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Chapter 12. Secondary hypertension

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OVERVIEW AND SCREENING

Hypertension is classified into essential and secondary hypertension according to cause. Although secondary hypertension is less frequent compared with essential hypertension, it may be cured by appropriate treatment. Therefore, its diagnosis is important, and the cause of hypertension should be considered in evaluating hypertensive patients.

Secondary hypertension has many types, as shown in Table 12-1. Renal parenchymal hypertension is caused by various kidney diseases such as chronic glomerulonephritis and polycystic kidney disease (PKD), and usually occurs along with reduced renal function. Renovascular hypertension (RVHT) is caused by renal artery stenosis and is usually accompanied by hyperactivity of the renin–angiotensin (RA) system. Primary aldosteronism (PA), Cushing's syndrome and pheochromocytoma are due to an excessive production of aldosterone, cortisol and catecholamines, respectively. Both a deficiency and excess of thyroid hormone may cause hypertension, and hyperparathyroidism is characterized by hypercalcemia. In aortic coarctation, blood pressure is high in the upper but low in the lower limbs. Sleep apnea syndrome is often accompanied by obesity, and blood pressure increases markedly during apneic periods. In brainstem vascular compression, compression of the ventrolateral medulla oblongata by blood vessels is observed. Neurogenic hypertension is also caused by increases in intracranial pressure due to brain tumor or other causes, cerebrovascular disorders, hyperventilation and panic disorder. Hypertension may also be brought on by various drugs that cause Na retention or sympathetic activation.

Although the frequency of secondary hypertension varies among populations, it has been reported to be approximately 5% in the general population. However, it is 50% or higher in young patients with severe hypertension. Renal hypertension is considered to be the most frequent form of secondary hypertension, but PA has been reported to be more prevalent than previously considered, and accounts for 3–10% of all hypertensive patients.[643,644] Hypothyroidism, sleep apnea syndrome and brainstem vascular compression are also observed in many hypertensive patients. Therefore, secondary hypertension is considered to account for about 10% of all hypertension.

Screening for secondary hypertension involves a close evaluation of history, physical examinations, and blood and urine tests. The possibility of secondary hypertension is higher in hypertension with an early onset, severe hypertension and resistant hypertension. Table 12-1 presents findings suggestive of major types of secondary hypertension and tests necessary for their differential diagnosis. Cushing's syndrome and pheochromocytoma usually present characteristic clinical features, but symptoms may not be clear, and similar symptoms are often observed in other diseases. The possibility of secondary hypertension should be considered in the diagnosis and treatment of all hypertensive patients.

POINT 12A

Renal parenchymal hypertension

1. **Renal parenchymal hypertension is hypertension occurring with renal parenchymal disorders and is one of the most frequent forms of secondary hypertension.**
2. **Although hypertension occurs from an early stage in glomerular disorders, it occurs in the terminal stage in renal interstitial disorders. However, hypertension occurs frequently from an early stage in PKD, one of the tubulointerstitial disorders.**
3. **As hypertension accelerates the progression of nephropathy, antihypertensive treatment is important for both the prevention of cardiovascular events and the protection of the kidney.**
4. **In glomerular disorders (glomerulonephritis and diabetic nephropathy), the glomerular capillary pressure generally increases and the urinary protein level remains high. An aggressive antihypertensive treatment (target: $<$125/75 mm Hg) primarily using RA system inhibitors is necessary.**
5. **In renal interstitial disorders (pyelonephritis and PKD) and hypertensive nephrosclerosis, the glomerular capillary pressure is generally normal or low, and the urinary protein level is low. The control of blood pressure to $<$130/80 mm Hg using antihypertensive drugs (of any type) should be attempted. However, if proteinuria increases, a more aggressive blood pressure control using RA system inhibitors would be required, as with glomerular disorders.**

1) RENAL PARENCHYMAL HYPERTENSION

Renal parenchymal hypertension, caused by renal parenchymal disorders, is a common form of secondary hypertension, accounting for 2–5% of all hypertension.[645–647] In the Hisayama Study, which followed up a general population aged $\geqslant$40 years, autopsy was performed on 131 hypertensive patients during the 20 years after 1961, and the frequency of secondary hypertension was 3.8%, with that of renal hypertension being 3.1%.[645]

Although the incidence of and mortality rates due to stroke and heart diseases have decreased due to improvements in antihypertensive treatment, the incidence of end-stage renal failure continues to increase. In the 35 192 patients in whom hemodialysis was initiated in 2006, the most frequent underlying disease was diabetic nephropathy (42.9%), with chronic glomerulonephritis being the second most frequent (25.6%) and nephrosclerosis being the third (9.4%). Together with PKD, which was the fourth most frequent underlying disease (2.4%), these four diseases accounted for 80%.[138] Most of these

Table 12-1 Major types of secondary hypertension, their suggestive findings and examinations necessary for differential diagnosis

Underlying disease or condition	*Suggestive findings*	*Examinations necessary for differential diagnosis*
Renal parenchymal hypertension	Proteinuria, hematuria, kidney dysfunction, a history of kidney disease	Seroimmunological test, renal ultrasonography/CT, kidney biopsy
Renovascular hypertension	Young age, rapid blood-pressure increase, abdominal vascular bruit, hypokalemia	PRA, PAC, renal Doppler ultrasonography, renal scintigraphy, angiography
Primary aldosteronism	Weakness of the limbs, nocturnal pollakiuria, hypokalemia	PRA, PAC, adrenal CT, saline or furosemide load test, adrenal venous blood collection
Cushing's syndrome	Central obesity, moon face, striated skin, hyperglycemia	Cortisol, ACTH, abdominal CT, brain (pituitary) MRI
Pheochromocytoma	Paroxysmal/labile hypertension, palpitation, headache, sweating, neurofibroma	Blood/urinary catecholamines and their metabolites, abdominal ultrasonography/CT, MIBG scintigraphy
Hypothyroidism	Bradycardia, edema, hypoactivity, increases in the levels of lipids, CPK and LDH	Thyroid hormone/autoantibody, thyroid ultrasonography
Hyperthyroidism	Tachycardia, sweating, weight loss, a decrease in the cholesterol level	Thyroid hormone/autoantibody, thyroid ultrasonography
Hyperparathyroidism	Hypercalcemia	Parathyroid hormone
Aortic coarctation	Differences in blood pressure between the upper and lower limbs, vascular murmurs	Thoracic (abdominal) CT, MRI/MRA, angiography
Brainstem vascular compression	Resistant hypertension, facial spasm, trigeminal neuralgia	Brain (medullary) MRI/MRA
Sleep apnea syndrome	Snoring, daytime sleepiness, obesity	Overnight sleep monitoring
Drug-induced hypertension	Previous drug administration, resistant hypertension, hypokalemia	Confirmation of previously administered drugs

Abbreviations: LDH, lactate dehydrogenase; MRA, magnetic resonance angiography; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

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.[648,649] As there is no radical treatment for CKD at present, blood pressure control by antihypertensive drug therapy primarily using RA system inhibitors, angiotensin receptor blockers (ARBs) or agiotensin-converting enzyme (ACE) inhibitors, is extremely important for the prevention of end-stage renal failure. In Japan, marked regional differences are observed in the incidence of end-stage renal failure[650,651] and, as a negative correlation exists between its incidence and the prescribed amount of RA system inhibitors,[652] RA system inhibitors are considered to actually prevent the progression of CKD.

On account of the close relationship between CKD and hypertension, it is often difficult to determine 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 or proteinuria/renal dysfunction (superimposed pre-eclampsia) from an early period of pregnancy 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 abnormality persists, kidney morphology must be examined by ultrasonography or CT.

