EDITORIAL REVIEWS

Vasodilator and Inotropic Therapy for Severe Chronic Heart Failure: Passion and Skepticism

MILTON PACKER, MD, FACC
New York, New York

Although substantial progress has been made in the last 5 years in the development of vasodilator and inotropic drugs for the management of patients with severe chronic heart failure, much of the enthusiasm that surrounded the introduction of many of these agents has subsequently been tempered by reports of drug failure or adverse reactions. In this review and analysis, currently available vasodilator and inotropic agents are critically and comparatively evaluated to assess their respective advantages and limitations.

It is apparent that the ability of most of these drugs to produce substantial clinical benefits in patients with severe heart failure has probably been overstated. Therapy fails to achieve the desired clinical results all too frequently, possibly as the result of: the choice of an ineffective drug; the administration of an effective drug in subtherapeutic doses; the administration of an effective drug to improperly selected patients; the failure of initial hemodynamic benefits to be sustained; the occurrence of severe or serious adverse reactions; and the failure to alter concomitant therapy appropriately.

The present analysis indicates that there is no uniformly effective or safe vasodilator or inotropic drug for patients with severe heart failure; all agents have important limitations. Of the available therapeutic choices, however, long-term converting enzyme inhibition appears to produce more consistent hemodynamic and clinical benefits with an acceptable degree of adverse reactions than other pharmacologic approaches for the management of these severely ill patients.

Passion makes the best observations and draws the most wretched conclusions.

Richter

Nothing fortifies skepticism more than that there are some who are not skeptics; if all were so, they would be wrong.

Pascal

Five years ago when orally active systemic vasodilator drugs were first being used for the management of patients with severe chronic heart failure, we reviewed the advantages and disadvantages of the drugs available at that time and appealed for caution (1), because no single drug or drug combination appeared to fulfill the prerequisites of efficacy and safety that were needed before this therapeutic approach could be recommended for widespread use. Over the last 5 years, however, substantial progress has been made, new vasodilator and inotropic agents have been developed and the enthusiasm surrounding the use of these drugs is greater than ever. Hence, it is appropriate to reexamine the advantages and limitations of existing therapeutic approaches for severe chronic heart failure and ask: Is the caution we advised in our original review still warranted?

The number of orally active vasodilator drugs that have been advocated for use in chronic heart failure has multiplied dramatically in the last 5 years (Table 1) (2). The list now includes: the direct-acting vasodilator agents: nitrates, hydralazine and minoxidil; the neurohumoral antagonists: prazosin, trimazosin, captopril and enalapril; the calcium channel antagonists: nifedipine, verapamil and diltiazem; the beta-adrenergic agonist drugs with vasodilator activity: prenalterol, pirbuterol, salbutamol and terbutaline; and the noncatecholamine nonglycoside inotropic drugs with vasodilator actions: amrinone, milrinone, MDL 17043 and MDL 19205.

Direct-Acting Vasodilator Drugs

Nitrates

Therapeutic properties. Orally active nitrates, particularly isosorbide dinitrate, were the first oral vasodilator drugs widely used in the management of patients with severe
The hemodynamic effects of nitrates during long-term therapy in some patients with heart failure, but the frequency of their occurrence is not known. Leier et al. (15) have shown that during long-term treatment, tolerance occurs primarily to the arterial vasodilating actions of these agents, but not to their effects on venous capacitance. Accordingly, sustained decreases in right and left ventricular filling pressures during rest and exercise without increases in cardiac output occur in most patients receiving long-term nitrate therapy (15,16). However, the lack of improvement in cardiac output appears to be clinically unimportant because exercise tolerance improves even in the absence of an increase in forward flow (15,17). Maximal oxygen consumption is enhanced during long-term treatment with nitrates despite little change in oxygen delivery to the peripheral circulation because systemic oxygen extraction is increased by the training effects of more comfortable repeated submaximal exercise (17). Because the short-term effects of these drugs on cardiac output appear to be of minor significance, the concern about the use of nitrates in patients with low ventricular filling pressures before therapy may not be warranted. Although cardiac output may decline in these patients as preload is excessively compromised (18,19), nitrates will effectively attenuate exercise-induced increases in ventricular filling pressure (12,13) and reduce exertional dyspnea, regardless of the pretreatment level of filling pressure. This attenuation leads to an improvement in peripheral oxygen extraction and exercise tolerance during long-term therapy (by means of a training effect), regardless of the observed direction and magnitude of acute changes in cardiac output at rest (20).

