with previous reports (55-73%) [10, 13, 26]. In contrast, the “cure” rate of PTA (13%) was lower in our study than in those reported by other authors, including one report from China (23.1-37%) [10, 11, 13, 26]. We propose that this lower cure rate may be a result of the higher proportion of patients with CVD in our study (40%) compared with previous studies (18-22%) [11, 13]. The majority of the patients with CVD were MMD patients; therefore, we set the target BP higher to prevent aggravation of brain ischemia, and these patients were therefore categorized as “improved” rather than “cured”. As a result, the higher proportion of MMD as the etiology of RVHT may have contributed to the lower “cure” rate in our cohort.

PTA has been reported to be less efficacious in FMD [26] and of variable efficacy in MMD [7, 30, 34]. This variability in PTA effectiveness based on underlying conditions has been considered to be the result of different pathologies. In TA, for example, inflammatory processes fragment the elastic fibers of vessels, while FMD exhibits medial fibroplasia but preserves the intima and MMD results in fibrous thickening of the intima [35-37]. Beyond the different pathological factors that affect the efficacy of PTA, restenosis varied according to underlying conditions. While none of the TA patients experienced restenosis, half of the FMD patients experienced restenosis after PTA but showed relatively good long-term outcomes, with 70% experiencing clinical benefit even after repeated PTA. In contrast, only one-third of MMD patients achieved long-term clinical benefit (33.3%) from PTA, while many cases of MMD experienced restenosis. Collectively, the patients with CVD comorbidity developed restenosis in 50% of the treated arteries, whereas patients without CVD developed restenosis in 31.6% of the treated arteries, suggesting that patients with CVD are more prone to restenosis. The CVD comorbidity along with RAS implies the presence of systemic vasculopathy, which may be progressive, leading to restenosis. Intriguingly, the restenosis rate (40%) of balloon-dilated renal arteries in our study was higher than the previously reported rate of less than 10% [13]. While we could not find similar reports in the literature, a higher proportion of MMD as the underlying etiology of RVHT may contribute to the higher restenosis rate observed in our cohort. Although TA is a chronic inflammatory disease, none of our patients with TA had active disease, which may explain why none of the patients with TA experienced restenosis.

A surgical approach was considered in our center when the renal artery stenotic lesion was not amenable to angioplasty or when BP control was not satisfactory after PTA. Reported outcomes in previous studies on revascularization surgeries, such as bypass and auto-transplantation, were clinical benefit rates of 81-100% and cure rates of 59-88% [27, 28, 38]. All of the patients in our study who underwent bypass surgery (n=4) achieved clinical benefit (1 cured, 3 with improved BP). The four remaining patients underwent nephrectomy of atrophic kidneys, and only one was cured of RVHT. Two of the patients who underwent unilateral nephrectomy experienced aggravation of contralateral RAS, and the other patient experienced progression of underlying CKD. Overall, two patients who were surgically cured had isolated main RAS without additional vasculopathy, while 4 patients had CVD and the remaining 2 patients had MAS. Therefore, the addition of vasculopathy may be a partial explanation for the low cure rate among our surgically treated patients.

Based on the long-term follow-up, BP control was considered to be fair in all patients in the present study, regardless of the treatment modality. Despite the fact that many (36.2%) of the affected kidneys became smaller, renal function was preserved in most of them (93%), and proteinuria persisted in only a few patients (n=3, 7% of 43 patients).

Conclusion

In Korean children, the long-term outcome of pediatric RVHT after aggressive treatment is fair, resulting in well-controlled hypertension and preserved renal function. PTA, if successful, can be a good treatment modality that can preserve the involved kidneys and

achieve fair BP control. While the surgical procedure is typically successful, its efficacy may be limited in cases of bilateral RAS. Interestingly, CVD comorbidity was associated with less favorable outcomes and a higher incidence of restenosis after PTA. To confirm these findings, larger cohort studies with longer follow-up periods are warranted.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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References