As prognosis may be improved by early treatment in CKD, it is recommended to refer patients suspected of having renal parenchymal disorders to nephrologists. Hypertensive nephrosclerosis, which causes renal dysfunction on the basis of essential hypertension, and diabetic nephropathy are discussed in Chapter 6.

a. Chronic glomerulonephritis

Patients with chronic glomerulonephritis frequently develop hypertension from an early stage. Blood pressure increases further with the progression of renal dysfunction, and hypertension occurs in nearly all patients with end-stage renal failure.[653] Hypertension is observed more often with the exacerbation of kidney biopsy findings. It may be caused by body fluid expansion due to Na retention (increased salt sensitivity), inappropriate activation of the RA system and an involvement of the sympathetic nervous system.[648,649,654,655]

The therapeutic strategy for hypertension associated with chronic glomerulonephritis is basically the same as that for diabetic nephropathy (Table 12-2). Generally, the urinary protein excretion is often $1\,g\,day^{-1}$ or higher, reflecting an increase in the glomerular capillary pressure. The basic treatment consists of reductions in salt and protein intake combined with guidance on smoking cessation.[423] Concerning antihypertensive drug therapy, aggressive treatment to reduce blood pressure to $<125/75$ mm Hg primarily using RA system inhibitors is important. Combination drug therapy including diuretics is often necessary.[387,440,656]

As RA system inhibitors reduce proteinuria even in normotensive IgA[657] and diabetic[416,487] nephropathy, they are used as kidney-protecting drugs. On the other hand, the kidney-protecting effect of RA system inhibitors on CKD that is not accompanied by proteinuria has not been established.

b. Chronic pyelonephritis

In renal interstitial disorders, typically chronic pyelonephritis, hypertension is rarely observed at an early stage and occurs only after renal dysfunction has progressed, unlike glomerular diseases such as glomerulonephritis and diabetic nephropathy.[653,658] It is the sixth most frequent disease leading to end-stage renal failure (0.8%), following rapidly progressive glomerulonephritis.[138] The glomerular capillary pressure is generally normal or low, and the urinary protein level is low (see Table 12-2). The target level of blood pressure control is $<130/80$ mm Hg, and the type of antihypertensive drug is not specified.

Chronic pyelonephritis often shows few symptoms in contrast to acute pyelonephritis. It rarely presents symptoms directly caused by

Table 12-2 Level of proteinuria and the goal of antihypertensive therapy with respect to underlying disease of CKD

Underlying disease	*Glomerular capillary pressure*	*Proteinuria*[a] *(g day^{-1})*	*Target blood pressure (mm Hg)*	*Recommended antihypertensive drugs*
Diabetic nephropathy, glomerulonephritis	High	Usually $\geqslant 1$ g day^{-1}	$<$125/75[b]	RA system inhibitors
Nephrosclerosis, polycystic kidney, renal interstitial disorders	Normal–low	Usually <1 g day^{-1}	$<$130/80	Any types[c]

Abbreviations: CKD, chronic kidney disease; RA, renin–angiotensin.
Some patients with diabetic nephropathy or glomerulonephritis are treated with RA system inhibitors to protect the kidney even in the absence of hypertension.
In CKD patients without proteinuria, kidney-protecting actions of RA system inhibitors have not been established.
[a]A reference urinary protein level of 1 g day^{-1} was roughly established.
[b]In diabetic nephropathy or glomerulonephritis patients showing a urinary protein level of <1 g day^{-1}, the target blood pressure values are $<$130/80 mm Hg.
[c]As urinary protein level increases, strict blood pressure control with RA system inhibitors should be recommended to lower glomerular capillary pressure.

urinary tract infection, and asymptomatic bacteriuria, lower urinary tract symptoms such as pollakiuria, discomfort of the lateral or dorsal lumbar region, and intermittent mild fever may be the only findings. If tubulointerstitial damage progresses, hypertension, Na loss, impairment of urine-concentrating ability, hyperkalemia and acidosis develop. Clinically, as the ability to concentrate urine is reduced and Na is lost, patients are likely to develop dehydration. Hypertension occurs only after renal dysfunction has markedly progressed. If the urinary protein level is 1 g day^{-1} or higher, focal glomerulosclerosis based on tubulointerstitial damage is possible.[659] This condition requires aggressive antihypertensive treatment primarily using RA system inhibitors with a target blood pressure level of $<$125/75 mm Hg.

As chronic pyelonephritis occurs more frequently in women as a complication of vesicoureteral reflux, urological diagnosis and treatment are also important.

c. Polycystic kidney disease

Polycystic kidney disease 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 ultrasound tomography or CT is necessary for diagnosis.[660] The genes responsible for PKD are PKD1 (short arm of chromosome 16) and PKD2 (long arm of chromosome 4); the disease is transmitted by autosomal dominant inheritance in most patients and rarely by autosomal recessive inheritance. PKD1 accounts for 80–90% of the disease, with PKD2 accounting for the rest.[661] The number of patients treated for PKD at medical institutions accounts for 1 in 2000–4000 of the population.[662] The disease is progressive, and renal function decreases gradually, causing end-stage renal failure in about 40% of patients in their 50s.[662]

Hypertension is observed in about 60% of patients at an early stage, when renal function remains normal,[653,663] and it occurs in all patients with end-stage renal failure.[664] Cysts displace blood vessels, causing ischemia in local kidney tissues, and the resultant increase in renin secretion is involved in the occurrence of hypertension.[665] RA system inhibitors often show blood pressure-lowering effects, occasionally inducing rapid decreases in blood pressure and renal function. PKD is complicated by cerebral aneurysm in about 10% of patients, and as aneurysmal rupture causes intracranial hemorrhage, control of the blood pressure to $<$130/80 mm Hg is recommended, as with other CKDs.

It is not known whether RA system inhibitors also show kidney-protecting effects in PKD.[660,666-670] There are many reports that other treatments to reduce the glomerular capillary pressure; for example, strict blood pressure control[671] and dietary protein restriction,[672] are ineffective for the renal protection of PKD. Histopathologically, kidney ischemia rather than glomerular hypertension is considered to play a central role in the progression of kidney damage.

POINT 12B
Renovascular hypertension

1. **Renovascular hypertension 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 ischemic heart disease, carotid and peripheral arterial diseases. Bilateral renal artery stenosis/obstruction causes progressive renal failure called ischemic nephropathy.**
2. **Renovascular hypertension often presents as severe or resistant hypertension. Abdominal vascular bruit, lateral difference in the kidney size, kidney dysfunction and hypokalemia are clues to the diagnosis, but they are not observed in all patients. If the renal function deteriorates after the administration of an RA system inhibitor, bilateral RVHT should be suspected.**
3. **Morphological (CT angiography, magnetic resonance angiography and renal arteriography) and functional (plasma renin activity and renography) examinations are important for the definitive diagnosis of RVHT. Renal Doppler ultrasonography is useful for both morphological and functional screening.**
4. **Percutaneous transluminal renal angioplasty (PTRA) is performed for the treatment of RVHT, but its indications require further evaluation. Although PTRA is effective in reducing blood pressure, evidence for its kidney-protecting effect is insufficient. Surgical vascular reconstruction may also be indicated. As for conservative treatment, blood pressure control should be attempted using antihypertensive drugs. RA system inhibitors are effective for unilateral RVHT, but must be avoided in bilateral RVHT.**

2) RENOVASCULAR HYPERTENSION

Renovascular hypertension is hypertension caused by stenosis or obstruction of the renal artery and is observed in about 1% of hypertensive patients. Its etiological mechanism is the activation of the RA system by a reduction in the renal perfusion pressure. 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 occasionally 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.[673]

Atherosclerosis of the renal artery suggests advanced systemic arteriosclerosis, and is often complicated by other atherosclerotic vascular diseases. According to reports in Japan, renal artery stenosis was disclosed by autopsy in 12[674] and 10%[675] of patients with myocardial infarction and stroke, respectively, 7%[676] of those who underwent cardiac catheterization, and 27% of those with severe carotid artery stenosis.[677] 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 the blood pressure are often noted.

