Introduction

Hypertension

Hypertension is recognized as a state of abnormally elevated blood pressure. It is not easy to defined a level of blood pressure which can be represent hypertension. However, in man, blood pressure in excess of 140 mmHg systolic or 90 mmHg diastolic has been characterized as "hypertension". The levels of blood pressure vary with age, sex or race. Many factors can influence the blood pressure: body posture, exercise, gastrointestinal activity, emotion or painful stimuli, environmental factors and drugs. Blood pressure frequently associated with anatomic and physiologic abnormalities of many organs, particularly of the blood vessels, heart, kidneys, nervous system, and adrenal glands. It is estimated that 10 to 15 percent of the general population has an abnormally elevated blood pressure (Ross, 1976).

Classification of hypertension

Hypertension may be classified in two ways:

A) According to types of hypertension.

B) According to the degree of severity.

A. Classification of hypertension according to types of hypertension.

I. Systolic hypertension in which only systolic pressure is raised.

1. Increased stroke volume of the left ventricle. (Complete heart block, patent ductus arteriosus, fever, thyrotoxicosis, pregnancy).

2. Increased regidity of aorta due to degenerative disease of wall.

3. Decreased capacity of aorta in coarctation.

II. Hypertension in which both systolic and diastolic pressure are raised.

1. Secondary hypertension : hypertension occuring as manifestation of known disease.

a. Disease of the kidneys and urinary tract :

- Chronic pyelonephritis
- Renal stone and other lesions
- Diabetes mellitus
- Hereditary nephritis

b. Coarctation of the Aorta

c. Pheochromocytoma

d. Primary aldosteronism

2. Essential hypertension (more than 80% of case).

The common type of hypertension, the precise etiology of this type is unknown.

B. Classification of hypertension according to the degree of severity.

I. The malignant phase.

The malignant hypertension occurs at any age but is more frequently found in the young than in the old. It is characterized by neuroretinopathy and by a rapid decline in renal function. The pressure is usually very high. Unless the arterial pressure is reduced at an early stage, the patient dies after a few months or years either of renal failure, left ventricular failure or cerebral hemorrhage. Its pathology is fibrinoid arteriolar necrosis.

II. The benign phase.

It usually occurs in rather older subjects in whom the pressures are not as high as the malignant. The patient's condition remains relatively stable for years ; and death, when it occurs, is either due to heart failure, stroke or intercurrent disease.

Hormone in high blood pressure

When diastolic blood pressure is elevated, there is an excessive resistance of flow of blood through the small arteries. Although numerous factors can affect the caliber of the small arteries but the primary importance factor is a control of hormones. These are noradrenaline, aldosterone and substance renin.

Noradrenaline, Which is contained within special nerve fiber locates in the wall of the small arteries. This hormone also found in

the adrenal gland. The reflexes of the autonomic nervous system normally regulate the amount of noradrenaline release in the blood vessel walls. This hormone reduces the caliber of the small arteries which leads to increased resistance to flow and hence elevates the blood pressure.

Aldosterone. It is secreated normally by the adrenal glands and also plays a role in the control of blood pressure. Over secretion of this hormone causes a retention of the sodium ion in the body, which inturn increases blood volume resulting high blood pressure.

Renin, a protein normally released from the kidney, which reacts with a precursor, angiotensin I in the blood to produce and active substance "angiotensin II". Angiotensin II increases the blood pressure by constricting small arteries, in addition it stimulates aldosterone secretion from the adrenal gland, resulting sodium retention.

Normally,the levels of all of these hormones are regulated both by the nervous system and the body's complex hormonal regulatory mechanism to maintain a normal level of blood pressure.

Complication of high blood pressure.

With persistent diastolic pressure elevation, there is abnormal thickening of the muscular wall of the smallest arteries. This change is followed by a progressive decrease in the size of the channel within these vessels, and later all layers of the arterial wall are destruction.

These changes may occur in any and all parts of the circulation, including the coronary arteries, the retinal vessels, kidney and brain. Small areas of cell and tissue death may occur in these organs as a result of inadequate blood supply.

