Hypertension Research (2014) 37, 349–361

www.nature.com/hr

GUIDELINES (JSH 2014)

Chapter 13. Secondary hypertension

Hypertension Research (2014) **37,** 349–361; doi:10.1038/hr.2014.16

OVERVIEW AND SCREENING

Hypertension related to a specific etiology is termed secondary hypertension, markedly differing from essential hypertension, of which the etiology cannot be identified, in the condition and therapeutic strategies. Secondary hypertension is often resistant hypertension, for which a target blood pressure is difficult to achieve by standard treatment. However, blood pressure can be effectively reduced by identifying its etiology and treating the condition. Therefore, it is important to suspect secondary hypertension and reach an appropriate diagnosis.

Frequent etiological factors for secondary hypertension include renal parenchymal hypertension, primary aldosteronism (PA), renovascular hypertension and sleep apnea syndrome. Renal parenchymal hypertension is caused by glomerular diseases, such as chronic glomerulonephritis and diabetic nephropathy, interstitial kidney diseases, such as chronic pyelonephritis, and polycystic kidney disease (PKD). Hypertension is observed in approximately 50–70% of patients with CKD.[981] The incidence of hypertension increases with the degree of renal hypofunction. In patients with PA, an excessive production of aldosterone in the adrenal glands is involved in the pathogenesis of hypertension. As therapeutic strategies differ between unilateral and bilateral lesions, localized diagnosis is important. Concerning renovascular hypertension, renal artery stenosis-related hyperactivity of the renin–angiotensin (RA) system contributes to an increase in blood pressure. In patients with sleep apnea syndrome, various factors such as hyperactivity of the sympathetic nervous and RA systems cause hypertension, increasing blood pressure fluctuation. As other etiological factors for secondary hypertension, the following conditions have been reported: in endocrine hypertension, pheochromocytoma and Cushing's syndrome are related to an excessive production of catecholamines and cortisol, respectively. Hypo-/hyperthyroidism, hyperparathyroidism and acromegaly are also etiologically involved in hypertension. In vascular hypertension, angiitis syndrome, such as aortitis syndrome, polyarteritis nodosa (PN) and systemic scleroderma, aortic coarctation and aortic insufficiency have been reported. Compression of the rostral ventrolateral medulla by brainstem blood vessels causes hypertension through hyperactivity of the sympathetic nerves. Furthermore, hypertension is also observed in patients with brain tumors or cerebrovascular disease. In addition, hereditary or drug-induced hypertension has been reported.

It has been recognized that secondary hypertension accounts for ~10% of hypertensive patients,[982,983] but a study indicated that the incidence of PA was higher than previously reported; at least 10% of hypertensive patients may have secondary hypertension. As secondary hypertension is often resistant to treatment, the incidence of secondary hypertension in patients with a resistance-resistant hypertension may be higher. According to several studies, PA accounts for approximately 5–10% of hypertensive patients,[984,985] and it is the most frequent in endocrine hypertension. In addition, frequent etiological factors for secondary hypertension include renal parenchymal hypertension and renovascular hypertension. A study reported that sleep apnea syndrome was the most frequent factor for secondary hypertension.[517] The number of patients with secondary hypertension may further increase with the widespread diagnosis of sleep apnea syndrome.

Generally, the presence of severe or resistant hypertension, juvenile hypertension and the rapid onset of hypertension suggest the possibility of secondary hypertension. In such hypertensive patients, a close inquiry on medical history, medical examination and adequate examinations must be performed, considering the possibility of secondary hypertension. Table 13-1 shows findings suggestive of major types of secondary hypertension and tests necessary for their differential diagnosis. The possibility of secondary hypertension should be considered in the diagnosis and treatment of all hypertensive patients. It is important to conduct appropriate examinations without overlooking findings of secondary hypertension.

1. RENAL PARENCHYMAL HYPERTENSION

Renal parenchymal hypertension is caused by renal parenchymal disorders and is the most common form of secondary hypertension, accounting for 2–5% of all hypertensive patients.[982,986–991] In the Hisayama Study, which followed up a general population aged over 40 years, autopsy was performed on 131 hypertensive patients during the 20 years after 1961, and the incidence of secondary hypertension was 3.8%. Renal parenchymal hypertension was observed in 3.1% of hypertensive patients, accounting for ~80% of patients with secondary hypertension.[991]

The incidence of end-stage renal failure has increased despite advances in antihypertensive treatment, but has recently decreased slightly. In 38 613 patients in whom hemodialysis was initiated in 2011, the most frequent underlying disease was diabetic nephropathy (n=16 803, 44.3%), with chronic glomerulonephritis being the second most frequent (n=7670, 20.2%) and nephrosclerosis being the third (n=4475, 11.8%). Together with PKD, which was the fourth most frequent underlying disease (n=957, 2.5%), these four diseases accounted for ~80%.[992] Most of these chronic kidney diseases (CKDs) induce hypertension, but hypertension promotes the progression of kidney damage and establishes a vicious circle leading to end-stage renal failure.[993,994] As there is no radical treatment for CKD at present, blood pressure control by antihypertensive drug therapy primarily using RA system inhibitors (angiotensin II receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors) is extremely important for the prevention of end-stage renal failure.[995] In Japan, there are marked regional differences in the incidence of

Table 13-1 Findings suggesting major types of secondary hypertension and examinations necessary for differential diagnosis

Underlying disease	*Suggestive findings*	*Examinations necessary for differential diagnosis*
Secondary hypertension in general	Severe hypertension, resistant hypertension, hypertensive crisis and juvenile hypertension	
Renovascular hypertension	Rapid deterioration of the renal function after the administration of RA system inhibitors, laterality in the kidney size, hypokalemia and abdominal vascular bruit	Renal artery ultrasonography, abdominal CTA, abdominal MRA, renoscintigraphy, PRA and PAC
Renal parenchymal hypertension	Increase in the serum Cr level, proteinuria, hematuria and a history of kidney disease	Seroimmunological test, abdominal CT, ultrasonography and kidney biopsy
Primary aldosteronism	Hypokalemia, adrenal incidentaloma	PRA, PAC, load test, adrenal CT and adrenal venous blood collection
Sleep apnea syndrome	Snoring, obesity, daytime sleepiness and morning/nighttime hypertension	Polysomnography
Pheochromocytoma	Paroxysmal/labile hypertension, palpitation, headache and sweating	Blood/urinary catecholamines and their metabolites, abdominal ultrasonography/CT and MIBG scintigraphy
Cushing's syndrome	Central obesity, moon face, striated skin and hyperglycemia	Cortisol, ACTH, abdominal CT, cephalic MRI and dexamethasone suppression test
Sub-clinical Cushing's syndrome	Adrenal incidentaloma	Cortisol, ACTH, abdominal CT and dexamethasone suppression test
Drug-induced hypertension	Previous drug administration, hypokalemia	Confirmation of previously administered drugs
Aortic coarctation	Differences in blood pressure between the upper and lower limbs, vascular murmurs	Thoracic/abdominal CT, MRI/MRA and angiography
Hypothyroidism	Bradycardia, edema, hypoactivity and increases in the levels of lipids, CPK and LDH	Thyroid hormone, TSH, autoantibody and thyroid ultrasonography
Hyperthyroidism	Tachycardia, sweating, weight loss and a decrease in the cholesterol level	Thyroid hormone, TSH, autoantibody and thyroid ultrasonography
Hyperparathyroidism	Hypercalcemia	Parathyroid hormone
Brainstem vascular compression	Facial spasm, trigeminal neuralgia	Brain MRI/MRA

Abbreviations: ACTH, adrenocorticotropic hormone; CPK, creatine phosphokinase; CTA, CT angiography; LDH, lactate dehydrogenase; MIBG, metaiodobenzylguanidine; MRA, magnetic resonance angiography; PAC, plasma aldosterone concentration; PRA, plasma renin activity; RA, renin–angiotensin; TSH, thyrotropin-releasing hormone.

end-stage renal failure.[996,997] As a negative correlation exists between its incidence and the prescribed amount of RA system inhibitors,[998,999] RA system inhibitors may actually suppress the progression to renal failure. Recently, however, an increase in the incidence of renal failure has been more markedly inhibited in regions in which its incidence had been higher. The regional differences in the incidence of end-stage renal failure have almost disappeared.[1000]

As there is a close relationship between CKD and hypertension, it is often difficult to determine which came first, CKD or hypertension, if they are concurrent. If abnormal findings have been obtained on urinalysis, or renal dysfunction has appeared before hypertension, or if the presence of hypertension, proteinuria or renal dysfunction from an early phase of pregnancy (superimposed pre-eclampsia) can be confirmed, hypertension is likely to be caused by CKD. Also, if hypertension is mild relative to abnormal urinary findings or kidney damage, or if there are few hypertensive cardiovascular complications concurrent with the kidney disorders, CKD is considered to underlie the hypertension. Urinalysis and measurement of the serum creatinine concentration should be performed in all hypertensive patients, and, if an abnormality persists, kidney morphology must be evaluated using abdominal ultrasonography or CT.

As the prognosis of CKD, especially renal parenchymal disease, may be improved by early treatment, it is strongly recommended to promptly refer patients suspected of having renal parenchymal disorders to nephrologists.[439] Hypertensive nephrosclerosis, which causes renal dysfunction on the basis of essential hypertension, and diabetic nephropathy are discussed in Section 3 of Chapter 6, KIDNEY DISEASE.

