Journal of the American Heart Association

VIEWPOINTS

Cardiovascular Disease Prevention in Patients With Atherosclerotic Renovascular Disease-Induced Resistant Hypertension: Further Considerations for 24-Hour Blood Pressure Profiles

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In a recent issue of the *Journal of the American Heart Association (JAHA)*, Reinhard et al. report that, in a prospective observational study with 2-year follow-up regarding the effect of renal artery stenting in patients with resistant hypertension, 24-hour systolic blood pressure (BP) evaluated by ambulatory BP monitoring (ABPM) was decreased by 25.7 mm Hg from a baseline of 166.2 mm Hg, and an improvement in renal function was observed.[1] Although participants were using 2 to 3 classes of antihypertensive medications and office BP measurements were used in the former studies,[2–4] the novelty of Reinhard et al.'s observational study is the feature of "true resistant hypertension" among subjects who had used at least 4 different classes of antihypertensive medications and whose uncontrolled BP was evaluated by multiple ABPM measurements. All prospective observational studies, including that of Reinhard et al., reported that percutaneous transluminal angioplasty (PTRA), such as renal artery stenting, had a favorable effect on elevated BP. From these findings, PTRA for renovascular hypertension should be considered a reasonable treatment for the management of hypertension. Of course, PTRA is an invasive procedure with a risk of adverse complications. Before it can be widely applied to patients with renovascular hypertension, it must be shown that PTRA is superior to antihypertensive drug therapy.

See Viewpoint by Cooper et al.

There are cases of uncontrolled blood pressure in patients who take appropriate medications and have adhered to recommended dietary and exercise interventions. In fact, their resistant hypertension may be due to secondary hypertension. A previous study reported that among patients with hypertension, 10% have secondary hypertension, including 3% with renovascular hypertension.[5] In addition, it has been reported that 24% of older patients (mean age, 71 years) with resistant hypertension have significant renovascular disease.[6] From these findings, renovascular hypertension is one of the important etiologies for resistant hypertension. Almost all cases of renal artery stenosis can be treated by stents. In addition, the causes of renal artery stenosis neatly divide into fibromuscular

Key Words: atherosclerotic renovascular disease ■ cardiovascular disease prevention ■ management on hypertension ■ treatment resistant hypertension

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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dysplasia and atherosclerosis, with patient groups of differing demographics and comorbidities. As an intervention therapy, PTRA is more strongly recommended for renovascular disease due to fibromuscular dysplasia than atherosclerosis. Compared with those of antihypertensive medications, the effects of PTRA for atherosclerotic renovascular disease on BP levels, improvement of renal function, and cardiovascular disease (CVD) outcomes have been controversial.

Table shows previous studies including prospective observational studies and randomized controlled trials for the effects of PTRA on atherosclerotic renal artery stenosis. Almost all prospective observational studies after the 2000s have shown improved BP control or renal function.[2–4,7–9] Some previous observational studies have reported a decrease in systolic BP (SBP) of as much as 10 to 30 mm Hg 1 to 3 years after renal artery stenting.[2–4] In the results of the Sapoval et al.'s study, BP decreased from 171/89 at baseline to 141/80 mm Hg at the 1-year follow-up.[2] Likewise, in the REFORM (Reducing Falls with Orthoses and a Multifaceted Podiatry Intervention) study, BP decreased from 150/74 at baseline to 141/78 mm Hg at the 9-month follow-up; patients with higher baseline BPs (SBP>180 mm Hg) showed a much stronger effect (a 48-mm Hg decrease in SBP).[3] Additionally, the HERCULES (Herculink Elite Renal Stent to Treat Renal Artery Stenosis) study showed the effect of renal artery stenting on lowering BP was long lived, with a 3-year follow-up showing a decrease in SBP from 162 to 146 mm Hg.[4]