High blood pressure also affects the heart muscle, causing hypertrophy of the left ventricular wall. This results from increased muscle protein synthesis, stimulated by the increased workload placed on this pumping chamber by the high systolic blood pressure required during each heart beat. The complication which commonly occurs is heart failure, the result of damage to the heart muscle from long-standing overwork.

Another complication of hypertension is the enlargement of aorta and thickening or destruction of the muscle in its wall. Sometimes, rupture of an area of outpouching of the aortic wall (aneurysm) occurs, resulting in bleeding into the chest, or even sudden death. The destruction of localized areas of kidney tissue may have poor function. The damage and narrowing of the small arteries supplying the brain leads to an insufficient cerebral blood flow, to bleeding into the brain due to a ruptured blood vessel, or to atherosclerosis and blockade of one of the larger blood vessels which supply the brain.

Treatment of high blood pressure.

If the cause of hypertension can be revealed, we usually cures the problem or the cause of hypertension. Some types of hypertension

can be cured by operating such as adrenal pheochromocytoma or removing the kidney which is damage by any diseases or inadequate blood supply.

The aim of effective drug therapy for hypertension is to control both systolic and diastolic blood pressure with a view to bring them to normal levels and to prevent the onset and progression of blood vessel damage. Medical treatment including a low salt diet and diuretics which increase the excretion of sodium by the kidney should be applied.

Drugs used in the treatment of hypertension may act through the following sites :

1. Vessel wall unrelated to nerve endings, e.g. nitrite, xanthines, nitroprusside, diazoxide, methyldopa , hydralazine (?). Diuretics may act here as well as by reducing plasma volume.

2. At the sympathetic receptor, blocking of the adrenoceptor.

(a) α - adrenoceptor blocking drugs. (Phentolamine, Phenoxybenzamine, Thymoxamine).

(b) β - adrenoceptor blocking drugs. (Propranolol, Oxprenolol etc.).

3. Sympathetic nerve fibers (Post-ganglionic), or nerve terminals or adrenergic neurone blocking drugs (guanethidine, methyldopa, reserpine).

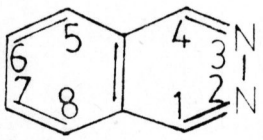
4. Sympathetic ganglia, e.g. pempidine, mecamylamine.

5. Central nervous system, e.g. reserpine, clonidine, methyldopa.

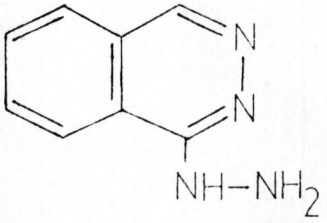
6. Afferent nerve ending, e.g. Veratrum.

Hydralazine

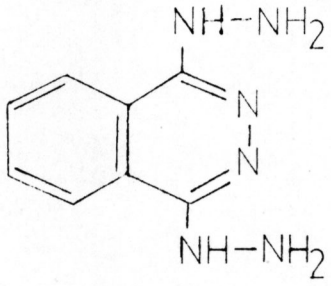
Hydralazine is an effective vasodilator drugs : it has been used in the treatment of hypertension for several years (Åblad, 1963 ; Finnertry et al, 1963 : Sellers and Koch-Weser, 1969 : Zacest, Gilmore, Koch-Weser, 1972 : Moyer, 1953 ; Schroeder, 1952). Hydralazine lowers peripheral vascular resistance by a direct relaxing effect on arteriolar smooth muscle but has little action on capacitance vassels (Åblad 1963 : Sellers and Koch-Weser 1969 ; Bhatia and Frohlich, 1973 ; Stunkard et al, 1954 ; Rubin et al, 1962).The hypotensive action of hydralazine is accompanied by marked increases in heart rate and cardiac output (Åblad; 1963 ; Finnertry et al, 1963 ; Zacest, Gilmore, Koch-Weser 1972 ; Bhatia and Fronlich, 1973 ; Rubin et al, 1963). This cardiac hyperactivity is the result of increased sympathetic tone of the heart due to activation of the baroreceptor reflex by the vasodilation induced hypotension (Åblad, 1963 ; Zacest, Gilmore and Koch-Weser, 1972 ; Bhatia and Frohlich, 1973 ; Koch-Weser, 1973). Reflex stimulation of the heart can be decreased by administering hydralazine together with β-adrenergic blocking agent, propranolol (Zacest Gilmore and Koch-Weser, 1972 ; Hansson et al, 1971) or other β-adrenergic antagonist (Sannerstedt et al, 1971 ; Katila, Frick, 1970). Daily doses of 80-240 mg of propranolol predictably prevent increases in cardiac rate and output during hydralazine therapy (Zacest, Gilmore and Koch-Weser, 1972). Propranolol also minimizes increase in plasma renin activity which requlary accompanies treatment of hypertensive



