Vasodilator Therapy for Acute Myocardial Infarction and Chronic Congestive Heart Failure

KANU CHATTERJEE, MB, FRCP, FACC, WILLIAM W. PARMLEY, MD, FACC

San Francisco, California

Vasodilator therapy is useful adjunctive therapy in the management of both acute and chronic heart failure. Arteriolar dilators, such as hydralazine, increase cardiac output by decreasing the elevated peripheral vascular resistance that occurs in heart failure. Venodilators, such as nitrates, decrease ventricular filling pressures by redistributing blood so that more is pooled in peripheral veins. Vasodilators that produce both effects (nitroprusside, prazosin, captopril, for example) are usually helpful in short-term improvement of hemodynamics. Long-term treatment with nonparenteral vasodilators often reduces symptoms and increases exercise tolerance, although there is inconclusive evidence regarding the effects of these agents on mortality. In acute myocardial infarction, intravenous vasodilators frequently improve cardiac performance. Evidence regarding their beneficial effects on infarct size and immediate mortality is encouraging but inconclusive. There is little evidence that they prolong life in patients who survive cardiogenic shock and leave the hospital. Thus, vasodilators can improve hemodynamics and lessen symptoms, but more evidence is needed regarding their long-term effects on survival.

The potential benefits of vasodilation in the treatment of heart failure were observed more than 3 decades ago (1–3). However, it was not until the late 1960s and early 1970s that vasodilator therapy was shown to produce marked improvement in the cardiac performance of patients with acute or chronic heart failure (4–8) or mitral regurgitation (9). This renewed interest in vasodilator therapy was closely linked to the development of newer techniques for bedside hemodynamic monitoring. Use of balloon flotation catheters (10,11) has facilitated evaluation of the hemodynamic effects of a variety of vasodilator drugs and their application to the management of critically ill patients. Since the recognition of the potential benefits of vasodilators, there has been increasing interest in delineating their mechanisms of action, their effects on cardiac dynamics and regional circulations and their relative advantages and disadvantages. Furthermore, the search continues to identify newer, better vasodilator drugs for the treatment of heart failure. The purpose of this paper is to provide an overview of vasodilator therapy for heart failure, and to describe in detail some of the specific effects of the currently available drugs. Because this is a rapidly changing field, no attempt will be made to provide all-inclusive information: instead, areas of practical and clinical interest will be emphasized.

Mechanisms of Action

Afterload Reduction

Vasodilator therapy for low cardiac output is based on the principle of afterload reduction in the failing heart. From studies of the mechanics of contraction of isolated heart muscle, it is known that increasing the load against which a muscle shortens (afterload) will decrease the magnitude of shortening and the velocity of shortening (12). Conversely, if one reduces the afterload, the muscle shortens further and with a greater velocity. Translation of this concept to the intact heart explains how decreased resistance to left ventricular ejection can enhance shortening of cardiac muscle fibers and thereby increase stroke volume and cardiac output.

In isolated heart muscle preparations, preload represents the initial load on the muscle that stretches it to its end-diastolic length before contraction. Afterload represents the additional load the muscle must lift as it shortens. If the concepts of preload and afterload, as defined in isolated muscle experiments, are used in the intact heart, it is necessary to calculate instantaneous wall stress from measurements of intraventricular pressure, radius and wall thickness

(13,14). However, such calculations are difficult to make in clinical practice. Therefore, other approximations of afterload, such as aortic pressure, aortic impedance and systemic vascular resistance, have been used.

Arterial pressure. Arterial pressure is the most easily measured index of afterload in the intact heart, because the left ventricle must generate that pressure before it can open the aortic valve. Increased intraventricular systolic pressure (aortic pressure in the absence of left ventricular outflow obstruction) is associated with decreased shortening of the left ventricular diameter during systole, and decreased mean velocity of circumferential shortening (V_{CF}) (14–16). Arterial pressure, however, should be regarded as a rough approximation of afterload, because it is only one of the variables that determines wall stress. Furthermore, changes in arterial pressure may not appropriately reflect changes in cardiac performance during vasodilator therapy. In certain circumstances, arterial pressure may not change when a vasodilator-induced decrease in systemic vascular resistance causes a proportional increase in cardiac output. This reflects the basic relation between blood pressure (BP), cardiac output (CO) and systemic vascular resistance (SVR): BP = CO × SVR.

Aortic input impedance. Some investigators believe that the external force to ventricular ejection (afterload) is better represented by the aortic input impedance, which can be described by the relation of aortic pulsatile pressure and flow waveforms throughout the cardiac cycle (17–25). In general, "impedance" implies a measure of the opposition to flow presented by a system and is a frequency-dependent function. Resistance conveys a meaning similar to impedance but is confined to average or steady state conditions. In the arterial system, blood pressure and flow exist as oscillatory (or pulsatile) waveforms superimposed on a mean (or nonpulsatile) component. Thus, total opposition to arterial blood flow encompasses both frequency-dependent pulsatile components and a frequency-independent nonpulsatile steady state component. Aortic input impedance provides information about both pulsatile and nonpulsatile components of the vascular load (17,19,24,25). The influence of each individual component of vascular load on ventricular ejection has been evaluated in experimental animals and human beings. Decreased arterial compliance (increased characteristic impedance) with constant resistance is associated with reduced stroke volume and mean aortic pressure (23). Increased resistance alone also causes a decrease in stroke volume but increases mean aortic pressure.

Aortic input impedance spectra were determined in patients with clinical and hemodynamic evidence of chronic heart failure and compared with those in subjects without heart failure, matched for age and arterial pressure. In patients with heart failure, both input resistance and characteristic impedance (index of aortic distensibility) were significantly greater than values in control subjects (26). It was also demonstrated that vasodilators like sodium nitroprus-

side can decrease characteristic impedance and increase ventricular ejection without changing arterial pressure (27). These studies indicate that a vasodilator-induced increase in arterial compliance is a potentially important mechanism for improving left ventricular function during vasodilator therapy. The calculation of aortic input impedance, however, is difficult and cannot be applied in routine clinical practice.

Systemic vascular resistance. Systemic vascular resistance, which can be determined more easily, is related to aortic input impedance. Whereas impedance is the instantaneous relation between pressure and flow, systemic vascular resistance is the average of this relation throughout the cardiac cycle. Systemic resistance is the ratio of the reduction in pressure drop across the arterial system and the mean flow. The use of systemic vascular resistance to represent afterload not only is helpful in understanding how vasodilators improve cardiac function but also can be applied in clinical practice (28). Reduction of systemic vascular resistance or aortic impedance appears to be the principal mechanism for the improvement of left ventricular function with vasodilators (Fig. 1) (29,30).

Relief of myocardial ischemia. A number of investigations have shown that relief of segmental myocardial ischemia might also be beneficial (31–34). Vasodilator agents can decrease myocardial oxygen requirements in heart failure by decreasing the determinants of myocardial oxygen demand. Intraventricular pressure and ventricular volume decrease, the heart rate either decreases or remains unchanged, and most vasodilator agents do not possess any direct positive inotropic effects. Thus, the overall myocardial oxygen demand tends to decrease during vasodilator therapy. Some vasodilator agents may also increase regional myocardial perfusion by enhancing collateral blood flow to ischemic myocardial segments (34,35). Furthermore, improved subendocardial blood flow has been demonstrated in heart failure due to experimental myocardial infarction, presumably as a result of an increased transmyocardial pressure gradient (aortic diastolic pressure-left ventricular diastolic pressure) or of increased collateral flow (36,37). It appears, therefore, that vasodilators have the potential to decrease segmental myocardial ischemia by decreasing myocardial oxygen requirements or increasing myocardial perfusion, or both. This net decrease in segmental myocardial ischemia might improve overall cardiac performance; supporting evidence is available from ventriculographic and radioisotope angiographic studies in patients with acute myocardial infarction as well as in patients with chronic coronary artery disease without heart failure (32,33,38,39).

Left ventricular diastolic compliance. Another possible mechanism by which vasodilators can produce beneficial effects in patients with heart failure is by increasing left ventricular diastolic compliance. The pressure-volume relation of the left ventricle is curvilinear, so that at small end-diastolic volumes, a given volume increment will pro-
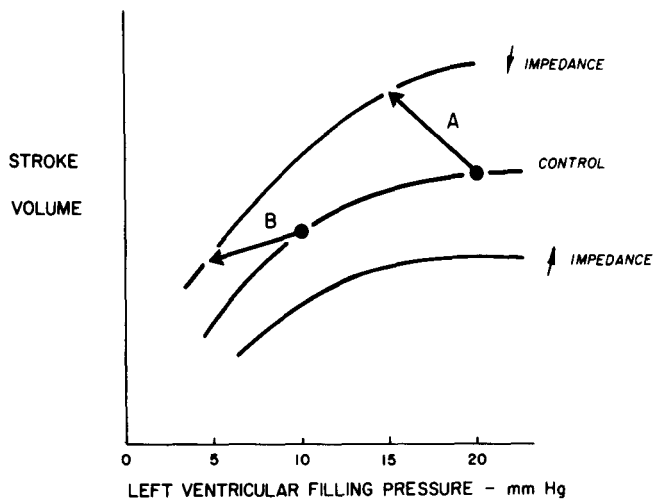
Figure 1. Left ventricular function curves plotting stroke volume versus left ventricular filling pressure are illustrated under control conditions and after decreased aortic impedance or increased aortic impedance. At a high filling pressure (20 mm Hg), with a decrease in impedance, there is a decrease in filling pressure to 15 mm Hg (**line A**) and an increase in stroke volume. Beginning at a low ventricular filling pressure (10 mm Hg), there is a similar reduction in the magnitude of filling pressure, but this is accompanied by a reduction in stroke volume (**line B**). This graph conceptually illustrates the importance of giving vasodilators only to patients with high left ventricular filling pressures. (Reprinted from Chatterjee K, Parmley WW [30], with permission.)

duce only a minor rise in ventricular diastolic pressure. At high end-diastolic volumes, as in patients with heart failure, however, there is a greater increase in diastolic pressure with each volume increment as the ventricle moves onto the steep portion of its curve. Because left ventricular end-diastolic volume is the most important determinant of stroke volume, it is apparent that a shift in ventricular compliance could markedly alter the relation between filling pressure and cardiac performance. Thus, if the pressure-volume relation were shifted to the right—that is, if there was a larger volume at the same end-diastolic pressure—a leftward shift of the left ventricular function curve might result, such as that seen with vasodilators.

