

Clinical approach to young hypertension

Norlela SUKOR

Endocrine Unit, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Malaysia

ABSTRACT

Hypertension affects approximately 30% of the population worldwide. It is a serious disease, expensive to treat, and can lead to long-term morbidity and mortality. Young hypertension, defined as hypertension occurring in patients aged 40 or younger, is now seen more frequently. A correct and holistic approach in the evaluation of patients with suspected young hypertension is essential, as the underlying cause is demonstrable in more than half of the cases. Among these causes include primary aldosteronism, pheochromocytoma, Cushing's syndrome, renal parenchymal disease and renal artery stenosis. The detection of these causes is important as it provides an opportunity to convert an incurable disease into a potentially curable disease, hence avoiding the long-term sequelae and complications of hypertension.

Keywords: Young hypertension, secondary hypertension, primary aldosteronism, pheochromocytoma, Cushing's syndrome

INTRODUCTION

Hypertension is a major long-term health condition, and is the leading cause of premature death among adults throughout the world. It is now established that hypertension detected at young age is not uncommon. Young hypertension is defined as hypertension diagnosed in patients at the age of less than 40 years. The challenges faced by clinicians include how to distinguish young or secondary hypertension from essential hypertension.

Correspondence author: Norlela SUKOR
Endocrine Unit, Department of Medicine,
Universiti Kebangsaan Malaysia Medical Centre,
Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur,
Malaysia. Tel: +60391456087, Fax: +60391456679.
E mail: drlela2020@yahoo.com

Hypertension in the young can be attributed to some underlying causes. This view stems from the study by Platt, who demonstrated secondary causes in 75% of 64 hypertensive patients under the age of 40.¹ In another study looking at 127 young hypertensive patients, an identifiable cause was found in 57%.² The incidence of secondary hypertension is variably estimated between five and 10%.³ The detection of a secondary cause is of important as it provides an opportunity to convert an incurable disease into a potentially curable disease.

A number of rare causes of secondary

hypertension have been identified. However, this review will focus only on the more common secondary causes and the diagnostic approach.

General clinical approach

Before instituting laborious evaluations in a young patient with hypertension, the clinician must be certain that the blood pressure readings obtained are indicative of the patient's blood pressure level. It is crucial to establish that the blood pressure measurement methods are valid and accurate as per established guidelines.⁴ Lack of attention to proper measurement techniques (including using an appropriate arm-cuff size, allowing a full 5-minute resting in a seated position, and keep-

minute resting in a seated position, and keeping the upper arm at heart level) can lead to false diagnoses of hypertension. Once the diagnosis is confirmed, evaluation of secondary causes should be pursued. Ambulatory blood pressure monitoring may be useful in certain patients due to diurnal variation.

A detailed medical history and review of systems should be obtained, complemented with a careful and complete physical examinations. These will provide information and guidance to the diagnostic approach. Table 1 illustrates some of the causes of secondary hypertension and the relevant history and clinical findings.

Table 1. Causes of secondary hypertension.

System	Diseases	Important history	Clinical findings
	Primary aldosteronism	Difficult to control blood pressure, hypertension with hypokalaemia, family history of intracerebral haemorrhage	Muscle or body weakness
	Pheochromocytoma	Headaches, palpitation and/or sweating	Significant postural drop or fluctuating blood pressure
	Cushing's syndrome	Easy bruising, unable to stand up from a squatting position, weight gain, fracture due to osteoporosis	Cushingoid appearance, facial plethora, thin skin, reddish purple striae, proximal myopathy
Endocrine	Acromegaly	Increasing in ring and/or shoe size, enlargement of extremities or visual disturbance, headache	Frontal bossing, thickening of the nose, macroglossia, prognathism
	Hyperthyroidism or Hypothyroidism	Weight loss, palpitation, irritability	Goiter, exophthalmos
	Hyperparathyroidism	Cold intolerance, tiredness and weight gain	Dry skin, coarse, brittle, straw like hair, goitre
		Polyuria, kidney stones, bone/joint pain, depression, epigastric pain	Muscle weakness, depression
Renal	Other mineralocorticoid hypertension (e.g., apparent mineralocorticoid excess, Liddle's syndrome)	Hypertension with hypokalaemia	Muscle or body weakness
	Renal parenchymal disease	Reduced urine output, facial or lower limb swelling, hypertension, haematuria	Facial or lower limb oedema, anaemia
	Renal artery stenosis	Difficult to control blood pressure, sudden deterioration in kidney function	Renal bruit
	Polycystic kidneys	Haematuria or flank pain or recurrent urinary infections	Ballotable kidneys
Cardiovascular	Coarctation of aorta	Hypertension, chest pain	Systolic murmur at left infra-clavicular area, blood pressure difference >20 mmHg between arms and legs
Others	Systemic lupus erythematosus	Small joint pain, mouth ulcers, rashes	Malar rash, small joints polyarthropathy, oral ulcers, alopecia
	Obstructive sleep apnoea	Snoring or fall asleep during daytime	Morbid obesity
	Exogenous drug use	Drug abuse or taking over-the-counter medications	Cushingoid appearance (if exogenous drug contain steroids)

Table 2: Reported effects of drugs on the aldosterone/renin ratio.