1) Chronic glomerulonephritis

Patients with chronic glomerulonephritis frequently develop hypertension from an early stage. Blood pressure is elevated further with the progression of renal dysfunction, and hypertension occurs in nearly all patients with end-stage renal failure.[1001] Hypertension is observed more often in patients with marked tissue damage on kidney biopsy. It may be caused by body fluid expansion due to Na retention (increased salt sensitivity), inappropriate activation of the RA system and due to an involvement of the sympathetic nervous system.[993,994,1002,1003]

Therapeutic strategies for hypertension related to chronic glomerulonephritis should be basically determined in accordance with those for CKD complications (see Section 3 of Chapter 6, KIDNEY DISEASE).

2) Polycystic kidney disease

PKD is a disease in which a large number of cysts develop in the bilateral kidneys. Confirmation of the presence of many cysts in the bilateral kidneys by abdominal ultrasonography or CT is necessary for diagnosis.[1004] The genes responsible for PKD are mostly autosomal dominant *PKD1* (short arm of chromosome 16) and *PKD2* (long arm of chromosome 4), and the disease is transmitted rarely by autosomal recessive inheritance. PKD1 accounts for 80–90% of the disease, with PKD2 accounting for the rest.[1005] The number of patients treated for PKD at medical institutions accounts for 1 in 2000–4000 of the population.[1006] The disease is progressive, and renal function reduces gradually, resulting in end-stage renal failure in about 40% of patients in their 50s.[1006]

Hypertension is observed in about 60% of patients at an early stage, when renal function remains normal,[1001,1007] and it occurs in all patients with end-stage renal failure.[1008] Cysts displace blood vessels, causing ischemia in local kidney tissues, and the resultant increases in renin section and sympathetic activity are involved in the genesis of hypertension.[1009] Therapeutic strategies should be determined in ac-

cordance with those for CKD complications (see Section 3 of Chapter 6, KIDNEY DISEASE).

3) Ischemic nephropathy

Ischemic nephropathy is a disease in which atherosclerosis-based bilateral renal artery stenosis causes renal dysfunction. It is not necessarily a renal parenchymal disease in a narrow sense, but the condition resembles bilateral renovascular hypertension. Although its incidence is increasing in Europe and the United States,[1010,1011] this disease name is absent in Japan, and this disease may be overlooked as nephrosclerosis. According to data, the incidence of end-stage renal failure associated with nephrosclerosis has steadily increased,[992] possibly because the number of patients with ischemic nephropathy is increasing, as reported in foreign countries (for antihypertensive treatment, see Section 2 of Chapter 13, RENOVASCULAR HYPERTENSION).

2. RENOVASCULAR HYPERTENSION

POINT 13A

1. **Renovascular hypertension (RVHT) is hypertension caused by stenosis or obstruction of the renal artery and is observed in about 1% of all hypertensive patients. Its primary cause is atherosclerosis in middle-aged and elderly patients and fibromuscular dysplasia in younger patients. Atherosclerotic RVHT is often complicated by other vascular diseases such as peripheral and coronary artery diseases. Significant unilateral or bilateral renal artery stenosis and renal dysfunction cause progressive renal failure called ischemic nephropathy (Evidence level: II).**
2. **In patients with juvenile hypertension, severe or resistant hypertension, exacerbating hypertension, abdominal vascular bruit, a lateral difference in kidney size or deterioration of renal dysfunction after the administration of an RA system inhibitor, RVHT should be suspected (Recommendation: Grade C1, Evidence level: IVa).**
3. **A diagnosis of RVHT should be made on the basis of morphological evaluation involving diagnostic imaging. If necessary, functional assessment should be performed as an auxiliary procedure. Initially, renal artery ultrasonography, which is useful for morphological and functional screening, must be considered. In addition, magnetic resonance angiography (MRA) and CT angiography (CTA) should be considered in accordance with renal function (Recommendation Grade: C1, Evidence level: IVa).**
4. **RVHT treatment is started with antihypertensive drugs in many cases. Combination therapy with RA system inhibitors, Ca channel blockers, diuretics and β-blockers should be administered until a target blood pressure is achieved (Recommendation Grade C1, Evidence level: IVa).**

The use of RA system inhibitors should be considered because they are useful for reducing blood pressure, maintaining renal function and improving the prognosis in patients with unilateral RVHT (Recommendation Grade C1, Evidence level: IVa).

In patients with bilateral RVHT, RA system inhibitors may rapidly induce renal dysfunction, and are contraindicated as a general rule (Recommendation Grade C2, Evidence level: IVa).

A combination of percutaneous transluminal renal angioplasty (PTRA) and antihypertensive drug therapy is useful for reducing blood pressure, but evidence regarding renoprotective effects is not sufficient. Although PTRA should be carefully indicated, it may be considered in accordance with individual patients (Recommendation Grade B, Evidence level: II).

However, in patients with fibromuscular dysplasia, potent hypotensive effects are achieved, and the long-term prognosis is relatively favorable. Therefore, PTRA should be performed (Recommendation Grade C1, Evidence level: IVa).

Renovascular hypertension is caused by stenosis or obstruction of the renal artery and is observed in about 1% of hypertensive patients. The most frequent cause of renal artery stenosis is atherosclerosis, which is common in middle-aged and elderly people, followed by fibromuscular dysplasia, which occurs more frequently in young people. Aortitis syndrome (Takayasu's arteritis), which frequently affects young women, is also rarely noted. RVHT may also be caused by congenital malformations, aortic dissection, compression of the renal artery by extrarenal masses and thromboembolism. Stenosis is either unilateral or bilateral. Atherosclerosis usually occurs at the origin of the renal artery, whereas fibromuscular dysplasia occurs more often in the middle to distal parts.[1012]

Atherosclerosis of the renal artery suggests advanced systemic arteriosclerosis and is often complicated by peripheral/coronary artery diseases, renal hypofunction and proteinuria. According to reports in Japan, 50% or greater stenosis of the renal artery was observed in 10% of patients who underwent coronary angiography, in 18% of hypertensive patients, in 25% of patients with peripheral artery disease, in 33% of those with abdominal aortic aneurysms[1013] and in 27% of those with marked carotid stenosis.[1014] Fibromuscular dysplasia has subtypes, such as intimal and medial thickening, and may be accompanied by other lesions of vascular stenosis. Aortitis syndrome is accompanied by findings of inflammation, stenosis or dilation of other large vessels, and lateral or vertical differences in blood pressure are often noted.

In many patients with renovascular hypertension, renal function is normal. On the other hand, hemodynamically significant unilateral or bilateral renal artery stenosis and renal dysfunction cause progressive renal failure called ischemic nephropathy. Ischemic nephropathy accounts for about 10% of underlying diseases of end-stage renal failure.[1015]

1) Diagnostic clues

Table 13-2 shows histories and clinical signs that suggest RVHT and ischemic nephropathy. However, these histories or signs are not observed in all patients.

Table 13-2 Diagnostic clues to renovascular hypertension

- Onset of hypertension before the age of 30 years or severe hypertension after the age of 55
- Accelerated, resistant or malignant hypertension
- Development of new azotemia or worsening renal function after administration of an ACE inhibitor or ARB agent
- Unexplained atrophic kidney or size discrepancy between kidneys of greater than 1.5 cm
- Sudden, unexplained pulmonary edema
- Unexplained renal dysfunction, including individuals starting renal replacement therapy
- Abdominal vascular bruit
- Other vascular diseases such as peripheral artery disease
- Hypokalemia

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin ii receptor blocker.
Reference 1018 was partially modified and quoted.

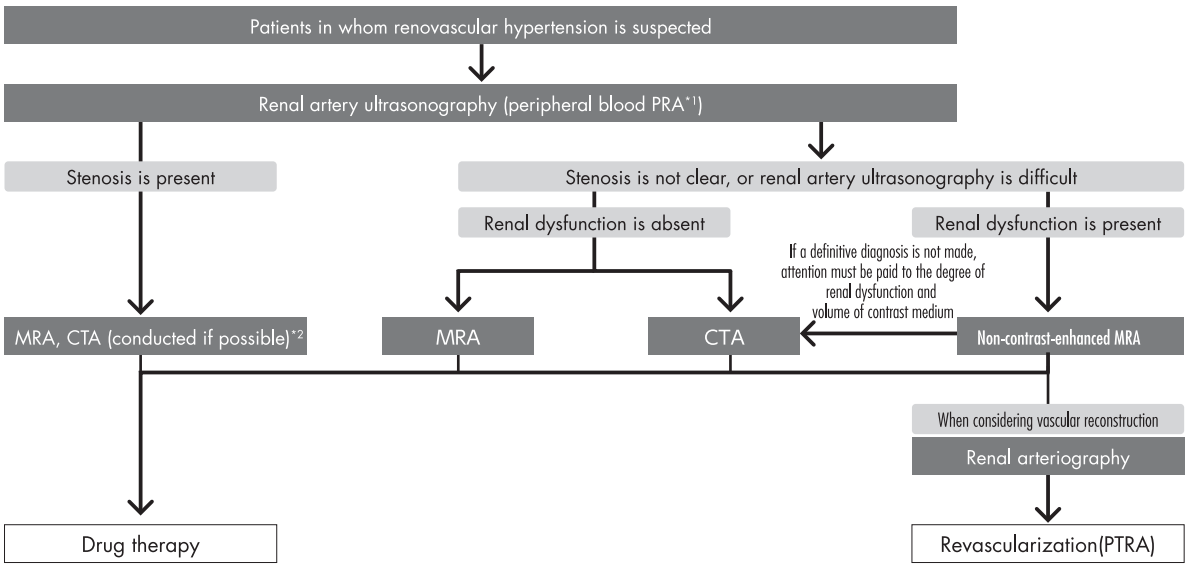

Figure 13-1 Examinations to make a definitive diagnosis of renovascular hypertension. *1Functional diagnostic procedures such as peripheral blood PRA, captopril-loaded PRA and renography should be used as auxiliary procedures. *2In patients with renal dysfunction, non-contrast-enhanced MRA or CTA should be considered. A full color version of this figure is available at the *Hypertension Research* journal online.