Renovascular hypertension is often grade III and may cause malignant hypertension. Renal function may be normal, but it is impaired if stenosis exists bilaterally. Renal failure caused by bilateral renal artery stenosis is called ischemic nephropathy. Ischemic nephropathy accounts for about 10% of underlying diseases of end-stage renal failure[678] and causes the rapid progression of kidney damage in middle-aged and elderly people. If pulmonary edema that cannot be explained by cardiac function is noted, the possibility of ischemic nephropathy should be considered.

a. Diagnostic clues

Table 12-3 shows histories and clinical signs that suggest RVHT and ischemic nephropathy. However, these histories or signs are not observed in all patients.

b. Examinations for a definitive diagnosis

For the diagnosis of RVHT, it is important to confirm the presence of stenosis in the renal artery (morphological diagnosis) and hyperactivity of the RA system due to stenosis, causing hypertension (functional diagnosis) (Figure 12-1).

Table 12-3 Diagnostic clues to renovascular hypertension

Hypertension that develops at $\leqslant$30 years of age, or at $\geqslant$50 years of age
Recent onset or rapid exacerbation of hypertension
Grade III or resistant hypertension
Symptoms or findings of vascular disease in other sites
Deterioration of renal function after the start of treatment with ACE inhibitors or ARB
Abdominal vascular bruit
Laterality in the kidney size
Hypokalemia
Progressive renal failure, congestive heart failure and pulmonary edema

If RVHT is suspected, the plasma renin activity (PRA) should be measured first as a functional examination. PRA usually increases in patients with unilateral renal artery stenosis but is occasionally normal in patients with a long clinical course and those with bilateral stenosis. It should also be noted that PRA is affected by antihypertensive medication. Renal scintigraphy (renography) is useful for the evaluation of a split renal function and lateral difference in the renal blood flow. With captopril loading, the difference between the stenosed and intact sides becomes clearer. Measurement of PRA before and after captopril administration is also useful, because PRA shows an excessive increase after loading in RVHT. Split renal vein sampling, although invasive, may also be useful, and hypertension is considered to be due to renal artery stenosis if PRA on the stenosed side is $\geqslant$1.5 times higher than that on the intact side.

Non-invasive renal Doppler ultrasonography is highly useful for both morphological and functional screening.[679] Renal artery stenosis is evaluated by detecting the blood flow at the origin of the renal artery and in the segmental and interlobular arteries in the kidney. The resistance index based on the intrarenal blood flow pattern has been suggested to be an index for the prediction of the effectiveness of PTRA.[680] CT angiography and magnetic resonance angiography have been reported to be useful,[681] but indications for both examinations must be evaluated carefully in patients with a reduced renal function. Confirmative morphological examination is made by aortography or selective renal arteriography. For the evaluation of indications for treatment, particularly PTRA, morphological and functional examinations should be performed in combination, and angiography employing a contrast medium should be conducted only in patients expected to respond to revascularization.

c. Treatments

Vascular reconstruction. Percutaneous transluminal renal angioplasty is now performed frequently for the treatment of RVHT and renal artery stenosis. This procedure is relatively non-invasive and can be performed repeatedly compared with surgical revascularization. The initial success rate of PTRA is high for fibromuscular dysplasia,[682] and is considered to be the first choice unless it is technically difficult. The long-term prognosis of fibromuscular dysplasia after PTRA is also relatively good, but restenosis may occur.[683] In atherosclerotic renal artery stenosis, the initial response rate to PTRA using a balloon alone was relatively low, the restenosis rate was high and therapeutic results were not always satisfactory.[684] The therapeutic results are reported to have improved after the introduction of stent use.[685]

However, in a prospective study comparing PTRA with drug therapy against atherosclerotic renal artery stenosis, PTRA was shown to be effective for blood pressure control, but its effects on renal function

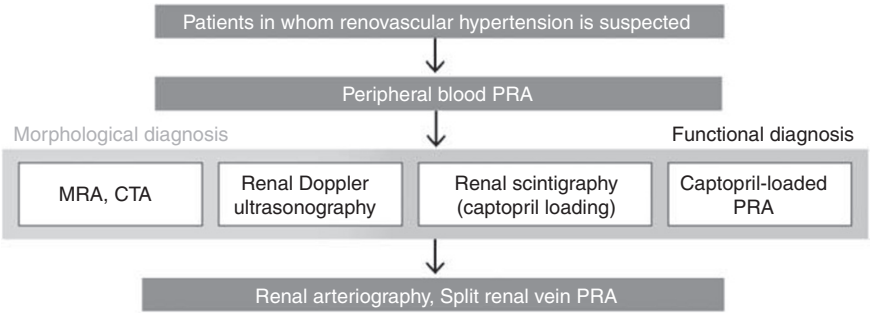


Figure 12-1 Examinations to make a definitive diagnosis of renovascular hypertension.

were unclear.[686] Recent systematic reviews reported that the blood pressure-reducing effect of PTRA was better than that of drug therapy in bilateral stenosis,[687] but was not statistically significant in overall analysis.[688] Also, in the PTRA group, the amount of antihypertensive drugs required was lower and cardiovascular or renovascular complications were fewer, but no difference was observed in renal function, compared with the drug therapy group.[688] Thus, no definite consensus has been reached regarding the usefulness of PTRA at present, and the results of large-scale clinical studies currently in progress are awaited. According to overseas guidelines for PTRA and stent placement, these treatments are recommended when a decrease in blood pressure, recovery of the kidneys and an alleviation of pulmonary edema due to ischemic nephropathy are expected.[689] Therefore, PTRA should be performed only after a sufficient evaluation of indications.

If vascular reconstruction by PTRA is difficult, or if hypertension is resistant to drug therapy, surgical reconstruction by bypass surgery or autologous kidney transplantation should be considered. Surgical vascular reconstruction has also been very effective in Japan. Further, in patients with severely impaired renal function but enhanced renin secretion on the stenosed side, blood pressure is expected to be reduced by nephrectomy.

Antihypertensive drug therapy. Treatment using antihypertensive drugs should be given until vascular reconstructive surgery and in patients in whom vascular reconstruction is impossible or should be avoided. Although β-blockers, which suppress the RA system, and ARB and ACE inhibitors are effective in lowering blood pressure, bilateral renal artery stenosis is a contraindication for ARBs and ACE inhibitors. Ca channel blockers have no marked effect on the RA system and are safe. The use of diuretics, which stimulate the RA system, should be limited to a complementary level, but the presence of renal failure may be an indication for use. 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. As hypertension is often severe, multiple drug regimens may be required to control blood pressure in patients with RVHT.