Medications	Renin	Aldosterone	Effects
No effect			
Non-dihydropyridine calcium channel blocker (verapamil)	Minimal	Minimal	No effect
Alpha blockers	Nil	Nil	No effect
Hydralazine (with verapamil)	Minimal	Minimal	No effect
False negative effect			
Diuretics (including spironolactone and amiloride)	Increased markedly	Increased	False negative
ACE inhibitors	Increased	Decreased	False negative
Angiotensin receptor blockers	Increased	Decreased	False negative (probably similar to ACEI)
Minoxidil	Increased	Minimal	False negative
Dihydropyridine calcium channel blocker (Amlodipine)	Minimal increased	Minimal decreased	False negative
False positive effect			
B-blockers	Decreased	Minimal decreased	False positive
α -methyldopa	Decreased	Minimal decreased	False positive
Clonidine	Decreased	Minimal decreased	False positive

Primary Aldosteronism

Primary Aldosteronism (PA) is characterised by overproduction of aldosterone by the adrenal cortex which causes salt and water retention, resulting in hypertension and potassium wasting, eventually leading to hypokalaemia. PA was previously considered to be a rare cause of hypertension, accounting for less than 1% of cases and only considered in patients with demonstrated with hypokalaemia. However, recent evidence has showed that PA is the most common specifically treatable and potentially curable form of hypertension, accounting for approximately 5-10% of cases.⁵⁻⁷ Importantly, hypokalaemia is only present in a minority of patients (9-37%)⁸ and normokalaemic hypertension constitutes the most common presentation of the disease.

Screening for PA involves measurement of plasma aldosterone concentration/plasma renin activity (PAC/PRA) ratio [or aldosterone/renin ratio (ARR)]. Plasma ARR is widely regarded as the most reliable screening test for PA. Although the ARR is predominantly renin-dependent, the reliability of aldosterone measurement is also critical for accurate determination of the ARR, and

appropriate interpretation of results.

Many factors can affect the ARR result and compromise its sensitivity and specificity. The most common confounders are anti-hypertensive medications⁹ (Table 2). β -blockers, α -methyldopa and clonidine are known to cause false positive ratios, while false negatives may be encountered with diuretics (including spironolactone and amiloride), dihydropyridine calcium channel antagonists, angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs).⁹⁻¹¹ Diuretics should be withheld for at least four weeks, and β -blocker, α -methyldopa, clonidine, dihydropyridine calcium channel antagonists, ACE-Is and ARBs should be withheld for at least two weeks prior to ARR testing.^{12, 13} Other agents that have lesser effect on the ratio such as slow release verapamil (with or without hydralazine) or prazosin are used to control the blood pressure during this period.^{9, 13} Hypokalaemia must be corrected prior to the testing as potassium influences aldosterone secretion and low potassium levels may be associated with false negative ratios. An ARR greater than 100 (plasma aldosterone in pmol/L, direct renin in mU/L) or 30 (plasma aldosterone in ng/dl,

direct renin in ng/ml/h) is considered highly suggestive of PA. However, different centres use different cut-off values. Some centres use the ARR alone ⁽¹⁴⁾ while others use a combination of the ARR with absolute PAC levels. ^{8, 15, 16}

As ARR is only a screening test, all positive results should be followed by a confirmatory test to definitively confirm or exclude the diagnosis of PA. The Endocrine Society Guideline recommends any of the four confirmatory tests commonly used; fludrocortisone suppression, saline infusion, oral salt loading and captopril challenge tests. Currently, there is insufficient evidence to recommend one over the other. The procedure and interpretation is as shown in Table 3.

It should be emphasised that all of the confirmatory tests have risks and should be used with care in patients with compromised left ventricular cardiac function. Confirmatory tests requiring oral or intravenous sodium loading should be avoided, or at least administered with great caution in patients with uncontrolled hypertension or congestive heart failure.

