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VASODILATOR THERAPY FOR CHRONIC HEART FAILURE

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INTRODUCTION

Over the past several years there has been increasing interest in the use of vasodilator drugs for the treatment of chronic heart failure. The principle of peripheral vasodilation for the treatment of pulmonary edema was postulated as early as 1944 (1). Its clinical application, however, with the use of vasodilator agents has gained popularity only recently. With the advent of balloon flotation catheters (2), which allow safe and prolonged bedside hemodynamic monitoring, it has been possible to quantitate more precisely the hemodynamic effects of various vasodilator drugs in patients with chronic heart failure. These monitoring techniques have also been useful to evaluate the qualitative and quantitative differences in the hemodynamic responses to individual vasodilator agents. With increasing experience, it has become apparent that although most vasodilator agents produce similar qualitative hemodynamic effects, the hemodynamic response may quantitatively vary. This is due not only to their different pharmacologic properties, but also to the different subsets of patients being treated. In this review, the hemodynamic effects of various nonparenteral vasodilator agents that are used for the treatment of chronic heart failure are discussed relative to their specific advantages and disadvantages.

MECHANISM OF ACTION

The ability of vasodilator drugs to improve cardiac performance in patients with heart failure is not related to their direct effect on the heart, since most

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of these agents have been demonstrated to have no direct positive inotropic effects on the myocardium (3). The major mechanisms by which these agents improve cardiac function appear to be related to their effects on precapillary arteriolar resistance and postcapillary venous capacitance beds. In patients with heart failure, several compensatory mechanisms interplay to maintain circulatory homeostasis. Although these compensatory mechanisms are designed to produce the most favorable effect on the cardiovascular system in the face of heart failure, the peripheral vascular response may not be always appropriate and may produce deleterious effects on cardiac performance. Vasodilator drugs may improve cardiac function by altering these inappropriate peripheral vascular responses.

In many patients with clinical heart failure, the contractile function of the left ventricle is depressed. Disturbance of the contractile function may be caused by ischemic heart disease, primary cardiomyopathy, or chronic pressure or volume overload as in patients with long-standing hypertension or valvular heart disease. This myocardial failure, irrespective of the underlying cause, produces depression of overall cardiac performance and initiates a number of compensatory mechanisms. With an intact circulation, cardiac output is regulated by four major determinants: contractile state, preload, afterload, and heart rate (4, 5). When stroke volume decreases due to myocardial failure associated with depressed contractile state, the heart tends to dilate. Dilatation of the left ventricle (i.e. an increase in left ventricular end-diastolic volume or preload) can be viewed as a compensatory mechanism to maintain forward stroke volume according to the Frank-Starling principle. There may be an increase in the adrenergic stimulation of the heart, secondary both to a rise in sympathetic tone and circulating catecholamines. This enhanced adrenergic state will increase heart rate and contractile state and, thereby, will tend to increase cardiac output. In addition, in response to low cardiac output, total systemic vascular resistance tends to increase to maintain arterial pressure (6) (arterial pressure = cardiac output X vascular resistance).

Initially, by virtue of these compensatory mechanisms, adequate cardiac output, stroke volume, and arterial pressure may be maintained, particularly at rest. However, in patients with myocardial failure, cardiac reserve is limited and, therefore, cardiac performance during stress is impaired. Clinically, then, patients with mild or moderate heart failure may remain asymptomatic at rest, but develop symptoms of diminished cardiac reserve during stress. With progressive myocardial failure and decrement in cardiac reserve, symptoms of heart failure eventually manifest at rest.

The circulatory adjustments and the compensatory mechanisms to maintain stroke volume, cardiac output, and perfusion pressure to the vital organs may also produce deleterious effects on cardiac performance. An

increase in left ventricular diastolic volume or preload, associated with ventricular dilatation will cause elevation of left ventricular diastolic pressure. Increased left ventricular diastolic pressure causes a passive increase in left atrial and pulmonary venous pressures—the major determinants of pulmonary venous congestion and edema. Furthermore, left ventricular dilatation will increase its wall stress according to the Laplace relation and thereby will increase myocardial oxygen requirements. Increased myocardial oxygen demand may be deleterious, particularly in patients with ischemic heart disease. Increased heart rate and contractile state due to enhanced sympathetic activity will also increase myocardial oxygen demand and may produce adverse effects.

Increased systemic vascular resistance in response to low cardiac output is an important compensatory mechanism and is necessary to maintain arterial pressure. Inappropriate and excessive increase in systemic vascular resistance, however, adversely affects cardiac performance. An increase in systemic vascular resistance also leads to an increase in the resistance to left ventricular ejection or arterial impedance. Because an inverse relation exists between left ventricular ejection impedance and its stroke volume, an increase in systemic vascular resistance can further reduce cardiac output. Thus, a vicious cycle may develop that will ultimately lead to a lower steady state level of cardiac output and inappropriately high systemic vascular resistance (7). Reduction of the elevated systemic vascular resistance may be helpful to break this vicious cycle.

The predominant mechanism whereby vasodilators increase cardiac output is by reducing systemic arteriolar tone and systemic vascular resistance. The terms afterload or impedance reduction have been used to describe this particular action of vasodilator drugs. The concept of afterload reduction and its effect on cardiac performance is relatively straightforward. In studies of isolated heart muscle, if one reduces the load against which a muscle must shorten, it shortens further and with a greater velocity (8). Translation of this concept into the intact heart makes it easy to visualize how a reduction of the resistance to ejection can promote myocardial shortening and thus increase stroke volume.

In terms of ventricular function curve, Figure 1 illustrates how reduction in arterial impedance (closely related to systemic vascular resistance) tends to increase stroke volume at any given left ventricular filling pressure. The control ventricular function curve is illustrated in the middle of Figure 1. An increased impedance, which occurs in many patients with heart failure (9), can potentially shift the curve down and to the right, indicating a decreased stroke volume at any given left ventricular filling

versely, if one decreases the impedance to aortic ejection, the curve is shifted up and to the left, so that there is an increase in stroke volume at the same

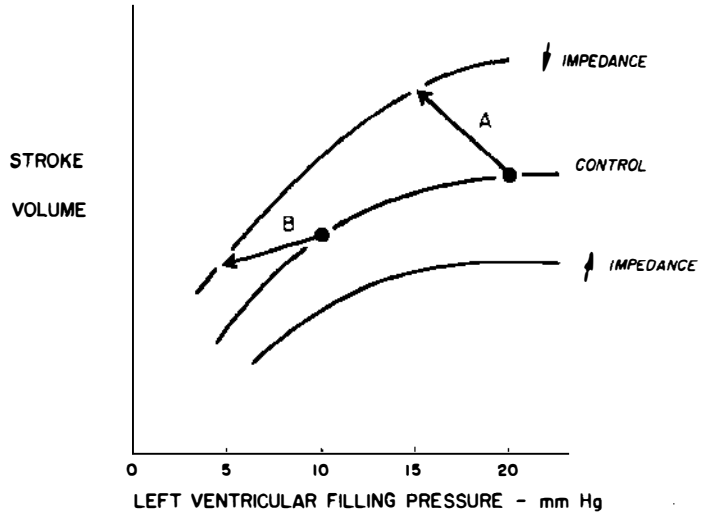

Figure 1 Left ventricular function curves plotting stroke volume as a function of left ventricular filling pressure. The control curve is in the middle. With a vasodilator drug there would be a decrease in impedance, which would shift the curve up and to the left. Note that if a patient on the control curve were given a vasodilator with an initial filling pressure of 20 mm Hg, the reduction of filling pressure would be accompanied by an increase in stroke volume (Line *A*). However, if the same patient began at a filling pressure of 10 mm Hg, there would be a decrease in stroke volume (Line *B*).

filling pressure. Vasodilator drugs capable of reducing systemic vascular resistance shift ventricular function curve up and to the left indicating improved cardiac performance.

Many vasodilator drugs, however, predominantly dilate systemic veins and increase the volume of these capacitance vessels and thus effectively redistribute circulating blood volume. This results in a transient reduction in venous return, although as a new steady-state level is reached venous return may be maintained or even increased if forward cardiac output is also increased. This pooling of blood, however, is effective in reducing filling pressure and intracardiac volume of the right and left sides of the heart. Reduction of left and right filling
and symptoms of pulmonary and systemic venous congestion. The effects of a venodilator on cardiac performance is dependent on the initial level of left ventricular filling
(e.g. 10 mm Hg), a further reduction of filling
pooling of blood will tend to decrease stroke volume as the ventricle moves down the steep portion of the ascending limb of ventricular function curve.

Under these circumstances there may be a compensatory increase in heart rate to maintain forward cardiac output. If, however, initial left ventricular filling
flat portion of the ventricular function curve and, therefore, will not produce a marked reduction in stroke volume, provided filling pressure does not fall to a very low level (usually less than 15 mm Hg).

Changes in cardiac performance induced by a vasodilator agent with balanced arteriolar and venodilating effects is also influenced by the initial level of left ventricular filling pressure. In a patient with heart failure with an elevated filling pressure, a reduction in arterial impedance will shift the curve upward while an increase in venous capacitance will reduce filling pressure. The overall result is a shift in ventricular function up and to the left (Line *A,* Figure 1). On the other hand, if the initial left ventricular filling pressure is normal, although a reduction in arterial impedance will shift ventricular function to the new curve, this is more than offset by the further reduction in filling pressure so that there may be an actual reduction in stroke volume (Line *B,* Figure 1).