2) Examinations for a definitive diagnosis

For the diagnosis of renovascular hypertension, it is necessary to demonstrate the presence of hypertension and involvement of renovascular stenosis as its etiological factor (Figure 13-1). Examinations include functional diagnosis based on plasma renin activity (PRA), renal scintigraphy findings (renograms) and captopril-loaded PRA and morphological diagnosis by renal artery ultrasonography, MRA and CTA.

Renal artery ultrasonography is inexpensive and noninvasive and facilitates a morphological and functional diagnosis. This procedure should be first considered due to its accuracy.[1016] In particular, a high-level accuracy can be obtained using the peak systolic velocity as an index (sensitivity: 84–98%, specificity: 62–99%).[1017,1018] However, this examination has limitations: obesity or intestinal gas makes it difficult to visualize the renal artery, and, when the unilateral renal artery consists of multiple vessels, its visualization is affected. Furthermore, this procedure depends on operators, and there are regional or facility-related differences in special technician skills.[1019]

MRA and CTA should be considered if renal artery ultrasonography is impossible or if the above screening does not reach a conclusion. If renal artery ultrasonography suggests stenosis, its presence should also be morphologically confirmed using MRA or CTA. Contrast-enhanced MRA is highly accurate,[1020] but may cause renal systemic fibrosis; therefore, as a rule, it should be avoided in patients with an eGFR of $<30\,ml\,min^{-1}$ per $1.73\,m^2$.[1021] According to a recent study, the sensitivity and specificity of non-contrast-enhanced MRA without contrast medium have become similar to those of contrast-enhanced MRA,[1022] and this procedure should be predominantly used. However, it must be considered that both the sensitivity and specificity markedly depend on devices and examiner skills. CTA is also highly accurate.[1020] In particular, its spatial/temporal resolution is more favorable than that of MRA or arteriography, and clearer, high-quality images can be obtained. Contrast medium must be carefully used in accordance with renal function.[1023] On the other hand, stenosis may be overestimated in the presence of calcified lesions on CT. On MRI, it is difficult to evaluate intra-stent stenosis due to metallic artifacts. If noninvasive examinations do not lead to a definitive diagnosis and whether or not indications for percutaneous angioplasty is examined, aortic angiography with a catheter or left and right selective renal arteriography should be finally considered. Although PRA can be simply measured, it is not high in some patients with bilateral renal artery stenosis.

Moreover, PRA is normal in 20–37% of patients with renovascular hypertension, and there is also an increase in PRA in some patients with essential hypertension.[1024,1025] The sensitivity and specificity of captopril-loaded PRA and captopril-loaded renography are slightly lower than those of MRA and CTA.[1020] On the other hand, captopril-loaded renography is useful for evaluating a split renal function and lateral difference in the renal blood flow. Currently, most international guidelines claim that the above functional diagnosis, which has been conducted, is not appropriate for screening in comparison with morphological diagnosis primarily using images; it should be used as an auxiliary procedure.[1018]

A diagnosis of renovascular hypertension is predicted on the basis of medical history, supported by laboratory data, and confirmed by imaging procedures. Considering the characteristics of individual patients and the facility's examination capacity, it is important to review the merits and limitations of morphological and functional diagnoses.

3) Treatment

(1) Antihypertensive drug therapy. The treatment of renovascular hypertension is started with antihypertensive drugs in many cases. Several large-scale clinical studies compared antihypertensive drug therapy with a combination of antihypertensive drug therapy and PTRA, and indicated that the hypotensive and renoprotective effects of the former were similar to those of the later.

According to some studies, ACE inhibitors contributed to improvement in the prognosis and renal function in both the antihypertensive drug therapy and PTRA-combined groups in comparison with other antihypertensive drugs.[1026,1027] A study reported that, in patients taking ACE inhibitors or ARBs, the risk of heart failure-related admission, that of dialysis introduction, and mortality rate were lower than in those taking other antihypertensive drugs.[1028] In

patients with unilateral renal artery stenosis-related hypertension, the use of RA system inhibitors should be considered. However, a study indicated that the use of these drugs increased the risk of acute renal failure-related admission.[1028] As there is always a risk of the rapid progression of renal dysfunction or an excessive decrease in blood pressure in a specific percentage of patients, caution is needed for the use of RA system inhibitors.

In patients with bilateral renal artery stenosis, RA system inhibitors may induce the rapid exacerbation of renal function[1029] and are contraindicated as a general rule. When using ARBs and ACE inhibitors, they should be started at a low dose, and the dose should be adjusted by paying attention to excessive decreases in blood pressure, hyperkalemia and renal function. If the renal function deteriorates rapidly, administration should be discontinued, and the drugs should be substituted for other antihypertensive agents. Combination therapy with Ca channel blockers, diuretics and β-blockers should be performed until a target blood pressure level is achieved.

(2) Vascular reconstruction. For vascular reconstruction, PTRA is initially considered because of its low-level invasiveness. In patients with fibromuscular dysplasia, the initial success rate of PTRA is high,[1030] and PTRA may be a first-choice procedure unless it is technically difficult. The long-term prognosis of fibromuscular dysplasia after PTRA is also relatively favorable, but restenosis may occur.[1031] On the other hand, in patients with atherosclerotic renal artery stenosis, the initial response rate to PTRA using a balloon alone was slightly low, and the restenosis rate was high; the results of treatment were not always satisfactory.[1032] Since the introduction of a stent, the results of treatment have improved, with marked improvement in renal function and blood pressure.[1033]

The results of previous clinical studies have not demonstrated any marked difference between antihypertensive drug therapy alone and a combination of antihypertensive drug therapy and PTRA.[1034–1039] In 2009, two large-scale randomized clinical trials (RCTs) were reported. The results of the two trials did not show any further prognosis improving the effects of PTRA in combination with antihypertensive drug therapy with respect to the hypotensive effects, renal function and prevention of complications such as chronic kidney disease, supporting antihypertensive drug therapy alone from the perspective of the risk of PTRA-related complications.[1040,1041] These trials, however, had methodological limitations. The latest randomized trial (CORAL study) also failed to show a clear benefit for PTRA except for a slight improvement in blood pressure with stenting.[1042] At present, PTRA may be considered for (I) patients with hemodynamically significant renal artery stenosis and <1> resistant hypertension in whom the target of blood pressure control is not achieved despite the use of three or more antihypertensive drugs including a diuretic, <2> exacerbating hypertension, <3> malignant hypertension, <4> hypertension with idiopathic unilateral kidney atrophy, <5> idiopathic pulmonary edema that suddenly develops, <6> repeated heart failure, <7> unstable angina or <8> fibromuscular dysplasia, as well as (II) patients with bilateral renal artery stenosis and (III) progressive chronic kidney disease patients with renal artery stenosis of a single kidney that functions.[1018]

In some patients in whom vascular reconstruction by PTRA is difficult or hypertension is resistant to drug therapy, surgery may also be an option. Several studies compared PTRA with surgery, and reported that the patency rate and prognosis in the surgery group were similar to or more favorable than those in the PTRA group,[1043,1044] whereas another study indicated a high mortality rate.[1045] Internationally, the number of patients for whom surgical procedures such as nephrectomy and bypass are indicated has decreased, and PTRA should be initially considered.

For antihypertensive drug therapy alone or a combination of antihypertensive drug therapy and PTRA, serial changes in the serum creatinine level, the kidney size on ultrasonography and peak systolic velocity must be carefully examined.

3. ENDOCRINE HYPERTENSION

POINT 13B

1. **As appropriate diagnosis and treatment of endocrine hypertension are essential, patients in whom endocrine hypertension is suspected should be referred without delay to the specialists of The Japanese Society of Hypertension and/or the Japan Endocrine Society (Recommendation Grade: B, Consensus).**
2. **The incidence of PA is high. The disease can be cured, but often causes organ damage. Early diagnosis and treatment are therefore important. In hypertensive patients, especially in those at a high risk of PA, screening should be positively performed, and a definitive diagnosis should be made based on the results of confirmatory tests and localization diagnosis (Recommendation Grade: B, Consensus, Evidence level: IVa).**
3. **For the diagnosis of Cushing's syndrome, attention should be paid first to characteristic physical findings, followed by measurement of blood cortisol and adrenocorticotropic hormone (ACTH) levels and the dexamethasone suppression test. In cases of adrenal incidentaloma, subclinical Cushing's syndrome should be differentiated (Recommendation Grade: B, Consensus, Evidence level: IVa).**
4. **Pheochromocytoma/paraganglioma should be suspected on the basis of symptoms such as headache and paroxysmal hypertension. Diagnosis should be made on the basis of the measurement of catecholamines and their metabolites and imaging examinations. As about 10% of pheochromocytomas/paragangliomas are malignant, follow-up should be carefully continued after initial surgery (Recommendation Grade: B, Consensus, Evidence level: IVa).**
5. **Characteristic physical findings are clues to the diagnosis of acromegaly, hyperthyroidism and hypothyroidism. Hypercalcemia suggests primary hyperparathyroidism (Evidence level: IVa).**

Endocrine hypertension is a group of diseases in which hypertension is caused by excessive hormone secretion from the endocrine organs, represented by PA, Cushing's syndrome and pheochromocytoma. Although endocrine hypertension can be cured by the treatment of the primary disease, a delay in diagnosis is involved in the progression of target organ damage. Early diagnosis and treatment are therefore important. Patients in whom endocrine hypertension is suspected should be referred without delay to the specialists of The Japanese Society of Hypertension and/or the Japan Endocrine Society.

