Editorial:

How Much Can We Expect From Vasodilator Therapy in Congestive Heart Failure?

ROBERT ZELIS, M.D., STEPHEN F. FLAIM, PH.D., RALPH M. MOSKOWITZ, M.D.,
AND STEPHEN H. NELLS, PH.D.

The “Gee, Whiz” Phase of vasodilator therapy has passed. We know that a wide variety of vasodilator compounds produce some combination of reduction in left ventricular filling pressure and enhancement of systemic cardiac output in patients with refractory congestive heart failure who are symptomatic at rest. Now, we are asking more probing questions. Some answers are available; others will require more sophisticated or imaginative investigative approaches. The symposium recently published in the American Journal of Medicine1 is an excellent presentation of the evolution of research in vasodilator therapy. A second review2 presents a more cautious optimism and critically examines the limitations of the more common drugs currently used. This editorial will explore some of the questions that characterize the directions of the current phase of vasodilator research.

Which Patients Respond Best to Vasodilator Therapy?

Vasodilators have been classified as venodilators (e.g., nitrates), which reduce left ventricular filling pressure and relieve pulmonary congestion; arteriolar dilators (e.g., hydralazine), which enhance cardiac output; and balanced vasodilators (e.g., nitroprusside, prazosin), which dilate both resistance and capacitance vessels. It has been suggested that a hemodynamic profile should be obtained before beginning vasodilator therapy in order to match the patient with the proper drug.3,4 It has been reasoned that a correct hemodynamic classification will prevent adverse results such as the fall in cardiac output that occurs when arteriolar dilators or venodilators are used in patients with normal left ventricular filling pressures.

Vasodilator therapy could be more effective if it were related to a better classification of heart failure patients based on an understanding of which compensatory mechanisms are used to maintain circulatory homeostasis. Therefore, it is important to consider why and how systemic vascular resistance is increased in heart failure before deciding on the best approach to lower it. We probably understand why vascular resistance is increased. It is an effort to maintain systemic arterial pressure to perfuse vital organs (brain and heart) at the expense of less essential circulations (skin and kidney). However, it is too simplistic to explain the mechanism of the vasocostriction as an increased “sympathetic tone.” Different forms of heart failure may have one or more of the following: 1) increased neurogenic vasconstrictor tone (i.e., neuronally released norepinephrine); 2) increased humorally delivered vasoconstrictors (e.g., norepinephrine or angiotensin); and 3) altered vascular smooth muscle reactivity (e.g., enhanced responsiveness to norepinephrine, reduced responsiveness to metabolic vasodilator stimuli).5-11

Heart failure of different etiologies may use different compensatory mechanisms. For example, in animal models,4 some types of congestive heart failure (e.g., aortic stenosis with reduced stimulation of carotid arterial baroreceptors) are more likely to result in enhanced neurogenic constrictor tone than others (e.g., pulmonic stenosis, where there is an enhanced vascular constrictor response to norepinephrine). Furthermore, it has been suggested that another mechanism for activation of the sympathetic nervous system in congestive heart failure is hypoperfusion of skeletal muscle; the resultant hypoxia stimulates somatic afferent receptors in muscle which then leads to a reflexly mediated sympathetic efferent response and systemic arteriolar constriction.6 7 Recent reports have shown that enhanced circulating levels of angiotensin may play an important but variable role in the increased systemic arteriolar resistance noted in some patients with heart failure.6-10

How might these observations be related to the choice of a vasodilator? In a preliminary report, Vrobel et al. evaluated the hemodynamic responses to teprotide (SQ 20,881) and nitroprusside.10 Teprotide, an angiotensin-converting enzyme inhibitor, was most effective in patients with the highest elevation in plasma renin activity. The dose requirements were inversely related to the level of plasma renin activity. However, patients with high plasma renin activity were much less sensitive to nitroprusside. In both groups of patients, hemodynamic improvement was accompanied by a drop in circulating catecholamine levels. This might be explained if both nitroprusside and teprotide result in enhanced skeletal muscle perfusion.

We are just beginning to understand who will respond to which vasodilator, based on the definition of the pathophysiologic circulatory derangements of congestive heart failure of different etiologies. Whether

From the Division of Cardiology and the Department of Physiology, The Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, Pennsylvania.