Other previous randomized controlled trials have compared the effect on BP levels and improvement of renal function between patients in whom PTRA is added to drug therapy and those with drug therapy alone and have reported no advantage of adding PTRA to drug therapy.[10–13] In the STAR (Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function) trial in 2009, 145 patients who had a stable BP control (BP <140/90 mm Hg) and ostial renal artery stenosis of at least 50% were included. These patients were randomized to optimal drug therapy including antihypertensives, statins, and aspirin or to renal artery stenting in addition to optimal drug therapy. No significant difference between the 2 groups was found for estimated glomerular filtration rate declines, BP levels, and CVD outcomes at the 2-year follow-up.[11] The ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) study in 2009 was a larger trial in 806 patients who were randomized to drug therapy alone or drug therapy plus renal artery stenting; at baseline, the mean BPs were 152/76 and 149/76 mm Hg, respectively. Similar to the results of the STAR trial, there were no differences between the 2 groups in BP change or mortality at the 5-year follow-up.[12] Moreover, the largest randomized controlled trial, the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial in 2014, was conducted in 947 patients, all of whom had SBP >150 mm Hg and were taking 2 or more antihypertensive agents. Although there were no significant differences in CVD outcomes or worsening estimated glomerular filtration rate between the 2 groups, adding renal artery stenting to drug therapy showed a modest advantage in BP lowering compared with drug therapy alone (–2.3 mm Hg [95% CI, −4.4 to −0.2 mm Hg], P=0.03).[13] Based on these findings, current international guidelines do not recommend catheter or surgical angioplasty for all cases with renal artery stenosis.[14] The current US guideline from the Society for Cardiovascular Angiography and Intervention recommends PTRA for patients who have complications of cardiac disturbance syndrome (flash pulmonary edema or unstable angina), chronic kidney disease stage IV, recurrent congestive heart failure, and resistant hypertension.[14] The findings from Reinhard et al.'s study thus may support the benefit of renal artery stenting for patients with resistant hypertension due to renal artery stenosis.

Who is the best responder to PTRA? Radermacher et al. used a renal artery resistive index evaluated by Doppler ultrasonography to predict the outcome of PTRA for renal artery stenosis.[8] They reported that a renal resistive index value <80 is a predictor for improvement of BP level in response to PTRA. Courand et al.'s prospective observational study using ABPM reported that younger age, lower body mass index, and preserved renal function (higher estimated glomerular filtration rate) were associated with achievement of good BP control by renal artery stenting in patients with resistant hypertension due to renal artery stenosis.[15] Similarly, Fujihara et al. reported that response factors for PTRA were younger age and higher BP at baseline.[16] The previous study using ABPM also reported that higher ambulatory BP at baseline was related with a good response to PTRA, but this relationship was not shown in office BP.[17] In this issue of the *JAHA*, we find that the participants in the study of Reinhard et al. had uncontrolled BP by ABPM despite their use of multiple medications. Especially in patients with uncontrolled resistant hypertension or refractory hypertension, PTRA would be effective at lowering BP. Moreover, from a previous study's findings, the presence of resistant hypertension, younger age, lower body mass index, and preserved renal function may be favorable conditions for good response of PTRA.

Figure shows the suspected mechanisms of BP elevation in renal artery stenosis and recommendations for management of renovascular hypertension. Renal hypoperfusion due to renal artery stenosis induces excessive activation of the renin angiotensin aldosterone system, causing both sympathetic nervous system activation and fluid retention, which may lead to

Table. Previous Studies (Post-2000) Regarding the Effect of Renal Artery Angioplasty on Blood Pressure and Renal Function