Although vasodilator drugs improve cardiac performance principally by their peripheral vascular effects, there are other potential mechanisms by which these agents can improve cardiac function. There is evidence that some vasodilator agents may reduce segmental myocardial ischemia and therefore improve overall cardiac performance (10–12). Myocardial ischemia usually results from an imbalance of myocardial oxygen demand and supply. The major determinants of myocardial oxygen demand are heart rate, contractile state, arterial pressure, and heart size. Some reduction in arterial pressure is commonly observed during vasodilator therapy. Left ventricular diastolic volume may decrease, particularly with the use of venodilators. In patients with heart failure with elevated left ventricular filling pressure, heart rate either does not change or may even decrease slightly during vasodilator therapy. Most vasodilator agents do not possess any direct positive inotropic effect on the myocardium. Thus, vasodilator agents have the potential to reduce myocardial oxygen demand and influence the myocardial oxygen supply/demand ratio favorably. A decrease in segmental myocardial ischemia with consequent improvement in regional and global myocardial function may therefore occur. In addition to the reduction of the determinants of myocardial oxygen demand, some vasodilator agents like nitroglycerin or nitroprusside can also improve myocardial perfusion. When there is a significant
diastolic pressure, transmyocardial pressure gradient increases with a potential to promote subendocardial blood flow. Nitroglycerin and nitrates may also increase collateral blood flow to the ischemic myocardial segments

(13). It is apparent that in patients with heart failure due to ischemic heart disease vasodilator agents have the potential for decreasing myocardial ischemia which might be contributory to improved cardiac performance.

Increased left ventricular compliance is another possible mechanism by which vasodilator drugs may cause improvement in cardiac function in patients with heart failure (14). The pressure-volume relationship of the left ventricle is curvilinear, so that at small end-diastolic volumes, a volume increment will produce only a small rise in diastolic pressure. At larger end-diastolic volume, volume increment of similar magnitude will cause a much greater increase in diastolic pressure as the ventricle moves onto the steep portion of its curve. Because end-diastolic volume is the major determinant of stroke volume (Frank-Starling principle), a shift in left ventricular pressure-volume curve will also influence the relationship between the left ventricular filling pressure and stroke volume, i.e. ventricular function curve. Thus, if the pressure volume relation were shifted to the right, a leftward shift of left ventricular function curve might result, indicating improved cardiac performance. Recent experimental and clinical studies have suggested that some vasodilators can cause an acute increase in left ventricular compliance. The precise mechanism of increased left ventricular compliance with vasodilators remains unclear. Reduction of ischemia and relief of ischemic contracture, increased ventricular relaxation, and changes in the interaction of the right and left ventricles in a confined space (15, 16) all have been suggested as possible causes. Irrespective of the underlying mechanism, an increase in left ventricular diastolic compliance is an important action of vasodilators that has the potential to improve left ventricular function.

It is apparent that there are a number of interacting variables that influence the response of a particular patient to vasodilator therapy. The most important of these appear to be venodilation and arteriolar dilation, although relief of myocardial ischemia and alteration of left ventricular diastolic compliance may also play an important role in certain circumstances.

CLASSIFICATION OF NONPARENTERAL VASODILATOR DRUGS

It is useful to classify the vasodilator drugs in terms of their principal peripheral vascular effects (Table 1). One group of vasodilators predominantly dilates systemic veins, a second group predominantly dilates arterioles, and the third has more or less a balanced effect on arteries and veins. Vasodilators that predominantly dilate systemic veins cause a significant reduction in systemic and pulmonary venous pressures, but may not increase cardiac output. Vasodilators with a predominant effect on arteriolar

Table 1 Nonparenteral vasodilators for the treatment of chronic heart failure

Venodilators	Arteriolar dilators	Arteriolar and venodilators
Nitroglycerin	Hydralazine	Prazosin
Nitrates	Minoxidil	Trimazosin
		Captopril
		Phentolamine
		Phenoxybenzamine

resistance beds decrease systemic vascular resistance and increase cardiac output with little or no change in systemic or pulmonary venous pressures. Drugs with balanced effects on arteriolar and venous beds cause an increase in cardiac output and a decrease in systemic and pulmonary venous pressures. It needs to be emphasized, however, that none of the vasodilator drugs currently available has pure arteriolar or venodilative effects. Furthermore, the response of the peripheral vascular beds to vasodilator agents in individual patients may be variable and hemodynamic effects of a given vasodilator agent may not be always similar in all patients with chronic heart failure. Nevertheless, the classification
their principal mechanism of action and major hemodynamic effects is useful for clinical application.

HEMODYNAMIC EFFECTS

Nitroglycerin and Nitrates

Nitroglycerin and organic nitrates exert their effects through dilatation of smooth muscle in blood vessel walls (17–19). Their actions are maximal on the large veins (capacitance vessels) and least on the arteriolar resistance vessels. These agents have little effect on precapillary sphincters but cause dilation of postcapillary vessels.

Nitroglycerin and nitrates appear to act on a specific receptor site in the vascular wall (17–20). The active nitrate molecules react with a sulfydryl group at the receptor and are subsequently reduced, releasing a nitrite ion which causes vascular relaxation. Decreased responsiveness to nitrates might occur consequent to depletion of sulfydryl groups with the formation of disulfide bridges in the vascular smooth muscle (20, 21).

Nitroglycerin and nitrates are readily absorbed from the sublingual mucosa. They are metabolized in the liver by the enzyme glutathione reductase to mono- and dinitro metabolites which have virtually no vasodilative effects (22–24). Gastrointestinal absorption of oral nitrates occurs readily,

but because of hepatic degradation much larger doses than those used for sublingual administration are required to produce physiologic effects. Transcutaneous absorption of nitroglycerin also occurs when it is applied topically.

Nitroglycerin, whether administered sublingually, orally or topically, produces similar hemodynamic effects in patients with chronic congestive heart failure. The hemodynamic effects of topical nitroglycerin (1–3 in.) in a group of patients with chronic heart failure are summarized in Table 2 (25). There was no significant

Pulmonary capillary wedge and right atrial pressures decreased significantly. There was also a modest increase in cardiac index, stroke volume, and stroke work indices along with some decrease in systemic vascular resistance. The fact that there was some reduction in systemic vascular resistance and a modest increase in cardiac output suggests that nitroglycerin produces some dilative effect on arteriolar resistance bed. A decrease in myocardial ischemia and an increase in left ventricular diastolic compliance might also contribute to improved cardiac performance.

In patients with normal left ventricular filling

tricular filling

cardiac output may decrease along with a further decrease in left ventricular filling

The hemodynamic effects of sublingual, oral, or chewable isosorbide dinitrate are similar to those of nitroglycerin. The principal hemodynamic effects of oral isosorbide dinitrate (40 mg every 4 hr) in patients with chronic congestive heart failure are shown in Table 3 (26). The hemodynamic response included a modest reduction in mean arterial pressure, and a

Table 2 Hemodynamic effects (mean ± SEM) of topical nitroglycerin (1–3 in.) in 14 patients with chronic congestive heart failure

Parameter	Control	Nitrol	*P*
Heart rate (beats/min)	83 ± 4.5	76 ± 4.1	NS[a]
Mean arterial pressure (mm Hg)	89 ± 3.4	85 ± 4.3	NS
Pulmonary capillary wedge pressure (mm Hg)	28 ± 1.5	21 ± 1.5	< 0.001
Right atrial pressure (mm Hg)	12 ± 1.4	8 ± 1.2	< 0.01
Cardiac index (liters/min/m^2)	1.9 ± 0.12	2.3 ± 0.15	< 0.01
Stroke volume index (ml/m^2)	23 ± 1.6	31 ± 1.9	< 0.002
Stroke work index (g-m/m^2)	24 ± 2.6	33 ± 2.9	< 0.001
Systemic vascular resistance (dynes-sec-cm^{-5})	1,996 ± 187	1,654 ± 200	< 0.05
Pulmonary vascular resistance (dynes-sec-cm^{-5})	300 ± 44	233 ± 44	NS

[a] NS = not significant.

Table 3 Hemodynamic effects of oral isosorbide dinitrate in patients with chronic heart failure ($N = 13$)

Parameter	Control	Oral nitrate
Heart rate (beats/min)	89 ± 4.7	89 ± 6
Left ventricular filling pressure (mm Hg)	23 ± 2.3	19 ± 1.6[a]
Cardiac output (liters/min)	3.6 ± 0.29	3.8 ± 0.24
Stroke volume index (ml/m^2)	24.3 ± 1.9	25.6 ± 2.1

[a] $p < 0.05$.

substantial decrease in pulmonary capillary wedge pressure. Cardiac index and stroke volume index, however, either did not change or only increased slightly. There was also little or no change in calculated systemic vascular resistance. Heart rate, as with nitroglycerin, also did not change.

In general, nitroglycerin and nitrates cause a greater decrease in systemic and pulmonary venous pressures and a lesser increase in cardiac output. This is because the major site of action of nitroglycerin and nitrates is on the peripheral venous capacitance bed. The dilating effect on the arteriolar resistance bed is relatively small. As a result of marked venodilation, a significant reduction occurs in effective circulating blood volume, that in turn reduces ventricular end-diastolic volume or preload. A reduction in stroke volume, therefore, tends to occur. Nitroglycerin and nitrates produce beneficial hemodynamic effects in patients with mitral or aortic regurgitation (27, 28). Regurgitant volume usually decreases along with a reduction in left ventricular diastolic volume and pressure. Pulmonary venous pressure, therefore, also falls. Forward stroke volume and cardiac output, however, may not increase because of marked reduction in left ventricular end-diastolic volume.

