For more than 30 years, hydralazine has been known as an antihypertensive agent. Its therapeutic spectrum was relatively broad until the occurrence of major side effects became known. Dose reduction and combination with diuretics or beta-adrenergic receptor blocking agents led to a renewed increase in its use for the management of hypertension.

Within the last few years, since about 1972, hydralazine has been used increasingly for the management of chronic heart failure (Chatterjee et al. 1976a, b; 1979).

I. Pharmacokinetics of Hydralazine

Among the various phthalazine derivatives, the most frequently used agents are hydralazine and dihydralazine. Both agents are rapidly and almost completely absorbed. Only 10 percent of the oral dose is excreted in the stools. Peak blood levels are reached after 0.5 to 2 hours, and hydralazine is predominantly bound to serum protein. Following oral administration, the onset of action occurs within 20 to 30 minutes, whereas after intravenous administration it occurs within 10 to 20 minutes. Blood levels are significantly lower after oral administration than with intravenous administration. The oral administration of 100 mg hydralazine produces serum concentrations similar to those obtained with a dose of 25 mg intravenously. Accumulation of hydralazine can be demonstrated in the vascular walls of arteries in the kidney, liver, spleen, heart, lungs, brain and muscle.

The serum half-life of hydralazine is 2 to 4 hours. Biologic half-life is clearly prolonged as a result of higher concentrations of hydralazine in the muscularis layer of arterial walls (Koch-Weser 1976).

During the initial pass through the liver, 40 percent of the hydralazine is acetylated which is the main reason for its reduced oral bioavailability. Furthermore, there are genetic differences in the concentrations of hepatic N-acetyl transferase. ‘Slow’ acetylators, with a low level of N-acetyl transferase, have distinctly higher hydralazine plasma concentrations even at low doses. Therefore, the probability of toxicity is higher in this patient group. About 50 percent of the population belong to this slow acetylator phenotype.

Further metabolic reactions include hydroxylation and conjugation with glucuronic acid. Within 48 hours the majority of hydralazine and its metabolites is excreted, a process which is prolonged in renal failure. Accumulation is not uncommon. In ‘rapid’ acetylators, complications such as the lupus-like syndrome or polyneuropathy are less common, even with high doses. The status of acetylation can be determined with the help of the isoniazide assay (Chatterjee et al. 1976a, b; Massie et al. 1981a, b, c). In ‘slow’ acetylators, half of the recommended dose is given to these patients.
II. Mechanism of Action of Hydralazine

1. Hemodynamic Effects

Hydralazine is a direct-acting vasodilator that causes relaxation of smooth muscle, primarily of the arteriolar resistance vessels. It demonstrates only minor activity on venous capacitance vessels of the skin and skeletal muscles, whereas it has a significant action on coronary, renal and splanchnic arteries and cranial vessels. Its effect on the pulmonary vasculature is variable. In heart failure and with hydralazine producing a marked increase in cardiac output, a decrease in pulmonary resistance can occur though pulmonary artery pressure remains unchanged.

The reduction of systemic resistance following the use of hydralazine is associated with a definite increase of cardiac output. Thus, a precipitous drop in blood pressure is avoided in patients with chronic heart failure. However, in patients with hypertension but without heart failure, hydralazine causes a decrease in blood pressure which occasionally results in hypotension associated with reflex tachycardia. The heightened sympathetic tone leads to enhanced myocardial contractility. Due to the increase in stroke volume and cardiac output, reflex tachycardia and hypotension are uncommon in patients with heart failure. Some authors believe that even in the presence of heart failure, hydralazine enhances myocardial contractility (Kment 1981; Khatri et al. 1977).

The reduction of peripheral resistance associated with a dramatic increase in cardiac output should be critically evaluated. Although the administration of hydralazine resulted in a substantial improvement in cardiac function at rest and during exercise, an improvement of exercise capacity or an increase in total oxygen consumption was not observed (Chatterjee et al. 1979). Hydralazine increases cardiac output during exercise but oxygen extraction decreases proportionately resulting in no net change in oxygen consumption of the organism (Fig. 134). In spite of a higher blood flow and oxygen supply, muscular tissue does not extract more oxygen necessary to achieve better performance. The reason for this has not yet been determined. Evidently there exists a negative influence on the microcirculation and the increased blood flow is counteracted by the opening of arterio-venous shunts.

The extent of increase in stroke volume and cardiac output with hydralazine depends on the diastolic ventricular size. The greater the diastolic diameter, the larger the increase in stroke volume. Packer et al. (1980) reported an increase in stroke volume above a ventricular diameter of 55 mm and below 55 mm a decrease in stroke volume (Fig. 135).

a) Renal Blood Flow

The reduction in renovascular resistance leads to an augmentation of renal blood flow and an improved glomerular filtration rate (Cogan et al. 1979). Studies by Mathey demonstrated a mild increase in renal blood flow with acute therapy and a pronounced effect after 6 months of treatment (Fig. 136) (Mathey 1983). No changes in glomerular filtration rate were observed in hypertensive patients without heart failure.