

REFRACTORY HYPERTENSION

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Introduction

Refractory or resistant hypertension is not an uncommon problem for doctors who manage patients with hypertension. The proper assessment and management of these patients is important to prevent the development of complications related to poorly controlled hypertension.

Definition

According to the JNC VI definition, hypertension should be considered refractory or resistant if blood pressure cannot be reduced below 140/90 mmHg (below 160 mmHg systolic blood pressure for the elderly patient with isolated systolic hypertension) with adequate doses of a triple-drug regimen that includes a diuretic⁽¹⁾. Secondary hypertension also needs to be excluded and enough time given (usually up to 6 weeks) for the medication to reach full effect.

Prevalence

The prevalence of refractory hypertension has been reported to be as high as 20%.

Etiology

The categories of causes of refractory or resistant hypertension include⁽²⁾:

- κ Inaccurate blood pressure measurement
- κ White-coat hypertension
- κ Disease progression
- κ Suboptimal treatment
- κ Non-compliance with prescribed treatments
- κ Drug interactions
- κ Coexisting conditions
- κ Secondary hypertension.

It is important to exclude pseudoresistance, where the blood pressure is falsely elevated. The sphygmomanometer should always be checked for faults. This can occur when the blood pressure is wrongly measured (e.g. using a regular cuff on a very obese arm). The standard cuff with a rubber bag 20x12 cm is too small for 30% of patients (those with big arms) and can readily cause an overestimation of 10-15 mmHg. A cuff with an inflatable rubber bag that is about 30-40 cm long and 14-15 cm wide should be used.

White-coat hypertension is not an infrequent phenomenon. The effect of both the office setting and the physician in elevating blood pressure reading has been repeatedly shown. Laughlin et al found that 17% of a group of hypertensive patients had diastolic blood pressure 10 mmHg higher in the office than

at home⁽³⁾. In a study of hospitalized patients, the mean arterial blood pressure increased by 8.6 mm Hg when the doctor came into the room to take the blood pressure⁽⁴⁾. It is useful to look for discrepancies between blood pressure levels and target organ damage, especially in the fundi and cardiovascular system. If the pressure is always around 110 mmHg diastolic despite the fundi and other target organs being quite normal, these are grounds for suspecting that the blood pressure may be selectively elevated in the doctor's presence.

With time, the blood pressure in adults with hypertension will gradually increase⁽⁵⁾. There is however no recent data to demonstrate how often disease progression is the cause of resistant hypertension. Hence it is unwise to accept it as such until other causes have been excluded. Hypertension resulting in progressive renal damage will also result in hypertension being more difficult to control.

An important cause for "refractory hypertension" may actually be due to suboptimal treatment or failure to dose in accordance with the duration of action of each medication. The suboptimal treatment may also be due to inappropriately low dosage or when diuretics are not used. Occasionally, it is because wrong combinations of drugs are used. Often, medication is not changed or added by the physician despite failure to achieve goal blood pressure levels.

For patients with true persistently resistant hypertension after triple drug therapy, studies point to non-compliance with treatment (both pharmacological and non-pharmacological) as the most common cause. Non-pharmacological causes include excessive salt intake or alcohol consumption and failure to lose weight in the obese patient. Failure of drug therapy may be due of poor compliance in the patient, especially in the elderly. Compliance with drugs may be investigated by talking to the patient's spouse and relatives. Counting medications prescribed and number of medications left between visits may be useful. In patients on beta-blockers, presence of bradycardia suggests that the patient is compliant. It is important not to lower the blood pressure too quickly. This often causes unnecessary and severe side-effects and can lead to poor compliance.

Drugs may interact with the control of hypertension and include the following:

- κ Sympathomimetics
- κ Nasal decongestants
- κ Appetite suppressants
- κ Cocaine and other illicit drugs
- κ Caffeine
- κ Oral contraceptives
- κ Adrenal steroids
- κ Liquorice (as it may be found in chewing tobacco)

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- κ Cyclosporine, tacrolimus
- κ Erythropoietin
- κ Anti-depressants
- κ NSAID and Cox inhibitors

Associated medical conditions may aggravate hypertension. Increasing obesity, sleep apnoea, anxiety and chronic pain may result in refractory or resistant hypertension.

Finally, secondary hypertension should be excluded if hypertension is still unexplained, or for patients who fit specific patterns suggesting secondary hypertension. A selective, sequential evaluation for secondary causes of hypertension should be considered, starting with relatively common conditions, such as renovascular causes and renal parenchymal disease or adrenal causes (phaeochromocytoma and hyperaldosteronism). The prevalence of secondary hypertension in primary care however is uncertain but it is probably an uncommon cause of refractory hypertension.

Assessment of the patient with refractory hypertension

- κ Recheck blood pressure repeatedly.
- κ Ensure proper cuff size
- κ Check for patient compliance with medications
- κ Repeat patient history and physical examination
- κ Drug history – for drugs that aggravate blood pressure control
- κ Look for end-organ damage – fundi, cardiac, renal
- κ Look for secondary cause of hypertension
- κ Consider home blood pressure monitoring or ambulatory blood pressure monitoring
- κ Advise and institute non-pharmacological measures
- κ Optimize drug therapy

Physical examination

- κ Height and weight – Body Mass Index to assess obesity
- κ Blood pressure measurements – both arms and standing
- κ Skin – neurofibromata or cafe-au-lait spots suggests pheochromocytoma
- κ Peripheral pulses – radiofemoral delay suggest coarctation of aorta
- κ Fundi – for evidence of hemorrhages, exudates or papilledema
- κ Heart – evidence of displaced apex beat. Fourth heart sound suggests LV strain and third heart sound suggests heart failure.
- κ Abdomen – palpable kidney suggesting polycystic kidney, renal bruit for renal artery stenosis

Investigations

Urine analysis

Proteinuria, hematuria, glycosuria should be looked for.