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Address for reprints: Robert Zelis, M.D., Division of Cardiology, The Hershey Medical Center, Hershey, Pennsylvania 17033.

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this understanding will significantly affect our use of vasodilator therapy is unknown. However, simple principles can guide outpatient therapy because our present choice of chronically effective drugs is limited.

**Is Chronic Vasodilator Therapy Associated with Drug Tolerance?**

Of the three most commonly used nonparenteral preparations (nitrates, hydralazine and prazosin), nitrates are the most likely to become ineffective due to tolerance during chronic therapy. Tolerance was described nearly a century ago, when tincture of nitroglycerin was used to treat hypertension secondary to Bright’s disease.12 Anecdotal reports of tolerance and perhaps even nitrate dependence among munitions handlers and dynamite factory workers are well known,13 and the physiological basis has been carefully described (disulfide bridges form in vascular smooth muscle at the nitrate receptor site, rendering the receptor temporarily unresponsive).14 Because venodilation (and preload reduction) is supposed to be the predominant mechanism by which nitrates relieve pulmonary congestion in heart failure, it was distressing to note, when these vessels were studied by means of limb plethysmography, that chronic nitrate administration blunted the venodilator response, but not the arteriolar dilator response, to acutely administered nitroglycerin.15 Despite decades of acceptance of the reality of nitrate tolerance, and despite a firm scientific basis, many experienced clinicians suspect that tolerance might be a highly overrated phenomenon. How many patients with angina pectoris taking significant quantities of long-acting and sustained-release nitrates failed to have their anginal episodes respond to sublingual nitroglycerin? It was argued, however, that heart failure patients are being treated with much larger doses of nitrates. A recent preliminary report suggests that 3 months of chronic therapy of heart failure patients with isosorbide dinitrate did not result in significant tolerance to the hemodynamic effects of the drug when administered acutely.16 Therefore, the fear of clinically meaningful nitrate tolerance appears to be unfounded. This seems to be true for hydralazine as well, because the hemodynamic responses to this drug were also unchanged after therapy lasting, on average, 8 months.17

Such is not the case with prazosin, however. Although some observers have reported a sustained clinical improvement with chronic prazosin,17 and others have documented a sustained improvement in exercise tolerance during 6 weeks of therapy,18 at least two laboratories have presented objective hemodynamic data to suggest that tolerance to prazosin is significant and develops rapidly.19,20 A recent report noted that tolerance is only partial. The initial improvement in cardiac output after administration of prazosin was not sustained, and could not be restored by doubling the dose. The reduction in left ventricular filling pressure was maintained somewhat better, especially when higher doses were used.20 In summary, the “first-dose effect” noted when prazosin is used to treat hypertension is very apparent when the drug is used to treat heart failure. Tolerance to chronically administered nitrates and hydralazine, however, does not appear to be a problem.

**How Do Vasodilators Alter the Distribution of the Cardiac Output?**

Drugs can affect the fractional distribution of cardiac output by their direct and sometimes different effects on vascular smooth muscle of the various regional circulations, and they can have different actions on various reflex arc. The triggering of afferent nerves from one receptor system can lead to a differential and sometimes species-specific nonuniform alteration in sympathetic adrenergic nerve traffic.21 Understanding these interactions in congestive heart failure is more complex because the basal level of vasomotor tone is altered by neural, humoral and intrinsic factors.5–11,22,23 In heart failure, vasoconstriction is most pronounced in the cutaneous, renal and splanchnic circulations (perhaps excluding hepatic arterial flow, which is preserved).22,23 Although most drugs have not been evaluated in this context, nitroglycerin has. In normal, conscious dogs and rats, intravenous nitroglycerin administration results in a reflex arteriolar constriction in heavily innervated circulations. This effect is probably caused by baroreceptor stimulation24,25 secondary to peripheral venous pooling. In the rat with heart failure, this is less pronounced, especially at high nitrate infusion levels, where a direct arteriolar dilation ensues.25

Although other drugs have not been similarly studied, hydralazine can probably improve renal blood flow significantly,26 making diuretic therapy more effective. In fact, improved diuresis may cause the prolonged and increasing improvement in congestive heart failure with chronic hydralazine therapy.2 This effect may ultimately allow nitrate therapy to be discontinued in patients initially treated with hydralazine-nitrate combinations. The first-dose phenomenon with prazosin therapy might be used to advantage by preparing the slowly decompensating patient for diuretic therapy using one or a few acute doses of prazosin. The concept of preparing a patient for diuretic therapy is not new. Before the loop diuretics were introduced, patients were commonly pretreated with carbonic anhydrase inhibitors, ammonium chloride, and sometimes a methylxanthine in order to increase the effectiveness of mercurial diuretics.