1) Primary aldosteronism

In typical PA patients, hypertension, hypokalemia and hypomagnesemia are observed. The major disease subtypes of PA are aldosterone-producing adenoma and idiopathic aldosteronism. The incidence of PA in hypertensive patients is reported to be ~5% (1.6–11.2%)[984,1046] and that in hypertensive patients with various complications is ~20%

Table 13-3 Hypertensive patients at a higher risk of PA in whom a screening test is strongly recommended

- Hypertension complicated by hypokalemia (including diuretic-induced hypokalemia)
- Hypertension in young patients
- Grade II or severer (moderate/severe) hypertension
- Resistant hypertension
- Hypertension with adrenal incidentaloma
- Hypertension complicated by cerebrovascular disease at $\leqslant$40 years of age

Abbreviation: PA, primary aldosteronism.

Table 13-4 Influence of various antihypertensive drugs on PAC, PRA and ARR

	PAC	*PRA*	*ARR*
ACE inhibitors/ARBs	↓	↑↑	↓[a]
β-blockers	↓	↓↓	↑[b]
Renin inhibitor	↓	↓↓	↑[b]
Ca channel blockers	→~↓	↑	↓[a,c]
Aldosterone antagonists, Thiazide diuretics	↑	↑↑	↓[a]

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin ii receptor blocker; ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity.
[a]Possibility of false-negative results.
[b]Possibility of false-positive results.
[c]The influence is less marked than that of ACE inhibitors and ARBs.

(11.3–31%), being higher than previously estimated. As PA is often associated with target organ damage including the brain, cardiovascular system and kidneys,[1047,1048] it is the most important cause of endocrine hypertension. Guidelines for PA treatment were also published by the Endocrine Society (USA)[1049] and the Japan Endocrine Society.[1050]

(1) Diagnostic clues. A recent study indicated that many patients with PA showed normal K levels.[1051] As PA is difficult to differentiate from essential hypertension, screening should be performed in all hypertensive patients. However, evidence regarding cost-effectiveness has not been established, and screening should be performed particularly in hypertensive patients at a high risk of PA. These patients include those with hypokalemia (including those with diuretic-induced hypokalemia), young patients with hypertension, patients with grade II or severer hypertension (7%),[1052] those with resistant hypertension (11.3–20%),[1053,1054] those with adrenal incidentaloma (4%)[1055] and those, aged under 40 years, with cerebrovascular diseases (Table 13-3). A recent study reported that the incidence of PA was high in patients with sleep apnea syndrome.[1056] Although extremely rare, screening for familial hyperaldosteronism should be performed, if there is a family history of PA. Even when there is a family history of hypertension, PA cannot be ruled out. A study reported that the urinary K/Na ratio increased in patients with PA.[1057]

(2) Screening tests. A plasma aldosterone concentration (PAC) to plasma renin activity (PRA) (or plasma active renin concentration: ARC) ratio (ARR)[1058,1059] of $>$200 (PAC/ARC $>$40) is used for screening. However, considering that it is necessary to prevent false-positive findings evaluated on the basis of a low PRA alone, and that there are many PA patients with a PAC of $<$150 pg ml^{-1}, patients with a PAC of $>$120 pg ml^{-1} are regarded as screening-positive. Values are influenced by conditions for blood collection, but, initially, measurement should be taken after sitting for 15–30 min. If a positive reaction is detected, an additional examination under stricter conditions (after fasting, early in the morning, after a 30-min rest)[1060] or referral to specialists should be considered. As antihypertensive medication can cause a false-positive or false-negative result (Table 13-4), measurement is preferably taken in an untreated condition or after a 2-week medication-free period. If discontinuation is difficult due to the necessity of blood pressure control, measurement should be taken after switching the drugs to Ca channel blockers, α-blockers or hydralazine, which have less marked effects on the PRA or PAC. As spironolactone has marked effects, it should be withdrawn for 2 months or more. For blood pressure control, antihypertensive drugs should be discontinued or switched, considering their advantages and risks.[1061] As a rule, evaluation is performed on a single session of measurement, but an additional examination should be conducted if necessary, considering changes related to various factors.[1062] As PAC is expressed in pg ml^{-1} or ng dl^{-1}, caution is needed.

(3) Confirmatory tests. If a positive reaction is detected on screening, it must be confirmed on at least one of the confirmatory tests presented in Table 13-5 to demonstrate the autonomous secretion of aldosterone.[1063] The confirmatory tests should be performed after correcting hypokalemia using K preparations. Captopril challenge and oral salt-loading tests can be performed at the outpatient clinic. The furosemide-upright test is physically stressful. The saline infusion test has been reported to have excellent specificity, but requires a long duration; it is not appropriate for patients with heart/renal hypofunction. If the ARR and PAC are high (ARR $>$1000, PAC $>$250 pg ml^{-1}), the confirmatory tests can be spared.[1064]

(4) Localization of the lesion site. In patients with positive reactions on confirmatory tests, the localization of the lesion site should be evaluated. Initially, adrenal CT (1- to 3-mm slices, contrast-enhanced CT) should be performed to investigate the presence or absence of a tumor. The tumor detection rate is higher than that of MRI. If a tumor is detected in the unilateral adrenal gland, aldosterone-producing adenoma should be suspected. However, the possibility that the tumor may be a nonfunctional lesion cannot be ruled out. Microadenoma measuring 5 mm or smaller, which cannot be confirmed on CT, has also been reported. ^{131}I-adosterol adrenal scintigraphy should be performed under dexamethasone suppression, but the proportion of patients with positive reactions is low in those with microadenoma or nonfunctional lesions. When selecting surgery, it is necessary to accurately evaluate the localization of the lesion site, and adrenal venous sampling should be performed.[1065,1066] The concomitant use of ACTH loading is useful for successfully achieving catheterization and evaluating the localization of the lesion site. On the other hand, this procedure is invasive, and has the following limitations: no localization-evaluating method (parameter, cutoff) has been standardized,[1067,1068] and the success rate for the right adrenal vein is low, raising technical issues. Therefore, whether or not adrenal venous sampling is indicated should be determined, considering the presence or absence of indications for surgery and the patient's wishes. In addition, adrenal venous sampling is recommended to be performed in a skilled, special facility.[1069,1070]

(5) Treatment. In patients with unilateral lesions, laparoscopic adrenalectomy is a first-choice procedure. After surgery, improvement in hypertension, electrolyte abnormalities and organ damage is achieved. The postoperative blood pressure normalization rate

Table 13-5 Type and outline of confirmatory tests

	Methods	*Criteria for positive results*	*Adverse effects*
Captopril challenge test	Oral administration of captopril at 50 mg	ARR (60 or 90 min) $\geqslant 200$[a]	A decrease in blood pressure
Furosemide-upright test	Intravenous injection of furosemide at 40 mg and upright posture for 2 h	PRAmax $\leqslant 2.0\,ng\,ml^{-1}$ per h	Orthostatic hypotension, a decrease in the serum K level
Saline infusion test	Intravenous drip infusion of saline at 2 l per 4 h	PAC (4 h) $\geqslant 60\,pg\,ml^{-1}$	A rise in blood pressure, a decrease in the serum K level, not performed in patients with heart/kidney hypofunction
Oral salt-loading test	24-h urine collection at the outpatient clinic[b]	Urinary aldosterone $\geqslant 8\,\mu g$ per day (urinary Na $\geqslant 170$ mEq per day[c])	A rise in blood pressure, heart failure

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin ii receptor blocker; ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity.
[a]ARR is calculated with PAC in the unit of $pg\,ml^{-1}$.
[b]After the consumption of salt at 10–12 g per day for 3 days in inpatients.
[c]It should be confirmed that salt loading is sufficient.

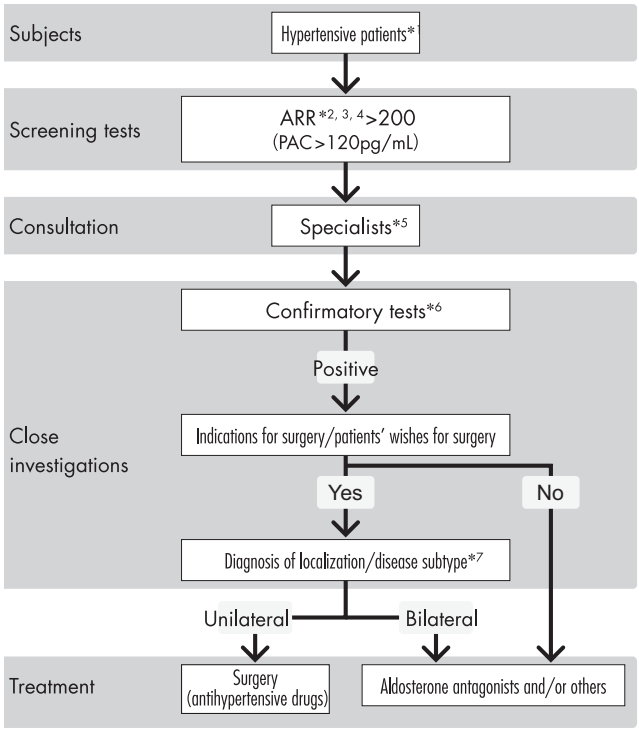

Figure 13-2 Algorithm for the diagnosis of primary aldosteronism. *1Especially those at a higher risk. *2ARR: PAC/PRA ratio. *3Antihypertensive drugs: Test after switching drugs to Ca channel blockers and/or á-blockers. *4Additional examinations should be performed if necessary. *5Patients should be referred to the specialists of The Japanese Society of Hypertension and/or the Japan Endocrine Society. *6At least one positive test should be confirmed. *7Adrenal CT, adrenal scintigraphy and/or adrenal venous sampling.[985] A full color version of this figure is available at the *Hypertension Research* journal online.

depends on the duration and severity of hypertension and the presence or absence of essential hypertension. In patients with no indication or wish for surgery, those with bilateral lesions, or those before surgery, hypertension and hypokalemia must be treated using aldosterone antagonists and other antihypertensive drugs. The preoperative administration of an aldosterone antagonist reduces rapid postoperative changes in hemodynamics through the activation of the RA system, preventing electrolyte abnormalities and renal hypofunction.[1071] Eplerenone less frequently causes adverse effects such as gynecomastia, compared with spironolactone.[1072] However, this drug is contraindicated for diabetics with proteinuria and for patients taking K preparations. Ca channel blockers suppress aldosterone secretion. It remains to be clarified whether aldosterone antagonists are more useful than other antihypertensive drugs for improving the prognosis even in patients with normal serum K levels.