POINT 12C
Endocrine hypertension

1. **As endocrine hypertension is often cured by appropriate treatment, patients should be referred without delay to the specialists of The Japanese Society of Hypertension and/or the Japan Endocrine Society.**
2. **It is noted that primary aldosteronism (PA) is a more common cause of hypertension than previously considered and that it often causes target organ damage. In hypertensive patients, especially in those at risk, it is recommended to measure both plasma aldosterone concentration (PAC) and PRA. If the PAC to PRA ratio (ARR) is >200 (PAC: pg ml^{-1}), confirmatory tests for aldosterone excess should be performed, followed by investigations to determine the localization of the lesion site. If the disease is unilateral, laparoscopic adrenalectomy is the treatment of choice. If it is bilateral, antihypertensive agents such as aldosterone antagonists are indicated.**
3. **For the diagnosis of Cushing's syndrome, attention should be paid to characteristic physical findings and the dexamethasone suppression test should be performed. In cases of adrenal incidentaloma, subclinical Cushing's syndrome should be diagnosed according to the diagnostic criteria of the Ministry of Health, Labour and Welfare, Japan.**
4. **Pheochromocytoma is diagnosed based on the measurement of catecholamines and their metabolites and imaging examinations. The tumor is occasionally found as adrenal incidentaloma even in elderly people. An α-blocker is the first choice of treatment. As about 10% of pheochromocytomas are malignant, a careful follow-up is necessary after initial surgery.**
5. **Characteristic physical findings are clues to the diagnoses of acromegaly, Basedow's disease and hypothyroidism. Hypercalcemia suggests primary hyperparathyroidism. In all these conditions, hypertension is often alleviated by the treatment of the causative disease.**

3) ENDOCRINE HYPERTENSION

Endocrine hypertension is a group of diseases in which hypertension is caused by excessive hormone secretion due to a tumor or hyperplasia of the endocrine organs. PA, Cushing's syndrome and pheochromocytoma are the major causes of endocrine hypertension. Although these causes of hypertension are often cured by treatments of the primary lesion, target organ damage may develop if not appropriately treated. In addition, some tumors causing hypertension could be histologically malignant. Appropriate diagnosis is therefore essential and patients should be referred to specialists of The Japanese Society of Hypertension and/or the Japan Endocrine Society without delay.

a. Primary aldosteronism

PA is typically associated with hypertension, suppressed renin secretion, hypokalemia, hypomagnesemia and metabolic alkalosis due to excess aldosterone secretion. Prevalence appears to be more frequent than previously considered and is reported to account for about 3–10% of all hypertensive patients, although lower prevalence has been suggested.[690–692] As the disease often damages target organs including the brain, cardiovascular system and kidneys,[693] early diagnosis and treatment are important. It occurs more often in women, with a male–female ratio of 1:1.5.

Diagnostic clues. PA should be suspected in all patients with hypertension, especially untreated patients. A screening test is strongly recommended in patients at higher risk,[694] including patients with hypokalemia (serum K level $\leqslant 3.5$ mEq l^{-1}, including hypokalemia induced by diuretics), grade II–III hypertension (about 10%), resistant hypertension (about 20%), adrenal incidentaloma (about 3%) and those aged $\leqslant 40$ years with target organ damages (Table 12-4). As the serum K level has recently been reported to be normal in about three out of four patients with PA,[695] PA cannot be excluded even in patients without hypokalemia.

Table 12-4 Hypertensive patients at higher risk of PA in whom a screening test is strongly recommended

Hypokalemia (including diuretic-induced hypokalemia)
Grade II/III hypertension
Resistant hypertension
Adrenal incidentaloma
Patients aged $\leqslant 40$ years with target organ damage

Abbreviation: PA, primary aldosteronism.

Screening tests.

Measurement of PRA and PAC. PRA and PAC should be measured simultaneously, particularly in the high-prevalence group mentioned above. As the values are affected by the time of blood sampling, posture, and antihypertensive medication, blood sampling under standard conditions (untreated, between early morning and 0900 hours, fasting, after at least 30 min of recumbancy) is desirable. As antihypertensive medication can cause a false-positive or false-negative result (Table 12-5), measurement is preferably performed in an untreated condition or after a 2-week medication-free period. If withdrawal of medication is difficult due to the necessity of blood pressure control, measurement is recommended to be performed after replacing the drugs with Ca channel blockers, α-blockers, and/or hydralazine, which have less marked effects on the PRA or PAC. As spironolactone has marked effects, it should be withdrawn for at least 2 months. Also, as values can show considerable variation even in the same patient, repeated measurements are recommended.[696] As PAC is expressed in ng per 100 ml or pg ml^{-1}, caution is required that absolute values expressed in the latter units are 10 times higher than those in the former.

Evaluation of the aldosterone to renin ratio (ARR). As the ARR increases in PA, it is useful for screening.[697] Although cutoff values ranging from 200 to 1000 (PAC: pg ml^{-1}) have been reported, 200 is recommended for screening. ARR is, however, markedly affected by a low renin level; PAC > 150 pg ml^{-1} has been proposed as a supplementary condition in addition to the ARR alone.[698]

Confirmatory tests. If the screening tests are positive, confirmatory tests should be performed to establish autonomous secretion of aldosterone independent of the RA system. The captopril challenge test[699] shows an excellent sensitivity despite a relatively low specificity and can be performed at the outpatient clinic because of its simplicity. The furosemide-upright test has been commonly performed in Japan, but it has a slightly lower sensitivity and specificity and may involve considerable physical stress. The saline infusion test,[700] commonly performed in the United States and other countries, has been reported to be excellent in sensitivity and specificity but is not indicated for patients with impaired cardiac and/or renal function (Table 12-6). If at least one of these tests is positive, investigations to determine the disease subtype and site of the lesion should be initiated.

Disease subtype and localization of the lesion site. Aldosterone-producing adenoma and idiopathic hyperaldosteronism due to bilateral adrenal hyperplasia are major types of PA, but there are also rare types including glucocorticoid-remediable aldosteronism, adrenal cancer and unilateral adrenal hyperplasia. Comprehensive diagnosis is made by adrenal CT, adrenal scintigraphy and adrenal vein sampling.

Treatments. For unilateral aldosterone-producing adenoma, laparoscopic adrenalectomy is the treatment of choice. As the serum K level rapidly normalizes after surgery, blood pressure decreases slowly. Hypertension may not be completely normalized in patients with a 5-year or longer history of hypertension, essential hypertension, renal damage and resistance to spironolactone. The control of hypertension is usually improved. Strict control of hypertension and hypokalemia should be continued in patients with no surgical indications and those awaiting surgery. Although an aldosterone antagonist is the first-choice antihypertensive agent, blood pressure should be controlled through its concomitant use with Ca channel blockers, which have been reported to suppress aldosterone secretion after initiating administration. Eplerenone more selectively binds to mineralocorticoid receptors than spironolactone and less frequently causes adverse effects including gynecomastia. The efficacy of eplerenon in PA awaits investigation in a large number of patients. The preoperative administration of an aldosterone antagonist has been reported to reduce rapid postoperative changes in hemodynamics through the activation of the RA system or other mechanisms and to prevent electrolyte abnormalities and renal dysfunction.[701] On the other hand, as hypoaldosteronism after operation may cause hyperkalemia and hyponatremia, a careful postoperative management of body fluid volume and electrolyte concentration is mandatory.