Evidence suggests that vasodilator drugs may produce an acute increase in left ventricular compliance (40–42). In general, drugs that lower aortic and pulmonary artery pressures increase compliance, while those that raise pressures tend to decrease compliance. There has been considerable speculation as to the mechanism of these effects. Some investigators (43) have said that the increase in compliance produced by vasodilators may be due to a reduction in ischemia and relief of ischemic contracture. Others (40) have suggested that this change in compliance is a result of the interaction of the right and left ventricles in a confined pericardial space. Because the pericardium is a very stiff structure, at high filling pressures it tends to maintain a constant overall heart volume. A vasodilator that reduces right-sided pressures will also reduce the end-diastolic vol-

ume of the right ventricle and allow for a larger left ventricle at the same left ventricular diastolic pressure. Thus, agents that lower right-sided pressures will tend to produce an apparent increase in the compliance of the left ventricle and a beneficial shift in the ventricular function curve. This mechanism has been carefully described in experimental studies with animals, and there are enough clinical data to suggest that it is of some value in the clinical situation, but further studies are required to assess the relative importance of its role.

Overall, it is apparent that the vasodilators can improve left ventricular function of patients with heart failure by a number of related mechanisms. The most important of these appears to be the reduction of left ventricular ejection impedance, although relief of segmental myocardial ischemia and an increase in ventricular compliance may also play significant roles in certain circumstances.

Mechanism of Systemic Vasoconstriction in Heart Failure

Catecholamine release. The mediators of the systemic vasomotor response to heart failure have been discussed in recent review articles (44,45). An understanding of the different mechanisms that contribute to vasoconstriction and maintain an elevated systemic vascular resistance has important implications regarding the mechanisms of vasodilation and the hemodynamic effects of the different vasodilator agents. In patients with severe heart failure associated with a reduced cardiac output, systemic vascular resistance is markedly elevated (46–48). It appears that this vasoconstriction results from increased stimulation of vascular $alpha_1$-receptors due in part to neurogenic mechanisms as well as to high levels of circulating norepinephrine. Circulating norepinephrine levels are frequently elevated in patients with heart failure (Table 1) (49–52), and it has been postulated that this results primarily from spillover into the circulation of catecholamines released during peripheral neurogenic vasoconstriction.

Angiotensin II. In addition to increasing levels of circulating norepinephrine, angiotensin II contributes to an elevated systemic vascular resistance (53–63). The precise mechanism for the activation of the renin-angiotensin-aldosterone system in heart failure is not entirely known. Increased renal sympathetic activity with beta-receptor stimulation, renal vasoconstriction with redistribution of cortical blood flow to medullary glomeruli and a reduction in perfusion pressure in the afferent arterioles—all can promote renin release from the juxtaglomerular apparatus. Irrespective of the mechanism, increased renin release is accompanied by increased levels of angiotensin II, which elevate systemic vascular resistance. Angiotensin also facilitates norepinephrine release at neuromuscular junctions and thus further contributes to the increase in systemic vascular resistance. Increased aldosterone levels promote salt and water

Table 1. Plasma Catecholamine Levels and Hemodynamics at Rest in Patients With Severe Chronic Ischemic Cardiomyopathy and Patients With Coronary Artery Disease Without Heart Failure

	Chronic Congestive Heart Failure	Coronary Artery Disease Without Heart Failure	p
Number of patients	9	15	
Arterial norepinephrine (pg/ml)	520 ± 72	185 ± 27	0.001
Arterial epinephrine (pg/ml)	45 ± 8	55 ± 18	NS
Heart rate (beats/min)	95 ± 5	73 ± 3	0.001
Mean blood pressure (mm Hg)	89 ± 6	95 ± 3	NS
Cardiac index (liters/min per m^2)	2.1 ± 0.2	3.2 ± 0.2	0.002
Stroke work index (g-m/m^2)	22 ± 3	63 ± 6	0.001

Data are mean values ± standard deviation.
NS = not significant; p = probability.

retention with consequent deterioration in heart failure. In some patients with severe heart failure, angiotensin II contributes significantly to elevating systemic vascular resistance. When these patients are treated with angiotensin-converting enzyme inhibitors, systemic vascular resistance decreases and renal function and cardiac function improve.

Vasopressin. In many patients with chronic heart failure, a higher level of the antidiuretic hormone, vasopressin, has been observed (64,65). The increase in vasopressin occurs despite cardiac dilation and left atrial stretching, which usually inhibits the secretion of antidiuretic hormone. The significance of this increase is not apparent; however, it might contribute to plasma volume expansion and to the increase in systemic vascular resistance.

Increased vascular stiffness. Increased vascular stiffness in congestive heart failure has been considered an important contributing factor in elevating systemic vascular resistance (44,66). Increased sodium content of blood vessels has been suggested as the possible mechanism for this stiffness based on the observation that the vascular sodium content of the large and small arteries of animals with heart failure is higher. Furthermore, increased tissue pressure associated with apparent or subclinical edema may also be contributory. Thus, there are several interacting mechanisms that may contribute to the elevation of systemic vascular resistance.

Classification and Hemodynamic Effects of Vasodilators

Classification

Primary effects. A number of vasodilator agents decrease vascular tone by direct relaxation of the smooth muscle of the peripheral vascular bed. Nitroprusside, nitroglycerin and other organic nitrates, molsidomine, hydralazine

and minoxidil belong to this class. Other agents cause vasodilation by decreasing or inhibiting the vasoconstricting effects mediated by the sympathetic adrenergic system. Drugs like phentolamine, prazosin and trimazosin decrease vascular tone and systemic vascular resistance primarily by alpha-adrenergic blockade. Reduction of systemic vascular resistance and arterial pressure also occurs after ganglionic blockade with hexamethonium and trimethaphan, which produce beneficial effects in heart failure. Beta$_2$-adrenergic receptor stimulation also causes peripheral vasodilation, and agents like salbutamol and pirbuterol appear to decrease systemic vascular resistance by this mechanism. The principal mechanism by which slow channel blocking agents such as nifedipine cause vasodilation and reduction of systemic vascular resistance is thought to be inhibition of the inward calcium current to the smooth muscle of the vascular bed. Prostacyclin and prostaglandin E increase cyclic adenosine monophosphate levels in the smooth muscle of the vascular bed and cause vasodilation.

Because the renin-angiotensin-aldosterone system is frequently activated and contributes to the increased systemic vascular resistance seen in heart failure, inhibition of the vasoconstricting effect of angiotensin II is a logical approach for decreasing systemic vascular resistance and increasing cardiac output. Saralasin is a competitive antagonist of angiotensin II. Captopril, teprotide and MK-421 decrease the formation of angiotensin II from angiotensin I by inhibiting the converting enzyme. Attenuation of the effects of angiotensin II decreases arterial pressure and systemic vascular resistance (66).

Many of these vasodilator drugs possess additional pharmacologic properties that might be contributory to peripheral vasodilation. For example, although phentolamine is an alpha-adrenergic blocking agent, it also directly relaxes the smooth muscle of arteries and veins (47). Phentolamine also possesses beta-adrenergic stimulating effects that may contribute to peripheral vasodilation (67). Similarly, captopril, in addition to decreasing the vasoconstricting effects of angiotensin II, also inhibits the degradation of bradykinin, a vasodilator that might also be contributory to reducing systemic vascular resistance.

Site of action. Irrespective of their primary mechanisms of vasodilation, the hemodynamic effects of the vasodilator drugs appear to be related to their principal site of action on the peripheral vascular bed. One group of vasodilators predominantly dilates systemic veins (for example, nitroglycerin), a second group predominantly dilates arterioles (for example, hydralazine) and a third group has a more or less balanced effect on arteries and veins (for example, nitroprusside). Vasodilators that predominantly dilate systemic veins 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. However, this pooling of blood in the veins is effective in reducing filling pressures and intracardiac volumes of the right and left sides of the heart, thus relieving pulmonary and systemic venous congestion.

Venous dilators. The effects of a predominant venodilator drug on cardiac performance are also dependent on the initial level of left ventricular filling pressure. If one starts at a normal filling pressure, pooling of blood and a further reduction of filling pressure will tend to lower stroke volume as the ventricle moves down the ascending limb of its curve (Fig. 1). In order to maintain cardiac output under these circumstances, there may be a compensatory increase in heart rate. If one starts at a high filling pressure, a reduction in filling pressure will occur along the flat portion of the ventricular function curve and therefore will not produce a marked reduction in ventricular performance. Thus, it is apparent that caution should be taken in giving a venodilator to a patient with a very low filling pressure. A further reduction in filling pressure may reduce forward stroke volume and cardiac output to produce a precipitous fall in blood pressure; this potential harmful effect must be considered before administering any venodilator to a patient with a low initial filling pressure, especially after acute myocardial infarction.

Arteriolar vasodilators and drugs with combined effects. Vasodilators that primarily decrease arteriolar tone cause a reduction in systemic vascular resistance and an increase in cardiac output with little or no change in ventricular filling pressures. Drugs with balanced effects on arteriolar and venous beds decrease systemic vascular resistance and systemic venous tone and cause an increase in cardiac output and a decrease in ventricular filling pressures. The net increase in cardiac output with these agents is necessarily less than that expected from their arteriolar dilating effect because of the concomitant reduction of filling pressure related to venodilation. None of the vasodilator drugs currently available has pure arteriolar or venodilator effects. The response of the peripheral vascular beds to vasodilator agents in individual patients may be variable and the hemodynamic effects of a given vasodilator agent may not be identical in all patients. Moreover, the relative effects of the vasodilator drugs on the systemic veins versus systemic arteries cannot be assessed solely from changes in right or left ventricular filling pressures and systemic vascular resistance. Changes in right atrial and pulmonary venous pressures are related not only to the changes in ventricular preload and afterload but also to the compliance characteristics of the right and left ventricles and of the pulmonary vascular bed. Thus, the preferential effects of a vasodilator drug on arteries or veins should be assessed, whenever possible, by direct determinations. Nevertheless, a knowledge of the principal site of action on the peripheral

vascular beds provides the clinician with an understanding of the expected hemodynamic effects of a vasodilator drug.