(6) Timing of referral to specialists. Figure 13-2 shows the procedure for the diagnosis of PA in clinical practice. In hypertensive patients, particularly those at a higher risk for PA, screening should be positively performed. If a positive reaction is detected, the patient must be referred to a specialist.

2) Other conditions associated with mineralocorticoid excess

Congenital adrenocortical hyperplasia (17α- and 11β-hydroxylase deficiency) and deoxycorticosterone (DOC)-producing tumors cause hypertension and hypokalemia. Usually, the PRA and aldosterone levels are low to normal.

3) Cushing's syndrome

Cushing's signs, hypertension and diabetes mellitus are caused by the autonomous and excessive secretion of cortisol. The disease conditions are classified into ACTH-dependent and ACTH-independent types. The former includes Cushing's syndrome due to adrenal adenoma, whereas the latter includes Cushing's disease due to ACTH-producing pituitary tumors and ectopic ACTH-producing tumors. Cardiovascular complications such as heart failure influence the prognosis.[1073]

(1) Diagnostic clues. Attention must be paid to central obesity, moon face, buffalo humps, red striae, skin thinning, polytrichosis and acne. Nonspecific findings include hypertension, diabetes mellitus, dyslipidemia, osteoporosis, urolithiasis and nail trichophytia. On general laboratory tests, considerable attention should be paid to eosinopenia and hypokalemia. Cushing's syndrome accounts for ~8% of patients with adrenal incidentaloma.[1074] Adrenal subclinical Cushing's syndrome does not show any characteristic physical findings. Therefore, a differential diagnosis should be carefully made if adrenal incidentaloma is detected.

(2) Diagnosis. Increases in the plasma and urinary free cortisol levels, the absence of cortisol suppression on the dexamethasone suppression test (overnight method) (cortisol after dexamethasone administration at 1 mg: $>5\,\mu g\,dl^{-1}$) and the disappearance of diurnal changes in the plasma cortisol level must be confirmed. Subsequently, whether the condition is dependent on or independent of ACTH must be differentiated through blood ACTH and corticotropin-releasing hormone challenge tests, and adrenal and pituitary lesions should be investigated using adrenal CT and pituitary MRI, respectively.

Subclinical Cushing's syndrome should be diagnosed in accordance with the diagnostic criteria established by the Study Group of the Ministry of Health, Labour and Welfare.[1075]

(3) Treatment. First-choice procedures for adrenal adenoma, Cushing's disease and ectopic ACTH-producing tumors are laparoscopic adrenalectomy, trans-sphenoidal hypophysectomy and resection of the causative mass, respectively. If the tumor diameter is 4 cm or larger or there is a slight increase in its size in patients with subclinical Cushing's syndrome, resection should be performed, considering the possibility of malignancy. In subclinical Cushing's syndrome patients with hypertension, obesity or impaired glucose tolerance, surgery should also be considered.[1076]

(4) Timing of referral to specialists. If Cushing's signs, the concurrence of resistant hypertension and diabetes mellitus, or adrenal incidentaloma is detected, patients should be referred to specialists.

4) Pheochromocytoma/paraganglioma

Adrenal medulla-derived pheochromocytoma and paraganglion-derived paraganglioma have been reported. These lesions are associated with hypertension and impaired glucose tolerance due to catecholamine excess. Extra-adrenal, bilateral, multiple and malignant pheochromocytoma accounts for ~10% of cases, respectively. Diagnosis and treatment should be performed in accordance with the treatment guidelines established by the Study Group of the Ministry of Health, Labour and Welfare.[1077] Malignant pheochromocytoma is the most important issue. Recently, various etiological gene mutations have been reported in patients with malignant pheochromocytoma/paraganglioma.[1078]

(1) Diagnostic clues. Symptoms including headache, palpitation, sweating and pallor, as well as paroxysmal hypertension, are suggestive of pheochromocytoma/paraganglioma. Hypertensive crisis is induced by exercise, stress or excretion. It may also be induced by intravenous metoclopramide injection. The disease may be found as adrenal incidentaloma.

(2) Diagnosis. Increases (threefold the upper limit of the normal range or greater) in the plasma catecholamine level, 24-h urinary catecholamine excretion and urinary excretions of its metabolites, metanephrine and normetanephrine, must be confirmed. Provocation (glucagon, metoclopramide) and phentolamine tests are not recommended because of problems with specificity and safety. The localization of the tumor is determined by CT. However, as the use of contrast medium is essentially contraindicated because of possible induction of hypertensive crisis, phentolamine and propranolol must be prepared if contrast enhancement is indicated. On MRI, a low signal intensity on T1-weighted and a high signal intensity on T2-weighted images are characteristic findings. If the localization of the tumor is unclear, the whole body should be scanned by iodine-123 metaiodobenzylguanidine (123I-MIBG) scintigraphy, whole-trunk CT and/or 18F-FDG-PET.

(3) Treatment. Resection of the tumor is the treatment of choice. For preoperative blood pressure management, correction of the circulating plasma volume and prevention of intraoperative crises, α1-blockers, such as doxazosin, should be administered. Beta-blockers are concomitantly used for the treatment of tachycardia and arrhythmia. However, the administration of β-blockers alone is contraindicated because it enhances α-actions. Malignant pheochromocytoma is the most important issue. As it is difficult to differentiate benign from malignant diseases based on histopathological findings, long-term postoperative follow-up is recommended. Pheochromocytoma crises should be treated by the intravenous injection or drip infusion of phentolamine, followed by the administration of α1-blockers.

(4) Timing of referral to specialists. If paroxysmal hypertension or adrenal tumors suggest pheochromocytoma/paraganglioma, patients should be referred to specialists.

5) Other endocrine hypertension

(1) Acromegaly. Hypertension is noted in about 40% of patients with acromegaly. The diagnosis is suggested by characteristic physical findings, including enlargement of the peripheral parts of limbs, and is established by high blood growth hormone and insulin-like growth factor-1 levels, the absence of growth hormone suppression on the 75-g oral glucose tolerance test, paradoxical responses on the thyroid-releasing hormone test and the presence of a pituitary tumor. Trans-sphenoidal hypophysectomy is the treatment of choice.

(2) Hyperthyroidism. Systolic hypertension with an increased pulse pressure is characteristic. Palpitation, finger tremor, increased appetite, weight loss, goiter and exophthalmos suggest the disease. A diagnosis of hyperthyroidism is made by measuring the fT_3, fT_4, thyrotropin-releasing hormone and thyroid autoantibody (TSAb or TRAb) levels. The disease is treated by the administration of antithyroid drugs. Patients should be referred to specialists for the differentiation of the disease from other thyrotoxic disorders such as painless thyroiditis.

(3) Hypothyroidism. Hashimoto's disease is the major cause of hypothyroidism. Although the concomitant development of hypertension is known, hypothyroidism is rarely diagnosed due to hypertension. Nonspecific symptoms such as malaise, goiter and dyslipidemia are clues to the diagnosis. For treatment, Levothyroxine replacement therapy should be performed.

(4) Primary hyperparathyroidism. Hypertension is observed in about 20% of patients with primary hyperparathyroidism, but it rarely leads to diagnosis. Hypercalcemia and/or urolithiasis are clues to the diagnosis. Resection of the morbid parathyroid gland should be performed.

4. VASCULAR HYPERTENSION

POINT 13C
Vascular hypertension

1. Diseases that cause vascular hypertension include aortitis syndrome (Takayasu's arteritis), other forms of vasculitis syndrome (PN, progressive systemic scleroderma), aortic coarctation and diseases with an increase in cardiac output (aortic valve insufficiency, patent ductus arteriosus and arteriovenous fistula). Treatment should be performed in accordance with the condition of each disease for blood pressure control (Recommendation Grade: C1, Evidence level: IVa).