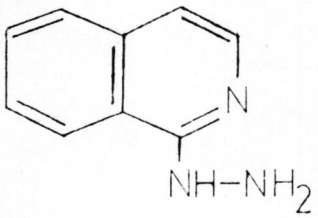
Phthalazine ring



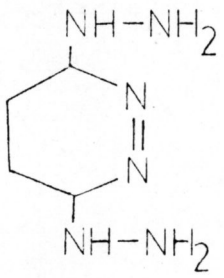
1-hydrazinophthalazine
[hydralazine]



1,4 - dihydrazinoph
thalazine



1-hydrazino -
isoquinoline



3,6 - dihydrazino -
pyridazine

Structureal formulae of 1-hydrazinophthalazine (hydralazine) and related compounds.

(after Arthur R. Schulert, 1961)

patients with hydralazine or other vasodilator drugs (Koch-Weser, 1974). Hydralazine must be administered with a diuretic in order to prevent sodium and water retention, expansion of plasma and extracellular fluid volume, weight gain, and edema formation (Zacest, Gilmore, Koch-Weser, 1972 ; Moyer, 1953 ; Wilkinson, 1952). These disturbances in electrolyte and fluid balance do not reflect decreases in renal blood flow and glomerular filtration rate, both of which are either increased or unchanged during hydralazine therapy (Moyer, 1953 ; Stein, Hecht, 1955; Wilkinson, Backman, Hecht, 1952 ; Judson, Hollander, Willkins, 1956).

Hydralazine can decrease total peripheral resistance by more than 60 % of hypertensive patients (Freis et al, 1953). Its hypotensive effect was characterized by gradual onset, limited degree and long duration (Craver, Yonkman, 1950). The peripheral vasodilation of hydralazine is not uniform, and vascular resistance in the coronary, cerebral, splanchnic, and renal circulations decreases more than in skin and muscle (Åblad, 1963 ; Freis et al, 1953). Postcapillary capacitance vessels are affected much less by hydralazine than precapillary resistance vessels (Åblad, 1963 ; Freis et al, 1972).

In well-tolerated doses of up to 50 mg, four times per day, the antihypertensive effect of hydralazine, when administered to patients receiving a diuretic and propranolol, is limited to a reduction of about 20 mmHg. Not exceeding 200 mg/day are sufficient in most patients and this amount rarely causes adverse effects (Zacest, Gilmore, Koch-Weser,

1972). However, the vasodilator effectiveness of such doses is inadequate for satisfactory control of severe hypertension. Prolonged treatment with hydralazine may produce a syndrome resembling lupus erythematosus (Perry and Schroeder, 1954). The incidence of this type of hydralazine toxicity increases with dosage and duration of exposure (Perry 1973). It eventually appears in 10 % to 20 % of individuals treated with doses of 400 mg or more. The syndrome is reversible when hydralazine is stopped, but months to years may be required for complete clearing (Perry, 1973).

Hydralazine is rapidly absorbed after oral administration and the hypotensive action is fully developed within one hour (Zacest, Koch-Weser, 1972). Postingestion serum concentrations are lower than after intravenous injection of the same dose. This may be due to incomplete intestinal absorption or to inactivation of hydralazine during its first passage through the liver. Acetylation of hydralazine is an important pathway of biotransformation in the liver, (McIsaac, Kanda, 1964) and the rate of this process is dependent on the genetically determined activity of hepatic N-acetyltransferase (Zacest, Koch-Weser, 1972). Slow acetylators have higher serum concentrations of hydralazine than fast acetylators (Zacest, Koch-Weser, 1972). With any given daily dosage, slow acetylators have a greater antihypertensive effect (Zacest, Koch-Weser, 1972) and are more likely to develop antinuclear antibodies and the rheumatoid type of hydralazine toxicity (Perry et al, 1970). Patients with impaired renal function also show unusually high serum concentrations of hydralazine (Zacest, Koch-Weser, 1972 ; Perry et al ;1954), indicating that renal

excretion of unchanged drug is an important route of elimination.