One deleterious regional circulatory abnormality has been noted with the use of nitroprusside and nitroglycerin. When these drugs are given to patients with heart failure, there appears to be a small but significant reduction in systemic arterial oxygen content related to an increased physiologic shunt flow through the pulmonary circulation.28

**Do Vasodilators Affect Exercise Capacity?**

Franciosa and Cohn address this important question in this issue.27 Vasodilators might improve exercise capacity in heart failure by a variety of mechanisms. If there is a sustained reduction in left
ventricular filling pressure, exercise duration might be prolonged because of reduced effort dyspnea. If cardiac output and its distribution to skeletal muscle were improved, fatigue might occur at a higher level of exercise. Franciosa and Cohn found that maximum exercise capacity was not improved by an oral hydralazine-isosorbide dinitrate combination; however, hemodynamics at submaximal work loads were slightly improved.

This should not be taken as an indictment of vasodilator therapy. A third response was also possible: Vasodilator therapy might have been harmful. The circulatory compensatory mechanisms in heart failure appear to be at least partially protective. The exaggerated sympathoadrenal response to exercise (and attendant vasoconstriction in skin, renal and splanchic circulations) and the reduced capacity of skeletal muscle resistance vessels to respond to metabolic vasodilator stimuli may be considered protective in that systemic arterial pressure is preserved despite a diminished cardiac output response to exercise. If vasodilator therapy critically reduced vascular resistance, and cardiac output did not increase, exercise syncope might result. Such a situation may occur with exercise after extensive diuresis where the skeletal muscle resistance vessels are no longer sodium-loaded and "stiff." The improvement of the vasodilator response to exercise coupled with a contracted plasma volume are two mechanisms by which exercise syncope after diuresis can be explained.

Similarly, if vasodilator therapy interrupted normal reflex arteriolar constriction upon assuming an upright position, or if there were excessive peripheral venous pooling, orthostatic symptoms might be experienced; neither was observed in the patients studied by Franciosa and Cohn. Their seemingly negative result is, in fact, encouraging. The protective increase in systemic vascular resistance seen in heart failure may be "overprotective," and thus harmful by increasing the impedance to left ventricular ejection. Most heart failure patients will respond to reduced arteriolar resistance with increased cardiac output, thereby preserving systemic arterial pressure even during exercise.

The hydralazine-nitrate combination Franciosa and Cohn have suggested did not interfere with mild exercise (perhaps improved it slightly), nor did it interfere with reflex adjustments to changing body position. However, it did provide sustained relief of symptoms at rest, the situation in which most patients find themselves throughout the day. A number of investigators have found a variety of favorable but minimal responses to exercise with other vasodilators.

When considering the effects of vasodilator therapy on blood flow to skeletal muscles during exercise, it is important to recognize that many factors regulate the intramuscular distribution of flow. Normal autoregulatory phenomena effectively distribute flow selectively to exercising fibers because metabolites accumulating in their vicinity open local precapillary sphincters. A "little bit" of norepinephrine may, in fact, be helpful and aid in this redistribution process. Presumably, its constrictor effect is most felt by those vessels perfusing inactive skeletal muscle fibers. Unfortunately, norepinephrine in higher concentrations is deleterious, and reduces nutritional flow to exercising skeletal muscle, presumably by severely restricting flow at the arteriolar level. Because flow is so reduced, local autoregulatory mechanisms appear to be ineffective. The increased vascular stiffness noted in heart failure also appears to work at the large vessel level. In effect, vascular stiffness can be considered analogous to partial large vessel occlusion, which is a much more potent factor than high-dose norepinephrine in limiting nutritional blood flow to skeletal muscle during exercise.