Study (y)	Number	Baseline				Outcomes		
		Mean age	No. of antihypertensive drugs	BP	Renal function	Changes in BP	Changes in renal function	CVD outcomes
Prospective, PTRA								
Beutler et al. (2001)[7]	N=63	68 y	2	180/110 mm Hg	s-Cr 171 mmol/L	SBP levels were 180, 160, and 160 mm Hg at baseline, 6 mos, and 12 mos.	In 56 cases, s-Cr improved from 182 to 154 mmol/L.	2 cases of death after <6 mos.
Radermacher et al. (2001)[8]	N=131	RI≥0.8: 67 y RI<0.8: 55 y	RI≥0.8: 3.3 RI<0.8: 3.2	RI≥0.8: 164/83 mm Hg RI<0.8: 150/89 mm Hg (24-h BP in ABPM)	CCr 33 mL/min in RI ≥0.8, 68 mL/min in RI <0.8, Using the evaluation of echography RI	In RI ≥0.8, 164/83 to 163/86 mm Hg at 5y (NS). In RI <0.8, BP was reduced from 150/89 to 135/80 mm Hg at 5y	Poor prognosis in RI ≥0.8, end-stage renal disease 46%, death 29% at 5y-FU.	
Zeller et al. (2003)[9]	N=215	67 y	3	145/79 mm Hg	s-Cr 1.51 mg/dL	147/79 mm Hg at 1 yr (NS).	s-Cr improved from 1.51 to 1.19 mg/dL	…
Sapoval et al. (2010)[2]	N=251	70 y	≥3	171/89 mm Hg	s-Cr 283 mmol/L, eGFR 54 mL/min per 1.73 m^2, CKD 33%	141/80 mm Hg at 1 yr, 71% improved BP control.*	s-Cr, from 283 to 209 mmol/L at 12 mos	…
Bersin et al. (2013),[3] REFORM	N=100	72 y	-	150/74 mm Hg	s-Cr 1.3 mg/dL, eGFR 61 mL/min per 1.73 m^2, CKD 59%	141/78 mm Hg at 9 mos (160–180 mm Hg at baseline, –30 mm Hg; >180 mm Hg at baseline, –48 mm Hg)	NS. at 9 mos	…
Chrysant et al. (2014),[4] HERCULES	N=202	-	≥2	162/78 mm Hg	s-Cr 1.2 mg/dL, eGFR 58 mL/min per 1.73 m^2	SBP levels were 162, 145, 145, 144, and 146 mm Hg at baseline, 1 mo, 9mos, 2 and 3y.	NS. at 3 y	…
Jujo et al. (2016)[17]	N=31	-	-	135/74 mm Hg (24-h BP in ABPM)	s-Cr 1.18 mg/dL	Responders showed a higher 24-h BP at baseline than non-responders (148/81 mm Hg vs 126/70 mm Hg), but this relationship was not shown in office BP (149/75 vs 144/78 mm Hg).	…	…
Randomized controlled trial, PTRA adding DT vs DT alone								
van Jaarsveld et al. (2000),[10] DRASTIC	PTRA (n=56) DT (n=50)	PTRA: 59 y DT: 61 y	2.3 vs 1.8 (NS)	185/107 mm Hg vs 179/101 mm Hg (NS)	s-Cr <2.3 mg/dL	There were no differences in BP levels, daily drug use, or renal function at 12 mos.	NS.	…
Bax et al. (2009),[11] STAR	PTRA (n=64) DT (n=76)	PTRA: 66y DT: 67 y	2.8 vs 2.9 (NS)	160/83 mm Hg vs 163/82 mm Hg (NS)	eGFR 46 mL/min per 1.73 m^2	There were no differences in BP levels or daily drug use at 2 y FU.	NS.	No differences in mortality and CVD events at 2 y FU
ASTRAL Investigators, (2009),[12] ASTRAL	PTRA (n=403) DT (n=403)	PTRA: 70y DT: 71 y	2.8 vs 2.8 (NS)	149/76 mm Hg vs 152/76 mm Hg	s-Cr 179 mmol/L vs 178 mmol/L; eGFR 40 mL/min per 1.73 m^2 vs 40 mL/min per 1.73 m^2	There were no differences in BP levels at 5yrs FU (141/73 mm Hg vs 141/70 mm Hg).	NS.	No difference in overall mortality at 5 y FU

(*Continued*)

Table 1. Continued

Study (y)	Number	Baseline		BP	Renal function	Outcomes		
		Mean age	No. of antihypertensive drugs			Changes in BP	Changes in renal function	CVD outcomes
Cooper et al. (2014),[13] CORAL	PTRA (n=467) DT (n=480)	PTRA: 68y DT: 69y	2.1 in the group of all participants	SBP 150 mm Hg vs 150 mm Hg.	eGFR 58 mL/min per 1.73 m^2 vs 57 mL per min per 1.73 m^2	The PTRA group showed an advantage (−2.3 mm Hg); number of meds: 3.3 vs 3.5.	NS.	No difference in cardiovascular mortality at 5 y