All patients with confirmed PA, should

undergo adrenal computed tomography (CT) scanning as the initial study in subtype testing, and to exclude large masses that may represent adrenocortical carcinoma (Figure 1). However, adrenal CT lacks reliability as it fails to detect many (at least half in some series ^{12, 17} aldosterone producing adenomas (APAs), and yet may demonstrate non-functioning nodules in the contralateral gland and apparently unilateral lesions in patients with bilateral adrenal hyperplasia (BAH). In a systematic review of 38 studies in a total of 950 patients with PA, adrenal CT/magnetic resonance imaging (MRI) results were discordant with results of adrenal venous sampling (AVS) in 359 of 950 patients (38%). If only CT/MRI results are used to determine lateralisation, inappropriate exclusion from surgery would occur in 19%, inappropriate surgery 15% and surgery on the wrong side in 4%. ¹⁸ Therefore, it is importance that clini-



Figs. 1: a) Computed tomography scan showing a 9-mm left adrenal aldosterone producing adenoma (arrow), and b) left adrenocortical carcinoma.

Table 3: Different confirmatory tests used to diagnose primary aldosteronism.

Type of tests	Methods	Confirmation of primary aldosteronism
Fludrocortisone suppression test	Fludrocortisone acetate (0.1 mg every 6 h), Slow Na (30 mmol thrice daily) and sufficient dietary salt to maintain a urinary excretion rate of at least 3 mmol sodium/kg/day, with sufficient potassium supplementation (given every 6 h) to maintain normokalaemia	Upright PA > 6 ng/dl (166 pmol/l) at 1000 on day 4, provided upright PRA < 1.0 ng/ml/h, lower cortisol level at 1000 than 0700, and normal plasma potassium
IV saline suppression test	IV infusion of 2L of 0.9% sodium chloride over 4 h (500 ml/h)	Post-infusion PA > 5 or > 10 ng/dl (139 or 277 pmol/l)
Oral sodium load	Oral sodium chloride supplementation (300 mmol of sodium per day for 3 days) and potassium supplementation (if required) to maintain normokalaemia	Urinary aldosterone on the third day > 12 or > 14 ug (33 or 39 nmol)/24 h, and urinary sodium > 200 mmol in 24 h
Captopril suppression test	Measurement of ARR 2 h after oral 25-50 mg captopril	Post-captopril ARR > 12 (ng/dl) /(ng/ml/h) or 40 (pmol/L)/(mU/L) AND PA > 12 ng/dL (330 pmol/L)

cians do not use imaging studies as the first line of investigation as confirmation of diagnosis can only be proven with biochemical testing. The presence of a nodule/mass on imaging does not indicate the activity or functionality of a particular mass. Most incidentally found nodule/mass on imaging are non-functioning tumour, the so called 'incidentaloma'

AVS is considered the gold standard for differentiating unilateral from bilateral PA. Lateralisation of aldosterone excess is mandatory to guide the management as treatment differs. APA is treated with unilateral adrenalectomy, whereas targeted medical therapy is the treatment approach for bilateral PA. Unilateral adrenalectomy may result in cure of hypertension in 50-60% with significant improvement in the remainder.²² Quality of life has been shown to improve markedly following adrenalectomy with restoration of normokalaemia in all patients.^{20, 21}

Phaeochromocytoma/Paraganglioma

Phaeochromocytoma is defined as a tumour arising from the catecholamine-producing chromaffin cells in the adrenal medulla, whereas closely related tumours of extra-adrenal sympathetic or parasympathetic paraganglia are classified as extra-adrenal paragangliomas. In general, approximately 80% of phaeochromocytomas are located in the adrenal medulla.¹⁹⁾ Pheochromocytomas and paragangliomas are rare and occur in approximately 0.05% to 0.1% of patients with sustained hypertension.

Improvements in genetics, diagnosis, and treatment of phaeochromocytomas have changed the approaches to these tumours.²³

The formerly used rule of 10% for phaeochromocytoma is no longer applied. Currently, it is estimated that at least 24% to 27% of phaeochromocytomas or paragangliomas are associated with known genetic mutations.^{24, 25} Pheochromocytomas may occur sporadically or as part of a hereditary syndrome. Hereditary phaeochromocytoma is associated with the von Hippel-Lindau (VHL) syndrome, neurofibromatosis type 1 (NF-1), multiple endocrine neoplasia type 2 (MEN-2A or MEN-2B), and familial paragangliomas and phaeochromocytomas due to germ-line mutations of genes encoding succinate dehydrogenase subunits B, C, and D (SDHB, SDHC, SDHD).

Who should be screened for genetic mutations and what cost-benefit factors should be considered? At present, genetic testing is not recommended for every case as it is not cost-effective. It is recommended in cases with high genetic predisposition for hereditary phaeochromocytoma, such as patients with onset of hypertension at aged less than 20 and/or in those found to have bilateral phaeochromocytoma.²⁶ Before choosing the appropriate genetic test, the biochemical profile of catecholamine secretion, patient's age, localisation of the primary tumour and previous family history must be carefully evaluated. Specifically, MEN-2 and NF-1-related phaeochromocytomas always secrete epinephrine; VHL-related phaeochromocytomas secrete norepinephrine; and some SDHB-related paragangliomas causes elevation of dopamine together with norepinephrine. MEN-2, VHL, and NF-1 tumours are almost always found in the adrenal gland, whereas SDHB-related tumours are found in the extra-adrenal locations. In patients with malignant disease secondary to extra-adrenal paragan-

gliomas, almost 50% will have SDHB mutations. The implications of identifying a germline mutation are profound. It may help to predict patient at risk of multifocal tumours or risks of malignancy, recurrent disease and risks to other family members early.