- 1 Falkner B: Hypertension in children and adolescents: epidemiology and natural history. *Pediatr Nephrol* 2010;25:1219-1224.
- 2 Jung JW: Hypertension in children and adolescents. *Korean J Pediatr* 2009;52:745-751.
- 3 Courtel JV, Soto B, Niaudet P, Gagnadoux MF, Carteret M, Quignodon JF, Brunelle F: Percutaneous transluminal angioplasty of renal artery stenosis in children. *Pediatr Radiol* 1998;28:59-63.
- 4 Safian RD, Textor SC: Renal-Artery Stenosis. *N Engl J Med* 2001;344:431-442.
- 5 Wang PR, Kitamura H, Shimizu A, Yamanaka N: Glomerular Damage in Experimental Proliferative Glomerulonephritis Under Glomerular Capillary Hypertension. *Kidney Blood Press Res* 2015;40:188-199.
- 6 Guzman RP, Zierler RE, Isaacson JA, Bergelin RO, Strandness DE, Jr: Renal Atrophy and Arterial Stenosis: A prospective Study With Duplex Ultrasound. *Hypertension* 1994;23:346-350.
- 7 Choi Y, Kang BC, Kim KJ, Cheong HI, Hwang YS, Wang KC, Kim IO: Renovascular hypertension in children with moyamoya disease. *J Pediatr* 1997;131:258-263.
- 8 Tullus K, Brennan E, Hamilton G, Lord R, McLaren CA, Marks SD, Roebuck DJ: Renovascular hypertension in children. *Lancet* 2008;371:1453-1463.
- 9 Tullus K: Renovascular hypertension--is it fibromuscular dysplasia or Takayasu arteritis. *Pediatr Nephrol* 2013;28:191-196.
- 10 Zhu G, He F, Gu Y, Yu H, Chen B, Hu Z, Liang W, Wang Z: Angioplasty for pediatric renovascular hypertension: a 13-year experience. *Diagn Interv Radiol* 2014;20:285-292.
- 11 Kari JA, Roebuck DJ, McLaren CA, Davis M, Dillon MJ, Hamilton G, Shroff R, Marks SD, Tullus K: Angioplasty for renovascular hypertension in 78 children. *Arch Dis Child* 2015;100:474-478.
- 12 Ladapo TA, Gajjar P, McCulloch M, Scott C, Numanoglu A, Nourse P: Impact of revascularization on hypertension in children with Takayasu's arteritis-induced renal artery stenosis: a 21-year review. *Pediatr Nephrol* 2015;30:1289-1295.
- 13 Shroff R, Roebuck DJ, Gordon I, Davies R, Stephens S, Marks S, Chan M, Barkovics M, McLaren CA, Shah V, Dillon MJ, Tullus K: Angioplasty for renovascular hypertension in children: 20-year experience. *Pediatrics* 2006;118:268-275.
- 14 Kang B-C, Ha I-S, Kim I-O, Cheong H-I, Choi Y, Ko K-W: Renovascular Hypertension in Children. *Child Kidney Dis* 1997;1:101-108.
- 15 Lee CG, Moon JS, Choi J-M, Nam CM, Lee SY, Oh K, Kim YT: Normative blood pressure references for Korean children and adolescents. *Korean J Pediatr* 2008;51:33-41.
- 16 Foster BJ, Mackie AS, Mitsnefes M, Ali H, Mamber S, Colan SD: A Novel Method of Expressing Left Ventricular Mass Relative to Body Size in Children. *Circulation* 2008;117:2769.