Hemodynamic Effects

Nitrates. The principal hemodynamic effects of the commonly used vasodilator drugs for the treatment of acute or chronic heart failure are summarized in Table 2. Nitrates, whether administered sublingually, topically or intravenously, tend to produce qualitatively similar hemodynamic effects in patients with acute or chronic heart failure (68–72). A reduction in pulmonary capillary wedge and right atrial pressures is the most consistent effect. There is usually a modest decrease in arterial pressure. Pulmonary artery pressure and pulmonary vascular resistance tend to decrease in most patients. Changes in systemic vascular resistance, cardiac output and stroke volume are variable. However, a very large oral dose of isosorbide dinitrate (100 mg) has been reported to increase cardiac output considerably in some patients with chronic heart failure (73).

Hydralazine and minoxidil. By contrast, these drugs, which are predominantly arteriolar dilators, cause a significant reduction in systemic vascular resistance and a marked increase in cardiac output with little or no change in pulmonary venous pressure (74–76). Arterial pressure is only slightly decreased, and there is usually no change in heart rate. However, in some patients, marked hypotension and tachycardia may occur during hydralazine or minoxidil therapy. Salbutamol, pirbuterol and nifedipine appear to produce very similar hemodynamic effects (77–80).

Nitroprusside, phentolamine, prazosin, trimazosin and captopril. These vasodilator agents have a relatively balanced effect on both arteriolar and venous beds; they decrease both afterload and preload. The usual hemodynamic effects are a reduction of arterial pressure and systemic vascular resistance and an increase in cardiac output and stroke volume. Pulmonary capillary wedge, right atrial and pulmonary artery pressures also decrease. Heart rate either decreases or remains unchanged, even when there is a decrease in arterial pressure, except with phentolamine, which tends to cause some tachycardia (8,28,36,58–60,81–95). Despite the different mechanisms for vasodilation, these agents produce qualitatively and quantitatively similar hemodynamic effects. Nitroprusside, a direct vasodilator, prazosin, an alpha-receptor blocking agent, and captopril, an angiotensin-converting enzyme inhibitor, decrease systemic and pulmonary venous pressures and increase cardiac output concurrently. The hemodynamic effects outlined in Table 2 are the usual and expected response to these vasodilator agents in patients with heart failure. Significant variability, however, can be observed in different patients.

Comparative Hemodynamic Effects

To determine the relative advantages of the various vasodilator agents that are potentially useful for the treatment

Table 2. The Principal Hemodynamic Effects of Vasodilators Used for Treatment of Heart Failure

Vasodilator	Heart Rate	Blood Pressure	Cardiac Output	Systemic Vascular Resistance	Pulmonary Venous Pressure	Right Atrial Pressure	Pulmonary Vascular Resistance
Nitroglycerin	No change	Slight decrease	No change or slight increase	No change or slight decrease	Marked decrease	Marked decrease	Decrease
Isosorbide dinitrate	No change	Slight decrease	No change or slight increase	No change or slight decrease	Marked decrease	Marked decrease	Decrease
Hydralazine	No change or slight increase	Slight decrease or no change	Marked increase	Marked decrease	No change or slight decrease	No change	Slight decrease
Minoxidil	No change or slight increase	Slight decrease or no change	Marked increase	Marked decrease	No change or slight decrease	No change	Slight decrease
Prazosin	No change or slight decrease	Moderate decrease	Moderate increase	Moderate decrease	Marked decrease	Marked decrease	Decrease
Trimazosin	No change or slight decrease	Moderate decrease	Moderate increase	Moderate decrease	Marked decrease	Marked decrease	Decrease
Captopril	No change or slight decrease	Moderate decrease	Moderate increase	Moderate decrease	Marked decrease	Marked decrease	Decrease
Pirbuterol	Increase or no change	No change or slight decrease	Moderate increase	Moderate decrease	Moderate decrease	Moderate decrease	Slight decrease
Salbutamol	Increase or no change	No change or slight decrease	Moderate increase	Moderate decrease	No change or slight decrease	No change or slight decrease	Slight decrease
Nifedipine	Increase or no change	Decrease	Increase	Decrease	Decrease or no change	Decrease or no change	Decrease
Nitroprusside	Increase or no change	Slight decrease	Increase	Decrease	Decrease	Decrease	Decrease
Phentolamine	Increase	Slight decrease	Increase	Decrease	Decrease	Decrease	Decrease

of heart failure, it is necessary to evaluate the hemodynamic effects of these agents in the same patients. Studies of hemodynamic effects have been performed comparing hydralazine with nitrates and nitroprusside, prazosin with nitroprusside and captopril, and nitroprusside with captopril.

Armstrong et al. (96) compared the hemodynamic effects of both intravenous sodium nitroprusside and intravenous nitroglycerin in the same group of patients with acute myocardial infarction. A greater increment in the ratio of systemic vascular resistance to pulmonary capillary wedge pressure was noted with nitroglycerin than with nitroprusside at a comparable decrease in arterial pressure. Stinson et al. (97) compared the hemodynamic effects of intravenous nitroglycerin and nitroprusside in early post-surgical patients. Although both drugs decreased left atrial pressure, nitroprusside increased stroke volume and cardiac output, while nitroglycerin decreased cardiac output and stroke vol-

ume. Flaherty et al. (98), however, observed that at similar levels of left ventricular filling pressures in postoperative patients there was no significant difference in the magnitude of the increase in cardiac output or stroke volume with nitroglycerin or nitroprusside. These patients, however, did not have pump failure. In most studies in patients with heart failure, a greater increase in cardiac output has been observed with nitroprusside than with nitroglycerin. Awan et al. (99) reported that the magnitude of increase in cardiac output with captopril (+21%) was less than that with prazosin (+30%), although left ventricular filling pressure fell by a similar magnitude (captopril −29%, prazosin −30%).

Recently, Rouleau et al. (100) reported the comparative hemodynamic effects of captopril, prazosin and hydralazine in the same patients with chronic ischemic heart failure (Table 3). The magnitude of increase in cardiac output after captopril (19%) was less than that with prazosin (29%) or

Table 3. Comparative Systemic Hemodynamic Effects of Captopril, Prazosin and Hydralazine (101)

	HR (beats/min)	Mean BP (mm Hg)	Diastolic BP (mm Hg)	PCWP (mm Hg)	SWI (g-m/m^2)	CI (liters/min per m^2)	SVR (dynes s-cm^{-5})
Captopril (n = 8)							
C	90 ± 12	83 ± 12	62 ± 10	23 ± 6	29 ± 12	2.1 ± 0.5	1465 ± 258
Peak	83 ± 9	64 ± 12	46 ± 8	15 ± 4	28 ± 9	2.5 ± 0.4	938 ± 126
p	<0.05	<0.001	<0.001	<0.025	NS	<0.001	<0.001
Prazosin (n = 8)							
C	89 ± 15	80 ± 8	61 ± 5	21 ± 7	26 ± 13	2.0 ± 0.5	1553 ± 379
Peak	97 ± 13	62 ± 10	46 ± 7	13 ± 6	25 ± 9	2.7 ± 0.4	863 ± 215
p	<0.05	<0.001	<0.001	<0.005	NS	<0.001	<0.001
Hydralazine (n = 8)							
C	91 ± 14	77 ± 7	57 ± 4	21 ± 8	27 ± 12	2.1 ± 11	1445 ± 279
Peak	94 ± 15	72 ± 11	50 ± 8	18 ± 7	34 ± 16	2.9 ± 0.7	955 ± 271
p	NS	<0.025	<0.005	<0.05	·<0.01	<0.001	<0.005

Data are mean values ± standard deviation. Peak values indicate variables measured when there was a 10 mm Hg decrease in diastolic pressure.

C = control; CI = cardiac index; Diastolic BP = diastolic arterial pressure; HR = heart rate; Mean BP = mean arterial pressure; P = probability; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance; SWI = stroke work index.

hydralazine (36%). However, heart rate decreased with captopril, while it increased with both prazosin and hydralazine; thus, the increase in stroke volume was similar with all three agents—29, 24 and 34%, respectively. The decrease in pulmonary capillary wedge pressure with captopril and prazosin was considerably greater than with hydralazine (Fig. 2) (101). In their study, the comparative hemodynamic effects were evaluated after a single dose of prazosin and hydralazine. With continued administration of either agent for 24 or 48 hours more pronounced differences in their hemodynamic effects have been observed (102). The magnitude of decrease in systemic vascular resistance was greater with hydralazine (44%) than with prazosin (20%). Consequently, the increase in cardiac output was also greater with hydralazine (52%) than with prazosin. In this group of patients pulmonary capillary wedge pressure did not decrease significantly either with prazosin or with hydralazine. The lack of a significant reduction of pulmonary capillary wedge pressure after hydralazine is expected because of its weak venodilatory effects. It is not clear why there was no change with prazosin; attenuation of the hemodynamic response after subacute therapy remains a possible explanation.