1) Aortitis syndrome (Takayasu's arteritis)

Aortitis syndrome (Takayasu's arteritis) refers to idiopathic, non-specific large-vessel arteritis that induces obstructive or dilating lesions in the aorta, its major branches or pulmonary/coronary arteries.[1079] In Japan, this disease is observed more frequently in women.[1080] This disease is relatively rare, and sometimes requires a long period until a definitive diagnosis can be made. Therefore, common complaints on

the initial consultation include vertigo, syncope, vision disorder, numbness of the hands and hypertension, which suggest the progression of vascular lesions. It is important to prevent the progression of vascular lesions by starting the administration of adrenocorticosteroids or immunosuppressive drugs early, for improving the patient's prognosis/QOL. Even when nonspecific symptoms such as fever and malaise are present, this disease should be considered. Its primary findings are lateralities in the pulse and blood pressure, neck or abdominal bruit and an enhanced carotid sinus reflex. An aortitis syndrome is an important etiological factor for secondary hypertension, and hypertension is observed in about 40% of patients with this disease, and markedly affects the prognosis of this disease.[1081] In patients with bilateral subclavian artery stenosis, the upper limb blood pressure is lower than the aortic pressure, leading to underestimation. Advances in noninvasive diagnostic procedures such as diagnostic imaging and medical treatment have facilitated early therapeutic intervention. In patients who developed aortitis syndrome after 2000, the incidences of hypertension and aortic valve insufficiency have decreased.[1082] The pathogenesis of hypertension in the presence of this disease varies: (1) renovascular hypertension, (2) hypertension due to aortic coarctation (atypical aortic coarctation), (3) hypertension due to aortic valve insufficiency and (4) hypertension due to aortic wall sclerosis.[1079,1080]

Renovascular hypertension is observed in about 20% of patients with aortitis syndrome.[1083] Revascularization is indicated for aortic coarctation and RVHT when (1) antihypertensive drugs have become ineffective for the sufficient control of blood pressure, (2) antihypertensive treatment causes renal dysfunction, (3) congestive heart failure has occurred and (4) the renal artery has narrowed bilaterally.[1079] PTRA for RVHT is mildly invasive and is performed as a first-choice procedure. Its postoperative hypotensive effects and decreases in the doses of antihypertensive drugs have been reported, but the long-term patency rate is lower than that after bypass.[1084] Moreover, aortic valve insufficiency is an important complication that influences the prognosis of this disease; hence, under appropriate antihypertensive treatment, aortic valve replacement (including Bentall's operation) should be indicated in accordance with indication criteria for aortic valve insufficiency in general.[1085]

Surgical treatment for this disease should be performed after the complete resolution of active inflammation or control of inflammation with corticosteroids. Although the long-term prognosis of Japanese patients with this disease undergoing surgery is generally good, attention must be paid to the occurrence of anastomotic aneurysms and dilation of the rest of the ascending aorta.[1086] Hypertension due to renal artery stenosis or aortic coarctation, congestive heart failure due to aortic valve insufficiency, coronary artery disease, dissecting aortic aneurysms and aortic aneurysm rupture are considered to be important clinical conditions that influence the prognosis. Therefore, early, appropriate medical treatment (steroid therapy, antihypertensive therapy) and appropriate surgery for severe cases may improve the long-term prognosis.[1084]

Antihypertensive treatment for this disease is basically the same as that for renovascular or essential hypertension. However, as cerebral blood flow may be reduced in patients with stenotic lesions in the carotid artery, sufficient evaluation and attention for the cerebral blood flow is necessary for conducting antihypertensive treatment.

2) Other forms of vasculitis

Vasculitis syndrome, other than aortitis syndrome, such as PN and progressive systemic scleroderma, contributes to hypertension.[1087] Necrotic arteritis of systemic small- and medium-sized muscular arteries, including the renal artery in PN patients[1088] and spasms of the renal vessels in PSS patients, is involved in the etiology of hypertension. PN is complicated by hypertension ($\geqslant$160/95 mm Hg) in about 30% of patients,[1089] and some patients develop rapidly progressing nephritis. Patients with PSS often show renal crisis (malignant hypertension, renal failure). Other than PSS, causes of death in the acute phase are cerebral hemorrhage, myocardial infarction, heart failure and renal failure, all of which are closely related to the hypertension they complicate; therefore, the importance of blood pressure control must be recognized. For conditions other than PSS, steroid pulse and immunosuppressive therapies are performed in combination in the acute phase. The strategy for blood pressure control is the same as that for renal parenchymal or essential hypertension. In PSS patients, a treatment basically the same as that for malignant hypertension is indicated, and ACE inhibitors and Ca channel blockers are markedly effective.[1090]

3) Coarctation of the aorta

Coarctation of the aorta is suspected, based on vascular bruit ranging from precordium to back along the descending aorta, a reduction in lower-limb vascular pulsation and differences in blood pressure between the upper and lower limbs. In this condition, blood pressure is increased in the upper limb proximal to the site of stenosis and reduced in the lower limb distal to the site of stenosis, with a systolic blood pressure difference between the upper and lower limbs of 20–30 mm Hg or greater. In patients with this disease, the progression of systemic vascular remodeling,[1092] RA/sympathetic nervous systems[1093] and mechanical factors, such as an increase in the arterial reflection waves from the site of aortic coarctation,[1091] an increase in the peripheral vascular resistance in the upper body and weakening of the Windkessel effect of the aorta, are involved in the etiology of hypertension. As a rule, the surgical relief of stenosis or angioplasty using a balloon catheter is indicated in childhood, and a better outcome has been reported on earlier treatment.[1094] Postoperative recrudescence of hypertension is observed in $\sim$33% of patients,[1095] and in this case antihypertensive treatment should be performed in accordance with the condition. Some studies suggest that not only an increase in blood pressure at rest but also that on ABPM or exercise loading is a prognostic factor for recrudescence of hypertension in the postoperative chronic phase.[1096,1097]

4) Vascular hypertension accompanied by an increase in cardiac output

In patients with aortic valve insufficiency, patent ductus arteriosus or arteriovenous fistula, systolic hypertension may be caused primarily by an increase in stroke volume. Antihypertensive treatment should be performed in accordance with individual conditions. However, radical treatment for the primary disease may reduce hypertension.

5. HYPERTENSION RELATED TO DISEASES OF THE BRAIN OR CENTRAL NERVOUS SYSTEM

POINT 13D

1. In patients with hypertension related to an increase in intracranial pressure (Cushing's response) due to cerebrovascular disorders, brain tumors, encephalitis (myelitis) or brain injury, treatment for each cause should be performed first (Recommendation Grade: C1, Evidence level: VI).

2. **Compression by arteries around the rostral ventrolateral medulla induces an increase in blood pressure through the enhancement of sympathetic activities (neurovascular compression syndrome). In patients with neurological symptoms, surgical decompression may also be considered (Recommendation Grade: C1, Evidence level: V).**

Hypertension associated with stroke is described in detail in another chapter. In patients with central nervous diseases such as brain tumors (particularly those in the posterior cranial fossa), encephalitis (myelitis) and brain injury, sympathetic activities are increased through ischemia related to increased intracranial pressure at the brainstem, possibly causing hypertension (Cushing's response). Furthermore, the pathogenesis of neurovascular compression syndrome, in which compression of the rostral ventrolateral medulla, which is the vasomotor center of sympathetic activities, by surrounding arteries causes an increase in blood pressure or hypertension through the enhancement of sympathetic activities, and a surgical decompression-related decrease in blood pressure, was reported in the 1980s.[1098]

Thereafter, it was reported that this syndrome was an etiological factor for hypertension with the enhancement of sympathetic activities, and that it was related to blood pressure changes and the functional prognosis after the onset of ischemic stroke.[1098–1102] In patients with neurological symptoms such as unilateral facial spasm and trigeminal neuralgia, surgical decompression should be considered. In Japan, four patients in whom decompression reduced blood pressure and sympathetic activities have also been reported.[1103] On the other hand, neither the efficacy nor safety of decompression in patients without concomitant neurological symptoms has been established. In nonresponders to treatment with antihypertensive drugs, whether this procedure should be indicated must be carefully examined. As antihypertensive drugs, α-blockers, β-blockers and centrally acting sympatholytic drugs are effective from the perspective of their pressor mechanisms. RA system inhibitors and Ca channel blockers, especially drugs with sympatholytic actions, are useful.[1104,1105]

6. HEREDITARY HYPERTENSION

POINT 13E

1. **Essential hypertension is a multifactorial disorder in which genetic and environmental factors are involved. Approximately 30–70% of interindividual differences are influenced by genetic factors. For genetic factors, many common variants have been identified.**
2. **The influence of individual variants on blood pressure in the general population is not marked (~1 mm Hg). Despite the potential racial diversity, salt sensitivity candidate gene variants are frequently observed in the Japanese population.**
3. **On the other hand, genetic variants that markedly influence blood pressure have also been reported, although they are rare.**
4. **Hereditary blood pressure abnormalities caused by single-gene disorder exist, but are rare.**

Essential hypertension is a multifactorial disease in which many genetic and environmental factors are involved. The morbidity of hypertension is reported to be ~3.5 times higher in pairs of hypertensive siblings than in the general population,[1106] and the contribution of genetic factors is estimated to be approximately 30–70%.[1107] Common interindividual variations in the nucleotide sequence of the genome observed in the general population are called 'genetic polymorphisms or variants', showing a wide range of frequency, from common to rare. Among the genetic factors, common variants have been identified through a genome-wide association study. However, the influence of individual common variants on blood pressure in the general population is only slight (~1 mm Hg),[1108] and it may be difficult to make a diagnosis of essential hypertension solely on the basis of information on these variants alone. In a genome-wide association study involving different racial groups, while some genetic factors have been identified across the populations, there should be marked racial differences in the frequency of variants and their influence on blood pressure.[1109] In the Millennium Genome Project conducted in Japan, hypertension-associated gene loci such as *ATP2B1* were identified.[1110] In a large-scale meta-analysis of a genome-wide association study in East Asians, gene loci were comprehensively investigated/verified.[1111] Furthermore, a study reported that the frequency of candidate gene polymorphisms for salt sensitivity was relatively high in the Japanese population.[1112] Therefore, information on gene polymorphisms may be useful for recommending lifestyle modifications, including salt reduction,[1113] and for selecting antihypertensive drugs.[1114]

On the other hand, among the genetic factors, some rare variants markedly influence blood pressure,[1115] and diagnosis and treatment may be determined/changed primarily based on such variant information, although it is rare, in a group of individuals. In contrast, rare heritable blood pressure abnormalities caused by single-gene mutation and diagnosed by gene analysis have been reported.[1116] In particular, many such blood pressure abnormalities result from gene mutations of ion channels or cotransporters regulating water and electrolyte balance at the renal tubular level. Recently, two genes causing Gordon syndrome[1117] have been newly identified, and a gene causing type III familial aldosteronism[1118] has also been clarified. Table 13-6 shows the genes responsible for and clinical characteristics of hereditary blood pressure abnormalities. In the setting of clinical practice, there may be few cases in which gene analysis is required. However, if patients with early-onset hypertension do not respond to treatment and have a low PRA value, an abnormal serum potassium level and acid–base balance disturbance, the possibility of hereditary hypertension must be considered. When suspecting hereditary hypertension based on family history or clinical characteristics and wishing to perform a detailed analysis, the attending physician should consult a specialist in hypertension, because analytical facilities differ depending on the gene abnormalities. In such cases, currently, the purpose of gene analysis is limited to research, and it is essential to conduct gene analyses in accordance with the Ethics Guidelines for Human Genome/Gene Analysis Research[1119] from the timing of informed consent regarding blood collection.