Diagnosis relies heavily on biochemical evidence of catecholamine production. Catecholamines are metabolised within chromaffin cells to metanephrines, and this process occurs independently of catecholamine release. Recent studies have showed that measurements of fractionated metanephrines (ie, normetanephrine and metanephrine measured separately) in urine or plasma provide superior diagnostic sensitivity over measurement of the parent catecholamines.^{27, 28} Plasma fractionated metanephrines has a sensitivity and specificity of 98% and 92%, as compared to urinary catecholamines, 85% and 86% respectively. A raised plasma metanephrine of more than 4-fold above the upper reference limit is associated with close to 100% probability of the tumour.²⁹ In patients with levels of plasma metanephrine above the upper reference limit but less than 4-fold, should undergo clonidine suppression test together with measurements of plasma catecholamines and normetanephrine.²⁹

The next step is tumour localisation is imaging with either CT or MRI (Figure 2). These two imaging modalities offer excellent sensitivity, but lack specificity.³⁰ [¹²³I]-labeled metaiodobenzylguanidine scintigraphy ([¹²³I]-MIBG) overcomes the specificity limitations of anatomical imaging. However, [¹²³I]-MIBG is less sensitive in familial paragangliomas and malignant disease.^{31, 32} Hence,

newer compounds such as [¹⁸F]-flurodopamine ([¹⁸F]-FDA), [¹⁸F]-flurodihydroxyphenylalanine ([¹⁸F]-FDOPA), and [¹⁸F]-fluro-2-deoxy-D-glucose ([¹⁸F]-FDG) have emerged for use in positron emission tomography (PET). [¹⁸F]-FDA PET imaging have been shown to be more superior to [¹³¹I]-MIBG scintigraphy, especially in malignant tumours⁽³³⁾. Recent studies have demonstrated that most phaeochromocytomas show uptake of [¹⁸F]-FDG PET. [¹⁸F]-FDG has been shown to be more superior in the evaluation of metastatic SDHB-associated adult phaeochromocytoma and paraganglioma.³⁴ Currently, functional imaging is recommended on all phaeochromocytomas and paragangliomas, except adrenal phaeochromocytomas, with raised plasma or urine metanephrine and are less than 5 cm in diameter. Surgery has been the main treatment of phaeochromocytoma and paraganglioma.

Cushing's syndrome

Cushing's syndrome is a disease caused by different aetiologies that is characterised by excess glucocorticoid secretion. The hypertension can be severe and is associated with a lack of a normal nocturnal decline in blood



Fig. 2: A computed tomography scan showing a right adrenal phaeochromocytoma (box).

pressure. The syndrome should be suspected in patients with depression and those presenting with clinical features predictive of Cushing's such as easy bruising, facial plethora, reddish purple striae, proximal myopathy, unexplained osteoporosis and in children, weight gain with decreasing growth velocity.

The diagnosis of Cushing's syndrome remains a challenge, especially in mild cases. Recently, the Endocrine Society has developed a clinical practice guideline and recommends one of the following tests as an initial testing:³⁵

- Urinary free cortisol (UFC) – at least two measurements
- Late night salivary cortisol - two measurements
- 1-mg overnight suppression test (DST)
- Longer low-dose DST (2 mg/d for 48h)

It is important to obtain a detailed drug history to exclude excessive exogenous glucocorticoid exposure (iatrogenic Cushing's syndrome) prior to conducting these biochemical testing. Traditional medications that contain glucocorticoid are widely used for the treatment of various conditions such as joint pain, eczema and chronic cough. It is also important to be aware that all forms of glucocorticoid delivery have the potential to cause Cushing's syndrome.