The effectiveness of short- and long-term therapy with nitrates administered by other than oral routes (for example, transcutaneous delivery) remains unproven. Preliminary evidence (21) suggests that continuous nitroglycerin therapy may result in the rapid development of tolerance to the drug’s beneficial hemodynamic effects, and this may be followed by rebound hemodynamic changes after the drug is withdrawn. Rebound events may follow the abrupt discontinuation of long-term oral nitrate therapy as well (14).

**Clinical perspective.** Present evidence indicates that oral nitrates are effective drugs in the treatment of severe chronic heart failure. Furthermore, these agents are easy to use, hemodynamic responses are usually sustained during chronic therapy and adverse effects requiring discontinuation of treatment are infrequent (Table 2). However, in our experience, the clinical benefits that accompany short- and long-term nitrate therapy are modest compared with those observed with other vasodilator drugs; most patients continue to experience disabling symptoms of heart failure, even though some improvement may have been experienced. Hence, many clinicians use nitrates as adjuvant therapy to other orally effective vasodilator drugs (22,23).

**Hydralazine**

**Therapeutic properties.** Because of its predominant direct arterial vasodilator actions, hydralazine primarily increases cardiac output and lowers systemic vascular resistance in patients with severe chronic heart failure (24,25). Although venous capacitance is minimally altered (25), left ventricular filling pressures may be markedly decreased by

---

**Table 1. Orally Active Vasodilator and Inotropic Drugs**

<table>
<thead>
<tr>
<th>Direct-acting vasodilator drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
</tr>
<tr>
<td>Hydralazine</td>
</tr>
<tr>
<td>Minoxidil</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurohumoral antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin</td>
</tr>
<tr>
<td>Tramazosin</td>
</tr>
<tr>
<td>Captopril</td>
</tr>
<tr>
<td>Enalapril (MK 421)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcium channel antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
</tr>
<tr>
<td>Verapamil</td>
</tr>
<tr>
<td>Diltiazem</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs with vasodilator activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-agonist agents</td>
</tr>
<tr>
<td>Prenalterol</td>
</tr>
<tr>
<td>Piritrexol</td>
</tr>
<tr>
<td>Salbutamol</td>
</tr>
<tr>
<td>Terbutaline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Noncatecholamine nonglycoside inotropic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amrinone (WIN 40680)</td>
</tr>
<tr>
<td>Milrinone (WIN 47203)</td>
</tr>
<tr>
<td>MDL 17043</td>
</tr>
<tr>
<td>MDL 19205</td>
</tr>
</tbody>
</table>

Chronic heart failure (3). Nitrates primarily lower right and left ventricular filling pressures by a direct dilating action on venous capacitance vessels (4–7); the immediate increases in cardiac output are usually small but may be great in specific clinical situations, such as, after the administration of large doses (40 to 100 mg orally [8]), in patients having a very low cardiac index before treatment (9,10) and in patients with severe mitral or aortic valve regurgitation (11). The initial beneficial hemodynamic effects at rest are also observed during exercise (12,13), dyspnea and fatigue are alleviated and exercise tolerance improves (14–17). Two double-blind randomized clinical trials in patients with severe heart failure (14,15) have demonstrated that long-term treatment with nitrates (isosorbide dinitrate, 160 mg orally daily for 3 months) produces significant hemodynamic and clinical improvement compared with treatment with placebo. Furthermore, nitrates are well tolerated; headaches, flushing and dizziness occur less frequently in patients with heart failure than in patients with angina pectoris, and a few patients with heart failure discontinue nitrates because of adverse reactions.

**Limitations and disadvantages.** Tolerance develops to the hemodynamic effects of nitrates during long-term therapy in some patients with heart failure, but the frequency of its occurrence is not known. Leier et al. (15) have shown that during long-term treatment, tolerance occurs primarily to the arterial vasodilating actions of these agents, but not to their effects on venous capacitance. Accordingly, sustained decreases in right and left ventricular filling pressures during rest and exercise without increases in cardiac output.
Hydralazine in patients with severe mitral or aortic valve regurgitation in whom aortic impedance plays a critical role in determining the magnitude of regurgitant volume (26,27). Hydralazine’s benefits are seen at rest and during exercise (28); in patients with a markedly dilated congestive cardiomyopathy with associated secondary valvular regurgitation, long-term hydralazine therapy lessens dyspnea and fatigue and enhances exercise tolerance (29,30). However, in most reports (22,23,30–33), hydralazine has not been the sole vasodilator drug used, but has usually been combined with nitrates. Because nitrates are effective alone (14,15), it is unclear to what extent the reported benefits with combined therapy are the result of concomitant drug treatment; in other words, it is uncertain to what extent hydralazine adds to the improvement expected after therapy with nitrates alone.