ABPM indicates ambulatory BP monitoring; ASTRAL, Angioplasty and Stenting for Renal Artery Lesions; BP, blood pressure; CCr, creatinine clearance; CORAL, Cardiovascular Outcomes in Renal Atherosclerotic Lesions; CVD, cardiovascular disease; DRASTIC, Dutch Renal Artery Stenosis Intervention Cooperative; DT, drug therapy; eGFR, estimated glomerular filtration; FU, follow-up; HERCULES, Herculink Elite Renal Stent to Treat Renal Artery Stenosis; Meds, medications; NS, not significant; REFORM, Reducing Falls with Orthoses and a Multifaceted Podiatry Intervention; RI, renal resistive index; SBP, systolic BP; s-Cr, serum creatinine; and STAR, Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function.

*Reduced diastolic BP to <90 mm Hg and/or SBP <140 mm Hg on the same or reduced number of meds, or reduced diastolic BP by at least 15 mm Hg with the same or reduced number of meds.

an elevated BP level at bedtime and/or an abnormal nocturnal BP dipping pattern.

Disturbed patterns of nocturnal BP dipping are more important risk factors for CVD. Our research group reported that in patients with resistant hypertension, nighttime BP assessed by home BP monitoring is a superior predictor for CVD incidence compared with daytime home BP.[18] Based on the known mechanisms of renovascular hypertension, we speculated that the nighttime BP level may be elevated in patients with resistant hypertension due to renal artery stenosis. This nighttime BP level in renovascular hypertension may be a favorable treatment target to prevent CVD incidence in these patients, as intensive management of nighttime BP is important in all resistant hypertension. From this viewpoint, scientific research evaluating the effect on nighttime BP of adding PTRA to drug therapy is needed.

Second, in clinical practice, atherosclerotic renal artery stenosis is typically comorbid with systemic atherosclerosis, which makes patients with atherosclerotic renal artery at high risk of CVD events. It has been reported that patients with renal artery stenosis have high frequencies of atherosclerotic cardiovascular disease as a complication: 10% develop stroke, 6% to 40% develop coronary artery disease, and 20% to 38% develop abdominal aortic aneurysm. Indeed, the incidence of atherosclerotic heart disease is about 4 times more likely in patients with renal artery stenosis than in the general population (304/1000 patient years versus 74/1000 patient years).[19] Patients with renal artery stenosis complicated with resistant hypertension thus require strict risk management for CVD including intensive control of BP. A current meta-analysis assessing total 344 716 participants in 48 randomized controlled trials regarding pharmacological BP lowering for prevention of CVD events has reported a hazard ratio of 0.90 (95% CI, 0.86–0.92) for each 5-mm Hg reduction in systolic BP for composite cardiovascular events.[20] Although a 5-mm Hg decrease in SBP may seem slight, it does have a risk-reducing effect for CVD events. Therefore, it may be important to add PTRA to drug therapy in patients with resistant hypertension due to atherosclerotic renal artery stenosis who have a high risk of CVD events.

The results of Reinhard et al.'s study in *JAHA* thus may support the benefit of renal artery stenting for patients with uncontrolled resistant hypertension due to renal artery stenosis. If limited to those predicted to be good responders, the addition of PTRA to drug therapy may lead to risk reduction of CVD events in patients with renal artery stenosis-induced resistant hypertension. Moreover, a greater freedom from the mechanisms of renovascular hypertension including excessive activation of the renal angiotensin aldosterone system and sympathetic nervous system, excessive fluid retention, nighttime BP elevation, abnormal nocturnal BP dipping, and elevated BP variability may