If the initial test is abnormal, either dexamethasone-CRH test or midnight serum cortisol test is recommended. As the levels of UFC in a patient with Cushing's syndrome are variable, at least two collections are required. The guideline recommends using the upper limit of normal for the particular assay as the criterion as a positive test provided the creat-

inine shows a complete collection and there is not excessive volume. For salivary cortisol, the level in normal subjects are less than 145 ng/dl (4 nmol/l) at bedtime, or between 2300 and 2400 hours. The late night salivary cortisol has a sensitivity and specificity of 92-100% and 93-100% respectively.³⁶ Failure to suppress cortisol to less than 1.8 ug/dl (50 nmol/l) with the 1-mg DST has a sensitivity and specificity rates of >95% and 80% respectively.³⁷ The 48-hr 2 mg/d low dose DST (LDDST) is the preferred initial test in certain psychiatric disorders (depression and anxiety), morbid obesity, alcoholism and diabetes mellitus due to its improved specificity compared to the 1-mg DST. These conditions cause hypercortisolism that is not autonomous and the measurement of UFC is less useful. Using the same cut-off value as the 1-mg DST, the sensitivity approaches 95% and specificity 70%.³⁸

To improve the sensitivity of LDDST, a combined CRH stimulation test is advocated. Dexamethasone suppresses the serum cortisol in individuals without Cushing's syndrome, but also in a small number of patients with Cushing's disease. With CRH administration, patients with Cushing's disease should respond with an increase in ACTH and cortisol. A sensitivity of 98% and specificity of 60% has been reported for the dexamethasone-CRH test.³⁹ In patients with Cushing's syndrome, the nocturnal nadir of serum cortisol values is lost. In one study, a midnight serum cortisol greater than 1.8 ug/dl (>50 nmol/l) was reported to have 100% sensitivity for the diagnosis of Cushing's syndrome.³⁸ In cases of simple obesity that has a mildly elevated UFC but without suppression with DST, a midnight serum cortisol less than 1.8 ug/dL effec-

tively excludes Cushing's syndrome.

Once biochemical diagnosis of Cushing's syndrome has been established, imaging studies are used to localise the aetiology. These comprises of the adrenocorticotrophic hormone (ACTH)-dependent forms (ACTH-secreting pituitary adenomas- Cushing's disease [85%] and ectopic ACTH-secreting tumours [15%]), and the ACTH-independent forms (cortisol-secreting adrenal adenomas, carcinomas or bilateral nodular hyperplasia). The adrenal glands should be imaged with CT or MRI in ACTH independent cases and pituitary in ACTH-dependent cases. It is of important to be aware that pituitary adenomas are visible on imaging in only 60% of cases. Therefore, a normal MRI pituitary does not rule out the disease.

The treatment of Cushing's syndrome is usually resection of the tumour. However, even in experienced hands, remission barely reach 80%.⁴⁰ Importantly, treatment of moderate to severe Cushing's syndrome clearly reduces mortality and morbidity.

Renal Parenchymal Disease

Renal parenchymal disease is a common but often unrecognised cause of hypertension. Chronic kidney disease and hypertension may coexist. Essential hypertension is an important cause of chronic kidney disease and renal parenchymal disease is a well-established cause of secondary hypertension. Renal parenchymal disease accounts for approximately 2.5-5.0% of all cases of systemic hypertension. Secondary hypertension may accelerate the decline in renal function if inadequately controlled.

Renal parenchymal disease may be caused by any disease of the renal parenchyma either involving the glomerular or interstitium such as post-infectious glomerulonephritis, focal segmental sclerosis, crescentic glomerulonephritis, renal vasculitis, lupus nephritis, polycystic kidney disease or chronic interstitial nephritis. Chronic glomerulonephritis and pyelonephritis were previously common causes of young hypertension secondary to renal parenchymal disease.²

When a patient is first seen with hypertensive crisis, it is of foremost important to evaluate the renal function through a renal chemistry profile and a complete urinalysis. Other more detailed tests (e.g., urine phase contrast, serum protein electrophoresis, etc.) may be appropriate depending on individual cases or clinical scenario. Although abnormalities may be the result of the hypertension, evaluation of acute renal processes such as glomerulonephritis, renal artery embolism, worsening of ischaemic nephropathy and obstructive uropathy should be considered.⁴¹ Prompt evaluation of the renal function and the degree of proteinuria are mandatory in all patients with difficult to control or worsening blood pressure. Many interstitial disease of the kidney may present with only minor defects of tubular function prior to any discernible decline of the GFR. Therefore, close follow-up and serial surveillance are needed to identify underlying renal disease. Diagnosis of the different types of renal parenchymal diseases can be obtained through renal biopsy and /or renal imaging.