Limitations and disadvantages. At Mount Sinai Hospital, we have used hydralazine as monotherapy for patients with severe heart failure for the past 7 years and have found that the hemodynamic and clinical responses to the drug vary greatly. Although some patients show marked clinical improvement, the therapeutic application of this drug has important disadvantages:

1) The dose requirements of hydralazine are highly variable (34,35). Although many patients respond favorably to a dose of 300 mg daily, patients will frequently require larger doses (400 to 3,000 mg daily) to produce hemodynamic effects; conversely, some patients may be exquisitely sensitive to small doses (35). The administration of an arbitrary dose of the drug (for example, 300 mg orally) may be subtherapeutic for some patients and excessive for others. Because empiric dose titration based on clinical symptoms is difficult, invasive hemodynamic testing appears mandatory to ensure the administration of effective doses of the drugs (36).

2) Even if pharmacologically effective quantities of hydralazine are administered, the hemodynamic and clinical responses to the drug still vary greatly. Patients with a markedly dilated left ventricle show marked increases in cardiac index and stroke work with minimal hypotension or tachycardia; these patients improve clinically with long-term hydralazine therapy as prerenal azotemia resolves (29). On the other hand, patients with small left ventricular dimensions show only modest hemodynamic benefits, and these are accompanied by marked decreases in blood pressure and increases in heart rate; during long-term treatment with hydralazine, such patients fail to improve symptomatically and some may show clinical deterioration (progressive lethargy and confusion, worsening azotemia and ventricular arrhythmias) (29).

3) Even if effective doses of hydralazine are administered and highly favorable hemodynamic responses are obtained, long-term clinical improvement may not be observed. This may occur in part because pharmacologic tolerance may develop to the initial beneficial effects of the drug during prolonged administration (37). Of 104 consecutive patients whose acute responses to hydralazine were confirmed by right heart catheterization, we identified 38 patients with marked initial favorable hemodynamic effects, who inexplicably failed to show improvement during long-term treatment. When the hemodynamic responses to hydralazine were reassessed in 11 of these patients after an average of 37 weeks of therapy, we found that the marked increases in cardiac output seen initially were no longer present and that hemodynamic variables had returned to prehydralazine values. Tolerance could not be reversed by increments in the dose of the drug, by its intravenous administration or by diuresis; furthermore, deterioration did not occur when the drug was withdrawn (37). In contrast, long-term clinical benefits with hydralazine are usually seen in patients who demonstrate sustained hemodynamic effects (30,38,39). On the basis of these data, we estimate that clinically important tolerance occurs in about 30% of patients with heart failure who receive long-term treatment with hydralazine.

4) Even when sustained hemodynamic and clinical benefits are seen with hydralazine, adverse reactions may occur that may warrant discontinuation of effective therapy. In