Summary of the diagnostic procedure and timing of referral to the specialists. The Endocrine Society, USA, issued the Clinical Guidelines of Primary Aldosteronism,[694] and the Japan Endocrine Society also presents a diagnostic and therapeutic guide on its homepage.[702] Figure 12-2 shows the procedure for the diagnosis of PA on routine clinical practice of hypertension. In hypertensive patients, particularly those at a higher risk of PA, simultaneous measurement of PRA and PAC is strongly recommended. If the ARR exceeds 200 (PAC: pg ml^{-1}) and particularly if the PAC exceeds 150 pg ml^{-1}, patients should be referred to specialists in hypertension and/or endocrinology. It is noted, however, that ARR values can vary in each determination[696]

Table 12-5 Influence of various antihypertensive agents on PAC, PRA and ARR

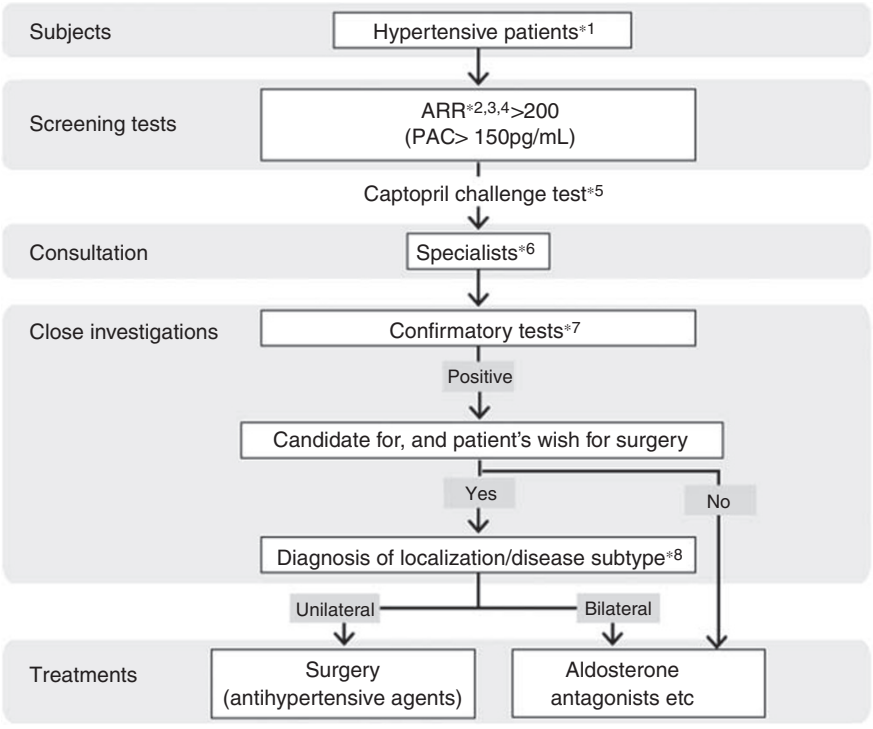
	PAC	*PRA*	*ARR*[a]
ACE inhibitors	↓	↑↑	↓[b]
ARB			
β-blockers	↓	↓↓	↑[c]
Ca channel blockers	→∼↓	↑	↓[b,d]
Aldosterone antagonists	↑	↑↑	↓[b]

Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity.
[a]ARR: PAC/PRA ratio.
[b]Possibility of false-negative results.
[c]Possibility of false-positive results.
[d]The influence is less marked than those of ACE inhibitors and ARBs.

Table 12-6 Confirmatory tests of aldosterone excess

	Methods	*Criteria for positive results*	*Adverse effects*
Captopril challenge test	Oral administration of captopril at 50 mg (crushed)	ARR (60 or 90 min) ⩾ 200 (or ⩾ 350)[a]	Hypotension
Furosemide-upright test	i.v. injection of furosemide at 40 mg and upright posture for 2 h	PRA_{max} ⩽ 1.0 ng ml^{-1} h^{-1} (or ⩽ 2.0)	Orthostatic hypotension, a decrease in the serum K level
Saline infusion test	i.v. drip infusion of saline at 2 l per 4 h	PAC (4 h) ⩾ 85 pg ml^{-1} (⩽ 50 ∼ 100)	Rise in blood pressure, not indicated in patients with impaired heart/kidney function, a decrease in the serum K level

Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity.
[a]ARR is calculated with PAC in the unit of pg ml^{-1}.



*1 Especially at higher risk (all patients if possible).
*2 ARR: PAC/PRA ratio
*3 Antihypertensive agents: Test after switching drugs to Ca channel antagonists and/or α-blockers.
*4 Repeated measurements are recommended.
*5 Cessation drugs in the morning of the test day, test should be done from early morning to 9 AM, fasting, after 30 minutes bed rest.
*6 Certified specialists of the Japan Society of Hypertension or Endocrinology.
*7 At least one of the following tests should be performed: captopril challenge, furosemide-upright, and saline infusion.
*8 Adrenal CT, adrenal scintigraphy, and/or adrenal vein sampling

Figure 12-2 Algorithm for the diagnosis of primary aldosteronism.

and so repeated measurements are recommended. Alternatively, patients may be referred after a captopril challenge test, which can be performed in the outpatient clinic. Specialists should perform at least one of the confirmatory tests and, if positive and surgery is indicated, decide on the execution of adrenal CT and adrenal vein sampling (Figure 12-2).

b. Other conditions associated with hypermineralocorticoid excess
Of the subtypes of congenital adrenocortical hyperplasia, deficiency of 17α-hydroxylase and 11β-hydroxylase causes hypertension with hypokalemia due to an increase in deoxycorticosterone. Glucocorticoid supplementation is the basic treatment of choice. Deoxycorticosterone (DOC)- and corticosterone-producing tumors are rare causes of mineralocorticoid excess.

c. Cushing's syndrome
Characteristic Cushing's signs, hypertension and diabetes mellitus are caused by the autonomous and excessive secretion of cortisol. The disease is observed more frequently in women, with a male–female ratio of 1:3–1:4. The disease conditions are classified into adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent forms. The former includes Cushing's syndrome due to adrenal adenoma and ACTH-independent macronodular adrenal hyperplasia, whereas the latter includes Cushing's disease due to ACTH-producing pituitary tumors and ectopic ACTH-producing tumors.

Diagnostic clues. Attention must be paid to characteristic physical findings including central obesity, moon face, buffalo humps, red striae, skin thinning and bruises and defeminizing symptoms such as hirsutism due to androgen excess. Additional findings, although not specific to the disease, include hypertension, diabetes mellitus, hyperlipidemia, osteoporosis, urolithiasis and nail trichophytosis. Cardiovascular complications such as heart failure are common and affect disease prognosis.[703] On general laboratory tests, eosinopenia and hypokalemia should be noted. As there is a report that 7.5% of patients with adrenal incidentaloma had Cushing's syndrome, a careful differential diagnosis is necessary.

Endocrinological examinations. Increases in plasma cortisol level and urinary free cortisol excretion, the absence of cortisol suppression on the dexamethasone suppression test (overnight method; 0.5 and 1 mg) and the disappearance of diurnal changes in the plasma cortisol level must be established. Then, whether the condition is ACTH dependent or independent must be determined by measuring the plasma ACTH and its response to a corticotropin-releasing hormone (CRH) challenge test. The adrenal and pituitary glands are subjected to imaging workup by adrenal CT and pituitary MRI, respectively.

Treatments. Treatments by laparoscopic adrenalectomy for adrenal adenoma, trans-sphenoidal hypophysectomy for Cushing's disease and surgical resection of the causative mass for ectopic ACTH-producing tumor are the treatments of choice. Although strict antihypertensive

therapy is necessary before surgery or in inoperable patients, Cushing's syndrome is generally refractory to medical treatment. Blockers of the RA system, Ca channel blockers, diuretics and α-blockers are used in combination.

Adrenal subclinical Cushing's syndrome. Although about 50% of adrenal incidentalomas are considered to be non-functioning, subclinical Cushing's syndrome is often observed in patients with 'apparently non-functioning' adrenal incidentaloma. The diagnostic criteria by the Ministry of Health, Labour and Welfare, Japan, include (1) the presence of an adrenal incidentaloma, (2) absence of Cushing's signs, (3) a normal basal blood cortisol level and (4) the absence of cortisol suppression on dexamethasone suppression test (overnight method) as essential findings. Diagnosis of adrenal subclinical Cushing's syndrome is made if there are additional subitems including the suppression of ACTH secretion. The syndrome is often complicated by hypertension, obesity and abnormal glucose tolerance, frequently exacerbated with time, but alleviated after surgery, so that surgery should be considered if possible. If the tumor is 4 cm or greater in diameter or increases in size, it should be resected, considering the possibility of malignancy.