Clinical Applications

In recent years vasodilator agents have been used for the treatment of heart failure due to a variety of causes. Vasodilator therapy has gained acceptance in the management of acute pump failure in patients with recent myocardial infarction, in patients after cardiac surgery and in patients with mechanical defects. There has been increasing interest in the use of nonparenteral vasodilator agents for the long-term management of patients with chronic congestive heart

Figure 2. Relative changes in cardiac index, pulmonary capillary wedge pressure (PCWP) and myocardial oxygen consumption (MVO$_2$) after administration of captopril, prazosin and hydralazine in patients with chronic congestive heart failure. With all three agents, left ventricular pump function improved; however, only with captopril MVO$_2$ decreased significantly. (Reprinted from Chatterjee K, Rouleau J-L [101], with permission.)
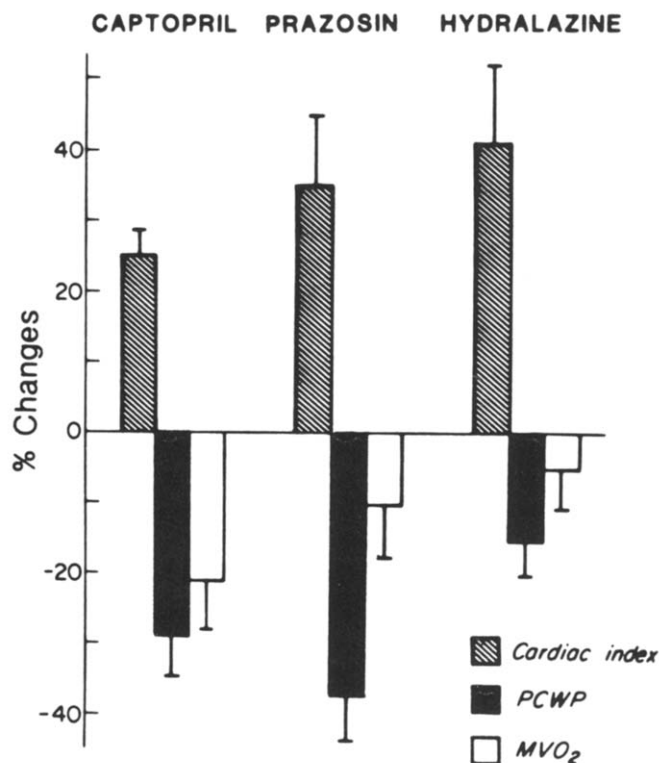
failure. The potential role of vasodilator agents for the therapy of predominantly right heart failure associated with pulmonary hypertension is currently under investigation.
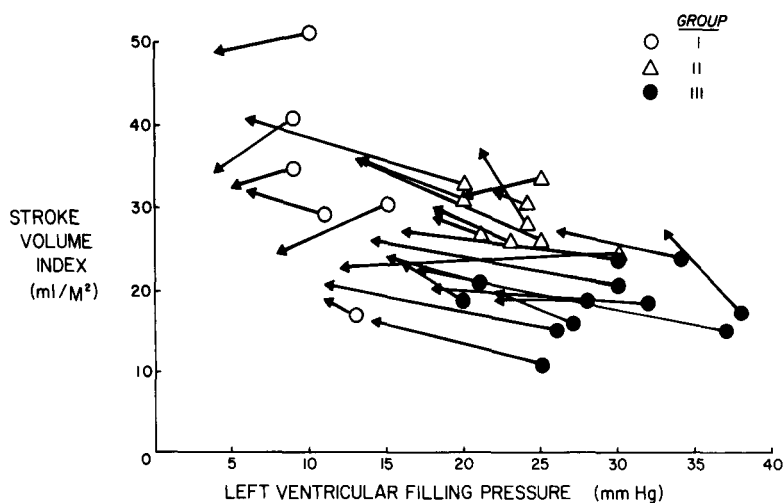
Acute Myocardial Infarction

Indications. In the management of pump failure complicating recent myocardial infarction, intravenous vasodilators with a rapid onset of action and short half-life are preferable. Sodium nitroprusside, nitroglycerin and phentolamine are the most frequently used vasodilator agents. Since the initial report of Franciosa et al. (8), the hemodynamic effects of sodium nitroprusside have been evaluated in a number of studies (28,36,96,103). These results indicate that in the presence of an elevated left ventricular filling pressure and reduced cardiac output, nitroprusside therapy improves left ventricular function (Fig. 3) (30). Cardiac output and stroke volume increase along with a decrease in left ventricular filling pressure. These beneficial hemodynamic effects are usually accompanied by clinical improvement and can be observed even in patients with severe pump failure with or without the clinical features of cardiogenic shock (Table 4) (103). Sublingual nitroglycerin and sublingual or oral isosorbide dinitrate also improve left ventricular function in patients with acute myocardial infarction if the initial left ventricular filling pressure is elevated (104–107). In patients with a normal left ventricular filling pressure and no pump failure, cardiac output and stroke volume may decrease as left ventricular filling pressure decreases, indicating no improvement in cardiac function (108).

Choice of vasodilator agent. Controversy exists regarding the choice of vasodilator agent for the treatment of pump failure complicating myocardial infarction. In some studies nitroglycerin has been shown to decrease the extent of myocardial injury, and nitroprusside, to enhance myocardial ischemia in the presence of experimental myocardial infarction (36). Transmyocardial blood flow and subendo-

cardial blood flow to the ischemic myocardial segments increased with nitroglycerin, and transmyocardial and subendocardial blood flow decreased with nitroprusside. An increase in collateral blood flow and decreased extravascular components of the coronary vascular bed resistance have been suggested as the likely mechanisms of enhanced perfusion to the ischemic myocardium with nitroglycerin. It has also been suggested that vasodilators, such as nitroprusside, with arteriolar dilating effects are more prone to cause diversion of blood flow from ischemic regions. This "coronary steal" might enhance existing myocardial ischemia and result in increased ST elevation or deterioration in regional mechanical function (36,109–111). Contrary to these reports, increased regional blood flow to ischemic myocardial segments (presumably collateral blood flow) associated with improved segmental myocardial function has been observed during nitroprusside therapy (34). Furthermore, improved regional metabolic function of ischemic myocardium was reported during nitroprusside infusion in experimental myocardial infarction (112,113). The effects of nitroprusside on the extent of myocardial injury were compared with those of phentolamine in dogs with experimental myocardial infarction. Nitroprusside decreased ischemic injury, but phentolamine enhanced it (114). In animal models, nitroprusside was shown to increase subendocardial blood flow provided that the initial left ventricular filling pressure was elevated; in the absence of heart failure, subendocardial blood flow decreased in the same experimental models (37).

Clinical results. In patients with recent myocardial infarction, conflicting results were obtained with these vasodilator agents. In some investigations, nitroprusside caused an increase in ST segment elevation and a higher level of serum creatine kinase (CK), suggesting an extension of myocardial injury (36,109,115). In other studies, however, a "reduction" in infarct size, as determined by a decrease in ST segment elevation, was noted (116). Amelioration of

Figure 3. Influence of nitroprusside infusion on left ventricular function in patients with acute myocardial infarction. Group I represents all patients with an initial left ventricular filling pressure of less than 15 mm Hg. These patients did not have pump failure. In Groups II and III, the patients had left ventricular failure with filling pressures greater than 15 mm Hg. Initial stroke work index was greater than 20 g-m/m² in Group II and less than 20 g-m/m² in Group III. In these two groups, nitroprusside infusion produced a reduction in filling pressure and an increase in stroke volume. In contrast, Group I patients with a low filling pressure tended to have a reduction in stroke volume and a reduction in filling pressure. (Reprinted from Chatterjee K, Parmley WW [30], with permission.)

Table 4. Hemodynamic Changes During Intravenous Vasodilator Therapy in Severe Pump Failure Complicating Acute Myocardial Infarction (n = 43) (30)

	Control	Vasodilator	p
Heart rate (beats/min)	100 ± 2.4	99 ± 2.7	NS
Arterial pressure (mm Hg)	83 ± 1.5	73 ± 1.7	<0.0005
Pulmonary artery pressure (mm Hg)	39 ± 1.2	28 ± 1.1	<0.0005
Right atrial pressure (mm Hg)	13 ± 0.8	9 ± 0.6	<0.0005
Left ventricular filling pressure (mm Hg)	31 ± 1.0	20 ± 0.8	<0.0005
Cardiac index (liters/min per m^2)	1.7 ± 0.05	2.2 ± 0.06	<0.0005
Stroke volume index (ml/m^2)	17.3 ± 0.2	22.8 ± 0.8	<0.0005
Stroke work index (g-m/m^2)	14 ± 0.7	19 ± 0.9	<0.005
Systemic vascular resistance (dynes cm^{-5})	2023 ± 112	1435 ± 65	<0.0005

All values are mean ± standard error of the mean.

postinfarction angina associated with a reduction in the magnitude of ST segment elevation was observed in some patients with acute myocardial infarction and persistent hypertension (117). In prospective randomized studies, early intervention (within 12 hours of the onset of symptoms) with sodium nitroprusside was associated with lower peak creatine kinase-MB isoenzyme levels compared with those in the control group (118,119). A similar reduction in infarct size calculated from CK and CK-MB activity curves was observed with intravenous nitroglycerin in a prospective randomized study (120). However, in a similar study, no significant decrease in the CK-MB activity was noted in the patients treated with nitroglycerin (121).

Effect on myocardial perfusion. It is apparent that both nitroprusside and nitroglycerin have the potential to decrease myocardial ischemia in appropriate subsets of patients with acute myocardial infarction. Global myocardial oxygen consumption tends to decrease and reduced relative ischemia of noninfarcted ischemic myocardial segments might contribute to improved left ventricular function. However, in most patients there is a thrombotic occlusion of the stenosed coronary artery supplying the infarcted territory. Increased perfusion to the peri-infarction zones, therefore, can occur only if there is an increase in collateral blood flow. Controversy exists regarding the effects of vasodilator agents on collateral flow, and to what extent vasodilators can increase collateral blood flow to infarcting myocardial segments in patients with acute myocardial infarction is unknown. Furthermore, it is not clear whether such an increase in collateral flow is sufficient to cause any significant decrease in the extent of myocardial injury. Decreased CK activity and a reduction of ST segment elevation, which are indicative of a reduction in myocardial injury, are not direct evidence for increased myocardial perfusion. Moreover, decreased serum levels may be related to slower washout (122), and the elevated ST segments may decrease spontaneously without enhanced perfusion to the infarcting myocardial segments. However, deep Q waves, the electrocardiographic evidence of myocardial necrosis, may develop rapidly despite increased regional myocardial perfusion, as occurs after coronary artery recanalization with thrombolytic therapy. Thus, enzymatic or electrocardiographic methods cannot conclusively show that vasodilator therapy decreases the extent of myocardial injury in patients with myocardial infarction.