Although the hemodynamic effects of various forms of nitroglycerin and nitrates are similar, their durations of action differ considerably. The hemodynamic effects of sublingual nitroglycerin last approximately for 20–30 min and of sublingual isosorbide dinitrate for about 2 hr (29). The duration of action of oral and chewable isosorbide dinitrate and that of topical nitroglycerin is considerably longer, approximately 4 hr (average 3–5 hr).

Very few complications and undesirable side effects are observed in patients with chronic heart failure during nitroglycerin or nitrate therapy. Headache is the most frequent side effect; however, it occurs less frequently in patients with chronic heart failure than in patients with angina without heart failure. Postural dizziness, weakness, and even frank syncope can result; these complications are more prone to occur in patients with normal left ventricular filling pressure in whom arterial pressure may fall substantially. Nausea infrequently occurs in patients with chronic heart failure

receiving nitroglycerin or nitrates. Drug rash may occur; a transient flushing of the skin is more common. Glaucoma has been thought to be a relative contraindication to the use of nitrates but this is poorly documented and nitrates can be given relatively safely to patients with increased intraocular pressure (30). Nitroglycerin or nitrates, however, should not be given to patients with increased intracranial pressure (31). Development of tolerance to the effects of nitroglycerin has been the subject of intensive investigation since late 1800s, when nitroglycerin was used for treatment of hypertension (32). It appears, however, that with continued use of nitroglycerin or nitrates tolerance tends to occur more frequently to their side effects such as headache rather than to their cardiovascular effects. Recent studies indicate that in patients with chronic heart failure nitrates produce sustained beneficial hemodynamic effects and tolerance usually does not develop (33–36).

Hydralazine

Hydralazine causes direct relaxation of the smooth muscle in the peripheral vascular bed (37, 38). Precapillary arteriolar resistance bed is predominantly affected by hydralazine and the relaxation of the capacitance vessels is much less pronounced (37–39). The vasodilative effects of hydralazine are neither uniform nor of equal magnitude on all peripheral vascular beds. The resistance vessels of the coronary, renal, splanchnic, and cerebral vascular beds are affected more than those in the skin and skeletal muscles. The effect of hydralazine on pulmonary vascular bed is variable; in patients without left ventricular failure, pulmonary vascular resistance may not change. Consequently, pulmonary artery pressure may increase if there is a concomitant increase in cardiac output (37). In contrast, in patients with left heart failure and elevated pulmonary vascular resistance, hydralazine not infrequently causes a decrease in pulmonary vascular resistance (40). Experimental studies suggest that hydralazine may decrease pulmonary artery pressure from active vasodilation of constricted pulmonary arteries and veins but has little effect on the normally dilated lung vessels (41).

Renal hemodynamics and function appear to improve with hydralazine in patients with heart failure and low output state (42). Renal vascular resistance along with total systemic vascular resistance decline; renal blood flow therefore increases. Filtration fraction falls, although glomerular filtration rate may remain unchanged. Enhanced sodium and potassium excretion may also occur during hydralazine therapy in patients with chronic heart failure. In hypertensive patients without cardiac failure, hydralazine does not produce any consistent changes in glomerular filtration rate or in tubular transport mechanism, although filtration fraction usually decreases (43, 44).

It has been suggested that the pharmacologic properties of hydralazine are related to its ability to act on sulfydryl—and carbonyl—groups of smooth muscle cells and to chelate certain metallic ions (45). Hydralazine is rapidly and almost totally (90%) absorbed from the gastrointestinal tract (46). Serum hydralazine is 85% protein bound (47). Peak serum concentrations are attained between 0.5 to 2 hr; onset of action after oral administration is between 20 to 30 min (48). Plasma half-life of hydralazine is between 2 to 4 hr, but biologic half-life is much longer (49, 50). Hydralazine remains in the muscular wall of the arteries long after it is cleared from the blood. Hydralazine undergoes biotransformation in the gut wall and during its passage through the liver (47, 51, 52). Genetically determined differences in the concentrations of hepatic *N*-acetyltransferase also influences the plasma concentrations of hydralazine (53, 54). In slow acetylators with low concentrations of this enzyme, plasma concentrations may be considerably higher even after a relatively small oral dose. Metabolism of hydralazine also involves ring hydroxylation and conjugation with glucuronic acid (55, 56). Over 80% of hydralazine and its metabolites are excreted within 48 hr (46). Hydralazine-induced changes in cardiac dynamics are of particular significance for management of patients with chronic heart failure. Hydralazine is a potent arteriolar dilator and usually causes a marked reduction in systemic vascular resistance. As systemic vascular resistance is one of the major components of the aortic impedance, decreased systemic vascular resistance is associated with an increase in cardiac output. That intravenous hydralazine therapy could be useful in improving cardiac performance of patients with hypertensive congestive heart failure was long recognized (44). More recent studies have demonstrated that oral hydralazine produces similar beneficial hemodynamic effects in normotensive or even hypotensive heart failure patients (40, 57–60). The principal hemodynamic effects of oral hydralazine in patients with severe congestive heart failure are summarized in Table 4 and Figure 2. A decrease in systemic vascular resistance was associated with a marked increase in cardiac output. Pulmonary vascular resistance decreased in the majority of patients. No consistent changes in mean arterial pressure, heart rate, and right or left ventricular filling pressures occurred in these patients. Stroke volume and stroke work indices increased in the majority of patients. It is noteworthy that with hydralazine significant tachycardia was infrequently observed in patients with chronic congestive heart failure. Similarly marked hypotension rarely occurred in these patients during oral hydralazine therapy. This is in contrast to what is observed in patients without heart failure in whom hydralazine frequently induces hypotension and reflex tachycardia mediated through enhanced sympathetic activity.

Table 4 Hemodynamic effects of oral hydralazine in patients with refractory heart failure ($N = 10$)[a]

	Control	Hydralazine	*P*
Heart rate (beats/min)	90 ± 6.9	90 ± 5.8	NS[b]
Arterial pressure (mean) (mm Hg)	89 ± 4.5	85 ± 4.0	NS
Pulmonary arterial pressure (mean) (mm Hg)	37 ± 3.4	38 ± 3.1	NS
Left ventricular filling pressure (mm Hg)	24 ± 2.0	23 ± 2.1	NS
Cardiac index (liter/min/m^2)	1.99 ± 0.15	3.39 ± 0.29	0.001
Stroke volume index (ml/m^2)	23 ± 3.0	38 ± 3.5	0.001
Stroke work index (gm-m/m^2)	23 ± 2.4	36 ± 3.7	0.001
Systemic vascular resistance (dynes sec cm^{-5})	1,748 ± 129	998 ± 115	0.001
Pulmonary vascular resistance (dynes sec cm^{-5})	328 ± 54	203 ± 32	0.001

[a] Reproduced by permission from (27).
[b] NS = not significant.

Following 50 or 75 mg of oral hydralazine, right or left ventricular filling pressures usually did not decrease significantly. With a larger (100 mg) dose, however, a modest decrease in pulmonary capillary wedge pressure has been observed (57). Lack of significant decrease in systemic and pulmonary venous pressure is probably related to weak venodilative effect of hydralazine. Nevertheless, increased cardiac output and stroke volume with little or no change in ventricular filling pressures suggest improved cardiac performance with hydralazine.

Hydralazine produces beneficial hemodynamic effects in patients with mitral regurgitation (61). In the presence of mitral regurgitation, the balance between forward cardiac output and regurgitant flow is influenced by aortic impedance to left ventricular outflow (62, 63). When aortic impedance is increased, forward cardiac output falls and regurgitant flow increases. Conversely, impedance reduction is associated with an increase in forward cardiac output and a fall in regurgitant volume. Hydralazine reduces aortic impedance and thereby improves forward cardiac output and causes a reduction in regurgitant volume. The hemodynamic effects of intravenous hydralazine (0.3 mg/kg) in patients with chronic severe mitral regurgitation are summarized in Table 5. Despite some decrease in mean arterial pressure, heart rate did not increase. Mean pulmonary artery pressure decreased in most patients. In contrast to patients with chronic heart failure but without mitral regurgitation, mean pulmonary capillary wedge pressure decreased consistently. There was also a significant reduction in the amplitude of the regurgitant "V" wave suggesting a reduction in the regurgitant volume. Indeed, when changes in regurgitant fraction were estimated from the difference between left ventricular total stroke volume