Do vasodilator drugs affect skeletal muscle nutritional flow? This question is just being asked and virtually no data are available to answer it. A preliminary report would suggest that nitroglycerin ointment does not improve nutritional flow to skeletal muscle during exercise, because lactate production and catecholamine liberation (presumably secondary to skeletal muscle hypoxia) were not improved significantly. Whether other vasodilators will behave similarly in isolated exercising muscle preparations remains to be determined.

Even though some clinical studies have shown that vasodilators can improve the cardiac output response to exercise, systemic oxygen consumption generally does not rise significantly. This suggests that skeletal muscle nutritional blood flow is not enhanced. What happens to the increased cardiac output? We have preliminary evidence in the exercising rat with heart failure that intravenous nitroglycerin enhances blood flow to the renal, splanchic and cutaneous circulations but not to skeletal muscle. Whether this increased flow enhances visceral function or reflects physiologic shunt flow has not been determined.

A Vein Is a Vein—Or Is It?

We have readily accepted the classification that nitrates are predominantly venodilators, hydralazine is predominantly an arteriolar dilator, and prazosin a mixed vasodilator. How has this classification system developed? There are basically two lines of evidence. First, this classification system is consistent with the observed changes in vascular resistance and venous tone in extremities measured by limb plethysmography. Second, we have assumed that vasodilators will preferentially reduce ventricular filling pressure and have a lesser effect on systemic vascular resistance; with arteriolar dilators, the converse is true.

In extrapolating the results of limb plethysmography studies to the circulation as a whole, one has to recognize that human extremities contain two major arterial circulations (skin and skeletal muscle) as well as two major categories of veins. The veins draining the cutaneous circulations are highly innervated and subserve the primary function of body temperature regulation. Veins draining skeletal muscle appear to lack the capacity to respond to venoconstrictor stimuli and contract poorly to humoral vasoactive sub-
The predominant mechanism by which blood is returned to the heart from veins that drain skeletal muscle is by skeletal muscle contraction and the presence of competent venous valves. The third major venous bed drains the splanchnic circulation. Although this has been extensively studied in dogs, we know very little about the regulation of splanchnic blood volume in humans. Because domestic dogs (along with raccoons and fur seals) have throttling veins which act as effective hepatic venous sphincters and contribute significantly to venous resistance, studies on the splanchnic venous system in that species cannot be readily extrapolated to humans. To confound the situation further, two additional factors must be considered. First, veins can empty and fill passively depending on body position and arterial inflow. Thus, an arteriolar dilator might actually lead to passive “venous pooling,” even though it may have little effect on venous smooth muscle tone. Second, animal studies have suggested that the venous system is best described in terms of its two major components—the small veins, which are the true capacitance vessels, and the large veins, which can be considered as venous resistance vessels. One can calculate these parameters in dogs for two venous circulations which have two time constants, the splanchnic and extrasplanchnic vessels. In dogs, one can produce venous pooling by selectively constricting the venous resistance vessels of one of these circuits (e.g., morphine increases splanchnic venous resistance) even though the tone of the venous capacitance vessels may not change. We do not know if the venous system of humans can be similarly characterized.

When considering the changes in ventricular filling pressure and systemic vascular resistance as indices of venodilation or arteriolar dilation, one ignores the concept that a drug effect in one portion of the circulation might induce reflex changes in another portion of the circulation and thereby mask a direct effect. An interesting study was recently reported that illustrates this phenomenon. Lower body negative pressure was used to reduce ventricular preload by pooling blood in the lower extremities. With a reduction in cardiac dimensions, a significant reflex arteriolar constriction occurred. When nitroglycerin was used to produce a comparable reduction in preload, the normal increase in systemic vascular resistance did not occur. Thus, it was argued that a direct arteriolar dilator effect of the nitroglycerin counterbalanced the reflex arteriolar constriction that should have occurred with stimulation of the low-pressure baroreceptors.