Some reduction in arterial pressure usually occurs during vasodilator therapy. If there is a marked reduction in arterial pressure, particularly in patients with hypotension or normotension, myocardial ischemia in patients with severe multivessel coronary artery disease is likely to be enhanced. When the objective of treatment is to improve pump function, beneficial hemodynamic effects of vasodilator therapy occur in most patients without a significant reduction in arterial pressure.

Prognosis After Vasodilator Therapy in Patients With Acute Myocardial Infarction.

Nitroprusside. Recently the influence of nitroprusside therapy on the mortality of patients with acute myocardial infarction was evaluated in prospective randomized studies. One group (118) reported a significant reduction in mortality at 1 week, with a decreased incidence of clinical cardiogenic shock and left ventricular failure after nitroprusside therapy. Late mortality at weeks 2 through 4 was also less in the nitroprusside-treated group. However, in the Veterans Administration cooperative study (119), nitroprusside therapy was not associated with any change in early or late mortality. In patients with a transient elevation of left ventricular filling pressure who received nitroprusside within 9 hours of the onset of symptoms, the early mortality was greater than in those receiving placebo. However, in patients with a persistent elevation of left ventricular filling pressure, the hospital mortality was less in the nitroprusside-treated group. Hockings et al. (123) found no reduction in hospital mortality with nitroprusside therapy in patients with acute myocardial infarction and an elevated left ventricular filling pressure.

The reasons for the different results of these investigations are not obvious. In the study demonstrating a reduced

mortality (118), nitroprusside therapy was started relatively earlier (mean 5 hours) after the onset of symptoms than in the studies showing no benefit. This suggests that nitroprusside may be effective in lowering mortality when given early after the onset of infarction, but further confirmation of these results is needed before the routine use of nitroprusside can be recommended in patients with acute myocardial infarction. It should be noted that patients with severe pump failure and cardiogenic shock were excluded from randomization in these studies.

Intravenous nitroglycerin. In a few prospective randomized studies, intravenous nitroglycerin was given to assess its influence on the prognosis of patients with mild or no left ventricular failure (120–124). Either no change or a slight reduction in mortality was reported. In these studies, however, the number of patients randomized was too small to draw any definitive conclusion. Thus, no conclusive evidence is available to suggest that the routine use of either nitroprusside or nitroglycerin improves the prognosis of patients with relatively uncomplicated myocardial infarction.

Cardiogenic shock. No controlled study has been performed to assess the effects of vasodilator therapy on the prognosis of patients with severe pump failure or cardiogenic shock. In an uncontrolled study, a lower hospital mortality was reported with vasodilator therapy compared with the expected mortality with conventional therapy (103). Forty-three patients with severe pump failure were treated: 40 patients with nitroprusside and 3 patients with phentolamine. Severe pump failure was defined on the basis of initial hemodynamics, that is, an initial stroke work index of 20 g-m/m^2 or less and a left ventricular filling pressure greater than 15 mm Hg. Clinically, all patients had frank pulmonary edema. Seventeen patients had clinical features of cardiogenic shock. Initially, a beneficial hemodynamic response was observed in almost all patients: cardiac output increased, while pulmonary capillary wedge pressure decreased. Nineteen patients (44%) died in the hospital, 15 (34%) from uncontrolled pump failure. These findings suggest a significant improvement in the immediate prognosis of patients with severe pump failure complicating myocardial infarction. Although the efficacy of vasodilator therapy cannot be firmly established without a control study, it is supported by the improvement in prognosis compared with reported mortality figures of approximately 75% with conventional therapy (125,126). However, when the stroke work index was extremely low (less than 10 g-m/m^2) and the left ventricular filling pressure was elevated, the prognosis was extremely poor. The mortality rate in this subset— even with vasodilator therapy—was 82%. In these patients the use of intraaortic balloon counterpulsation combined with vasodilator and inotropic therapy was occasionally effective.

Late prognosis. Despite an apparent improvement in the initial prognosis of some patients with severe pump failure

treated with vasodilator therapy, the late prognosis remains unfavorable in the survivors (103). Sixty-two percent of the patients surviving initial hospitalization died within 1 to 25 months (average 9.2) after discharge. The projected 2 year survival rate in these patients was only 28%. Currently, it is uncertain whether any other therapy will significantly improve the grave prognosis of these patients. Nevertheless, more aggressive therapy like myocardial revascularization with or without aneurysmectomy should be considered in such patients.

Heart Failure Complicating Mechanical Defects

Clinical and hemodynamic improvement is observed during vasodilator therapy in patients whose heart failure is precipitated or exacerbated by mechanical defects such as mitral and aortic regurgitation and ventricular septal defect.

The severity of mitral regurgitation is related not only to the degree of anatomic derangement of the mitral valve apparatus but also to changes in the aortic impedance (127,128). An increase in left ventricular ejection impedance is associated with an increased regurgitant volume and decreased forward stroke volume and cardiac output. Vasodilator agents like sodium nitroprusside, hydralazine and prazosin increase forward stroke volume and cardiac output and decrease the regurgitant volume as the aortic impedance decreases (9,129,132). Decreased regurgitation is associated with a decreased magnitude of the regurgitant V wave, mean pulmonary capillary wedge and pulmonary artery pressures (Fig. 4).

In patients with aortic regurgitation, sodium nitroprusside and hydralazine decrease regurgitant volume and increase forward cardiac output because of a decreased left ventricular ejection impedance (133–135). Left ventricular end-diastolic volume and pressure decrease, and the ejection fraction increases. These beneficial hemodynamic effects are particularly seen in patients with an elevated left ventricular filling pressure.

The magnitude of the left to right shunt due to a ventricular septal defect is influenced by the size of the defect and by the ratio of the pulmonary and systemic vascular resistances (136). Increased systemic vascular resistance is associated with an increased shunt volume and a proportional decrease in systemic output. Vasodilators like sodium nitroprusside, hydralazine, phentolamine and phenoxybenzamine reduce the left to right shunt and increase the systemic output by decreasing systemic vascular resistance (137,138). Pulmonary venous pressure and pulmonary artery pressure also decrease.

Clinical application. Although vasodilator agents produce beneficial hemodynamic effects, their clinical application in the management of heart failure associated with mechanical defects has not been clearly defined. In patients with severe mitral regurgitation or ventricular septal rupture complicat-

Figure 4. Hemodynamic effects of sodium nitroprusside in a patient with severe acute mitral regurgitation. Left ventricular pressure and pulmonary capillary wedge pressure are illustrated in each panel. On the **left panel**, note the large regurgitant V waves (up to 70 mm Hg) in the pulmonary capillary wedge pressure trace. During the administration of sodium nitroprusside (**right panel**) pulmonary capillary wedge pressure and left ventricular end-diastolic pressure returned almost to the normal range and the regurgitant V waves essentially disappeared. This patient illustrates the beneficial effects of vasodilator therapy in patients with mitral regurgitation. (Reprinted from Chatterjee K, Parmley WW [30], with permission.)
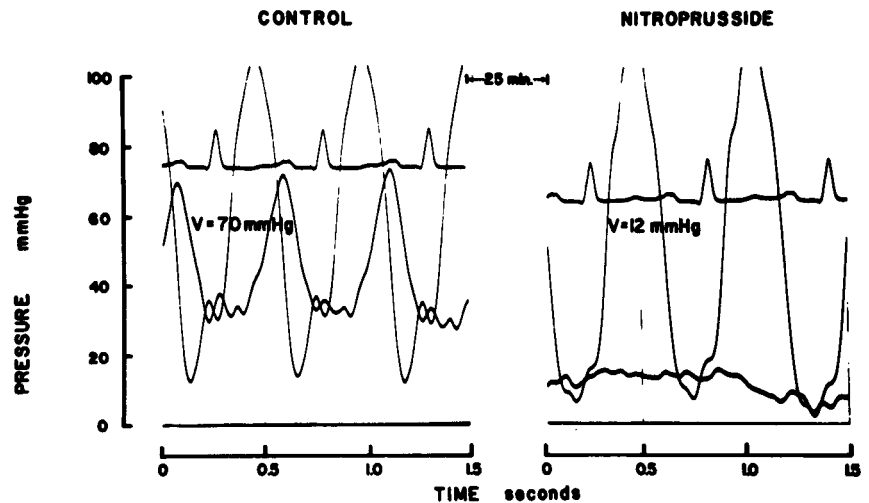
ing acute myocardial infarction, vasodilators such as nitroprusside or hydralazine can be used for immediate hemodynamic and clinical improvement. However, vasodilator therapy should be regarded as supportive rather than definitive treatment; surgical correction should be considered as soon as the patient's condition is stabilized.

In patients with bacterial endocarditis and acute mitral or aortic regurgitation with heart failure, there is a potential role for vasodilator therapy to tide the patient over the critical period until the infection is under control. Surgery should not be delayed if there is an inadequate hemodynamic response.