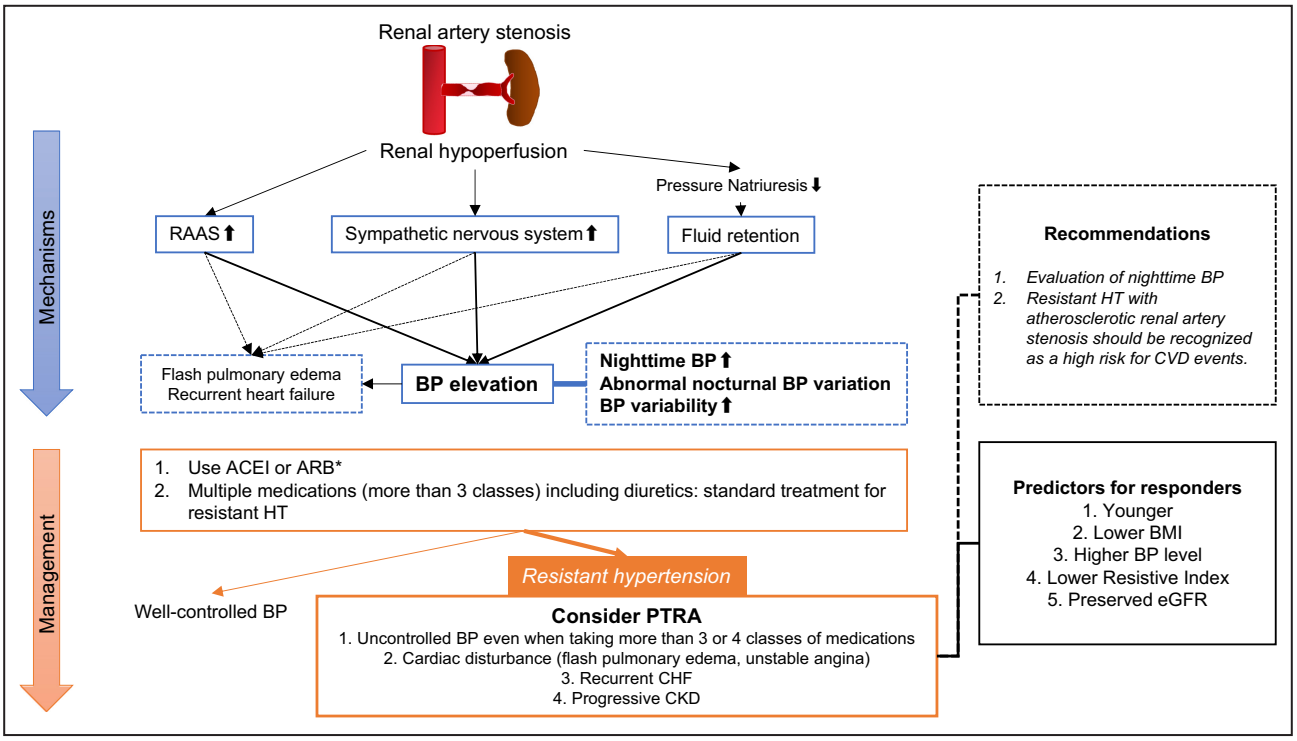

Figure. Mechanisms and management of renovascular hypertension.
Renal artery stenosis leads to renal hypoperfusion, which induces excessive activation of the RAAS and the sympathetic nervous systems, as well as fluid retention caused by the decrease in pressure natriuresis. These abnormalities cause elevation of BP levels and flash pulmonary edema. Based on the mechanisms of renovascular hypertension, we speculated that an increase in nighttime BP levels and abnormal nocturnal BP dipping may occur in patients with resistant hypertension due to renovascular disease. Nighttime BP is an important target to prevent CVD events especially in resistant hypertension. In the management of renovascular hypertension, interventional renal angioplasty including PTRA should be considered in patients with poor BP control despite adequate use of multiple antihypertensive medications. *Contraindicated in bilateral stenosis and taking care of renal dysfunction. ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor antagonist; BMI, body mass index; BP, blood pressure; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR; estimated glomerular filtration ratio; HT, hypertension; PTRA, percutaneous transluminal angioplasty; and RAAS, renin angiotensin aldosterone system.

occur. Again, from this perspective, the relationship of PTRA with nighttime BP control and BP variability should be assessed to discover new aspects of the effect of PTRA.

ARTICLE INFORMATION

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Disclosures

K. Kario has received research funding from Omron Healthcare Co., Fukuda Denshi, and A&D Co. The remaining authors have no disclosures to report.

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