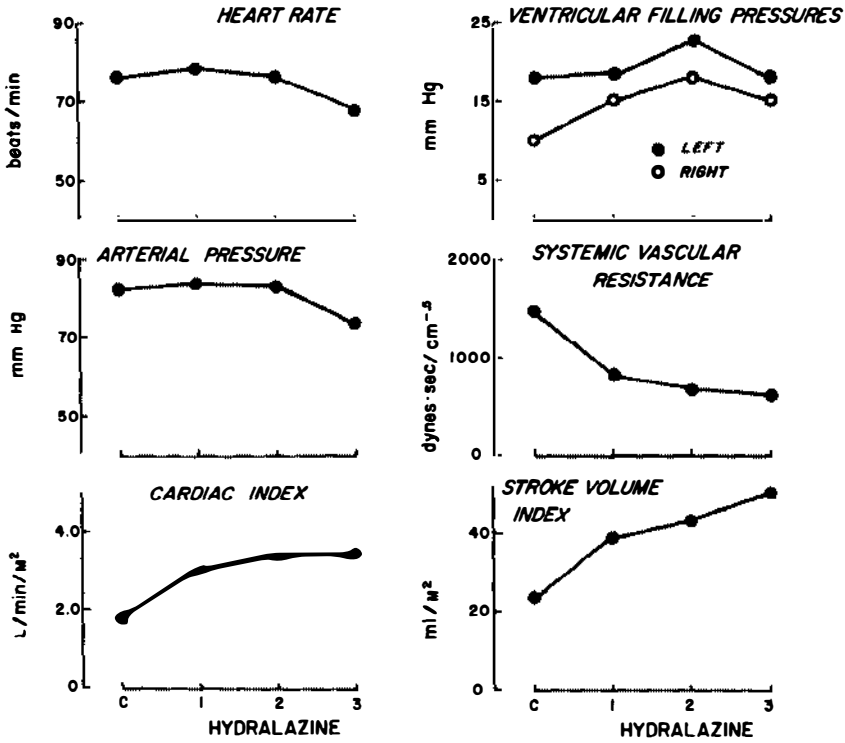

Figure 2 Hemodynamic effects of oral hydralazine in a patient with chronic congestive heart failure. C = control; HD 1 = hemodynamics 2–3 hr after 75 mg of oral hydralazine; HD 2 = hemodynamics after 6–8 hr; and HD 3 = hemodynamics after 24 hr. In this patient, during hydralazine therapy, there was no significant change in heart rate, despite some decrease in arterial pressure. Cardiac index and stroke volume index increased significantly along with a decrease in systemic vascular resistance. There was no significant change in pulmonary capillary wedge or right atrial pressures.

and its forward stroke volume, it was apparent that hydralazine caused a significant reduction in regurgitant fraction. Decreased regurgitant fraction was associated with an increase in forward stroke volume, although left ventricular total stroke volume remained unchanged. Thus, hydralazine, by reducing aortic impedance, caused a redistribution of the total stroke volume of the left ventricle—more blood was pumped forwards into the aorta and less to the left atrium. The hemodynamic effects of oral hydralazine in patients with mitral regurgitation were similar to those of intravenous hydralazine (61).

Increase in cardiac output is the major beneficial hemodynamic effect of hydralazine in patients with chronic heart failure. Reduction of systemic

vascular resistance and left ventricular ejection impedance appear to be the principal mechanism by which it improves cardiac performance in these patients. It has been suggested, however, that hydralazine produces a direct positive inotropic effect and increased contractile state may contribute to increasing cardiac output (64). Indeed, in isolated papillary muscle preparations, positive inotropic effect of hydralazine has been observed but only with a very high concentration. The dose of hydralazine that is used in clinical practice for the treatment of chronic heart failure is unlikely to produce such a high concentration. It appears therefore that the principal mechanism by which hydralazine improves cardiac performance is through its peripheral vascular effects.

Beneficial

a dose less than 200 mg per day (40). In the majority of patients, 300 to 400 mg of oral hydralazine per day produce adequate increase in cardiac output and a substantial decrease in systemic vascular resistance. It seems, therefore, that the dose of hydralazine required at least initially to produce beneficial

usually larger than that used for treatment of hypertension. Whether, during long-term therapy, hydralazine dose can be reduced to maintain the same beneficial

mined.

The incidence of untoward reactions and undesirable side effects of hydralazine in patients with chronic heart failure has not been determined.

Table 5 Hemodynamic effects of intravenous hydralazine in mitral regurgitation[a]

	Control	Hydralazine	*P*
Heart rate	90 ± 7 (SEM)	90 ± 5	NS
MAP (mm Hg)	99 ± 5	87 ± 5	< 0.001
PAP (mm Hg)	47 ± 6	41 ± 5	< 0.01
PCW (mm Hg)	33 ± 4	25 ± 3	< 0.005
PCW v wave (mm Hg)	48 ± 6	33 ± 5	< 0.005
LVEDP (mm Hg)	21 ± 3	18 ± 3	NS
Forward CI (1/min/m^2)	2.0 ± 0.1	3.0 ± 0.2	< 0.001
Forward SVI (ml/m^2)	22 ± 2	33 ± 3	< 0.001
SVR (dyne-sec/cm^5)	2,100 ± 170	1,290 ± 90	< 0.001
EDVI (ml/m^2)	130 ± 14	120 ± 12	NS
ESVI (ml/m^2)	67 ± 12	63 ± 11	NS
Total SVI (ml/m^2)	62 ± 6	60 ± 5	NS
Regurgitant SVI (ml/m^2)	40 ± 6	27 ± 6	< 0.001
Regurgitant fraction (%)	61 ± 5	42 ± 6	< 0.001
Ejection fraction (%)	51 ± 5	52 ± 5	NS

[a] CI = cardiac index; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; NS = not significant; PAP = mean pulmonary artery pressure; PCW = mean pulmonary capillary wedge pressure; SVI = stroke volume index; SVR = systemic vascular resistance.

Frequency of side effects of hydralazine in hypertensive patients has been reported to be approximately 19% (65). The nature of undesirable side effects of hydralazine when used for treatment of hypertension is variable and all these side effects are not necessarily observed in patients with chronic heart failure. Reflex tachycardia and orthostatic hypotension are distinctly rare in patients with chronic heart failure. Anorexia, nausea, and vomiting may occur at the initiation of therapy, but these symptoms tend to subside with continued therapy. Drug fever and skin rash are infrequent complications. Flushing, sweating, urticaria, and pruritus are rare complications of hydralazine therapy; hydralazine-induced inhibition of histaminase and consequent increased liberation of histamine might be the underlying mechanism (66, 67). An acute febrile illness resembling serum sickness occurring within 1–4 weeks of institution of hydralazine therapy in hypertensive patients has not been reported in patients with chronic heart failure (68).

Precipitation of angina has been reported in a few patients with chronic ischemic cardiomyopathy (69). Relief of angina associated with a decrease in the determinants of myocardial oxygen demand has also been observed during oral hydralazine therapy in patients with ischemic heart failure (70). It is apparent that the effects of hydralazine on coronary hemodynamics and myocardial metabolism are likely to be variable and are influenced by the relative changes in the determinants of myocardial oxygen demand and myocardial perfusion in individual patients.

Peripheral neuropathy secondary to pyridoxine deficiency is a recognized but rare complication of long-term hydralazine therapy. In most patients rapid amelioration of symptoms of the neuropathy occurs with the addition of pyridoxine (66, 71). Fluid retention and weight gain, possibly related to the interference with renin-angiotensin-aldosterone system has been observed in occasional patients (72).

The most serious complication of hydralazine therapy is the lupus syndrome (67). The incidence of this complication in patients with chronic heart failure is unknown. The important predisposing influence to develop this potentially serious complication appears to be one's ability to inactivate hydralazine by acetylation. In patients who are "fast acetylators," complications like lupus syndrome or polyneuropathy seldom occur even when larger doses of hydralazine are used. It is, therefore, desirable to determine the acetylation phenotype before long-term hydralazine therapy, particularly with larger doses, is contemplated.

Prazosin and Trimazosin

Prazosin is a quinazoline derivative and produces relaxation of the peripheral vascular beds by postreceptor α-blockade (73) and by its direct action by inhibition of the enzymic phosphodiesterase (74, 75). When administered

orally, it is well absorbed from the gastrointestinal tract and is rapidly distributed to the tissues of the heart, lung, and vascular system. Prazosin is primarily eliminated by the liver after its biotransformation by dealkylation and subsequent glucuronide formation (76, 77). Its urinary excretion is low. Plasma drug half-life in healthy subjects or in hypertensive non-heart-failure patients is between 2.5 and 4 hr (78, 79). Recent studies indicate, however, that the pharmacokinetics of prazosin in patients with severe chronic congestive heart failure may be different from those in healthy subjects (80). Plasma half-life in patients with heart failure may be as long as 6 hr. Peak plasma concentration of the drug was significantly higher in patients with heart failure than in normal subjects following a single oral dose of prazosin. Furthermore, the elimination rate constant of the drug in patients with heart failure was considerably less than that in normal subjects. Time to peak drug concentration and the plasma:blood concentration ratio in heart failure patients and in healthy subjects was similar. The fraction of the dose excreted unchanged in urine was low both in heart failure patients and in normal subjects. It has been suggested that higher plasma concentration of prazosin and its delayed elimination in patients with heart failure may be related to decreased hepatic blood flow associated with reduced cardiac output. The hemodynamic effects of prazosin in patients with chronic heart failure (Table 6) were characterized by a reduction in arterial, pulmonary arterial, right atrial, and pulmonary capillary wedge pressures along with an increase in cardiac output, stroke volume and stroke work. Calculated systemic and pulmonary vascular resistance also declined significantly whereas heart rate remained unchanged. Increased cardiac output, stroke volume, and stroke work associated with a decrease in left ventricular filling pressure indicated improved left ventricular performance. These beneficial hemodynamic effects last approximately 6 hr after a single oral dose of prazosin (81, 82).

A decrease in systemic and pulmonary venous pressure with prazosin is useful for the relief of signs and symptoms of pulmonary venous congestion. Concomitant increase in cardiac output is beneficial for amelioration of symptoms of low cardiac output.