<table>
<thead>
<tr>
<th>Dose requirements</th>
<th>Nitrates</th>
<th>Hydralazine</th>
<th>Prazosin</th>
<th>Captopril</th>
<th>Calcium Antagonists</th>
<th>Beta-Receptor Agonists</th>
<th>Noncatecholamine Inotropes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial hemodynamic response</td>
<td>Usually favorable</td>
<td>May be detrimental</td>
<td>Usually favorable</td>
<td>May be detrimental</td>
<td>Usually favorable</td>
<td>Usually favorable</td>
<td>Usually favorable</td>
</tr>
<tr>
<td>Hemodynamic tolerance</td>
<td>Occasional, arterial (30%)</td>
<td>Occasional (50%)</td>
<td>Common (15%)</td>
<td>Uncommon (60%)</td>
<td>Common, may be severe</td>
<td>Common, may be severe</td>
<td>Common, may be severe</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Occasional, mild</td>
<td>May be severe</td>
<td>Uncommon, mild</td>
<td>Occasional, manageable (60%)</td>
<td>Common, may be severe</td>
<td>Common, may be severe</td>
<td>Common, may be severe</td>
</tr>
<tr>
<td>Overall efficacy</td>
<td>Unknown</td>
<td>30 to 40%</td>
<td>30 to 40%</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
our experience, these appear to be more frequent with hydralazine than with most other vasodilator drugs used in the treatment of severe chronic heart failure. There are four adverse reactions that deserve special mention. Headaches, palpitation and flushing occur in about one-third of patients and may be severe, but are usually short-lived (< 1 week) and are almost never a cause for withdrawal of treatment. Nausea and vomiting occur occasionally, probably related to large oral doses required to produce hemodynamic effects and are the most common reasons for discontinuation of therapy. Myocardial ischemic events (unstable angina and myocardial infarction) may occur during initiation of treatment with hydralazine and are the most feared complications of therapy (40). Systemic lupus erythematosus may be induced when large doses of hydralazine are given for long periods to patients for treatment of systemic hypertension (41). However, this has been a minor problem with the use of hydralazine in the treatment of patients with heart failure, probably because the duration of therapy required to produce this syndrome may exceed the life expectancy of many patients with severe left ventricular dysfunction (32,33,42).

Clinical perspective. Because of these disadvantages (Table 2), we do not use hydralazine as a first line vasodilator drug for patients with severe chronic heart failure, except for patients with severe aortic regurgitation who are particularly sensitive to the modest decreases in aortic impedance achievable with small doses of the drug (27). The only randomized controlled clinical trial (43) using hydralazine as monotherapy failed to show significant differences between placebo- and hydralazine-treated patients; this supports our own experience, in which only 30 to 40% of consecutively evaluated patients with heart failure benefited from long-term treatment with the drug.

Minoxidil

A direct-acting arterial vasodilator drug similar to hydralazine, minoxidil, produces short- and long-term hemodynamic improvement in many patients with severe heart failure (44,45). Compared with hydralazine, however, minoxidil may have some advantages: the dose requirements of the drug appear to be more uniform (most patients respond to 20 mg twice daily [44]), and tolerance may occur less frequently (many patients who develop tolerance to hydralazine are still responsive to minoxidil [37,46]). However, experience with minoxidil in severe chronic heart failure remains limited, and it is not certain that clinical benefits are seen even when initial hemodynamic responses are sustained (45). Furthermore, adverse reactions (particularly fluid retention) are more frequent with minoxidil than with hydralazine (46,47). Such fluid retention is frequently severe and may be resistant to large doses of furosemide; in our experience, the addition of metolazone may be particularly helpful in such patients.

Neurohumoral Antagonists

Prazosin

Therapeutic properties. By attenuating the effects of the sympathetic nervous system on the peripheral circulation (48), the postsynaptic alpha-adrenergic blocking agent, prazosin, produces marked beneficial hemodynamic effects during the administration of first doses of the drug (49,50). These responses generally are highly favorable and do not appear to be dose-dependent; presumably, once complete alpha-receptor blockade is achieved, further increments in dose do not result in further postsynaptic receptor inhibition (51). Moreover, long-term therapy with prazosin over a wide range of doses (6 to 15 mg daily orally) is well tolerated; adverse reactions are uncommon. The first dose dizziness and syncope described in hypertensive patients (52–54), which probably resulted from an excessive lowering of normal left ventricular filling pressures, rarely occurs in patients with severe heart failure, whose filling pressures are markedly elevated before treatment.

Limitations and disadvantages. Considerable concern has been expressed, however, about the long-term effectiveness of prazosin in patients with severe heart failure. Although first doses of prazosin produce marked beneficial hemodynamic responses, these effects become rapidly attenuated within 48 hours of continuous therapy with the drug (55–58). The fale and clinical significance of this short-term tachyphylaxis have become a matter of considerable dispute. Some investigators (59,60) have suggested that hemodynamic tolerance to prazosin may occur only at rest and not during exercise. However, studies (61) of the long-term effects of the drug during exertion have demonstrated a pattern of attenuation similar to that seen at rest. Some investigators (58,62) have suggested that short-term tolerance to prazosin is spontaneously reversible and that long-term effects may exceed the benefits seen with first doses of the drug. In our experience (63), early hemodynamic tolerance is rarely reversible and is not responsive to increments in the dose of prazosin or that of concomitantly administered diuretic agents. Still other investigators have postulated that long-term tolerance may not be the result of a loss of the pharmacologic actions of prazosin, but a consequence of activation of counterposing neurohumoral forces, (the sympathetic nervous system or renin-angiotensin system) (51,64,65), so that tolerance may be reversed or prevented by treatment with aldosterone antagonists (62,66). However, in our experience as well as that of others, sustained increases in plasma renin activity or in plasma catecholamines are not seen during long-term prazosin therapy (67), and tolerance is not prevented or reversed by spironolactone (63).