7. DRUG-INDUCED HYPERTENSION

POINT 13F

Drug-induced hypertension

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs) raise the blood pressure and antagonize the antihypertensive effects of diuretics, β-blockers, ACE inhibitors and ARBs. Their effects tend to be more marked in elderly people (Evidence level: E-II).**

Table 13-6 Genes involved in congenital blood pressure abnormalities and their clinical features

Hereditary hypertension	*Causative genes*	*Clinical features*
Liddle syndrome	Epithelial Na channel β/γ subunits (*SCNN1B*, *SCNN1G*), AD	Low PRA, low PAC, metabolic alkalosis
Gordon syndrome (PHAIIB, IIC, IID, IIE)	Serine-threonine kinase (IIB: *WNK4*, IIC: *WNK1*), ubiquitinated protein (IID: *KLHL3*, IIE: *CUL3*), AD	High K, low PRA, metabolic acidosis, normal PAC, thiazide responsiveness
Apparent mineralocorticoid excess (AME) (New syndrome)	11β-hydroxysteroid dehydrogenase (*HSD11B2*), AR	Low PRA, low PAC, low K, delayed growth, metabolic alkalosis, spironolactone responsiveness
Glucocorticoid-remediable aldosteronism (GRA) (corresponding to type I familial aldosteronism (FH-I))	11β-hydroxylase (CYP11B1) and aldosterone synthase (*CYP11B2*) chimera, AD	Low PRA, high PAC, low K (rare), glucocorticoid/ spironolactone responsiveness
Type III familial aldosteronism (FH-III)	G protein-coupled inwardly rectifying potassium channel (*KCNJ5*), AD	Low PRA, high PAC, high 18-oxocortisol, adrenal hyperplasia, high 18-hydroxycortisol
11β-hydroxylase deficiency (11β-OHD)	11β-hydroxylase (*CYP11B1*), AR	Congenital adrenal hyperplasia, low PRA, high DOC, high ACTH, low cortisol, virilization
17α-hydroxylase deficiency (17α-OHD)	17α-hydroxylase (*CYP17*), AR	Congenital adrenal hyperplasia, low PRA, high DOC, high ACTH, low cortisol, feminization
Early-onset type hypertension with severe exacerbation during pregnancy	Mineralocorticoid receptor (MR)(*NR3C2*), AD	Onset at <20 years of age, development of eclampsia, blood-pressure increase through the actions of progesterone on mutant MR
Metabolic defects cluster (hypertension, hypercholesterolemia, hypomagnesemia)	Mitochondrial tRNA, isoleucine (*MTTI*), maternal inheritance	Low Mg, low K, permeability: 50%, onset at <50 years of age
Hereditary hypotension	*Causative genes*	*Clinical features*
Type 1/2 Bartter syndrome	Type 1: Na-K-2Cl cotransporter (*SLC12A1*), AR Type 2: ATP-sensitive K channel (*KCNJ1*), AR	Severe, low K, low Mg, metabolic alkalosis, hyperprostaglandin E2 syndrome, high PRA, high PAC
Type 3/4 Bartter syndrome	Type 3: kidney Cl channel (*CLCNKB*), AR Type 4: Barttin (*BSND*), AR	Onset during childhood, polyuria, tetanus (rare), low K high PRA, high PAC, hypercalciuria
Gitelman syndrome	Thiazide-sensitive Na-Cl cotransporter (*SLC12A3*), AR	Onset during adolescence, milder than Bartter syndrome, hypocalciuria, high PRA, high PAC, low K, low Mg
Type I pseudohypoaldosteronism (PHA I)	Mineralocorticoid receptor (*NR3C2*), AD, epithelial Na channel α/β/γ subunit (*SCNN1A/B/G*), AR	Onset during the neonatal period/infancy, high PRA, low Na, high K, age-related amelioration of symptoms

Abbreviations: ACTH, adrenocorticotropic hormone; AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; DOC, 11-deoxycorticosterone; PAC, plasma aldosterone concentration; PRA, plasma renin activity; RA, renin–angiotensin.

2. **The use of *kampo* drugs containing glycyrrhizin, a major active component of glycyrrhiza, drugs for liver/gastrointestinal diseases, or health foods may induce hypertension accompanied by hypokalemia (pseudoaldosteronism). Attention is necessary particularly when using *kampo* drugs. If there is an increase in blood pressure, the discontinuation of these drugs must be considered (Recommendation Grade: C2, Evidence level: VI).**
   If the discontinuation of administration is difficult, an aldosterone antagonist should be used (Recommendation Grade: C1, Evidence level: V).
3. **Massive therapy with glucocorticoids induces an increase in blood pressure. If their administration is unavoidable, Ca channel blockers, ACE inhibitors, ARBs, β-blockers, diuretics or aldosterone antagonists should be used (Recommendation Grade: C1, Evidence level: V).**
4. **The use of cyclosporine or tacrolimus may cause an increase in blood pressure. For antihypertensive treatment, Ca channel blockers, ACE inhibitors, ARBs or diuretics should be used (Recommendation Grade: C1, Evidence level: V).**
5. **The use of erythropoietin, estrogen or drugs with sympathomimetic actions may cause an increase in blood pressure. If blood pressure increases during the use of these drugs, a reduction in the dose or discontinuation of administration should be considered (Recommendation Grade: C2, Evidence level: VI).**
   If they cannot be discontinued, Ca channel blockers, ACE inhibitors, ARBs or α-blockers should be used (Recommendation Grade: C1, Evidence level: V).
6. **Molecule-targeting drugs, primarily anti-VEGF antibody preparations, induce hypertension. Its incidence depends on the type of drug or tumor. However, when using these drugs, changes in blood pressure must be monitored. Treatment with routine antihypertensive drugs should be performed (Recommendation Grade: C1, Evidence level: V).**

Drugs such as NSAIDs, glycyrrhizin preparations, glucocorticoids, cyclosporine, erythropoietin, oral contraceptives and sympathomimetic drugs are suggested to have hypertensive effects, to induce hypertension and attenuate the blood pressure-lowering effects of antihypertensive drugs if used concomitantly. Recently, hypertension induced by molecule-targeting drugs has been reported (Table 13-7). Many hypertensive patients also have other diseases and consult multiple medical organizations. Therefore, if the blood pressure management used to be adequate but has become difficult, or in cases of poorly controlled hypertension, the possibility of drug-

Table 13-7 Drugs causing drug-induced hypertension and hypertension treatment

Causative drugs	*Etiologies of hypertension*	*Strategies to treat hypertension*
NSAIDs	Water/Na retention and vasodilator suppression through the inhibition of renal prostaglandin production, attenuation of the antihypertensive effects of ACE inhibitors/ARBs/β-blockers/diuretics	Dose reduction/discontinuation of NSAIDs, dose elevation of an antihypertensive drug that has been administered, Ca channel blockers
Glycyrrhiza (licorice) Glycyrrhizin-containing drugs for liver disease, drugs for digestive disorders, *kampo* drugs, supplements, cosmetics	Water/Na retention and K reduction through the enhancement of intrinsic steroid actions related to the prolongation of the half-life of cortisol associated with the inhibition of 11β-hydroxylated steroid dehydrogenase	Dose reduction/discontinuation of *kampo* drugs, aldosterone antagonists
Glucocorticoids	Increases in renin-substrate and erythropoietin productions and the inhibition of NO production may be involved in the mechanism, but it remains to be clarified.	Dose reduction/discontinuation of glucocorticoids, Ca channel blockers, ACE inhibitors, ARBs, β-blockers, diuretics
Cyclosporine, tacrolimus	Nephrotoxicity, activation of the sympathetic nervous system, inhibition of calcineurin, vascular endothelial cell dysfunction	Ca channel blockers, combination therapy with Ca channel blockers and ACE inhibitors, diuretics
Erythropoietin	Enhancement of blood viscosity, vascular endothelial dysfunction, an increase in the intracellular Na level	Dose reduction/discontinuation of erythropoietin, Ca channel blockers, ACE inhibitors, ARBs, β-blockers, diuretics
Estrogen Oral contraceptives, hormone replacement therapy	An increase in renin-substrate production	Discontinuation of estrogen preparations, ACE inhibitors, ARBs
Drugs with sympathomimetic actions Phenylpropanolamine, tricyclic/tetracyclic antidepressants, monoamine oxygenase inhibitors	α-receptor stimulation, inhibition of catecholamine reuptake at the sympathetic nerve terminals	Dose reduction/discontinuation of drugs with sympathomimetic actions, α-blockers
Anti-VEGF antibody preparations	A decrease in the microvascular floor, a reduction in NO synthesis, renal hypofunction	Dose reduction/discontinuation of the drug if possible, treatment with standard antihypertensive drugs

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin ii receptor blocker; NSAID, non-steroidal anti-inflammatory drug.

induced hypertension should be considered. Also, if these drugs are used, attention must be paid to blood pressure control, and their administration simply as routine must be avoided.