Long-term vasodilator therapy for mechanical defects is occasionally indicated when surgical correction either is contraindicated or needs to be deferred because of associated noncardiac complications. Although vasodilators may potentially delay progressive ventricular dysfunction by decreasing left ventricular volume, regurgitant fraction and left ventricular work, information is not available regarding the effects of long-term vasodilator therapy in patients with mitral or aortic regurgitation.
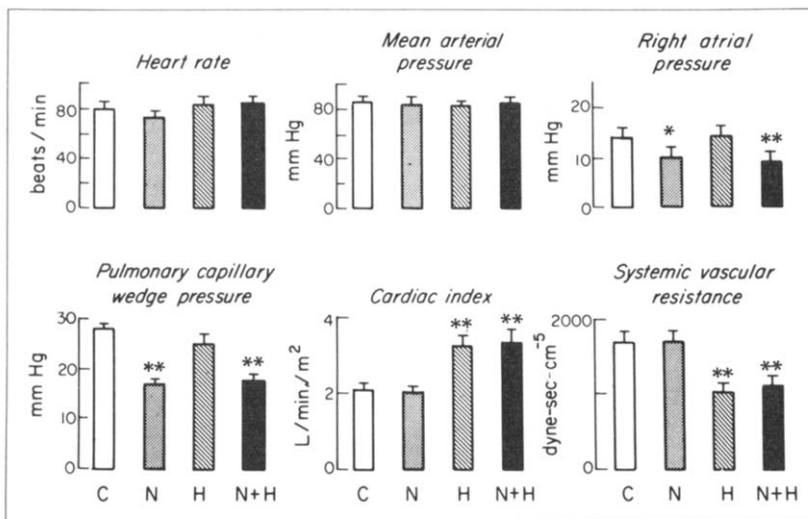
Chronic Congestive Heart Failure

Increased pulmonary venous pressure and low cardiac output are the two important hemodynamic correlates of the major symptoms of patients with chronic congestive heart failure. Dyspnea at rest or during physical activity is primarily a result of an elevated pulmonary venous pressure, and tiredness and fatigue are due to decreased cardiac output. The two major hemodynamic objectives of therapeutic interventions in these patients are to increase cardiac output and decrease pulmonary capillary wedge pressure. Intravenous vasodilators such as sodium nitroprusside or phentolamine decrease pulmonary venous pressure and increase cardiac output in patients with chronic heart failure (66,139). However, intravenous vasodilator therapy is applicable only for short-term treatment or to determine the magnitude of

the hemodynamic response prior to initiation of long-term vasodilator therapy.

Nitrates and hydralazine. Several vasodilators have been investigated in the long-term management of heart failure (140). The hemodynamic effects of nitroglycerin and other organic nitrates are similar and include a substantial reduction of right atrial and pulmonary capillary wedge pressures with little or no increase in cardiac output (140). In some studies, an increased cardiac output has been reported with nitrates (70,73), but the magnitude of increase appears to be substantially less than that expected with the use of a predominantly arteriolar dilator (141). With the use of arteriolar dilators, such as hydralazine and minoxidil, right atrial and pulmonary capillary wedge pressures either remain unchanged or decrease only slightly, although cardiac output increases considerably. It is apparent that the combination of an arteriolar dilator and a venodilator may provide hemodynamic advantages in the management of chronic heart failure. The hemodynamic effects of nonparenteral nitrates alone, hydralazine alone and combined nitrates and hydralazine therapy are illustrated in Figure 5 (141).

Prazosin. Prazosin and trimazosin are post-synaptic alpha-receptor blocking agents and produce beneficial hemodynamic effects in patients with chronic heart failure (86–92). Both agents cause a significant reduction in systemic and pulmonary venous pressures and a substantial increase in cardiac output. A modest decrease in mean arterial and pulmonary artery pressures, and in systemic and pulmonary vascular resistances, also occurs; heart rate remains unchanged (Table 5, Fig. 6). In many patients, profound hypotension may occur after the first dose of prazosin; therefore, prazosin therapy should be started cautiously.

Controversy exists regarding the continued efficacy of prazosin. In some studies, marked attenuation of the hemodynamic effects was observed within 48 to 72 hours (142). The increased cardiac output and decreased pulmonary capillary wedge pressure observed after the first dose were no

Figure 5. The hemodynamic effects of nitrates alone (N), hydralazine alone (H), and combined hydralazine and nitrates (N + H) in 12 patients with chronic congestive heart failure. The administration of nitrates resulted in a significant reduction in right atrial pressure and pulmonary capillary wedge pressure. Hydralazine produced a marked increase in cardiac index and a decrease in systemic vascular resistance. The combined therapy produced a decrease in both ventricular filling pressures along with an increase in cardiac index. Heart rate and arterial pressure were virtually unaffected. Statistically significant changes from control at the 0.01 and 0.001 levels are indicated by * and **, respectively. (Reprinted with permission from Chatterjee K, Massie B, Rubin S, et al. Long-term outpatient vasodilator therapy of congestive heart failure. Am J Med 1978;65:134–44.)

longer present after the fifth dose, despite a similar plasma concentration of the drug. Furthermore, the hemodynamic response was not regained by increasing the dose. In contrast, sustained beneficial hemodynamic and clinical effects of prazosin were reported in other investigations (143,144). Improved ejection fraction determined by radioisotope angiography was observed during continued prazosin therapy. The explanation for the different results in these studies is not obvious. Blunting of the hemodynamic effects of prazosin may occur only during subacute therapy (2 to 3 days), and the hemodynamic response is regained if therapy is continued for a longer period. It needs to be mentioned that, in most studies in which a sustained effect was observed, the dose of diuretic drugs was also increased. Increased plasma volume was observed in hypertensive patients who fail to respond to prazosin (145). Thus, decreased plasma volume with larger doses of diuretics might have contributed to the sustained hemodynamic effects of prazosin. Studies show that the addition of antialdosterone agents is helpful in maintaining the beneficial clinical response to prazosin (146). Increased plasma norepinephrine levels that occur in

some patients during long-term prazosin therapy might also be contributory to its attenuated hemodynamic effects (147).

Hydralazine. In a few studies, the hemodynamic effects of long-term hydralazine therapy were evaluated, and a sustained improvement in left ventricular function was seen (148,149). Withdrawal of hydralazine was associated with hemodynamic deterioration and decreased cardiac performance. Fluid retention and weight gain, however, occur in some patients during maintenance hydralazine therapy and additional diuretics are required to maintain the hemodynamic and clinical response. Furthermore, tolerance to hydralazine has occurred in some patients with chronic heart failure (150).

Captopril. Recently, there has been increasing interest in using the angiotensin antagonists for the treatment of chronic congestive heart failure. The hemodynamic effects of the oral angiotensin-converting enzyme inhibitor, captopril, were evaluated in a number of investigations (60,93,95). A significant reduction in systemic vascular resistance and an increase in cardiac output are consistently found. In many patients, heart rate decreases initially. Thus,

Table 5. Hemodynamic Effects (mean ± SEM) of Oral Prazosin Hydrochloride (3, 4 and 5 mg) in Patients With Chronic Congestive Heart Failure (102)

	HR (beats/min)	MAP (mm Hg)	MPAP (mm Hg)	LVFP (mm Hg)	RAP (mm Hg)	CI (liters/min per m^2)	SVI (ml/m^2)	SWI ($g\text{-}m/m^2$)	SVR (dynes s-cm^{-5})	PVR (dynes s-cm^{-5})
C	86 ± 7	87 ± 3	36 ± 2	24 ± 1	12 ± 1	2.0 ± 0.1	26 ± 2	22 ± 3	1776 ± 85	285 ± 40
P-3 mg	83 ± 4	80 ± 2	28 ± 2	19 ± 2	10 ± 2	2.5 ± 0.2	31 ± 2	26 ± 3	1373 ± 82	194 ± 41
P-4 mg	85 ± 5	84 ± 3	28 ± 2	19 ± 2	10 ± 1	2.4 ± 0.2	29 ± 2	25 ± 3	1631 ± 167	222 ± 31
P-5 mg	87 ± 7	79 ± 3	28 ± 3	19 ± 2	8 ± 1	2.5 ± 0.2	30 ± 3	25 ± 3	1410 ± 118	186 ± 29
C vs P	—	C>P*	C>P†	C>P§	C>P§	C<P‖	C<P§	—	C>PR¶	—
P-3 vs -4 vs -5 mg	—	—	—	—	—	—	—	—	—	—

*p < 0.05; †p < 0.025; §p < 0.001; ‖p < 0.005; ¶p < 0.001.
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.
Note that the hemodynamic responses to 3, 4 or 5 mg of prazosin were similar.
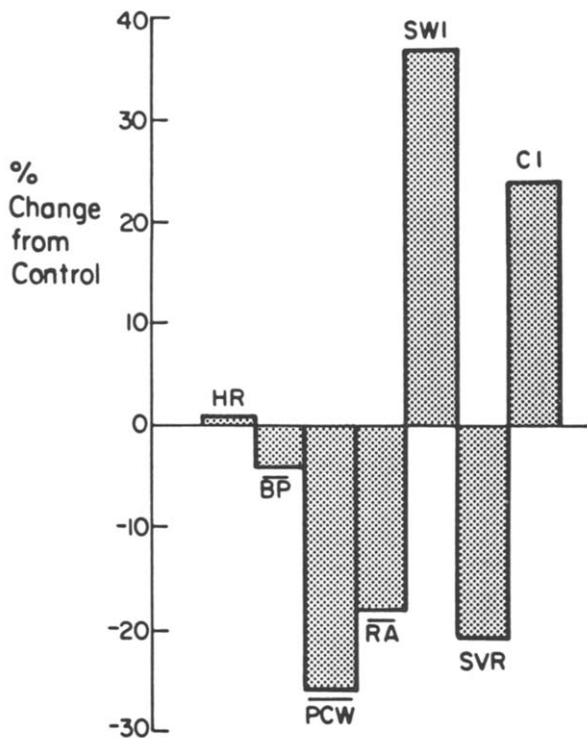
Figure 6. Percent change from control in heart rate (HR), mean arterial pressure (BP), pulmonary capillary wedge pressure (PCW), right atrial pressure (RA), stroke work index (SWI), cardiac index (CI) and systemic vascular resistance (SVR) after trimazosin therapy in patients with chronic congestive heart failure. There was a significant increase in stroke work index and cardiac index while pulmonary capillary wedge pressure, right atrial pressure and systemic vascular resistance decreased.

the average increase in stroke volume is usually greater than the increase in cardiac output. Despite a reduction in arterial pressure which occurs in almost all patients, left ventricular stroke work index increases. In most patients, captopril causes a marked decrease in pulmonary capillary wedge pressure and right atrial and pulmonary artery pressures, with a concomitant decline in pulmonary vascular resistance. The hemodynamic effects, after a single oral dose (25 mg), usually last for 6 to 8 hours (Fig. 7).