Parenteral administration of hydralazine is effective and is employed for treatment of hypertensive emergencies. However, the onset of action requires about 15 minutes (Åblad 1963 ; Brunner et al, 1967) ; doses and frequency of administration required for satisfactory blood pressure control are highly variable. The initial intravenous dose should not exceed 20 mg and may be repeated as necessary.

The untoward effects of hydralazine such as headache, dizziness, flushing, nasal congestion, palpitation, increases in cardiac work and oxygen consumption, anginal attacks, and electrocardiographic changes of myocardial ischemia are all related to the vasodilating action of the drug or to the reflex responses to that action. There are no problems when low doses of hydralazine are administered to patients treated with propranolol. Even hypertensive patients with limited coronary reserve and with symptoms or signs of myocardial ischemia can be succesfully treated with this combination of drugs (Koch-Weser, 1974 ; Koch-Weser,1976).

Effect of hydralazine on the heart

Among a series of phthalazines synthesized by Druey and Ringier in 1950, the most active hypotensive agent appeared to be L-hydrazinophthalazine (Hydralazine). The previous reports have been shown to exert a hypotensive action in the following species ; cat, dog, quinea pig and rat. The effects of hydralazine on the heart have been

reported by :

1. Craver, B.N. and Yonkman. F.F. (1950).

They studied in the canine heart-lung preparation, and suggested that doses up to 100 mg of hydralazine have no effect on the heart but higher doses of more than 100 mg decreased cardiac rate and output by the appearance of irregularities. Doses up to 2 mg were almost devoided of action on the perfused feline heart.

2. Moyer, J.H. et al (1951) suggested that the tachycardia may be due either to a central effect or to a local action of hydralazine on the heart of conscious dogs.

3. Bein, H.J. et al ; (1953) and Tripod, J. & Meier, R., (1954, 1958), reported that in the isolated perfused heart of the rabbit, hydralazine in a concentration of 5 mol/l, reduced the amplitude of contraction but had no effect on the rate of beating.

4. Gershin, M.E. & Smith, N.T. (1967), reported that hydralazine in a high concentration (1.3 mmol/l) produced an increase in the force of contraction of guinea-pig atria and they suggest that this effect was due to hydralazine releasing histamine, which in turn released noradrenaline with the consequent production of a positive inotropic effect.

5. Linet, O., Van Swieten, P.A. and Hertting, G ; (1967), have been shown that hydralazine cause a depletion of cardiac noradrenaline in the rat.

6. Bhatia, S.K. and Frohlich, E.D. (1973), Freis, E.D. (1964) ; Gershwin, M.E. & Smith, N.T. (1967), suggested that hydralazine may exert more proximate positive chronotropic and inotropic effects on the heart itself of kitten. It might produce such effects by releasing noradrenaline from myocardial sympathetic nerve ending, by stimulated cardiac β-adrenergic receptors, or by a direct myocardial action.

7. Koch-Weser, J. (1974), reported that hydralazine in a concentration of 3 mmol/l increased tension of both kitten papillary muscle and kitten aterial strip, and in a concentration of 10 mmol/l decreased in rate of beating of quinea pig isolated right atrium.

8. Songkittiguna, P. and Rand, M.J. (1982), suggested that low concentration 10 μmol/l - 0.1 mmol/l of hydralazine on rat isolated atria produce a negative chronotropic effect due to inhibition of spontaneous release of noradrenaline, but in concentration of 0.2 mmol/l or more the negative chronotropic effect was due to a more direct depression of pacemaker activity. In a concentration of 2 mmol/l produces a positive chronotropic effect due to release of noradrenaline. This effect was abolished by reserpine pretreatment or β-adrenergic blocking agents. A positive inotropic effect was produced by concentration of 0.6 - 2 mmol/l, this effect was not reduced by reserpine or β-adrenergic blocking agents, but it was absent in a calcium free medium and blocked by varapamil.