Changes in limb venous tone, venous capacitance, limb blood flow, and vascular resistance following prazosin have been investigated in patients with chronic heart failure by forearm plethysmography (82). Forearm venous tone decreased significantly by 30 min and remained low for about 6 hr. There was a concomitant decrease in forearm vascular resistance and an increase in forearm blood flow. The relative reduction in forearm vascular resistance was less than that in forearm venous tone indicating that prazosin produced relatively more venous than arteriolar dilation. These observations indicate, however, that prazosin, in contrast to hydralazine,

Table 6 Hemodynamic effects (mean ± SEM) of oral prazosin hydrochloride (3, 4, and 5 mg) in patients with chronic congestive heart failure[a,b]

	HR beats/min	MAP mm Hg	MPAP mm Hg	LVFP mm Hg	RAP mm Hg	CI L/min/m^2	SVI ml/m^2	SWI g·m/m^2	SVR dynes sec-cm^5	PVR dynes sec-cm^5
C	86 ± 7	87 ± 3	36 ± 2	24 ± 1	12 ± 1	2.0 ± 0.1	26 ± 2	22 ± 3	1,776 ± 85	285 ± 40
P – 3 mg	83 ± 4	80 ± 2	28 ± 2	19 ± 2	10 ± 2	2.5 ± 0.2	31 ± 2	26 ± 3	1,373 ± 82	194 ± 41
P – 4 mg	85 ± 5	84 ± 3	28 ± 2	19 ± 2	10 ± 1	2.4 ± 0.2	29 ± 2	25 ± 3	1,631 ± 167	222 ± 31
P – 5 mg	87 ± 7	79 ± 3	28 ± 3	19 ± 2	8 ± 1	2.5 ± 0.2	30 ± 3	25 ± 3	1,410 ± 118	186 ± 29
C vs P	—	C > PR[c]	C > PR[d]	C > PR[e]	C > PR[e]	C < PR[f]	C < PR[e]	—	C > PR[f]	—
P3 vs 4 vs 5 mg	—	—	—	—	—	—	—	—	—	—

[a] C = control hemodynamics before prazosin; CI = cardiac index; HR = heart rate; LVFP = left ventricular filling pressure; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; P = prazosin; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance; SWI = stroke work index.

[b] Note that the hemodynamic responses to 3, 4, or 5 mg of prazosin were similar.

[c] $P < 0.05$.

[d] $P < 0.005$.

[e] $P < 0.025$.

[f] $P < 0.001$.

causes dilation of both capacitance and resistance bed, and this balanced effect on the peripheral vascular beds might be the principal mechanism for both reduction in ventricular filling pressure

Effects of prazosin on left ventricular volumes and systolic function have been investigated by echocardiography and by radioisotope techniques. A reduction in left ventricular end-diastolic and end-systolic volume and an increase in ejection fraction and normalized circumferential fiber shortening rate have been reported (82). Reduction of left ventricular ejection impedance and a concomitant decrease in left ventricular preload with prazosin related to its peripheral vascular effects have been thought to be the principal mechanisms of these improved cardiac dynamics.

In most studies, the dose of oral prazosin that has been found to produce beneficial
action is approximately 6 hr, it needs to be administered every 6 hr. Postural hypotension and dizziness may be a troublesome complication of prazosin therapy. However, such complications occur relatively infrequently in patients with chronic heart failure. Occasionally, patients may complain of palpitations, drowsiness, depression, or nervousness. Gastrointestinal symptoms of nausea, vomiting, and diarrhea are infrequent side effects of prazosin therapy. Significant
curred rarely in some patients.

The major clinical problem with long-term prazosin therapy in patients with chronic heart failure is the development of tachyphylaxis to its hemodynamic effects (83–85). Several recent investigations indicate that a rapid attenuation of prazosin-mediated hemodynamic effect may occur in some patients with chronic heart failure (Figure 3). The changes in resting hemodynamics 2 hr after the first and fifth 5 mg dose of prazosin in 12 patients with chronic refractory heart failure are summarized in Table 7. Following the first dose, systemic vascular resistance decreased, and cardiac output, stroke volume, and stroke work increased. Following the fifth dose, however, changes in the hemodynamic variables were not significantly different from control. Even when the dose was increased to 10 mg every 6 hr, no appreciable change in systemic vascular resistance and cardiac output occurred. In this study, modest decreases in pulmonary capillary wedge and mean arterial pressures persisted during continued prazosin therapy (85). In other studies, attenuation of the magnitude of initial decrease in left ventricular filling
reported during continued prazosin therapy (83, 84).

The mechanism of attenuation of the hemodynamic effects of prazosin in patients with chronic heart failure remains unclear. It does not appear to be related to the inadequate plasma concentration of the drug (85). During the repeated administration of oral prazosin, its plasma concentration may

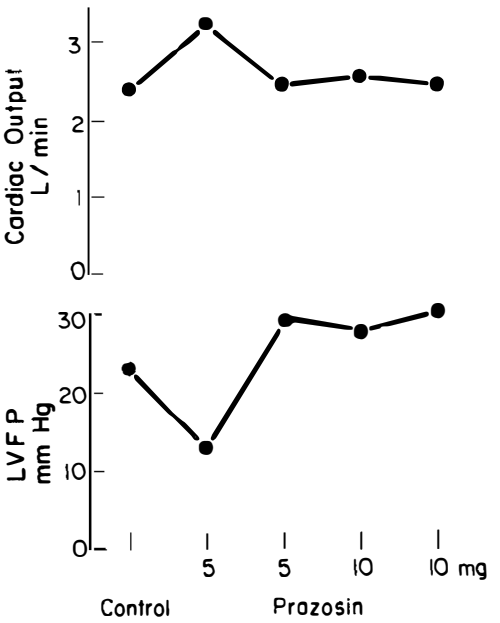

Figure 3 Rapid attenuation of hemodynamic effects of oral prazosin in a patient with chronic heart failure. Following the first dose of 5 mg, oral prazosin cardiac output increased and left ventricular filling pressure (LVFP) decreased. Following the fifth dose of 5 mg, hemodynamics returned to control. Increasing the dose to 10 mg did not restore the beneficial hemodynamic effects.

Table 7 Prazosin multidose hemodynamic evaluation[a, b]

		5 mg (N = 12)	
	Control	Dose 1[c]	Dose 5
CI (L/m/m^2)	2.3 ± 0.2	2.7 ± 0.2[d]	2.4 ± 0.2
HR (beats/min)	86 ± 4	85 ± 4	80 ± 2[d]
MAP (mm Hg)	91 ± 4	80 ± 4[e]	82 ± 4[e]
SVR (dsc^{-5})	1,568 ± 128	1,269 ± 108[d]	1,423 ± 128
PCW (mm Hg)	26 ± 3	19 ± 2[e]	21 ± 2[d]
RA (mm Hg)	14 ± 2	10 ± 1[d]	10 ± 1[d]
SWI (g-m/m^2)	28 ± 5	34 ± 5[d]	28 ± 3
SVI (cc/beat/m^2)	27 ± 3	33 ± 3[d]	29 ± 3

[a] Mean ± SEM.
[b] CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; PCW = pulmonary capillary wedge pressure; RA = right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance; SWI = stroke work index.
[c] Data obtained 2 hr after the respective dose.
[d] $P < 0.05$.
[e] $P < 0.01$ as compared to control.

equal or even be higher than the peak concentration after the first dose. And, yet, the beneficial hemodynamic effects of prazosin observed after the first dose may no longer be present during continued administration of the drug (Figure 4). Thus, inadequate plasma concentration of prazosin cannot be incriminated as the mechanism of attenuation of its hemodynamic effects. It has been suggested that changes in intra- and extravascular volume during prazosin therapy may play a significant role for the decrement of its beneficial hemodynamic effects. However, further studies will be needed to elucidate the mechanism of tachyphylaxis to prazosin.

Trimazosin, a newly developed antihypertensive agent (86), is also a quinazoline derivative. It appears to be well absorbed from the gastrointestinal tract following its oral administration. Peak plasma concentrations are noted after 1–2 hr and the plasma half-life is between 3–6 hr. The hemody-

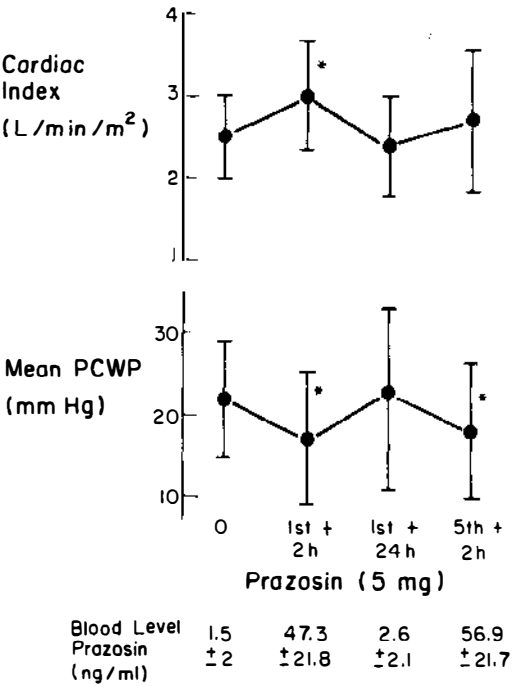

Figure 4 Relation between plasma concentration of prazosin and the hemodynamic changes in six patients with chronic heart failure. Hemodynamics and plasma concentration 2 hr and 24 hr after the first dose, and at 2 hr after the fifth dose of prazosin are shown. Plasma concentration 2 hr after the first dose and 2 hr after the fifth dose were similar. Decreased pulmonary capillary wedge pressure (PCWP) and increased cardiac index were observed after the first dose and these changes returned to control level during continued prazosin therapy, despite adequate plasma drug levels.

namic effects of trimazosin in patients with chronic heart failure appear to be similar to those of prazosin (87, 88). Systemic and pulmonary venous pressures decrease along with an increase in cardiac output, stroke volume, and stroke work, suggesting improved cardiac performance (Figures 5–7). Systemic venous tone and arteriolar resistance decrease indicating that trimazosin causes dilation of both venous capacitance and arteriolar resistance beds (88). The duration of action after 100–300 mg of oral dose exceeds 3 hr. Hemodynamic effects of tramazosin have been investigated

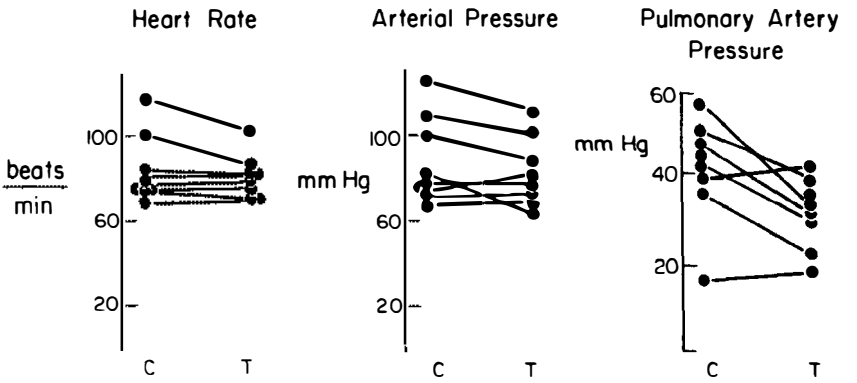

Figure 5 Changes in heart rate, arterial pressure, and pulmonary artery pressure following oral trimazosin (300 mg) in eight patients with chronic heart failure. There was no consistent change in heart rate or arterial pressure, but pulmonary artery pressure decreased in the majority of patients.