The hemodynamic effects of 25, 50 and 100 mg doses of captopril were evaluated in the same patients with chronic heart failure, and the magnitude of the hemodynamic response was similar (93). Thus, the left ventricular filling pressure decreased by an average of 46% after the 25 mg dose, and the decrease in filling pressure after 50 and 100 mg was similar. The average reduction in systemic vascular resistance (−41%), mean arterial pressure (−23%) and right atrial pressure (−27%) after the 25 mg dose was almost identical to that after the 50 to 100 mg dose. Thus, it seems that doses larger than 25 mg of captopril are usually not required for the treatment of congestive heart failure.

Maintenance captopril therapy appears to provide sustained improvement in left ventricular function in patients with chronic heart failure. In one study (Table 6) (93) after

the initiation of therapy, mean arterial pressure decreased by 21%, and at 8 weeks the decrease in arterial pressure was of a similar magnitude. Initially, captopril increased cardiac output by 21%, but at 8 weeks a larger increase (41%) was noted. The initial elevated stroke volume was maintained during long-term therapy. Mean pulmonary artery, right atrial and pulmonary capillary wedge pressures remained lower than control pressures. Similarly, a persistent decrease in systemic vascular resistance was also observed.

Fluid retention is extremely uncommon during maintenance captopril therapy, presumably related to the decreased aldosterone level secondary to reduced angiotensin II. In many patients, reduction of the diuretic dosage is required to prevent marked hypotension. During captopril therapy, the serum potassium level tends to increase, and the need for potassium supplementation decreases. Lack of fluid retention and reduction of the plasma aldosterone level appear to be the major advantages of captopril over other vasodilators in the long-term management of patients with chronic heart failure. The major disadvantage is marked hypotension which occurs in approximately 20% of patients, particularly after the first dose. Preliminary studies suggest that a dose titration with the use of much smaller doses (6.25 mg, for example) may help avoid sudden marked hypotension (151).

Figure 7. Changes in cardiac output (CO) and pulmonary capillary wedge pressure (PCW) after a single 25 mg dose of captopril in patients with chronic congestive failure. Within a half hour, cardiac output increased and pulmonary capillary wedge pressure fell and these hemodynamic changes lasted for 6 to 8 hours. (Reprinted from Ader R, Chatterjee K, Ports T, et al. [93], by permission of the American Heart Association, Inc.)
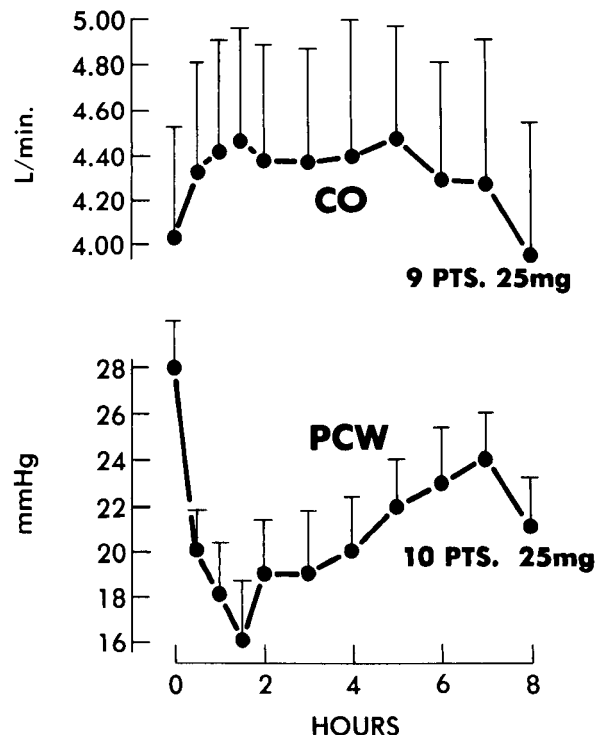
Table 6. Hemodynamic Effects at the Initiation of and After 8 Weeks of Maintenance Captopril Therapy in Seven Patients With Chronic Heart Failure (93)

| | Control | Immediate Response | 8 Weeks | p Value | |
				Control vs immediate response	Control vs 8 weeks
HR	78 ± 16	67 ± 15	73 ± 17	<0.05	<0.05
MAP	89 ± 16	70 ± 15	68 ± 9	<0.05	<0.05
PCW	29 ± 9	16 ± 4	13 ± 7	<0.05	<0.05
PAP	40 ± 10	28 ± 7	27 ± 14	<0.05	<0.05
RAP	12 ± 3	9 ± 3	5 ± 2	<0.05	<0.05
CO	3.54 ± 66	4.38 ± 1.30	5.09 ± 1.54	<0.05	<0.05
SV	46 ± 20	68 ± 22	72 ± 26	<0.05	<0.05
SWI	28 ± 12	36 ± 8	35 ± 7	NS	NS
SVR	1933 ± 753	1175 ± 384	1084 ± 327	<0.05	<0.05

CO = cardiac output (liters/min per m^2): HR = heart rate (beats/min): MAP = mean arterial pressure (mm Hg): PAP = mean pulmonary artery pressure (mm Hg): PCW = pulmonary capillary wedge pressure (mm Hg): RAP = right atrial pressure (mm Hg): SV = stroke volume (ml): SWI = stroke work index (g-m/m^2).

Another oral angiotensin-converting enzyme inhibitor, MK-421, is now under investigation; the preliminary results suggest that its hemodynamic effects are similar to those of captopril and it may also be useful in the long-term management of chronic congestive heart failure (152).

Effects on left ventricular function. The influence of vasodilator therapy on left ventricular function of patients with chronic heart failure during exercise has been evaluated. Cardiac output and stroke volume remain elevated during exercise after hydralazine therapy, although pulmonary capillary wedge pressure tends to increase by a similar magnitude with or without the addition of hydralazine to conventional therapy (153). Isosorbide dinitrate also improves cardiac performance during exercise; cardiac output increases and the exercise-induced elevation of pulmonary capillary wedge pressure is less marked. Similarly, with the addition of prazosin or trimazosin to conventional therapy, the increase in cardiac output during exercise is considerably greater than with conventional therapy (154). Although pulmonary capillary wedge pressure increases, the magnitude of increase is less with the addition of these vasodilators to conventional therapy. An increase in left ventricular ejection fraction during exercise determined by gated blood pool scintigraphy has been observed after prazosin therapy (144). Captopril produces beneficial hemodynamic effects during exercise. Cardiac output and stroke volume remain elevated and the left ventricular filling pressure is lower, suggesting improved left ventricular function during exercise (155). The radionuclide ejection fraction increases after captopril both at rest and during exercise (155). Thus, the cardiac performance of patients with chronic heart failure tends to improve after vasodilator therapy. Exercise tolerance and oxygen consumption also increase but usually not after short-term therapy. Long-term nitrate therapy improves exercise tolerance and oxygen consumption. Similarly, peak symptom-limited exercise capacity usually increases after long-term hydralazine, prazosin, trimazosin or captopril therapy (93,144,156,157).

Regional Hemodynamic Effects

Limb flow. A reduced cardiac output is accompanied by changes in the perfusion of regional vascular beds. Decreased limb and hepatic blood flow and a marked reduction of renal plasma flow occur in patients with congestive heart failure (158,159). Although cardiac output increases with most vasodilator drugs, little information is available regarding the distribution of the increased cardiac output. Vasodilators with arteriolar-dilating effects such as hydralazine and prazosin decrease limb vascular resistance and augment limb blood flow at rest (160). It is unknown whether a similar increase of flow occurs to the exercising limbs. However, despite an increase in cardiac output, it seems that the nutritional flow to the exercising skeletal muscles does not increase after the short-term administration of either hydralazine or prazosin (161). The peak serum lactate concentrations during exercise (at the same work load) were similar before and after the addition of these vasodilators, and the time constant for the lactate disappearance following cessation of exercise did not change after acute prazosin or hydralazine therapy. Similarly, during maximal and submaximal exercise, the increase in arterial lactate and catecholamine release were similar before and after the acute administration of nitroglycerin (162). These findings suggest that short-term vasodilator therapy does not increase nutritional flow to exercising muscles. It is unknown whether increased limb flow during exercise occurs after chronic therapy.

Hepatic flow. Hepatic vascular resistance and hepatic blood flow do not appear to change following the short-term administration of hydralazine, despite a considerable increase in cardiac output (160,163). Prazosin, on the other hand, decreases hepatic vascular resistance and increases

hepatic blood flow at smaller doses. With larger doses, however, these effects are markedly attenuated (160,163). Nitrates do not change hepatic blood flow in patients with chronic heart failure. Hepatic blood flow tends to decrease after captopril therapy, although cardiac output increases significantly (164,168).

Renal flow. The effects of vasodilator drugs on renal hemodynamics and function in the presence of chronic heart failure have been the subject of several investigations. An increased cardiac output with hydralazine is accompanied by increased renal blood flow and decreased renal-vascular resistance (160,163,165); these changes appear to be dose-related. Glomerular filtration rate remains unchanged but filtration fraction decreases. Excretion of sodium and potassium is also enhanced in these patients after hydralazine therapy.

Captopril tends to produce a marked increase in renal blood flow along with an increased ratio of renal to systemic blood flow in congestive heart failure. As with hydralazine, the glomerular filtration rate does not change, but the filtration fraction decreases. Urinary sodium excretion increases markedly along with decreased plasma aldosterone and norepinephrine concentrations. It has been suggested that converting-enzyme inhibition reverses renal vasoconstriction in congestive heart failure and redistributes regional blood flow. The increased urinary sodium excretion may be related to improved renal plasma flow and a decreased plasma aldosterone concentration. Decreased circulating catecholamines and a reduced filtration fraction might also be contributory. If marked hypotension occurs with captopril, renal function may not improve or may even deteriorate despite increased cardiac output and improved left ventricular function (166,167). Prazosin does not appear to affect renal blood flow or renal vascular resistance acutely (163). Similarly, isosorbide dinitrate does not alter renal hemodynamics and renal function in patients with chronic congestive heart failure (160). It appears, therefore, that hydralazine and captopril improve renal blood flow and renal function, which might be an advantage in the treatment of patients with chronic heart failure, associated with decreased renal function.