The controversy concerning the effectiveness of prazosin in heart failure is reflected by the results of double-blind placebo-controlled trials. Whereas early studies (68,69) showed marked clinical benefits with prazosin compared
with placebo, more recently published clinical trials (67,70,71) have shown little difference between prazosin- and placebo-treated patients, even when therapy is continued for up to 6 months.

Clinical perspective. Resolution of the controversy concerning the long-term efficacy of prazosin appears unlikely in the near future. It is probable that the appropriate role of prazosin in the management of severe heart failure lies between the extreme positions held by those who consider it to be uniformly beneficial or uniformly useless. In our experience, prazosin is an effective drug for some patients; those who do not develop tolerance to its long-term hemodynamic effects. Unfortunately, this group comprises only 30 to 40% of consecutively evaluated patients with severe chronic heart failure (Table 2). It is our belief that, rather than continuing to pursue the question of efficacy, future research efforts might more profitably be directed toward determining the nature of the mechanisms underlying the development of tolerance and developing means of preventing or reversing its occurrence.

Trimazosin

An analog of prazosin, trimazosin produces similar hemodynamic effects in patients with severe heart failure (72–74), presumably by postsynaptic alpha-adrenergic blockade. As with prazosin, initial reports (75–77) concerning its efficacy have been favorable, but the overall experience with the drug in severe chronic heart failure is limited.

Captopril

Therapeutic properties. The orally active angiotensin-converting enzyme inhibitor, captopril, produces marked hemodynamic improvement at rest and during exercise in patients with heart failure, and these effects are similar in many respects to that seen with other vasodilator drugs (78–85). Long-term treatment is accompanied by sustained hemodynamic responses, amelioration of dyspnea and fatigue and enhanced exercise tolerance (81,84,85). The hemodynamic and clinical benefits of captopril have been demonstrated in two double-blind placebo-controlled randomized clinical trials (86,87), the most recent of which was reported in the October issue of this journal. In that study (87) performed in 92 patients with class III or IV heart failure, patients treated with captopril had greater improvement in symptoms and in exercise tolerance than did patients treated with placebo. This multicenter study is the largest experience with the drug in severe chronic heart failure completed to date.

Dosage. As with prazosin but in contrast to hydralazine, determination of an effective dose of captopril is not complicated by highly variable dose requirements. Because only 10 to 20 mg of captopril is needed to completely inhibit the angiotensin-converting enzyme (88), doses of 25, 50, 100 and 150 mg of the drug produce nearly identical hemodynamic effects (80,81). The administration of doses greater than 25 to 50 mg orally may produce hemodynamic responses of longer duration than those seen with smaller doses (80,88). However, this enhanced duration has not been shown to be clinically important and the administration of larger doses may be associated with a higher frequency of adverse reactions (89). On the basis of these theoretical concepts, 25 to 50 mg three times daily may be a uniformly useful dose of captopril for most patients with severe heart failure; unfortunately, most of the clinical experience with the drug in the United States (both in double-blind and uncontrolled studies) has been with larger doses of the drug (150 to 300 mg daily).

Acute and long-term hemodynamic effects. Most patients demonstrate hemodynamic improvement with first doses of captopril, but the importance of these acute effects remains unclear. Although the early responses to converting enzyme inhibition are frequently sustained, the magnitude of these effects may be enhanced or attenuated during long-term treatment (90,91). Accordingly, some patients whose condition fails to improve with first doses of captopril show marked hemodynamic and clinical benefits during long-term therapy; conversely, some patients with dramatic initial hemodynamic responses fail to show long-term improvement. This may explain why the short-term hemodynamic effects of captopril may bear little relation to long-term changes in exercise tolerance (92–94). This may also explain why plasma renin activity correlates closely with the short-term responses to therapy but not with the long-term effects of the drug (80,95). Because the short-term hemodynamic effects of captopril may become greatly modified with time, it may not be possible to accurately assess the therapeutic efficacy of the drug in an individual patient with severe chronic heart failure for 3 to 6 weeks; this raises serious questions about the need for invasive hemodynamic testing during the initiation of therapy with converting enzyme inhibitors in patients with severe chronic heart failure (91,92,94). In our experience (90,91), long-term hemodynamic improvement is seen in approximately 70% of patients treated with captopril.