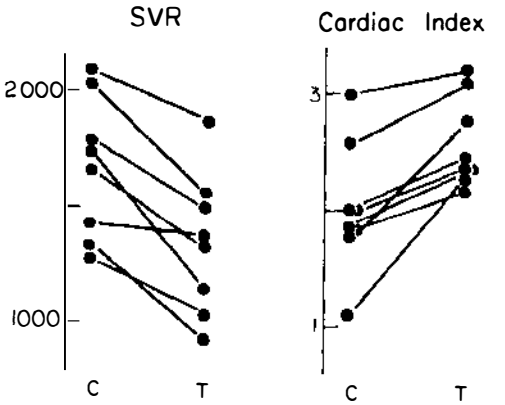

Figure 6 Trimazosin-induced changes in systemic vascular resistance (SVR) and cardiac index in patients with chronic heart failure. Cardiac index increased along with a decrease in SVR.

only in a limited number of patients with chronic heart failure. The advantages of its use over other vasodilator agents have not been determined. Furthermore, more studies will be needed to evaluate its long-term efficacy as well as its potential side effects.

Angiotensin-Converting Enzyme Inhibitor (Captopril)

Systemic vascular resistance is frequently elevated in patients with low cardiac output. The precise mechanism for an elevated systemic vascular resistance in individual patients is difficult to determine and several neural, humoral, or neurohumoral factors might be operative (21). In patients with heart failure accompanied by low cardiac output, the renin-angiotensin system may be stimulated and increased levels of angiotensin might contribute to an increased systemic vascular resistance (89–92). It seems logical, therefore, that attenuation or inhibition of the effects of angiotensin would be expected to reduce systemic vascular resistance and improve left ventricular performance. Saralasin (93), a specific competitive angiotensin antagonist, and teprotide (94, 95), an angiotensin-converting enzyme inhibitor, improve cardiac function in patients with congestive heart failure. However, both saralasin and teprotide need to be administered intravenously and therefore are not suitable agents for the long-term treatment of such patients. Captopril®, which also inhibits the conversion of angiotensin I to angiotensin II, can be administered orally and therefore is suitable for the long-term management of patients with chronic heart failure.

Peak plasma concentration of Captopril is attained between 1 and 1.5 hr after its oral administration. The plasma half-life is approximately 4.5 hr.

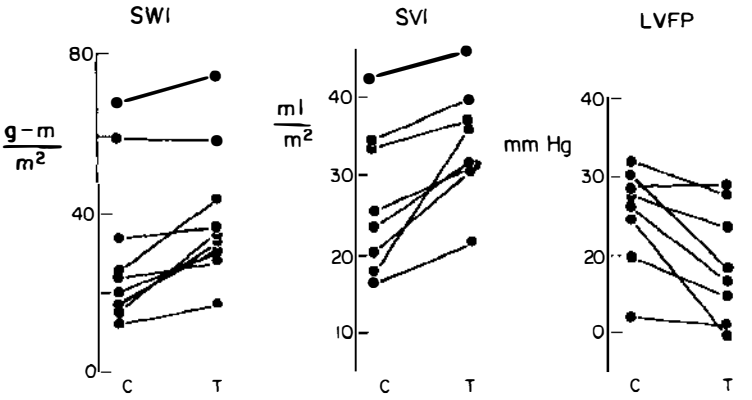

Figure 7 Changes in stroke work index (SWI), stroke volume index (SVI), and left ventricular filling pressure (LVFP) following oral trimazosin in patients with chronic heart failure. SWI and SVI increased, while LVFP decreased, indicating improved cardiac performance.

Over half of Captopril is excreted in the urine and about one third in the feces. In a number of recent studies, the hemodynamic effects of oral Captopril have been investigated in patients with chronic congestive heart failure (96–98). The hemodynamic changes were characterized by a significant reduction in right atrial, pulmonary arterial, and pulmonary capillary wedge pressures. Mean arterial pressure and systemic vascular resistance decreased significantly and cardiac output, stroke volume, and stroke work increased (Table 8). Increase in cardiac output and stroke volume along with a fall in left ventricular filling pressure indicated improved left ventricular performance (Figure 8). In one study, a consistent reduction in heart rate was observed (96); however, in other studies, no significant change in heart rate has been reported (98). Preliminary studies indicate that the maximum hemodynamic changes following 25, 50, or 100 mg of oral Captopril are quantitatively similar and the duration of action following each dose regimen exceeds 6 hr (99).

Although Captopril produces beneficial hemodynamic response in patients with chronic heart failure, the mechanism is not entirely clear. Previous studies have suggested that the hemodynamic effects of angiotensin-converting enzyme inhibitors are due predominantly to a fall in circulating levels of angiotensin II (100, 101). However, this does not appear to be the sole mechanism. In most studies, only a general correlation was found between the magnitude of fall in systemic vascular resistance and the initial level of plasma renin activity (98, 99) (Figure 9). Furthermore, no correlation was found between the initial level of systemic vascular resistance and

Table 8 Beneficial hemodynamic effects of angiotensin converting enzyme inhibitor in chronic refractory heart failure[a]

	CO (L/min)	PCW (mm Hg)	HR	MAP (mm Hg)	PA (mm Hg)	SVR (dynes-sec-cm^{-5})
C_1[b]	4.4	32	73	82	41	1,497
25 mg	5.1	18	61	63	28	939
C_2[c]	5.1	28	76	79	39	1,370
50 mg	5.5	17	63	59	26	986
C_3[d]	4.8	28	74	81	39	1,366
100 mg	5.7	17	61	62	28	880
	$P < 0.025$	$P < 0.005$	$P < 0.001$	$P < 0.001$	$P < 0.05$	NS

[a] CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; PA = mean pulmonary artery pressure; PCW = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

[b] C_1 = control before 25 mg of Captopril.

[c] C_2 = control before 50 mg of Captopril.

[d] C_3 = control before 100 mg of Captopril.

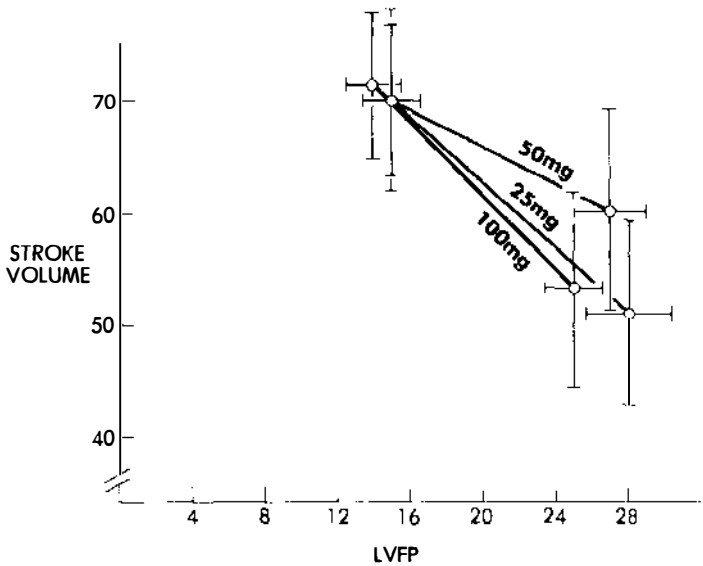

Figure 8 Changes in stroke volume and left ventricular filling pressure following 25, 50, and 100 mg of oral captopril in 11 patients with chronic heart failure. Following each dose, stroke volume increased, along with a decrease in LVFP, suggesting improved left ventricular function.

the control of plasma renin activity. These observations suggest that the reduction of systemic vascular resistance by Captopril in patients with chronic congestive heart failure may not be entirely due to a decrease in the levels of circulating angiotensin II. Captopril also inhibits the degradation of bradykinin (102, 103). Therefore, kinin-induced vasodilation with reduction of systemic vascular resistance remains a possibility. The mechanism of fall in systemic and pulmonary venous pressure with Captopril in patients with heart failure also remains unclear. It is generally accepted that angiotensin causes constriction of precapillary resistance vessels while the veins or capacitance vessels are relatively insensitive to the direct constricting effect of angiotensin (104–107). During the systemic administration of angiotensin, however, peripheral venous tone and central venous pressure usually increase, and this venoconstricting effect of angiotensin can be prevented by regional nerve block, suggesting that reflex neural mechanisms might be responsible (108–111). It is possible, therefore, that Captopril may cause venodilation by inhibiting this indirect venoconstricting effect of angiotensin. Circulating levels of norepinephrine are frequently elevated in patients with heart failure (97). In the capacitance vessels, there is an abundance of norepinephrine receptors (112), and therefore venous tone may increase considerably. Angiotensin-converting enzyme inhibitors may cause a fall in the level of circulating norepinephrine in patients with heart failure (94, 97) and therefore norepinephrine-induced increase in venous

tone may also decrease. It is possible that the fall in systemic and pulmonary venous pressures with the use of Captopril may be partly due to the attenuation of norepinephrine-induced venoconstriction. Whatever the mechanisms for a fall in systemic and pulmonary venous pressures, these hemodynamic effects of Captopril help relieve the signs and symptoms of systemic and pulmonary venous congestion.