1) Nonsteroidal anti-inflammatory drugs

NSAIDs cause water and Na retention and suppress vasodilation by inhibiting cyclooxygenase (COX) in the process of prostaglandin production from arachidonic acid in the kidney.[1120] In elderly patients and patients with renal dysfunction, renal prostaglandins maintain the renal function as a compensatory mechanism and contribute to the prevention of an increase in blood pressure. However, NSAIDs inhibit prostaglandin production and increase blood pressure by suppressing the renal function. COX has two isoforms, COX-1 and COX-2, which is induced in the presence of inflammation. Although classic NSAIDs nonselectively inhibit both, there are also selective inhibitors of COX-2. The harmful effects of nonselective and selective COX-2 inhibitors on the cardiovascular system are related to the suppression ratio between COX-1 and COX-2 and tissue-specific COX distribution, rather than the selectivity. Therefore, similar caution is necessary when using NSAIDs that are nonselective as well as for selective COX-2 inhibitors.[1121–1123]

In elderly people, NSAIDs often cause acute renal dysfunction, which further aggravates the rise in blood pressure, and they also increase the risk of heart failure if used concomitantly with diuretics compared with diuretics alone. Therefore, if NSAIDs are administered to elderly hypertensive patients, they should be used at a low dose for a limited period with careful observation and examination of the renal function. If renal hypofunction is observed and the drug cannot be discontinued, switching to acetaminophen should be considered.

Diuretics simultaneously inhibit the reabsorption of NaCl and stimulate prostacyclin production in the renal tubules. Therefore, the antihypertensive effects of diuretics are reduced when they are used with NSAIDs. The antihypertensive effects of ACE inhibitors and β-blockers are also reduced by their concomitant use with NSAIDs. The effects of their concomitant use with ARBs have not been evaluated sufficiently, but ARBs appear to be affected similarly as ACE inhibitors.[1124] The effects of NSAIDs on the antihypertensive effects of Ca channel blockers are considered to be minor.

2) Glycyrrhiza (licorice), glycyrrhizin

Glycyrrhiza is contained in drugs for liver and gastrointestinal diseases, in many other *kampo* drugs, in supplements and in cosmetics. Glycyrrhizin, a major active component of glycyrrhiza, inhibits 11β-hydroxylated steroid dehydrogenase, which metabolizes cortisol into inactive cortisone, enhances the actions of endogenous steroids by prolonging the half-life of cortisol[1125] and enhances Na and water retention and reduces the potassium level, causing pseudo-aldosteronism. The glycyrrhizin dose, administration period and age ($\geqslant$60 years) are considered to be risk factors for glycyrrhizin-induced hypertension.[1126] Glycyrrhizin-induced hypertension should be suspected if hypokalemia is concurrent with hypertension, and if the renin activity and plasma aldosterone level are reduced (pseudo-aldosteronism). As the use of *kampo* drugs or supplements is rarely reported by patients themselves, the possibility of their use must be carefully evaluated. Clinically, glycyrrhizin-induced hypertension is resolved by the withdrawal of glycyrrhiza for a few weeks (maximum: 4 months) or by concomitant administration of an anti-aldosterone drug.

3) Glucocorticoids

Glucocorticoids rarely cause hypertension at low doses even in the long-term treatment of asthma or rheumatoid arthritis. However, the

long-term administration of glucocorticoids at intermediate doses frequently induces hypertension.[1127] As with other drugs, blood pressure increased more notably in elderly patients with increases in the dose of prednisolone, and marked increases were observed when the dose was 20 mg per day or higher. Hypertension was observed in 37.1% of these elderly patients, and hypertensive patients more often had a familial history of hypertension compared with nonhypertensives.[1128] The mechanism of a glucocorticoid-induced increase in blood pressure remains to be clarified, although an increase in the angiotensin II level due to elevated renin substrate production,[1129] vasoconstriction due to an increase in erythropoietin production,[1130] vascular endothelial dysfunction through impairment of nitric oxide (NO) use related to the inhibition of NO production[1131] or excess production of superoxides,[1132] and stimulation of mineral corticoid receptors have been suggested.

Treatment is primarily a decrease in dose or withdrawal of the glucocorticoid. If this is difficult, blood pressure should be controlled with Ca channel blockers, ACE inhibitors, ARBs, β-blockers, diuretics or aldosterone antagonists.

4) Others

Cyclosporine and tacrolimus are used for immunosuppression after organ or bone marrow transplantation. Both of them frequently cause hypertension, although frequency varies with dose, treatment period and pathological conditions. Although the mechanism of the occurrence of hypertension has not been sufficiently clarified, the involvement of nephrotoxicity,[1133] stimulation of the sympathetic nervous system,[1134] inhibition of calcineurin[1135] and vascular endothelial cell dysfunction[1136] are suspected. Ca channel blockers are effective in the treatment of hypertension due to immunosuppressants, and their combination with ACE inhibitors has been reported to be even more effective.[1137] Although diuretics are also effective, caution regarding uric acid metabolism is necessary in patients after kidney transplantation. As Ca channel blockers may increase the blood concentrations of cyclosporine and tacrolimus, measurement of the blood concentrations of these immunosuppressants should be considered if necessary.

Although erythropoietin alleviates renal anemia, it increases the blood pressure. In Japan, an increase in blood pressure was reported in 29% of patients surveyed in postmarketing research.[1138] Its possible mechanism involves increases in the hematocrit and blood viscosity associated with recovery from anemia by erythropoietin treatment and a resultant increase in peripheral vascular resistance, but this possibility has been refuted by one report.[1139] An increase in the intracellular Na concentration,[1140] vascular endothelial dysfunction[1141] and genetic predispositions[1142] may also be involved. There is also a report that no increase in blood pressure due to erythropoietin was observed before hemodialysis.[1143] The dose of erythropoietin should be reduced or administration should be discontinued if hypertension develops or if blood pressure increases. However, if the increase is mild, antihypertensive drugs are also useful.[1144] On the other hand, a study indicated that blood pressure control was insufficient despite the administration of antihypertensive drugs in chronic dialysis patients (patients registered at the Japanese Society for Dialysis Therapy), of whom 82% were taking erythropoietin.[722]

Estrogen is used as an oral contraceptive and drug for climacteric disturbance, but has been considered to cause an increase in blood pressure or thromboembolism at a high dose. The details of the mechanism of estrogen-induced hypertension have not been clarified, although an increased renin substrate production in the liver has been proposed. An investigation of the relationship between the use of oral contraceptives and health showed that, although the blood pressure and lipid levels in users were slightly higher than in age-matched nonusers, the former's satisfaction with health and QOL was more favorable, suggesting the safety of oral contraceptives.[1145] Although the rate of increase in blood pressure was dose-dependent, caution is necessary even at a low dose. A sufficient analysis of the relationship between oral contraceptives and hypertension has not been made in Japan. When using oral contraceptives, blood pressure should be measured periodically, their use should be discontinued if an increase in blood pressure is observed and other contraceptive measures should be selected. If they cannot be discontinued, the administration of ACE inhibitors or ARBs should be considered. Concerning hormone replacement therapy, see Section 2 of Chapter 10, POSTMENOPAUSAL BLOOD PRESSURE.

Drugs with sympathomimetic actions may increase the blood pressure. An overdose of phenylpropanolamine, which is contained in drugs for the common cold, may increase the blood pressure. Caution is needed in its concomitant use during treatment with a β-blocker alone, because it may induce a state of dominant α-receptor stimulation and cause a marked increase in blood pressure. Tri- or tetracyclic antidepressants may also inhibit the antihypertensive effects of peripheral sympatholytic drugs by inhibiting catecholamine reuptake at the sympathetic nerve terminals and induce hypertensive crisis[1146] or hypertensive emergencies.[1147] Monoamine oxidase inhibitors, which are used for the treatment of Parkinson's disease, also cause an increase in blood pressure or orthostatic dysregulation.

A monoamine oxidase inhibitor and a tricyclic antidepressant must not be used simultaneously. The concomitant use of a monoamine oxidase inhibitor with ephedrine or methylephedrine may also cause an elevation in blood pressure and tachycardia. If hypertension is induced by these drugs, a reduction in the dose or discontinuation of administration is necessary, but if discontinuation is impossible α-blockers or central sympatholytic agents should be administered.

As metoclopramide, a dopamine (D2) receptor antagonist used for the treatment of gastrointestinal disorders, β-blockers and tricyclic antidepressants may cause clinical activation of pheochromocytoma as well as hypertensive crisis,[1148] caution is needed in their use.

Molecule-targeting drugs inhibiting angiogenesis, which are used for the treatment of malignant tumors or age-related macular degeneration, primarily anti-VEGF antibody preparations, may cause hypertension, myocardial infarction and cerebral infarction.[1149,1150] The incidence of hypertension is reportedly approximately from 2–3% to 90%, although it depends on the type of drug or tumor and race. The pathogenesis of hypertension remains to be clarified, but an increase in peripheral vascular resistance associated with a decrease in the microvascular floor or a VEGF inhibition-related reduction in NO production, as well as renal dysfunction, is suggested.[1151,1152] If hypertension is present before the start of treatment with anti-VEGF antibody preparations, strict blood pressure control should be performed. If hypertension develops, a reduction in the dose of the drug or discontinuation must be considered, and treatment with standard antihypertensive drugs should be conducted.[1152]

Citation Information

We recommend that any citations to information in the Guidelines are presented in the following format:

The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res* 2014; **37**: 253–392.

Please refer to the title page for the full list of authors.