Hemodynamic tolerance. Hemodynamic tolerance does occur during long-term therapy with captopril in some patients with severe heart failure, but it is uncommon (10 to 15% of consecutively treated patients) (91). Such patients manifest rapid or gradual loss of the hemodynamic benefits seen with first doses of the drug that is not reversed by dosage increments; hemodynamic deterioration does not occur when the drug is withdrawn. Of interest, such patients are not responsive to alternative inhibitors of the angiotensin-converting enzyme, but direct-acting vasodilator drugs are still effective (96). The incidence of hemodynamic and clinical tolerance with captopril in heart failure appears to
be significantly less common than that seen with hydralazine or prazosin (97).

Limitations and disadvantages. Three adverse reactions of captopril deserve emphasis. As with other vasodilator drugs, hypotension is a therapeutic effect of captopril and presents a concern only when accompanied by clinical evidence of end organ hypoperfusion (dizziness or blurred vision, or both); however, episodes of symptomatic hypotension occur more frequently with captopril than with other vasodilator drugs (86,89). Such hypotensive events usually occur within the first 24 hours of treatment, particularly in patients who have recently received intravenous diuretic drugs and those with severe hyponatremia (serum sodium concentration less than 130 mEq/liter) (89,98); hyponatremic patients appear to be dependent on the renin-angiotensin system for support of systemic pressure and, thus, are prone to hypotension when treated with converting enzyme inhibitors (99). Hypotension can be avoided by a reduction in the dose of captopril (to 6.25 to 12.5 mg orally) or of concomitantly administered diuretic drug. A pruritic erythematous maculopapular rash occurs in 5 to 8% of patients with heart failure treated with captopril (usually within 6 weeks) and is the most common adverse reaction that necessitates discontinuation of treatment; occasionally, the rash will disappear despite continued therapy or will not recur with rechallenge (100). An increase in blood urea nitrogen is seen in about 20% of patients with heart failure treated with captopril (89,101); this usually develops in patients in whom left ventricular filling pressures are excessively reduced during long-term treatment and is reversed by a reduction in diuretic dose (101). Although neutropenia and proteinuria are serious concerns when high doses of captopril are administered to hypertensive patients with renal insufficiency (89), these reactions have rarely been seen with the lower doses of this drug used in the management of patients with heart failure (86,87). Consequently, as with nitrates, adverse reactions to captopril are usually manageable and uncommonly warrant discontinuation of therapy.

Clinical perspective. In our experience, approximately 60% of patients with severe chronic heart failure improve during long-term treatment with captopril. This compares favorably with the 30 to 40% response rate we have observed during long-term therapy with hydralazine or with prazosin (Table 2). Nevertheless, approximately one-third of patients with heart failure fail to benefit from captopril therapy, and the magnitude of clinical improvement in some responders may be inadequate to restore an individual patient to a useful life-style (91,93). For these patients, the addition or substitution of second line therapy with hydralazine, nitrates or prazosin may be indicated (91,96,97,102).

Enalapril

A series of angiotensin-converting enzyme inhibitors are under development that are analogs of captopril and may prove useful in the treatment of severe heart failure (103). The most thoroughly investigated analog, enalapril, has a longer duration of action than captopril and does not possess a sulfhydryl group, which has been held responsible for some of captopril’s idiosyncratic adverse effects (104,105). Enalapril produces short- and long-term hemodynamic benefits in patients with severe chronic heart failure similar to those seen with captopril (106–108), but experience with this drug in the treatment of heart failure is still limited. Whether it will prove as effective as captopril with a lower incidence of adverse reactions remains to be determined.