Timing of referral to the specialists. If Cushing's syndrome is suspected due to characteristic Cushing's signs or the concurrence of resistant hypertension and diabetes mellitus, or if adrenal incidentaloma has been detected, patients should be referred to specialists.

d. Pheochromocytoma

Pheochromocytoma is associated with hypertension and abnormal glucose tolerance due to catecholamine excess. The disease is observed at any age, even in elderly people. As about 10% of the disease is either extra-adrenal, bilateral, multiple and malignant, it is called 'the 10% disease'. The disease may be observed as a lesion of multiple endocrine neoplasia, in which multiple lesions develop in endocrine glands, and attention to familial history is necessary. Pheochromocytoma can be diagnosed by the measurement of catecholamines and imaging examination, and blood pressure and catecholamine levels are normalized by resection of the tumor. The greatest problem is malignant pheochromocytoma. Its diagnosis is difficult at initial surgery if not associated with distant metastasis. Recently, the involvement of mutation of the pheochromocytoma-sensitive gene, particularly succinate dehydrogenase subunits B and D (SDHB and SDHD), has been suggested.[704] Pathophysiological significance and clinical implications, however, await further investigation.

Diagnostic clues. Symptoms including headache, palpitation, perspiration, pallor, weight loss and paroxysmal hypertension are suggestive of pheochromocytoma. Hypertensive crisis is induced by various stimuli including exercise, stress, excretion and alcohol consumption. It may also be induced by intravenous metoclopramide injection. The disease may be detected as adrenal incidentaloma.

Endocrinological examinations. Increases in the plasma catecholamine level, 24-h urinary catecholamine excretion and urinary excretions of the metabolites, metanephrine and normetanephrine, must be confirmed. Provocation tests (glucagon, metoclopramide) and the phentolamine (Regitin) test using a decrease in blood pressure as an index[1–12] are not recommended because of problems with specificity and safety. If the plasma noradrenaline level is increased, the clonidine, a central α_2-receptor agonist, test is useful.

Imaging workup. The localization of the tumor is determined by CT. However, as the use of a 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 unknown or extraadrenal, the whole body should be scanned by iodine-131 metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, MRI and/or CT. Although MIBG scintigraphy is useful for the detection of metastatic lesions of malignant pheochromocytoma, false-negative results are experienced if the lesion is small or functionally weak. Although 18-fluorine fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) is useful in patients with negative results on MIBG scintigraphy, it is not covered by medical insurance in Japan.

Treatments. 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, α_1-blockers, such as doxazosin, should be administered. β-blockers are used for the treatment of tachycardia and arrhythmias with concomitant administration of α_1-blockers. As the differentiation between benign and malignant diseases is difficult by histopathological examination, a periodic postoperative follow-up is recommended. Pheochromocytoma crises should be treated by the intravenous injection or drip infusion of phentolamine, followed by the administration of selective α_1-blockers.

Timing of referral to the specialists. Palpitation and paroxysmal hypertension are suggestive of pheochromocytoma. Patients should be referred to specialists if a high blood catecholamine level, high metanephrine or normetanephrine level (corrected for creatinine) in a spot urine sample ($>300\,\mathrm{ng\,mg^{-1}\cdot Cr}$) or adrenal incidentaloma is noted.

e. Other endocrine hypertension

Acromegaly. Acromegaly is caused by growth hormone-producing pituitary adenoma. Hypertension is noted in about 40% of patients. 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 (OGTT), paradoxical responses on the thyroid-releasing hormone (TRH) test and the presence of a pituitary tumor. Transsphenoidal hypophysectomy is the treatment of choice. Hypertension is treated with Ca channel blockers, blockers of the RA system, and others in combination.

Basedow's disease. Isolated systolic hypertension with an increased pulse pressure is characteristic. Signs and symptoms including palpitation, finger tremor, increased appetite, weight loss, goiter and exophthalmos suggest the disease. The diagnosis is based on the measurement of fT_3, fT_4, thyrotropin-releasing hormone (TSH) and thyroid autoantibody (TSAb or TRAb). The disease is treated by the administration of antithyroid drugs. β-blockers are effective for the control of palpitation, tachycardia, and systolic hypertension, and they are used from before the administration of antithyroid drugs until normalization of the thyroid function. Patients should be referred to specialists for the differentiation of the disease from other thyrotoxic disorders such as painless thyroiditis.

Hypothyroidism. Hashimoto's disease is the major cause of hypothyroidism. It is, however, rarely diagnosed due to hypertension. Nonspecific symptoms such as malaise, goiter and hypercholesterolemia are clues to the diagnosis. Sodium levothyroxine replacement therapy

comprises the treatment. Hypertension can be treated with Ca channel blockers, blockers of the RA system, and others in combination.

Primary hyperparathyroidism. The disease is caused by parathyroid adenoma or hyperplasia. Hypertension is observed in about 20% of patients, but it rarely leads to diagnosis. Hypercalcemia and/or urolithiasis are clues to the diagnosis. Resection of the pathological parathyroid gland is the treatment of choice.

POINT 12D
Vascular hypertension

1. **Vascular hypertension includes aortitis syndrome (Takayasu's arteritis), other forms of angiitic hypertension (polyarteritis nodosa, generalized scleroderma), aortic coarctation and vascular hypertension accompanied by an increase in cardiac output (aortic insufficiency, patent ductus arteriosus, arteriovenous fistula and so on). Therapeutic principles matched for various diseases must be followed.**

Hypertension due to brain or central nervous system disorders

1. **Hypertension due to brain or central nervous system disorders includes that caused by an increase in intracranial pressure due to cerebrovascular disorders (cerebral hemorrhage, cerebral infarction and chronic subdural hemorrhage), brain tumor, encephalitis (myelitis), brain injury, and so on (Cushing's response) or compression by arteries around the rostral ventrolateral medulla, which is the center of sympathetic activities. Radical treatment for each cause should be performed first.**

Hereditary hypertension

1. **Essential hypertension is a multiple-factor disorder in which genetic and environmental factors are involved. Genetic factors are considered to be involved in 30–70% of patients.**
2. **The contribution of each individual gene polymorphism to hypertension is small, but salt sensitivity gene polymorphism is frequently observed in the Japanese population.**
3. **Congenital blood pressure abnormalities caused by single-gene abnormalities exist but are rare.**

4) VASCULAR HYPERTENSION

a. Arteritis syndrome (Takayasu's arteritis)

Arteritis syndrome (Takayasu's arteritis) is an as-yet-unexplained non-specific large-vessel arteritis that causes obstructive or dilating lesions in the aorta and its major branches, the pulmonary and coronary arteries.[705] This disease is observed more frequently in women, and its primary findings are lateral differences in the pulse and blood pressure, neck or abdominal bruit, and an enhanced carotid sinus reflex.[706] Hypertension is observed in about 40% of patients with aortitis syndrome and markedly affects the prognosis of this disease. Its diagnostic method using FDG-PET has recently been established.[707] Hypertension of this disease occurs by more than one pathogenic mechanism, and its variations are (1) RVHT, (2) hypertension due to aortic coarctation (variant aortic coarctation), (3) hypertension due to aortic insufficiency and (4) hypertension due to aortic wall sclerosis.[705,706]

Renovascular hypertension is observed in about 20% of patients with aortitis syndrome. In patients with bilateral subclavian artery stenosis, it must be remembered that the upper limb blood pressure is lower than the aortic blood pressure, leading to underestimation. Vascular reconstruction 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.[705] PTRA for RVHT is mildly invasive and effective, but the restenosis rate is higher in this disease than in diseases such as fibromuscular dysplasia, and the long-term efficacy of this procedure is about 50%, which is lower than the 90% for successful bypass surgery. Moreover, aortic insufficiency is an important complication that determines the prognosis of this disease, so that, under an appropriate antihypertensive treatment, indications of aortic valve replacement (including Bentall's operation) should be evaluated following those for aortic insufficiency in general.