Renal Artery Stenosis

Renal artery stenosis (RAS) can be due to either an atherosclerotic process or fibromus-

cular dysplasia, both of which will result in hypertension. Fibromuscular dysplasia occurs mostly in children and young adults, especially in women, whereas atherosclerotic plaques are seen in men over 45 who have risk factors for atherosclerosis. However, the trend has changed and more young patients are presenting with atherosclerotic disease. Atherosclerotic RAS is primarily a disease of the renal artery ostium and the proximal one third of the renal artery. Since atherosclerosis is a systemic disease, RAS occurs in patients with other cardiovascular risk factors, and a substantial number of patients with atherosclerotic renal artery disease also have coronary disease.⁴²

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines on peripheral arterial disease agree that screening for RAS is only indicated if a corrective procedure would be considered when clinically significant renovascular disease were detected.⁴³ The gold standard for diagnosing RAS is renal arteriography. However, a variety of less invasive tests have been evaluated for screening purposes. False negative tests are the major concern with all non-invasive tests, since patients with a potentially correctable cause of hypertension will be missed. Non-invasive imaging with renal magnetic resonance angiography (MRA), Doppler ultrasonography, or CT has been used (Figure 3). MRA is promising and non-invasive. However, it has only been validated for the stenosis situated in the proximal 3-3.5 cm of renal arteries. Distal and segmental RAS were generally not analysed. The sensitivity of MRA was 90% for proximal RAS, 82% for main RAS, and 0% for segmental stenosis. Other tests such as selective

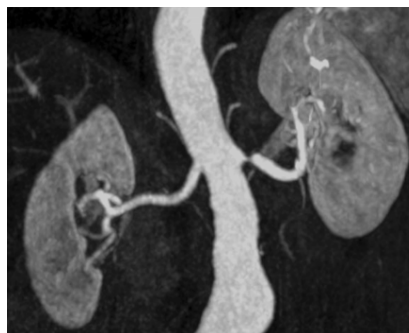


Fig. 3. Magnetic resonance angiogram showing left renal artery stenosis (RAS).

renal renin measurements and captopril renograms may further guide the decision of whether to perform revascularisation.

At present, there is no sufficiently accurate, non-invasive radiologic or serologic screening test that will completely exclude the presence of RAS. Thus, a clinical index of suspicion and the presence or absence of renal insufficiency is the primary determinants of the degree and type of evaluation. Over the decade, effort has been made to identify parameters that will help discern patients who will most likely benefit from procedures. Renal artery resistive indices measured by Doppler ultrasound and venous brain natriuretic peptide level have been demonstrated to be useful in predicting responsiveness to renal artery revascularisation.^{44, 45} In contrast to atherosclerotic RAS, renal artery fibromuscular dysplasia typically responds well to angioplasty without stenting. Since the disease involves the distal two third of the renal artery, most non-invasive imaging studies do not provide an adequate assessment of the distal two thirds of the renal arteries. Hence it is often necessary to perform arteriography if fibromuscular dysplasia is suspected.

Table 4. Screening and confirmatory tests for evaluating young hypertension.

Diseases	Screening tests	Confirmatory tests
Primary aldosteronism	ARR	Any one of four tests: FST SST OLT CCT
Phaeochromocytoma	Plasma/urine metanephrines	Clonidine suppression test CT adrenals ([¹²³ I]-MIBG)
Cushing's syndrome	Any one of four tests: UFC – at least two measurements Late night salivary cortisol - two measurements 1-mg DST Longer low-dose DST (2 mg/d for 48h)	Dexamethasone-CRH test Midnight serum cortisol Adrenal CT/MRI pituitary
Renal parenchymal disease	Renal profile Urinalysis	Renal biopsy Renal imaging
Renal artery stenosis	Captopril test Doppler ultrasonography	Renal angiography
Obstructive sleep apnea	Symptoms (snoring, daytime hypersomnolence)	Sleep study
Systemic lupus erythematosus	FBC, ANA, CRP, urinalysis	ds-DNA, Renal/skin biopsy
Coarctation of aorta	Symptoms and signs(BP in arm > leg, ischaemic symptoms in lower extremities, systolic murmur in thorax)	Aortography TO Echocardiography

Footnote: ARR denotes aldosterone renin ratio; FST, fludrocortisone suppression test; SST, saline suppression test; OLT, oral sodium loading test; CCT, captopril challenge test; CT, computed tomography; ([¹²³I]-MIBG, [¹²³I]-labeled metaiodobenzylguanidine scintigraphy; UFC, Urinary free cortisol; DST, overnight dexamethasone suppression test; CRH, corticotrophin-releasing hormone; MRI, magnetic resonance imaging; FBC, full blood count; ANA, antinuclear antibody; CRP, C-reactive protein; ds-DNA, double-stranded; deoxyribonucleic acid; BP, blood pressure; TOE trans-oesophageal

In general, patients with sudden onset of severe hypertension or rapid deterioration of hypertension control or renal function should be considered for renal artery evaluation, particularly if they have concomitant atherogenic risk factors.

CONCLUSION

Hypertension in the young has been found with increasing frequency and is increasingly recognised as having significant short and long-term health consequences. Improved pharmacologic and non-pharmacologic therapies offer potential for preventing or at least ameliorating early cardiovascular disease. A correct and holistic approach in the evaluation of young patients with hypertension is essential as an identifiable condition can be detected in more than half of the cases. Identifying such patients is of great importance as this can lead to cure of the disease, obviating the need for long-term medical therapy with

its attendant risks, and substantial reduction in the economic health expenditure.