Furthermore, one cannot discount the possibility that vasodilators might have a direct effect on pulmonary vascular compliance and reduce left ventricular filling pressure at a constant central blood volume. This phenomenon is almost impossible to document in humans because the stiffness of the pulmonary circulation is five to 10 times that of the systemic circulation. Because the pulmonary vessels are so stiff, if a systemic vasodilation produced a small reduction in pulmonary blood volume, a large change in pressure might result. Because a small volume change in human pulmonary blood volume cannot be detected by current methods, one cannot determine whether a vasodilator has its predominant effect on systemic or pulmonary capacitance vessels.

Last, vasodilators may reduce left ventricular filling pressure by shifting the diastolic pressure volume relationship downward. This downward shift could be a direct effect of these drugs on ventricular viscos properties, or an indirect effect that results in alterations of external constraints on the left ventricle. In addition, in patients with coronary artery disease, drugs such as nitroglycerin can improve regional blood flow to the ischemic myocardium. Left ventricular filling pressure would be expected to fall secondary to improved ventricular function and more complete ventricular relaxation.

How Much Can We Expect from Vasodilator Therapy in Congestive Heart Failure?

Can we make our patients more comfortable? Yes; at rest, certainly. Do we need a hemodynamic profile to pick the “right” vasodilator? Probably not. Certainly, we should use information available from indwelling catheters already in place. We know that the more ill patients respond best and that they are more likely to be studied and monitored hemodynamically.

However, Dr. George Burch has used hexamethonium, the ganglionic blocking agent, since 1950 and has used simple clinical parameters to guide therapy: the patient’s general appearance, arterial blood pressure, and distended neck veins. It is possible that noninvasive techniques (echocardiography, nuclear angiography) may be useful to monitor the cardiocirculatory response to a given agent or combination of agents; but noninvasive techniques are expensive. Empirically, a hydralazine-nitrate combination may work well for most patients, with more emphasis on the nitrate if the patient’s predominant symptoms are pulmonary congestion, and more emphasis on hydralazine if low-output symptoms (e.g., oliguria) predominate. Continuous nitrates may not be necessary for chronic therapy after the patient is stabilized. However, they may be particularly effective intermittently when given at night to improve sleep for the relief of nocturnal dyspnea. Since assuming the upright position is a very potent stimulus for peripheral venous pooling, nitrates may not be necessary during the day. Intermittent prazosin therapy might be used to augment diuresis.

Can we expect vasodilators to improve exercise performance? Probably not. The improvement might be measurable, but not noticeable. The improvement in symptoms experienced by patients on chronic vasodilator therapy is more a reflection of improved resting hemodynamics than of exercise hemodynamics. At least the vasodilators studied so far do not produce significant adverse effects during exercise.

Will we make our patient live longer? We doubt if the lives of the presently studied class IV patients will be significantly lengthened, although the quality may
be significantly improved. The answer to this question, however, awaits carefully controlled clinical trials.

What about the use of vasodilators as primary therapy for less severely ill patients? It is intriguing to think that vasodilator therapy might be used in place of digitalis. Many clinicians use diuretics rather than digitalis as primary therapy of heart failure, but this concept is not new. More than 15 years ago it was suggested that the sustained reduction in heart size by diuretic therapy in and of itself might produce a favorable long-term result. Furthermore, there is some evidence to suggest that exercise performance may not be significantly improved when digitalis is added to rigorous diuretic therapy. Considering the high prevalence of digitalis toxicity and its high fatality rate, if digitalis were used less because of a favorable response to diuretics or vasodilators, that alone might improve survival of the heart failure patient.

Last, a chronic reduction in ventricular dimensions might forestall the progression of ventricular hypertrophy and its attendant further depression of myocardial contractility. Unfortunately, the patients most likely to benefit from vasodilator therapy have been those with the most severely deranged hemodynamics. Patients with minimal hemodynamic dysfunction occasionally experienced a worsening of their hemodynamic profile with vasodilator therapy. Although that may be true for patients who have compensated hemodynamics with maximal inotropic and diuretic support, it might not be true if vasodilators were the primary therapy for early congestive heart failure, with diuretics and digitalis used as second and third line drugs.

The concept of vasodilator therapy is exquisitely simple. If the sick heart works less, it should get better. Yet hidden in this simplicity are a number of sophisticated questions that require answers. Considering that the most recent symposium on vasodilator therapy contained 643 bibliographic citations, there appears to be no shortage of investigators with enough interest to answer some of these questions.

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