Calcium Channel Antagonists

A number of reports have appeared concerning the application of the calcium channel antagonists, nifedipine (109–111), verapamil (112) and diltiazem (113), as vasodilator drugs in patients with severe chronic heart failure. Of the three, most of the experience in patients with heart failure has been gained with nifedipine.

Nifedipine

Like hydralazine and minoxidil, nifedipine is primarily an arterial vasodilator and, thus, increases cardiac output and lowers systemic vascular resistance with minimal effects on right and left ventricular filling pressures (109–111). Unlike other vasodilator drugs, however, nifedipine exerts a direct negative inotropic effect on the myocardium, consistent with its ability to block transmembrane calcium transport in cardiac muscle cells (114,115). In patients with a left ventricular ejection fraction greater than 30%, the peripheral vasodilator effects of nifedipine serve to offset its negative inotropic effects, so that significant increases in cardiac output are observed (109–111,116). This is particularly true in patients with aortic insufficiency or severe hypertension (117–119), who are exquisitely sensitive to even small reductions in peripheral resistance. In contrast, in patients with a left ventricular ejection fraction less than 30%, nifedipine’s effects on cardiac performance are unpredictable. Although increases in cardiac output may be seen in such patients, worsening of ventricular performance may also occur (120,121); in these patients the myocardium appears to be exquisitely sensitive to pharmacologic depression and, thus, severe heart failure may be exacerbated by nifedipine (Table 2) (122). When nifedipine and nitroprusside are titrated to produce similar decreases in systemic vascular resistance in the same patients with severe heart failure, the increase in cardiac output and decrease in left ventricular filling pressure with nitroprusside are greater than with nifedipine, whereas the hypotensive effects of nifedipine are greater than with nitroprusside (123). A similar deterioration of right ventricular function has been observed after nifedipine in patients with right heart failure due to severe pulmonary hypertension (124). Because the negative inotropic actions of calcium antagonists (including nifedipine) may cause worsening of heart
failure (120,121,124–126) and because experience with these agents in patients with severe heart failure remains limited, we do not use calcium antagonists as vasodilators in patients with severe heart failure unless additional clinical reasons for their administration exist; angina pectoris or systemic hypertension, or both.

### Inotropic Agents

A number of drugs have been developed over the last 5 years that increase cardiac contractility by mechanisms distinct from those utilized by digitalis. These include agents that act by stimulating beta-adrenergic receptors (prenalterol [127–129], pirbuterol [130–132], salbutamol [133] and terbutaline [134]) and agents that act independently of catecholamines (amrinone [135,136], milrinone (WIN 47203) [137], MDL 17043 [138] and MDL 19205 [139]). All of these agents exert peripheral vasodilator actions in addition to their inotropic effects, either directly or by withdrawal of reflex vasoconstrictor mechanisms deactivated by the improvement in the heart failure state (140–142). The relative importance of the inotropic versus vasodilator actions of these drugs in mediating the observed improvement in cardiac performance remains uncertain.

#### Beta-Adrenergic Receptor Agonists

The beta-receptor agonist drugs can be categorized into the beta-receptor agonists (prenalterol), which are thought to increase cardiac performance by a direct effect on cardiac contractility mediated by myocardial beta-receptors, and the beta-adrenoceptor agonists (pirbuterol, salbutamol and terbutaline), which are thought to improve cardiac performance by a systemic vasodilator effect mediated by vascular beta-receptors (143). Although such selectivity may be present when low doses of these drugs are administered, the doses utilized in the treatment of heart failure are large enough that receptor subsensitivity may be lost; hence, it is likely that both subpopulations of beta-receptors are stimulated by both groups of drugs (143). Significant increases in cardiac output and decreases in left ventricular filling pressure at rest and during exercise occur after short-term therapy with beta-agonist drugs in patients with severe heart failure (127–134,144), but this improvement may be accompanied by significant increases in heart rate (144). Furthermore, in many patients, the magnitude of hemodynamic benefit is modest (144), but attempts to increase drug dosage frequently lead to significant adverse reactions (palpitations, nervousness and tremulousness) (145). In our experience (132,146), the most serious adverse reactions with beta-receptor agonists have been their tendency to exacerbate angina pectoris and provoke ventricular arrhythmias.

