Therapeutic achievements of phosphodiesterase inhibitors and the future

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Heart failure remains a major therapeutic problem with a poor prognosis despite therapy with digitalis, diuretics and vasodilator drugs. Because impaired myocardial contractility is a principal feature of persistent heart failure, the development of phosphodiesterase inhibitors, e.g. milrinone, has presented important therapeutic possibilities. Milrinone exerts both positive inotropic and vasodilator activity, and improves systemic haemodynamics by increasing left ventricular stroke volume and decreasing left ventricular filling pressure and systemic vascular resistance. In addition to improving systolic pump function, milrinone has also been shown to improve impaired diastolic relaxation of the failing heart. Importantly, treatment with milrinone does not significantly increase myocardial oxygen consumption. In moderate to severe heart failure (NYHA class III and IV), intravenous and oral milrinone have been shown not only to produce acute haemodynamic improvement but also to relieve the associated symptom of breathlessness, with improvement in quality-of-life indices. In placebo-controlled, double-blind studies oral milrinone has enhanced exercise tolerance and increased total body oxygen consumption in mild (class II), moderate and severe heart failure. There is no evidence of a substantial pro-arrhythmic effect or other significant non-cardiovascular side-effects associated with the use of milrinone. The possibility of improved survival, which is still the ultimate goal of therapy with phosphodiesterase inhibitors, remains to be studied. Similarly, the role of these agents in the management of mild heart failure, alone or in addition to therapy with diuretics and angiotensin-converting enzyme (ACE) inhibitors, warrants further evaluation.

Introduction

Congestive heart failure remains a major cause of mortality and morbidity throughout the world[1]. The haemodynamic changes associated with congestive heart failure are a reduction in cardiac output, increase in intravascular volume, elevated left ventricular filling pressures and an increase in total peripheral resistance, the last being in part a response to circulating hormones including noradrenaline, angiotensin II and vasopressin. Impaired myocardial contractility is a major factor in the development of these haemodynamic features whether the heart failure is secondary to coronary artery disease, cardiomyopathy or the long-term effects of hypertension and/or valvular heart disease. Management of heart failure traditionally involves the administration of diuretics to reduce intravascular volume and filling pressures with or without addition of digitalis preparations to produce a modest increase in myocardial contractility. In recent years a third line of therapy has utilized the addition of vasodilator drugs to manipulate the preload and/or afterload.

Because depressed myocardial contractility is a primary feature of congestive heart failure, the search for more effective intravenous and oral inotropic drugs has continued and has resulted in the identification of a group of new agents which inhibit type-III phosphodiesterase, allowing intracellular accumulation of cyclic adenosine monophosphate (cAMP) in cardiac and vascular smooth muscle. The bipyridine derivative, milrinone, is the most extensively studied of these agents and has been shown to increase the contractility of isolated heart muscle and to possess an inotropic potency 10–30 times greater than that of its parent compound amrinone[2]. In addition, it is a potent vasodilator agent[3]. Extensive clinical studies of intravenous and oral milrinone have been reported and the initial therapeutic achievements can now be assessed.
The primary objectives of therapy with phosphodiesterase inhibitors, such as milrinone, are to improve the symptoms associated with heart failure, mostly breathlessness, impaired exercise tolerance, fatigue and peripheral oedema, and so improve the quality of life. Such symptomatic improvement is particularly important in severe heart failure, i.e. in New York Heart Association (NYHA) classes III and IV. It is essential that such symptomatic improvement should be achieved without serious cardiovascular side-effects and, in particular, the incidence of cardiac arrhythmias should not be increased. Similarly, non-cardiovascular side-effects should be minimal or non-existent. Finally, the goal of heart failure therapy is to improve patient survival and this is particularly important if treatment is directed at patients with milder degrees of heart failure, when symptomatic benefit may be marginal, but improved survival is the major goal.

**Haemodynamic benefits**

**SYSTOLIC FUNCTION**

Intravenous and orally administered milrinone has been conclusively demonstrated to increase cardiac index and stroke index, with associated reductions in left ventricular end-diastolic pressure and systemic vascular resistance. There is a clear increase in left-ventricular dP/dt\text{max} (Fig. 1). That this represents a positive inotropic effect has been confirmed in healthy volunteers, when a study of the left ventricular pressure/dimension relationships demonstrated a clear plasma level related increase in the left ventricular end-systolic pressure associated with a reduction in the left ventricular end-systolic dimension. We have demonstrated a similar leftward shift in the relationship between end-systolic pressure and dimension in patients with severe congestive heart failure (Fig. 2). This change suggests a positive

![Figure 1](image1.png)

**Figure 1** Effects of milrinone on (a) cardiac index, (b) left-ventricular end-diastolic pressure, (c) systemic vascular resistance, (d) left ventricular maximum dP/dt\text{max} in 12 patients. Mean (SEM) values are shown at baseline and 90 min after milrinone (5 mg) administration. (Based on a figure from the *British Heart Journal*.)