Coronary blood flow. In many patients with chronic heart failure, obstructive coronary artery disease coexists. Therefore, it is relevant to evaluate the changes in coronary hemodynamics and myocardial metabolic function produced by vasodilator drugs. In general, nitrates decrease coronary blood flow and myocardial oxygen consumption. The decrease in myocardial oxygen consumption appears to be due to a decrease in myocardial oxygen demand (101).

The relative changes in coronary blood flow, myocardial oxygen consumption and rate-pressure product following captopril, prazosin, and hydralazine in patients with chronic ischemic heart failure are illustrated in Figures 8 and 9 (100). With captopril, the rate-pressure product (heart rate times systolic blood pressure), a commonly used index of myo-

cardial oxygen demand, decreased in all patients; there was a concomitant reduction in coronary blood flow and myocardial oxygen consumption. Angiotensin II causes a sustained vasoconstriction of the large conductance vessels but a transient vasoconstriction of the smaller resistance vessels. An attenuation of the effects of angiotensin with captopril and the possible decrease in angiotensin-induced coronary vasoconstriction, therefore, might be expected to preserve autoregulation. However, it seems that the decrease in coronary blood flow with captopril in patients with congestive heart failure is largely produced by a reduction of the hemodynamic determinants of myocardial oxygen demand.

With hydralazine, there was also a general correlation between changes in coronary blood flow, myocardial oxygen consumption and changes in myocardial oxygen demand. In patients with cardiomyopathy without obstructive coronary artery disease, hydralazine decreased coronary vascular resistance and increased coronary blood flow. The increase in coronary blood flow in these patients occurred without any significant change in the rate-pressure product; also, coronary sinus oxygen content was higher and myocardial oxygen extraction was lower. These findings suggest that, in patients with heart failure and normal coronary arteries, coronary blood flow might increase from primary coronary vasodilation (169). In patients with fixed occlusive coronary artery disease, however, changes in coronary blood flow appear to be related to the changes in the determinants of myocardial oxygen demand. Changes in coronary blood flow and myocardial oxygen consumption parallel changes in the rate-pressure product (100).

With prazosin, no correlation has been found between changes in coronary blood flow and myocardial oxygen consumption and changes in the determinants of oxygen demand. Despite a significant reduction in arterial pressure, the rate-pressure product and left ventricular filling pressure, coronary blood flow increased in many patients. In others, coronary blood flow decreased together with a decreased rate-pressure product. The mechanism of this divergent response to prazosin remains unclear. Prazosin is a potent post-synaptic alpha-adrenergic blocking agent. Therefore, a primary decrease in coronary vascular resistance might cause an increase in coronary blood flow despite decreased myocardial oxygen demand. It is apparent that the effects of these vasodilator agents on coronary hemodynamics can be different although the systemic hemodynamic effects are similar. Only captopril, however, consistently improved left ventricular function at a decreased metabolic cost (Fig. 9).

Influence of Vasodilator Therapy on the Prognosis of Patients With Chronic Refractory Heart Failure

Mortality. The long-term prognosis of patients with severe chronic congestive heart failure is extremely poor. In patients with ischemic or nonischemic cardiomyopathy, the mortality rates with conventional therapy ranged from 39
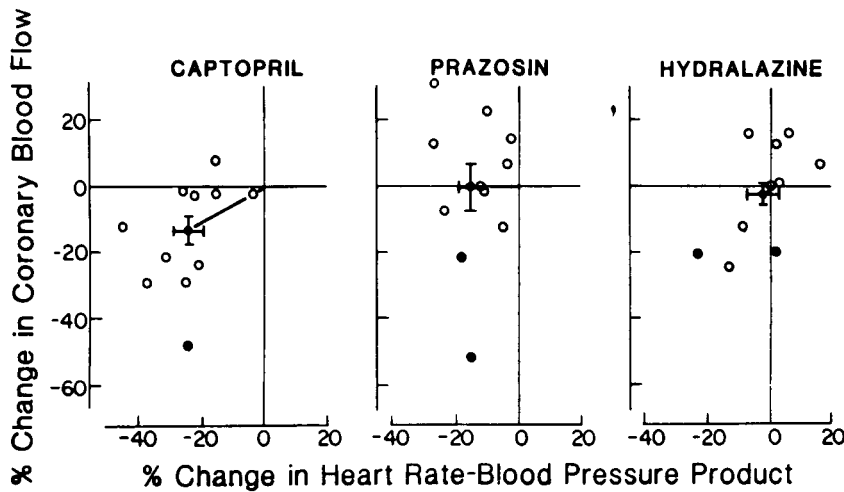
Figure 8. Captopril decreased the coronary blood flow in all but one patient and decreased the rate-pressure product in all 11 patients. Prazosin had no predictable effect on the coronary blood flow, but decreased the rate-pressure product in all 11 patients. Hydralazine tended to change the coronary blood flow in the same way it changed the rate-pressure product (r = 0.6, p = 0.05). With all three drugs, the patients that decreased their coronary blood flow produced the most lactate (•). Individual responses at the peak effect of each drug and the mean ± SEM are plotted for each drug. (Reprinted from Rouleau J-L, Chatterjee K, Benge W, Parmley WW, Hiramatsu B [100], by permission of the American Heart Association, Inc.)

to 80% in the initial 1 to 2 years' follow-up (170–175). No adequately controlled study has been performed to evaluate the influence of vasodilator therapy on the long-term prognosis of patients with chronic heart failure. Uncontrolled studies, however, suggest that the overall prognosis remains unfavorable, despite vasodilator therapy. An 80% mortality rate at 20 months has been reported in patients with severe chronic heart failure (most patients were in New York Heart Association class IV), despite combined prazosin and nitrate therapy (146). In a similar uncontrolled study, no significant improvement in the overall mortality was observed in 56 patients treated with hydralazine and nitrates (176). The mortality rates in this group at 6, 12 and 18 months were 22, 35 and 63%, respectively. Sudden death occurred in more than 50% of patients who died of cardiac causes. Thus, hydralazine and nitrate therapy did not improve the survival rate in these patients compared with that expected with

conventional therapy. Certain subsets of patients, however, appeared to have a better prognosis than others. The lack of progressive heart failure, as judged clinically, was associated with a better prognosis, but hemodynamic measurements were more helpful in assessing prognosis. The severity of depression of cardiac function based on hemodynamic indexes before the institution of hydralazine-nitrate therapy was related to the long-term prognosis. Thus, the patients with a pulmonary capillary wedge pressure of 30 mm Hg or more had a significantly greater mortality than that of patients with lower initial pulmonary capillary wedge pressures. Patients with an initial stroke work index of 30 g-m/m^2 or less also had a higher mortality rate. The combination of these two hemodynamic variables was better correlated with the subsequent outcome. Thus, the survival rate in patients with a stroke work index greater than 30 g-m/m^2 and a pulmonary capillary wedge pressure below 30
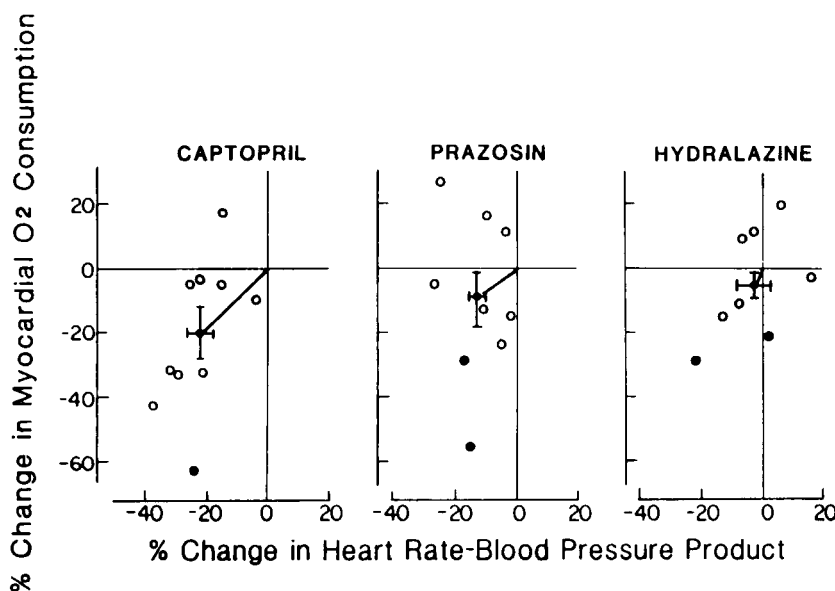
Figure 9. With captopril, the decrease in myocardial oxygen consumption paralleled the decrease in rate-pressure product (r = 0.6, p = 0.05). Prazosin had no predictable effect on the myocardial oxygen consumption, despite decreasing the rate-pressure product in these nine patients. Hydralazine tended to change the myocardial oxygen consumption in the same way as it changed the rate-pressure product (r = 0.06, p = 0.1). With all three drugs, the patients that decreased their coronary blood flow the most produced lactate (•). Individual responses at the peak effect of each drug and the mean ± SEM are plotted for each drug. (Reprinted from Rouleau J-L, Chatterjee K, Benge W, Parmley WW, Hiramatsu B [100], by permission of the American Heart Association, Inc.)

mm Hg was 69% compared with only 31% in patients with both a stroke work index of less than 30 g-m/m^2 and a pulmonary capillary wedge pressure greater than 30 mm Hg.

Hemodynamic improvement. The magnitude of hemodynamic improvement during the initiation of vasodilator therapy was also helpful in assessing long-term prognosis. In the subset with a stroke work index greater than 30 g-m/m^2 and a pulmonary capillary wedge pressure of less than 20 mm Hg after initiation of therapy, 75% of patients survived. In contrast, only 14% of patients with a stroke work index of less than 30 g-m/m^2 and a pulmonary capillary wedge pressure higher than 20 mm Hg after vasodilator therapy survived.

Although certain subsets of patients with chronic congestive heart failure may have a better survival rate (176,177), further long-term controlled studies are needed to assess the prognosis with vasodilator therapy. Furthermore, results with one vasodilator agent cannot be extrapolated when a different agent is used, because considerable differences exist among agents in their systemic and regional hemodynamic effects.

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