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 outcome of surgery in patients with this disease is generally good, attention must be paid to the occurrence of anastomotic aneurysm and dilation of the rest of the ascending aorta.[708] Hypertension due to renal artery stenosis and aortic coarctation, congestive heart failure due to aortic insufficiency, ischemic heart disease, dissecting aneurysm and aneurysmal rupture are considered to be important lesions that determine the prognosis. Therefore, the long-term prognosis is expected to be improved by early and appropriate treatments with medicine (steroids and antihypertensive drugs) and appropriate surgical treatments for severely ill patients.[705]

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

b. Other forms of angiitis

Hypertension due to angiitic syndrome other than aortitis syndrome includes polyarteritis nodosa and progressive systemic scleroderma (PSS). Necrotic arteritis of small- and middle-sized muscular arteries of the whole body, including the renal artery in polyarteritis nodosa and spasms of the renal vessels in PSS,[709] is involved in the etiology of hypertension. Polyarteritis nodosa is complicated by hypertension ($>160/95$ mm Hg) in about 30% of patients, and some patients develop rapidly progressing nephritis. Patients with PSS often show renal crisis (malignant hypertension and renal failure). Other than PSS, causes of death in the acute period 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 therapy and immunosuppressant therapies are performed in combination in the acute period. The method for blood pressure control is the same as that for renal parenchymal or essential hypertension. In PSS, a treatment basically the same as that for malignant hypertension is indicated, and ACE inhibitors and Ca channel blockers are markedly effective.

c. Coarctation of aorta

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. Proximal hypertension is an indication for the surgical relief of stenosis or

angioplasty using a balloon catheter in childhood, and a better outcome has been reported on earlier treatment.[710] In this disease, the RA system and sympathetic nervous system as well as mechanical factors such as an increase in the arterial reflection waves from the site of aortic coarctation,[711,712] an increase in the peripheral vascular resistance in the upper body and weakening of the Windkessel effect of the aorta are known to be involved in hypertension.[713] Hypertension may persist for a long period after repair depending on its preoperative duration, and antihypertensive treatments appropriate for the condition should be performed in such a situation.

d. Vascular hypertension accompanied by an increase in cardiac output

In patients with aortic insufficiency, patent ductus arteriosus, arteriovenous fistula, and so on, systemic hypertension may be caused primarily by an increase in the stroke volume.

Hypertension is cured by treatment of the primary disease in all these patients.

5) HYPERTENSION DUE TO DISEASES OF THE BRAIN OR CENTRAL NERVOUS SYSTEM

Hypertension due to cerebrovascular accidents (cerebral hemorrhage, cerebral infarction and chronic subdural hematoma) is described in detail in Chapter 6. In patients with intracranial diseases such as brain tumors (particularly those in the posterior cranial fossa), encephalitis (myelitis) and brain injury, peripheral sympathetic nervous system activities are increased through the mechanical stress increased intracranial pressure at the brainstem including the nuclei of the solitary tract of the medulla oblongata, possibly causing hypertension (Cushing's response),[648] but this rarely happens. Occasionally, patients with cerebrovascular accidents may present with paroxysmal hypertension and be misdiagnosed with pheochromocytoma. Also, the mechanism of hypertension caused by an increase in sympathetic activities due to the compression of the rostral ventrolateral medulla, which is the vasomotor center of sympathetic nervous system, by surrounding arteries, and patients in whom such hypertension was relieved by surgical decompression were reported in the 1980s.[714] Similar hypertensive cases have been reported on the involvement of an increased sympathetic activity due to the compression of the rostral ventrolateral medulla by surrounding arteries.[715–719]

Brain tumors should be detected promptly by head CT or MRI, and radical treatment such as removal or debulking of the tumor must be considered first. In patients with head trauma, early administration of an intravenous analgesic at a relatively high dose is considered useful in reducing intracranial pressure and controling hypertension. The therapeutic efficacy of decompressing rostral ventrolateral medulla has not been fully established, and the treatment is only considered for patients not responding to ordinary antihypertensive medication.[720] For medical treatment, β-blockers, α-blockers and centrally acting agents can be used first and may be combined with Ca channel blockers or other drugs if necessary.

6) HEREDITARY HYPERTENSION

Essential hypertension is a multifactorial disease in which many genetic and environmental factors are involved. The morbidity of hypertension is reported to be approximately 3.5 times higher in pairs of hypertensive siblings than in the general population,[721] and the contribution of genetic factors is estimated to be approximately 30–70%. Common individual variations in the nucleotide sequence of the genome observed in the general population are called 'genetic polymorphisms'. Many correlations between gene polymorphisms and the predisposition to hypertension or its complications have been reported primarily concerning the RA system, and multiple single-nucleotide polymorphisms[722] and candidate loci[723] were clarified by the genome-wide association study conducted in Japan as part of the Millennium Genome Project. However, the contribution of each gene polymorphism is relatively small, and the diagnosis of essential hypertension based on information concerning gene polymorphisms alone is considered difficult. On the other hand, the risk allele frequency of salt-sensitive hypertension was higher in the Japanese[724] population than in Caucasians. Therefore, the possible usefulness of information concerning gene polymorphisms for the design of lifestyle modifications, such as salt reduction, and selection of antihypertensive drugs has also been suggested.

In contrast, rare heritable blood pressure abnormalities caused by single gene mutation and diagnosed by gene analysis have been reported. Particularly, many such blood pressure abnormalities are due to gene mutations of channels or cotransporters regulating water and electrolyte balance at the renal tubular level,[725] and differential diagnosis should be considered when blood pressure abnormalities occur in children or are accompanied by electrolyte abnormalities. Table 12-7 shows the genes responsible for and clinical characteristics of hereditary blood pressure abnormalities.

In conducting gene analyses, adherence to the Ethics Guidelines for Human Genome/Gene Analysis Research[726] is essential.

POINT 12E
Drug-induced hypertension

1. **Non-steroidal 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 notable in elderly people.**
2. **The administration of glycyrrhizin, a major active component of glycyrrhiza, at a high dose may induce hypertension accompanied by hypokalemia (pseudoaldosteronism). Attention is necessary particularly when using *kampo* drugs. If the discontinuation of administration is difficult, use an aldosterone antagonist.**
3. **Glucocorticoids also induce an increase in blood pressure if used at a large dose. If their administration is unavoidable, common antihypertensive drugs (Ca channel blockers, ACE inhibitors, ARBs, β-blockers, diuretics, and so on) should be used.**
4. **The use of cyclosporine, tacrolimus, erythropoietin, estrogen and 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. If they cannot be discontinued, use Ca channel blockers, ACE inhibitors, ARBs or α-blockers.**

7) DRUG-INDUCED HYPERTENSION

Drugs such as NSAIDs, glycyrrhizin preparations, glucocorticoids, cyclosporine, erythropoietin, oral contraceptives and sympathomimetic drugs are suggested to have hypertensive effects, induce hypertension and attenuate the blood pressure-lowering effects of antihypertensive drugs if used concomitantly (Table 12-8). Many hypertensive patients also have other diseases and consult multiple medical organizations. Therefore, if the blood pressure management

Table 12-7 Genes involved in congenital blood pressure abnormalities and their clinical features