Renal function

Deterioration of renal function may explain why hypertension

has become more difficult to control. Sudden deterioration of renal function with use of ACE inhibitors should make the doctor suspect possible bilateral renal artery stenosis.

Ambulatory blood pressure monitoring

Ambulatory monitoring of blood pressure provides important insight into response to therapy and what, if any, additional therapy is necessary. It is also useful to ascertain whether there is a white-coat component superimposed on existing hypertension. A recent study showed that approximately one in four patients with apparent resistant hypertension referred for ambulatory blood pressure monitoring has controlled blood pressure⁽⁶⁾. Ambulatory monitoring of blood pressure is also helpful in patients with hypertension refractory to treatment because absence of a nocturnal dip in blood pressure can be determined. This finding would suggest the need to investigate possible secondary causes of hypertension.

Echocardiogram

The echocardiogram is useful to ascertain if hypertensive heart disease is present. This will confirm that the hypertension is significant and needs better control.

Investigate for secondary hypertension

Patients with refractory hypertension should be screened for secondary hypertension. These include a 24-hour urinary metanephrine for pheochromocytoma, renal ultrasound and duplex of the renal artery to exclude renal parenchymal disease and renal artery stenosis.

Treatment

Treatment should include both non-pharmacological and pharmacological treatment.

Non-drug Treatment

Salt restriction

Hypervolaemia resulting from a high intake of dietary sodium frequently plays an important part in refractory hypertension. This can be quantified by measuring the 24-hour urinary sodium excretion. Reduction of sodium from 200 to 100 mmol per day will convert a difficult patient to one whose hypertension is easy to control.

Weight reduction

Weight reduction is especially useful as a reduction of arm size decreases a falsely high reading of blood pressure. Weight reduction is also associated with a fall in blood pressure independent of arm size.

Reduction in alcohol intake

In some patients, fluctuation in blood pressure may be related to excessive alcohol intake. Reduction in alcohol may help by reducing fluid and salt intake (some alcoholic drinks e.g. beer

has a high salt content). The reduced caloric intake also leads to weight reduction. Tuomilhto et al reported that any use of alcohol correlated with poor blood pressure control and compliance independently⁽⁷⁾.

Relaxation therapy and exercise

This may help in some patients who have white-coat hypertension.

Drug treatment

Optimal blood pressure control may require use of multiple drugs. These include:

- κ ACE inhibitors
- κ Angiotensin receptor blockers
- κ Beta-blockers
- κ Ca antagonist
- κ Diuretics.

Additional drugs which may be useful include:

- κ Carvedilol
- κ Hydralazine
- κ Methyl-dopa
- κ Minoxidil
- κ Prazosin.

The optimal or additional use of diuretics is often the answer when a patient's blood pressure is difficult to control. Low-dose thiazides however do not achieve significant volume diuresis and it may be necessary to use either a loop diuretic or higher doses of a thiazide (≥ 50 mg daily), while presumably lowering blood pressure by vasodilation. Thiazides are also often ineffective in the presence of renal insufficiency (glomerular filtration rate of < 15 - 20 mL/min) and either a loop diuretic or metolazone is indicated in such patients. Loop diuretics however are not appropriate as initial therapy, particularly in patients with normal renal function⁽⁸⁾.

Carvedilol lowers blood pressure by blocking peripheral α_1 adrenoreceptors which causes arterial vasodilatation. In addition, it is a beta adrenoreceptor antagonist that prevents the development of reflex tachycardia and increased cardiac output in response to vasodilatation. It is especially useful in patients who have history of heart failure.

Prazosin may be effective in patients already on diuretic, beta-blocker and hydralazine. It is especially useful in elderly males who have benign prostatic hyperplasia.

Minoxidil, a potent arterial vasodilator, may be useful in resistant cases if a vasodilator has not been used. It is especially useful in those with renal impairment. However, it is not readily available in Singapore and needs to be combined with a diuretic to offset the fluid retention and/or a beta-blocker to attenuate the reflex tachycardia induced by minoxidil.

Combination drug regimens may not only be therapeutically more effective than single-drug therapy, but also may contribute to patient compliance by simplifying

and reducing the cost of the treatment regimen. Multiple-drug regimens should include drugs from different classes. Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACE/ARB) combinations and α_1 /beta blocker combinations may be helpful.

When to refer for specialist consultation

This should be considered in the following circumstances:

- κ If the blood pressure is still not under control after 3-4 months of compliant treatment.
- κ When end-organ damage appears or progresses despite treatment.
- κ When secondary hypertension is suspected and more complex investigations are required.

Take Home Messages

- Refractory hypertension may be due to multiple causes.
- Correct evaluation and management can result in successful treatment and prevention of the complications associated with poorly controlled hypertension.

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FURTHER READING

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