The incidence and the nature of side effects and potential complications cannot be evaluated from the presently available limited clinical experience. Gastrointestinal symptoms like nausea and abdominal pain may occur in some patients. Skin rash has been reported during long-term Captopril therapy, but this complication occurred in less than 10% of patients. Marked bradycardia and hypotension have been observed in some patients at the initiation of therapy, although these effects tend to be attenuated with continued therapy. Nevertheless, hypotension remains a potential complication of Captopril therapy.

Other Nonparenteral Vasodilator Agents

The hemodynamic effects of oral regitine and phenoxybenzamine, the α-adrenergic blocking agents, have been investigated in only a limited number of patients (113, 114). These preliminary studies indicate that these agents may produce beneficial hemodynamic effects in some patients with chronic

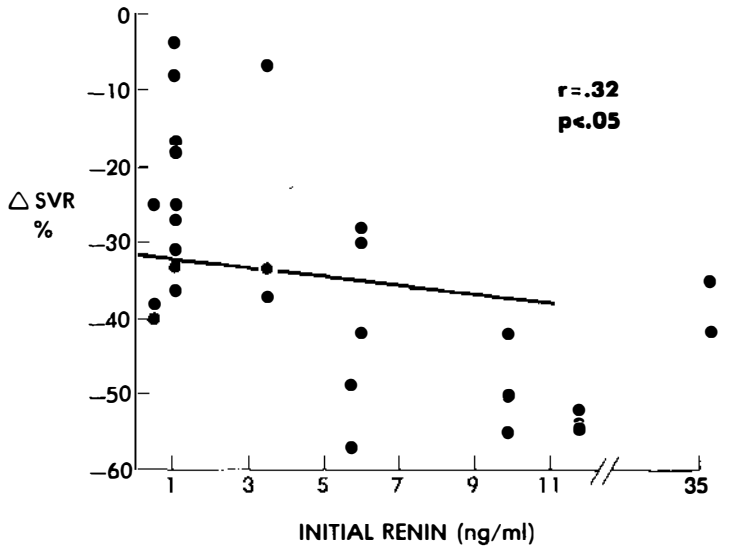

Figure 9 Relation between the magnitude of change in systemic vascular resistance (SVR) and the initial plasma renin level in a group of patients with chronic heart failure; only a general correlation was observed.

congestive heart failure. Decrease in systemic and pulmonary venous pressures and increase in cardiac output suggesting improved cardiac performance have been reported. Regitine may also cause reduction in pulmonary vascular resistance and pulmonary arterial hypertension in patients with right heart failure secondary to cor pulmonale (115). However, clinical experience is extremely limited and the role of regitine for the management of patients with chronic left or right heart failure remains uncertain at present. Furthermore, undue tachycardia and undesirable gastrointestinal symptoms may limit its use for the long-term management of such patients (114).

EFFECT OF VASODILATOR THERAPY ON EXERCISE HEMODYNAMICS IN PATIENTS WITH CHRONIC HEART FAILURE

Compromised left ventricular function in patients with chronic heart failure frequently deteriorates further during exercise (116, 117). In response to increased stress to the cardiovascular system during physical exercise, pulmonary venous pressure increases excessively causing dyspnea. An inappropriately small increase in cardiac output precipitates fatigue. Little or no increase in cardiac output with a large increase in left ventricular filling pressure also indicates a diminished cardiac reserve in these patients (118, 119).

Effects of various nonparenteral vasodilator agents on cardiac performance of chronic heart failure patients during exercise have been investigated. Short-term oral hydralazine therapy increased cardiac output not only at rest but also during exercise (120) (Table 9). The increase in stroke volume that was observed at rest following hydralazine therapy was maintained during exercise. Exercise-induced tachycardia before and after hydralazine was similar. Hydralazine did not produce any significant change in left ventricular filling pressure either at rest or during exercise. Nevertheless, increased cardiac output and stroke volume with little or no change in left ventricular filling pressure suggested improved cardiac performance during exercise.

Short-term prazosin therapy also improves exercise hemodynamics in patients with chronic heart failure (121). Addition of prazosin to conventional therapy increased cardiac outputs considerably during exercise. Prazosin-induced increase in cardiac output during exercise was mainly due to increase in stroke volume. During prazosin therapy, the magnitude of exercise-induced increases in left ventricular filling pressure was also less. Prazosin also significantly decreased the mean pulmonary artery pressure on exercise. Prazosin improved left ventricular performance more during

Table 9 Effects of oral hydralazine on hemodynamics at rest and during exercise[a]

Therapy	CO L/min	PA SAT %	SV ml	HR beats/min	LVFP mm Hg	$\overline{AP}$ mm Hg	$\overline{PA}$ mm Hg	$\overline{RA}$ mm Hg	W KPM
C R	3.2 ± 0.8	58 ± 10	37 ± 10	88 ± 23	23 ± 8	87 ± 11	35 ± 9	11 ± 8	
C E	4.6 ± 1.5	35 ± 7	40 ± 11	113 ± 30	33 ± 7	102 ± 11	48 ± 10	18 ± 11	180 ± 121
H R	4.8 ± 1.2	70 ± 7	49 ± 15	93 ± 22	23 ± 8	84 ± 10	33 ± 10	11 ± 10	
H E	5.9 ± 1.8	47 ± 8	48 ± 15	119 ± 31	33 ± 6	95 ± 13	50 ± 9	19 ± 12	100 ± 127
P of R–R	< 0.01	< 0.01	< 0.01	NS	NS	NS	NS	NS	
P of E–E	< 0.01	< 0.01	< 0.01	< 0.01	NS	< 0.05	NS	NS	

[a] AP = mean arterial pressure; C = conventional therapy; CO = cardiac output; E = exercise; H = hydralazine; HR = heart rate; LVFP = left ventricular filling pressure; PA = mean pulmonary artery pressure; R = rest; RA = mean right atrial pressure; RA SAT = mixed venous oxygen saturation; SV = stroke volume; W = peak exercise workload.

exercise than at rest because increases in cardiac output and decreases in left ventricular filling pressure were consistently larger during exercise than at rest.

Combined nitrates and hydralazine therapy also tends to improve cardiac performance during exercise. At similar workload, cardiac output tends to be higher and left ventricular filling pressure lower, suggesting improved left ventricular performance (122).

Although exercise hemodynamics and cardiac performance improve, exercise tolerance may not increase following short-term vasodilator therapy (120–122). Symptom-limited maximum exercise capacity of patients with severe chronic heart failure usually remains unchanged following initiation of vasodilator therapy. Changes in oxygen consumption, lactate metabolism, and exercise hemodynamics following short-term hydralazine and prazosin therapy in a group of patients with advanced heart failure are summarized in Table 10 (123). Following addition of hydralazine or prazosin to conservative therapy, cardiac output during exercise was considerably higher than that during conventional therapy. However, oxygen consumption did not change because increases in cardiac output were balanced by decreases in arteriovenous oxygen differences. Whether treated with hydralazine or prazosin, peak serum lactate concentration during exercise (at same workload) before and after addition of those vasodilator agents were similar. Furthermore, following short-term vasodilator therapy the time constant of lactate disappearance during recovery following cessation of exercise also did not change compared to control. The explanations for lack of increase in exercise tolerance and oxygen consumption, despite an increase in cardiac output following short-term vasodilator therapy, are not clear. It is possible that there is a maldistribution of the increase in cardiac output; more blood may be shunted to the nonexercising skeletal muscle than to the exercising muscles. It is conceivable that vasodilators do not affect the metabolically determined changes in vascular resistance and blood flow in exercising skeletal muscles but that blood flow increases in nonexercising limbs instead. It is also possible that short-term vasodilator therapy only increases shunt flow by altering the resistance at precapillary sphincters. Furthermore, if mitochondria and respiratory enzyme systems are decreased in patients with advanced heart failure associated with chronically reduced cardiac output tissue, oxygen utilization may not improve despite increased oxygen delivery. It is apparent that there are multiple possible explanations, although presently unproved, for the lack of increase in exercise tolerance and oxygen consumption, despite an increase in cardiac output induced by short-term vasodilator therapy.

Effects of long-term vasodilator therapy on exercise performance and oxygen consumption, however, may be different from those following short-

term therapy. If vasodilators chronically increase cardiac output and cardiac performance, exercise tolerance and oxygen consumption may also improve. Studies on exercise tolerance of heart failure patients treated with vasodilator agents have shown an increase in exercise capacity. Chronic nitrate therapy may improve exercise tolerance and increase oxygen consumption of patients with chronic heart failure (124). Similarly, peak symptom-limited exercise loads may increase during chronic long-term hydralazine, prazosin, or trimazosin therapy even though there may not be any change in exercise capacity during acute therapy (Figure 10) (125–127). However, further investigations will be needed to delineate more precisely the differences in exercise hemodynamics, exercise capacity, and oxygen consumption during short-term and long-term vasodilator therapy in patients with chronic congestive heart failure.