Hereditary hypertension	*Causative genes*	*Clinical features*
Early-onset type hypertension with severe exacerbation during pregnancy	Mineralocorticoid receptor (MR) (*NR3C2*), autosomal dominant	Onset at <20 years of age, development of eclampsia, blood-pressure increase through the actions of progesterone on mutant MR
Glucocorticoid-remediable aldosteronism (GRA) (FH-I)	11β-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) chimera, autosomal dominant	Low PRA, high PAC, low K (rare), glucocorticoid/spirono-lactone responsiveness
11β-hydroxylase deficiency (11β-OHD)	11β-hydroxylase (*CYP11B1*), autosomal recessive	Congenital adrenal hyperplasia, low PRA, high DOC, high ACTH, low cortisol, virilization
17α-hydroxylase deficiency (17α-OHD)	17α-hydroxylase (*CYP17*), autosomal recessive	Congenital adrenal hyperplasia, low PRA, high DOC, high ACTH, low cortisol, feminization
Liddle syndrome	Epithelial Na channel β/γ subunits (*SCNN1B, SCNN1G*), autosomal dominant	Low PRA, low PAC, metabolic alkalosis, Na retention, low K, triamterene responsiveness
Gordon syndrome (PHA IIC, IIB)	Serine–threonine kinase, (IIC: *WNK1*; IIB: *WNK4*), autosomal dominant	High K, low PRA, metabolic acidosis, normal PAC, thiazide responsiveness
Apparent mineralocorticoid excess (AME) (New syndrome)	11β-hydroxysteroid dehydrogenase (*HSD11B2*), autosomal recessive	Low PRA, low PAC, low K, delayed growth, metabolic alkalosis, spironolactone responsiveness
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		
Type 1/2 Bartter syndrome	Type 1: Na-K-2Cl cotransporter (*SLC12A1*), autosomal recessive Type 2: ATP-sensitive K channel (*KCNJ1*), autosomal recessive	Severe, low K, low Mg, metabolic alkalosis, hyperprosta-glandin E2 syndrome, high PRA, high PAC
Type 3/4 Bartter syndrome	Type 3: kidney Cl channel (*CLCNKB*), autosomal recessive Type 4: Barttin (*BSND*), autosomal recessive	Onset during childhood, polyuria, tetanus (rare), low K, high PRA, high PAC, hypocalciuria
Gitelman syndrome	Thiazide-sensitive Na-Cl cotransporter (*SLC12A3*), autosomal recessive	Onset during adolescence, milder than Bartter syndrome, hypocalciuria, high PRA, high PAC, low K, low Mg
PHA I	Mineralocorticoid receptor (*NR3C2*), autosomal dominant, epithelial Na channel α/β/γ subunit (*SCNN1A/B/G*), autosomal recessive	Onset during the neonatal period/infancy, high PRA, low Na, high K, age-related amelioration of symptoms

Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity.

used to be adequate but has become difficult, or in poorly controlled hypertension, the possibility of 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.

a. Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs cause water and Na retention and suppress vasodilation by inhibiting cyclooxygenase (COX) in the process of prostaglandin production from arachidonic acid in the kidney.[727] 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 inflammation. Although classic NSAIDs non-selectively inhibit both, there are also selective inhibitors of COX-2. The harmful effects of non-selective and selective COX-2 inhibitors on the cardiovascular system are related to the suppression ratio between COX-1 and COX-2, tissue-specific COX distribution and so on, rather than the selectivity. Therefore, similar caution is necessary when using NSAIDs that are non-selective as well as selective COX-2 inhibitors.[728–730]

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.

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 to ACE inhibitors. The effects of NSAIDs on the antihypertensive effects of Ca channel blockers are considered to be minor.

b. Glycyrrhiza (licorice), glycyrrhizin

Glycyrrhiza is contained in drugs for liver and gastrointestinal diseases, many other *kampo* drugs, supplements, cosmetics and so on. Glycyrrhizin, a major active component of glycyrrhizia, inhibits 11β-hydroxylated steroid dehydrogenase, which metabolizes cortisol into inactive cortisone, enhances the actions of endogenous

Table 12-8 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), therapeutic drugs containing glycyrrhizin, 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-hydroxy-lated steroid dehydrogenase	Dose reduction/discontinuation of *kampo* drugs, aldosterone antagonist
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 vascular 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, phenylpropa-nolamine, tricyclic/tetracyclic antidepressants, monoamine oxygenase inhibitors	α-Receptor stimulation, inhibition of catechola-mine reuptake at the sympathetic nerve terminals	Dose reduction/discontinuation of drugs with sympathomi-metic actions, α_1-blockers

Abbreviations: NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs.

steroids by prolonging the half-life of cortisol,[731] and enhances Na and water retention and reduces the potassium level, causing pseudoaldosteronism. The glycyrrhizin dose, administration period and age (>=60 years) are considered to be risk factors for glycyr-rhizin-induced hypertension, but the occurrence of hypertension is rare unless glycyrrhizin is administered at a high dose over a prolonged period.

Glycyrrhizin-induced hypertension should be suspected if hypoka-lemia is concurrent with hypertension, and if the renin activity and plasma aldosterone level are reduced (pseudoaldosteronism). 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 with-drawal of glycyrrhiza for a few weeks (maximum 4 months) or concomitant administration of an aldosterone antagonist.

c. 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.[732] 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 day^{-1} or higher. Hypertension was observed in 37.1% of these elderly patients, and hypertensive patients more often had a familial history of hypertension than non-hypertensives.[733] The clarification of the mechanism of glucocorticoid-induced hypertension remains insufficient, although an increase in angiotensin II due to elevated renin substrate production, vasoconstriction due to an increase in erythropoietin production, inhibition of nitrogen monoxide production and impairment of vascular endothelial function due to the inhibition of nitrogen monoxide use by the excess production of superoxides have been suggested.[734]

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, and so on.

d. Others

Cyclosporine and tacrolimus are used for immunosuppression after organ and 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, stimulation of the sympathetic nervous system, inhibition of calcineurin and vascular endothelial cell dysfunc-tion 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.[735] Although diuretics are also effective, caution regard-ing uric acid metabolism is necessary in patients with kidney trans-plantation. As Ca channel blockers may increase the blood concentration of cyclosporine and tacrolimus, measurement of the blood concentrations of these immunosuppressants should be con-sidered 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.[736] 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. An increase in the intracellular Na concentration, vascular endothelial dysfunction and genetic predisposition may also be involved. There is also a report that no increase in blood pressure due to erythropoietin was observed before hemodialysis.[737] However, although erythropoietin is reduced or discontinued if hypertension develops or if blood pressure increases, antihypertensive drugs have also been reported to be effective if the increase is mild.[738] On the other hand, blood pressure control has been reported to be 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.[739]

Estrogen is used in oral contraceptives and drugs for climacteric disturbance, but has been considered to cause an increase in blood pressure or thromboembolism at a high dose. 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 oral contraceptives were safe, although blood pressure was slightly higher in users than in nonusers.[740] However, although the increase in blood pressure was dose dependent, caution is necessary even at a low dose. No sufficient analysis of the relationship between oral contraceptives and hypertension has been made in Japan. When using oral contraceptives, blood pressure should be measured periodically, their use should be discontinued if an increase in the 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 hypertension related to menopause in Chapter 9.

Drugs with sympathomimetic actions may induce increases in the blood pressure. An overdose of phenylpropanolamine, which is contained in drugs for the common cold, may elevate 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 uptake by sympathetic nerve terminals and induce hypertensive crisis or hypertensive urgency.[741] 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 of the dose or discontinuation of administration is necessary, but if discontinuation is impossible, α_1-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 the clinical activation of pheochromocytoma and hypertensive crisis,[742] caution is needed in their use.

Citation Information

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

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