REFERENCES

- 1: Platt R. Severe hypertension in young person; a study of 50 cases. *Q J Medicine* 1948; 17:83-93.
- 2: Ooi BS, Chen BT, Toh CC, Khoo OT. Causes of hypertension in the young. *Br Med J.* 1970; 3:744-6.
- 3: Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res.* 2004; 27:193-202.
- 4: Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation.* 2005; 111:697-716.
- 5: Fardella CE, Mosso L, Gomez-Sanchez C, et al. Primary hyperaldosteronism in essential hyperten-

sives: prevalence, biochemical profile, and molecular biology. *J Clin Endocrinol Metab.* 2000; 85: 1863-7.

6: Gordon RD, Stowasser M, Tunny TJ, Klemm SA, Rutherford JC. High incidence of primary aldosteronism in 199 patients referred with hypertension. *Clin Exp Pharmacol Physiol.* 1994; 21:315-8.

7: Rossi GP, Bernini G, Caliumi C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *Journal of the American College of Cardiology.* 2006; 48:2293-300.

8: Mulatero P, Stowasser M, Loh KC, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab.* 2004; 89:1045-50.

9: Mulatero P, Rabbia F, Milan A, et al. Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. *Hypertension.* 2002; 40:897-902.

10: Gordon RD. Primary aldosteronism. *J Endocrinol Invest.* 1995; 18:495-511.

11: Young WF Jr. Minireview: primary aldosteronism--changing concepts in diagnosis and treatment. *Endocrinology.* 2003; 144:2208-13.

12: Stowasser M, Gordon RD. Primary aldosteronism--careful investigation is essential and rewarding. *Mol Cell Endocrinol.* 2004; 217:33-9.

13: Stowasser M, Gordon RD, Rutherford JC, et al. Diagnosis and management of primary aldosteronism. *J Renin Angiotensin Aldosterone Syst.* 2001; 2:156-69.

14: Stowasser M, Gordon RD. Primary aldosteronism. *Best Pract Res Clin Endocrinol Metab.* 2003; 17:591-605.

15: Rossi GP, Seccia TM, Pessina AC. Primary aldosteronism - part I: prevalence, screening, and selection of cases for adrenal vein sampling. *J Nephrol.* 2008; 21:447-54.

16: Young WFJ. Primary aldosteronism: update on diagnosis and treatment. *Endocrinologist.* 1997; 7:213-21.

17: Gordon RD, Stowasser M, Rutherford JC. Primary aldosteronism: are we diagnosing and operating on too few patients? *World J Surg.* 2001; 25:941-7.

18: Kempers MJ, Lenders JW, van Outheusden L, et al. Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. *Ann Intern Med.* 2009; 151:329-37.

19: Rutherford JC, Taylor WL, Stowasser M, Gordon RD. Success of surgery for primary aldosteronism judged by residual autonomous aldosterone production. *World J Surg.* 1998; 22:1243-5.

20: Sukor N, Kogovsek C, Gordon RD, Robson D, Stowasser M. Improved quality of life, blood pressure, and biochemical status following laparoscopic adrenalectomy for unilateral primary aldosteronism. *J Clin Endocrinol Metab.* 2010; 95:1360-4.

21: Ahmed AH, Gordon RD, Sukor N, Stowasser M. Quality of life in patients with bilateral primary aldosteronism before and during treatment with spironolactone and/or amiloride, including a comparison with our previously published results in those with unilateral disease treated surgically. *J Clin Endocrinol Metab.* 2011; 96:2904-11.

22: Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Pheochromocytoma. *Lancet.* 2005; 366:665-75.

23: Blanchet EM, Martucci V, Pacak K. Pheochromocytoma and paraganglioma: current functional and future molecular imaging. *Front Oncol.* 2011;1:58.

24: Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *J Clin Endocrinol Metab.* 2006; 91:827-36.

25: Neumann HP, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med.* 2002; 346:1459-66.

26: Pigny P, Cardot-Bauters C, Do Cao C, et al. Should genetic testing be performed in each patient with sporadic pheochromocytoma at presentation? *Eur J Endocrinol.* 2009; 160:227-31.

27: Eisenhofer G, Lenders JW, Linehan WM, et al. Plasma normetanephrine and metanephrine for detecting pheochromocytoma in von Hippel-Lindau disease and multiple endocrine neoplasia type 2. *N Engl J Med.* 1999; 340:1872-9.

28: Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma met-

anephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab.* 2003; 88:553-8.

29: Eisenhofer G, Goldstein DS, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *J Clin Endocrinol Metab.* 2003; 88:2656-66.