The most important limitation of beta-receptor agonist drugs in the treatment of severe chronic heart failure is the development of hemodynamic tolerance during long-term therapy (147–149). Long-term drug administration leads to a progressive loss of the marked hemodynamic response seen with initial doses, presumably because of a progressive decrease in the number of active beta-receptors (“down-regulation”) (149). Although such tolerance is reversible on discontinuation of the drug, it occurs with sufficient rapidity (within 1 week) to make effective long-term treatment with these agents unlikely. This probably explains why double-blind randomized clinical trials of these drugs have shown little difference between patients treated with an active drug and those treated with placebo (Table 2) (145).

#### Noncatecholamine Inotropic Agents

The noncatecholamine nonglycoside inotropic drugs include amrinone, milrinone, MDL 17043 and MDL 19205 (135–139). All of these agents directly increase cardiac contractility, but the molecular and biochemical mechanisms by which these effects are mediated remain unknown (150). In addition, these drugs produce direct dilator effects on the peripheral circulation that potentiate the improvement in cardiac performance (140,141,151).

**Amrinone.** Of the available agents, most of the clinical experience has been gained with amrinone. Administered either intravenously or orally, this inotropic drug produces marked hemodynamic benefit in most patients with severe heart failure with little hypotensive risk (135,136,152–154). Hemodynamic improvement is seen at rest and during exercise, and exercise tolerance improves with long-term therapy (154–156). However, the role of amrinone in the management of severe chronic heart failure remains uncertain. Like hydralazine, the dose requirements of the drug are variable. Whereas many patients respond to doses of 225 to 300 mg daily, some show little benefit even when 600 mg daily is administered orally (unpublished observations). This makes empiric therapy with amrinone difficult, and invasive hemodynamic testing may be necessary to determine an effective dose of the drug. Although hemodynamic and clinical deterioration has occurred on withdrawal of amrinone in some patients (155), others experience little deterioration when the agent has been discontinued (157); hence, the development of drug tolerance remains an unresolved issue. Adverse effects including gastrointestinal distress, thrombocytopenia, myalgias, fever, hepatic dysfunction and worsening arrhythmias have been reported with increasing frequency as experience with amrinone has grown (151–159). To what extent these can be modified by dose reduction and to what degree similar adverse effects occur with other inotropic agents remains to be determined (Table 2). Lastly, there is concern that the long-term administration of all inotropic drugs may hasten the progression of ventricular dysfunction in patients with severe heart failure and shorten survival (160); a similar fear has been expressed with conventional inotropic drugs such as digitalis (161,162).
Clearly, this new and interesting class of drugs requires further intensive study.

Conclusions

When the advantages and disadvantages of currently available drugs for the treatment of severe chronic heart failure are critically assessed, it appears that long-term converting enzyme inhibition produces more marked and more consistent hemodynamic and clinical benefits with an acceptable degree of adverse reactions than do other available approaches to the management of these patients. It is largely because of the evidence supporting such a conclusion (including the multicenter trial reported in the October issue of this journal [87]) that the U.S. Food and Drug Administration approved the use of captopril for patients with severe chronic heart failure in 1982. Captopril became the first orally active vasodilator drug to receive such official approval since the advocacy of oral vasodilator therapy for patients with heart failure began in earnest 5 years ago.

Despite the great strides made in the past 5 years, however, our original plea for caution (1) must be made once again with even greater conviction. We must remember that there is still no uniformly effective and safe vasodilator/inotropic drug for the treatment of severe chronic heart failure and that the development of such an agent in the future remains unlikely; all currently available agents have important limitations. The failure of therapy in an individual patient may be the result of a number of factors: the choice of an ineffective vasodilator drug; the administration of an effective drug in subtherapeutic doses; the administration of an effective drug to improperly selected patients; the failure of initial hemodynamic benefits to be sustained; the occurrence of severe or serious adverse reactions; and the failure to alter concomitant therapy appropriately. Furthermore, no vasodilator drug has been shown to reduce the high mortality rate that characterizes patients with severe left ventricular dysfunction (32,33,42).

Each of these limitations must be considered whenever we read initial enthusiastic reports of a new “breakthrough.” Early reports of the benefits of a new drug are commonly expressed with great passion and enthusiasm, and this enthusiasm is almost always subsequently tempered by reports of drug failure or adverse reactions. Hence, a healthy skepticism is always needed when favorable reports appear. With time, the proper role of a given agent will emerge, not only from the performance of double-blind placebo-controlled randomized clinical trials, but from the scrutiny and clinical experience of the individual physician.

References