- 17 Lee BH, Ahn HJ, Kang WH, Seo GH, Kim B, Lee SG, Oh DJ, Huh W, Kim YG, Kim DJ: Estimation of Kidney Size by Ultrasonography in Normal Korean Adults. *Korean J Nephrol* 1999;18:5.
- 18 Konuş OL, Ozdemir A, Akkaya A, Erbaş G, Celik H, Işık S: Normal liver, spleen, and kidney dimensions in neonates, infants, and children: evaluation with sonography. *Am J Roentgenol* 1998;171:1693-1698.
- 19 Rosenbaum DM, Korngold E, Teele RL: Sonographic assessment of renal length in normal children. *Am J Roentgenol* 1984;142:467-469.
- 20 Ozen S, Ruperto N, Dillon MJ, Bagga A, Barron K, Davin JC, Kawasaki T, Lindsley C, Petty RE, Prieur AM, Ravelli A, Woo P: EULAR/PreS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006;65:936-941.
- 21 Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, Lie JT, Lightfoot RW, Jr, et al.: The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum* 1990;33:1129-1134.
- 22 Pontes Tde C, Rufino GP, Gurgel MG, Medeiros AC, Freire EA: Fibromuscular dysplasia: a differential diagnosis of vasculitis. *Rev Bras Reumatol* 2012;52:70-74.
- 23 Burke GM, Burke AM, Sherma AK, Hurley MC, Batjer HH, Bendok BR: Moyamoya disease: a summary. *Neurosurg Focus* 2009;26:E11.
- 24 Sethna CB, Kaplan BS, Cahill AM, Velazquez OC, Meyers KE: Idiopathic mid-aortic syndrome in children. *Pediatr Nephrol* 2008;23:1135-1142.
- 25 Ellis D, Shapiro R, Scantlebury VP, Simmons R, Towbin R: Evaluation and management of bilateral renal artery stenosis in children: a case series and review. *Pediatr Nephrol* 1995;9:259-267.
- 26 Srinivasan A, Krishnamurthy G, Fontalvo-Herazo L, Nijs E, Keller MS, Meyers K, Kaplan B, Cahill AM: Angioplasty for renal artery stenosis in pediatric patients: an 11-year retrospective experience. *J Vasc Interv Radiol* 2010;21:1672-1680.
- 27 Kimura H, Sato O, Deguchi JO, Miyata T: Surgical treatment and long-term outcome of renovascular hypertension in children and adolescents. *Eur J Vasc Endovasc Surg* 2010;39:731-737.
- 28 Chalmers RT, Dhadwal A, Deal JE, Sever PS, Wolfe JH: The surgical management of renovascular hypertension in children and young adults. *Eur J Vasc Endovasc Surg* 2000;19:400-405.
- 29 Ladapo TA, Gajjar P, McCulloch M, Scott C, Numanoglu A, Nourse P: Impact of revascularization on hypertension in children with Takayasu's arteritis-induced renal artery stenosis: a 21-year review. *Pediatr Nephrol* 2015;30:1289-1295.
- 30 Yamada I, Himeno Y, Matsushima Y, Shibuya H: Renal Artery Lesions in Patients With Moyamoya Disease. *Stroke* 2000;31:733.
- 31 Balafa O, Kalaitzidis R, Siamopoulos KC: Optimal medical management in patients with renovascular hypertension. *Am J Cardiovasc Drugs* 2013;13:71-78.
- 32 Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, Baigent C, Carr S, Chalmers N, Eadington D, Hamilton G, Lipkin G, Nicholson A, Scoble J: Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;361:1953-1962.
- 33 Catena C, Colussi G, Nait F, Capobianco F, Sechi LA: Plasma Lipoprotein(a) Levels and Atherosclerotic Renal Artery Stenosis in Hypertensive Patients. *Kidney Blood Press Res* 2015;40:166-175.
- 34 Halley SE, White WB, Ramsby GR, Voytovich AE: Renovascular Hypertension in Moyamoya Syndrome: Therapeutic Response to Percutaneous Transluminal Angioplasty. *Am J Hypertens* 1988;1:348-352.
- 35 Vaideeswar P, Deshpande JR: Pathology of Takayasu arteritis: A brief review. *Ann Pediatr Cardiol* 2013;6:52-58.
- 36 Slovut DP, Olin JW: Fibromuscular Dysplasia. *N Engl J Med* 2004;350:1862-1871.
- 37 Ikeda E: Systemic vascular changes in spontaneous occlusion of the circle of Willis. *Stroke* 1991;22:1358.
- 38 Piercy KT, Hundley JC, Stafford JM, Craven TE, Nagaraj SK, Dean RH, Hansen KJ: Renovascular disease in children and adolescents. *J Vasc Surg* 2005;41:973-982.