30: Pacak K, Eisenhofer G, Goldstein DS. Functional imaging of endocrine tumors: role of positron emission tomography. *Endocr Rev.* 2004; 25:568-80.

31: Bhatia KS, Ismail MM, Sahdev A, et al. 123I-metaiodobenzylguanidine (MIBG) scintigraphy for the detection of adrenal and extra-adrenal pheochromocytomas: CT and MRI correlation. *Clin Endocrinol (Oxf).* 2008; 69:181-8.

32: Lumachi F, Tregnaghi A, Zucchetto P, et al. Sensitivity and positive predictive value of CT, MRI and 123I-MIBG scintigraphy in localizing pheochromocytomas: a prospective study. *Nucl Med Commun.* 2006; 27:583-7.

33: Ilias I, Yu J, Carrasquillo JA, et al. Superiority of 6-[18F]-fluorodopamine positron emission tomography versus [131I]-metaiodobenzylguanidine scintigraphy in the localization of metastatic pheochromocytoma. *J Clin Endocrinol Metab.* 2003; 88:4083-7.

34: Timmers HJ, Kozupa A, Chen CC, et al. Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. *J Clin Oncol.* 2007; 25:2262-9.

35: Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2008; 93:1526-40.

36: Viardot A, Huber P, Puder JJ, et al. Reproducibility of nighttime salivary cortisol and its use in the diagnosis of hypercortisolism compared with urinary free cortisol and overnight dexamethasone suppression test. *J Clin Endocrinol Metab.* 2005; 90:5730-6.

37: Wood PJ, Barth JH, Freedman DB, Perry L, Sheridan B. Evidence for the low dose dexamethasone suppression test to screen for Cushing's

syndrome--recommendations for a protocol for biochemistry laboratories. *Ann Clin Biochem.* 1997; 34 (Pt 3):222-9.

38: Nieman L. Editorial: The dexamethasone-suppressed corticotropin-releasing hormone test for the diagnosis of Cushing's syndrome: what have we learned in 14 years? *J Clin Endocrinol Metab.* 2007; 92:2876-8.

39: Gatta B, Chabre O, Cortet C, et al. Reevaluation of the combined dexamethasone suppression-corticotropin-releasing hormone test for differentiation of mild Cushing's disease from pseudo-Cushing's syndrome. *J Clin Endocrinol Metab.* 2007; 92:4290-3.

40: Hofmann BM, Hlavac M, Martinez R, et al. Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. *J Neurosurg.* 2008; 108:9-18.

41: Ghose RR, Harindra V. Unrecognised high pressure chronic retention of urine presenting with systemic arterial hypertension. *BMJ.* 1989; 298:1626-8.

42: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001; 285:2486-97.

43: White CJ, Jaff MR, Haskal ZJ, et al. Indications for renal arteriography at the time of coronary arteriography: a science advisory from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, and the Councils on Cardiovascular Radiology and Intervention and on Kidney in Cardiovascular Disease. *Circulation.* 2006; 114:1892-5.

44: van de Ven PJ, Kaatee R, Beutler JJ, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet.* 1999; 353:282-6.

45: Silva JA, Chan AW, White CJ, et al. Elevated brain natriuretic peptide predicts blood pressure response after stent revascularization in patients with renal artery stenosis. *Circulation* 2005; 111:328-33.

World Health Day 2013: High Blood Pressure



Silent killer, global public health crisis



3 April 2013 – The *Global brief on hypertension: silent killer, global public health crisis* describes why, in the early 21st century, hypertension is a global public health issue. It describes how hypertension contributes to the burden of heart disease, stroke and kidney failure and premature death and disability. The document also explains how hypertension is both preventable and treatable and how governments, health workers, civil society, the private sector, families and individuals can join forces to reduce hypertension and its impact.

[Read the global brief on hypertension](#)

Top stories

[Silent killer, global public health crisis](#)

[One in three adults has high blood pressure](#)

[Reducing blood pressure in Japan](#)

[Control your blood pressure](#)

Raised blood pressure

40%

of adults aged 25 and over had raised blood pressure in 2008.

Cardiovascular diseases

17.3 million

people died from cardiovascular diseases in 2008.

Noncommunicable diseases (NCDs)

80%

of NCD deaths occur in low- and middle-income countries.



World Health Day 2013 activity held at the Royal Wharf in Bandar Seri Begawan on the 14th April 2013 in Brunei Darussalam organised by the Ministry of Health. The aerobic session was participated by members and families of the Ministry of Health, from the very young to the old. Other activities included free medical check, exhibitions on healthy lifestyle and eating to prevent hypertension and stalls selling healthy food. A report on 'World Health Day 2013: Control blood pressure, prolong life' will be published in the June 2013 issue of the Brunei International Medical Journal.