HEMODYNAMIC EFFECTS OF CHRONIC VASODILATOR THERAPY

Although acute hemodynamic effects of various vasodilator agents have been investigated, relatively little information is available regarding the hemodynamic response of long-term vasodilator therapy in patients with chronic heart failure. Only in a small number of patients has the hemodynamic response to chronic hydralazine therapy been investigated (128, 129). Preliminary studies indicate that oral hydralazine produces sustained hemodynamic response in patients with chronic heart failure (Table 11). Changes in heart rate and mean arterial pressure were similar following initiation of therapy and during late hemodynamic study. The magnitude of decrease in systemic vascular resistance and increase in cardiac output was also similar during initial and late study. Increased stroke volume observed during initial study remained sustained during late study. There was no significant change in left ventricular filling pressure either at the time of initial study or during late hemodynamic study. These findings indicate that oral hydralazine produces sustained hemodynamic effects in patients with chronic heart failure. Persistent hemodynamic effects of nonparenteral nitrates and Captopril have also been demonstrated (99). In patients receiving chronic nitrate therapy, sustained decrease in pulmonary capillary wedge pressure has been observed (130). Similarly, in patients on chronic Captopril therapy, decreased pulmonary capillary wedge pressure, a modest hypotension and increased cardiac output have been reported not only at the time of the initiation of therapy but also during chronic therapy (Table 12). Combined phenoxybenzamine and nitrate therapy has been shown to produce sustained hemodynamic response in patients with chronic heart failure (113). It appears, therefore, that certain vasodilator agents produce

Table 10 Summary of metabolic and hemodynamic variables during exercise[a]

	HR (min^{-1})	MAP (mm Hg)	MPA (mm Hg)	PCW (mm Hg)	MRA (mm Hg)	CO (L/min)	AV-O_2 (ml/100 ml)	$\dot{V}O_2$ (ml/min)	Lp (mg/dl)	Lτ (min)
Hydralazine										
Control	121 ± 28	105 ± 11	53 ± 11	38 ± 4	14 ± 5	5.8 ± 2.3	11.7 ± 3.1	663 ± 249	49.7 ± 24.2	31.1 ± 16.7
Vasodilator	125 ± 26	105 ± 9	53 ± 11	36 ± 5	15 ± 6	6.9 ± 2.3	9.6 ± 1.7	651 ± 200	44.0 ± 21.4	29.8 ± 13.5
P	NS	NS	NS	NS	NS	0.001	0.01	NS	$0.10 < P < 0.05$	NS
Prazosin										
Control	122 ± 21	102 ± 14	54 ± 10	39 ± 5	21 ± 11	5.7 ± 2.1	12.1 ± 2.0	696 ± 246	33.8 ± 16.5	26.1 ± 7.8
Vasodilator	121 ± 22	97 ± 17	41 ± 13	29 ± 12	17 ± 9	7.6 ± 2.7	9.7 ± 1.8	734 ± 245	32.1 ± 12.2	38.9 ± 23.2
P	NS	NS	0.05	0.05	NS	0.005	0.025	NS	NS	NS

[a] Values are mean ± SD. AV-O_2 = arteriovenous oxygen difference; CO = cardiac output; HR = heart rate; Lp = peak lactate during recovery; Lτ = time constant of lactate disappearance during recovery; MAP = mean arterial pressure; MPA = mean pulmonary artery pressure; MRA = mean right atrial pressure; NS = not significant; PCW = mean pulmonary capillary wedge pressure; $\dot{V}O_2$ = oxygen consumption.

Table 11 Sustained beneficial hemodynamic effects during long-term hydralazine therapy in patients with chronic heart failure[a]

	N	CI (L/min/m^2)	SVI ml/m^2	SVR dynes sec cm^{-5}	LVFP mm Hg	MAP mm Hg
C	8	1.9 ± 0.4	21 ± 5	1,841 ± 530	24 ± 13	88 ± 14
HDI	8	3.2 ± 0.6	36 ± 9	1,068 ± 356	19 ± 9	83 ± 8
HDC	8	3.4 ± 0.7	42 ± 11	1,020 ± 188	19 ± 6	83 ± 12
HDO	4	2.0 ± 0.4	26 ± 8	1,753 ± 492	23 ± 7	83 ± 13

[a] C = initial control; CI = cardiac index; HDC = chronic hydralazine therapy; HDI = initial hydralazine therapy; HDO = off hydralazine therapy; LVEP = left ventricular filling pressure; MAP = mean arterial pressure; N = number of patients; SVI = stroke volume index; SVR = systemic vascular resistance.

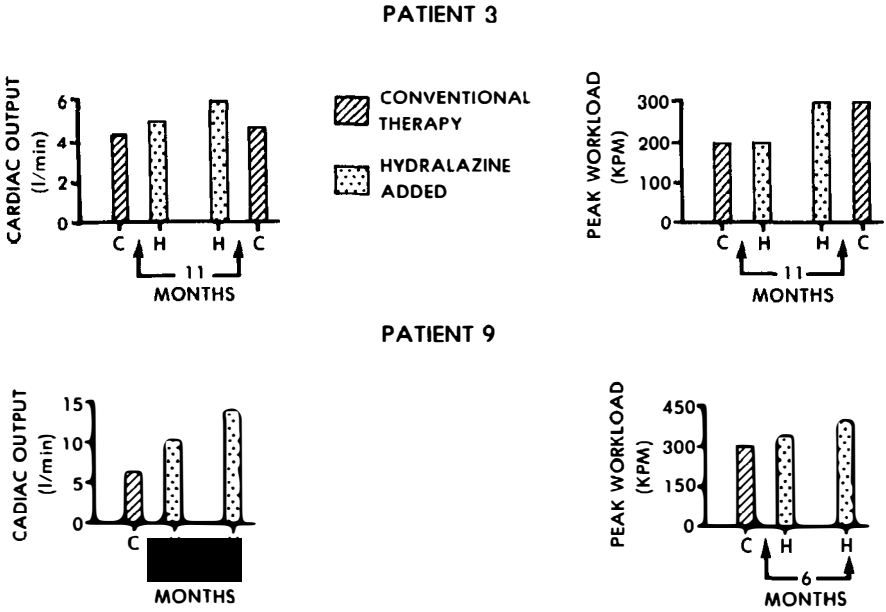

Figure 10 Comparison of acute and chronic exercise hemodynamics in two patients with chronic heart failure who received maintenance oral hydralazine therapy. Top (Patient 3): Cardiac output and peak exercise work load increased after long-term (11 months) therapy; although following initiation of therapy peak work load did not change, despite some increase in cardiac output. In patient 9 (bottom), also, following six months of therapy, peak work load increased significantly.

sustained hemodynamic response in patients with chronic heart failure. However, clinical experience to date with chronic vasodilator therapy for heart failure is extremely limited, and without further studies its role for routine long-term management of patients with chronic heart failure cannot be firmly established.

Table 12 Sustained beneficial hemodynamic effects of long-term oral angiotensin-converting enzyme inhibitor in chronic heart failure

	Control	Initial	Two month
Heart rate (heats/min)	78	67	71
Mean arterial pressure (mm Hg)	89	70	68
Pulmonary capillary wedge pressure (PCW) (mm Hg)	26	17	8
Stroke volume (SV) (ml/beat)	42	68	58

SUMMARY

It is apparent that the various nonparenteral vasodilator agents produce beneficial hemodynamic and clinical responses in patients with chronic heart failure. These beneficial responses are observed irrespective of the etiology of left ventricular failure. Hemodynamic improvements tend to be particularly pronounced in patients with primary or secondary mitral regurgitation.

As the hemodynamic effects of the various vasodilator drugs may be different, the choice of a vasodilator agent should be made according to the predominant symptoms and the specific hemodynamic deficits present in a given patient. When symptoms of pulmonary venous congestion are present and if pulmonary capillary wedge pressure is markedly elevated, nitroglycerin and nitrates are appropriate vasodilator agents. When fatigue and tiredness are the major symptoms, and if cardiac output is reduced and systemic vascular resistance is elevated, an arteriolar dilator like hydralazine is preferable. In the majority of patients with chronic left ventricular failure, however, not only the cardiac output is reduced but also the pulmonary capillary wedge pressure is elevated. In those patients, the drugs that cause a decrease in pulmonary venous pressure and an increase in cardiac output such as prazosin trimazosin or captopril can be used. Alternatively, a combination of venodilators, nitrates, and arteriolar dilator hydralazine can be used to achieve similar beneficial hemodynamic and clinical response (131). Nitrates reduce systemic and pulmonary venous pressures effectively but may not increase cardiac output. Hydralazine causes an increase in cardiac output without a significant change in pulmonary capillary wedge or right atrial pressure. Neither drug produces any significant change in heart rate or blood pressure. Thus, with the combination of nitrates and hydralazine, both the major hemodynamic objectives of treatment of heart failure, i.e. reduction of pulmonary and systemic venous pressures and increase in cardiac output, can be achieved.

Clinical experience with long-term vasodilator therapy, however, is limited and the incidence of side effects and complications with the long-term

use of the vasodilator agents remains unknown. Without further experience, the routine use of vasodilator agents for treatment of chronic heart failure, therefore, cannot be recommended, and the vasodilator therapy should be reserved only for refractory heart failure patients.

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