![Figure 2](image2.png)

**Figure 2** (a,b) Effects of milrinone on the relation between the left ventricular (LV) pressure and dimension in two separate patients. Values before treatment (C1 and C2) and 30, 60, and 90 min after milrinone administration (M30, M60, M90) are shown. O, pressure–dimension relation at end-systole. (Based on a figure from the *British Heart Journal*.)
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Both intravenous and oral milrinone have been demonstrated to reduce breathlessness on exertion and counteracts the increased oxygen requirement which would be necessary to support the enhanced contractility.

Therapeutic benefits from intravenous and oral milrinone

Milrinone, administered either intravenously or orally, produces a clear improvement in maximum exercise capacity. This change occurs acutely and persists for up to 3 months of oral administration. This is in contrast with the delayed development of improved exercise tolerance seen after administration of the vasodilator angiotensin-converting enzyme (ACE) inhibitor drugs captopril and enalapril. This initial observation, which was made in open studies, has been confirmed in the pivotal study described by DiBianco et al. In this multicentre, placebo-controlled evaluation, patients with NYHA class II or III heart failure received diuretic therapy, were randomly allocated to therapy, for a 3-month period, with either milrinone (10 mg every 6 h), placebo, digoxin, or a combination of milrinone and digoxin. Milrinone prolonged the exercise tolerance time by a mean of 83 s as compared with the placebo response, and this was highly significant. No additional improvement in exercise tolerance was demonstrated when digoxin was given together with milrinone.

It is known from open studies that milrinone increases acutely and chronically the total body oxygen consumption (peak VO₂). This has been confirmed in the multicentre, placebo-controlled trial referred to above, in which a sub-group of 60 patients in the randomized trial had peak VO₂ measurements taken. There was a statistically significant increase in the peak VO₂ in patients receiving milrinone over a 3-month period (+ 15.3%) as compared with the placebo group (− 14.8%). The difference was highly significant.

It is not clear why milrinone produces an early improvement in exercise tolerance. Studies of limb blood flow have suggested that the increased blood flow demonstrated after amrinone and milrinone administration may indicate improved blood supply to skeletal muscles, thereby delaying the appearance of anaerobic metabolism during exercise.

Symptomatic improvement

Both intravenous and oral milrinone have been demonstrated to reduce breathlessness on exertion
and at rest, and to improve the symptom of fatigue, as well as reducing peripheral oedema.

In the controlled oral milrinone multicentre study, the quality-of-life assessment made using the sickness impact profile demonstrated significant improvements in the ‘sleep and rest’ and ‘work’ categories when patients receiving milrinone were compared with the placebo group\(^\text{13}\). There was no change, however, in the NYHA classification of patients receiving milrinone compared with those receiving placebo.

In this study, the need for additional therapy to control heart failure during the trial, including increasing the diuretic dosage (the co-intervention rate), was significantly lower in patients receiving milrinone. This study established that milrinone’s effects were maintained throughout the 3 months of treatment and no evidence of tolerance to its action was noted.

**Adverse effects**

The incidence of adverse effects in the multicentre, oral placebo-controlled study and in a separate invasive haemodynamic study, have been carefully correlated. The only significant side-effects, which have been noted after milrinone administration in controlled studies, are the development of headaches and palpitations in approximately 9% of patients receiving the drug as compared with 3% of patients on placebo. A first-dose effect was observed in a small number of patients receiving milrinone in the controlled exercise tolerance study. This consisted of a small, but statistically significant, fall in the systolic blood pressure of approximately 6% of patients with a non-significant increase in heart rate of approximately 6%, at 60–90 min after drug administration with the patients in the erect posture.

In the multicentre, placebo-controlled milrinone study, 24-h ECG Holter monitoring was carried out in a sub-group of 103 patients. There was no significant difference in the incidence of ventricular arrhythmias between the milrinone, digoxin, milrinone plus digoxin, or placebo groups. However, using the clinical definition of pro-arrhythmia reported by Morganroth\(^\text{17}\), there was a marginally greater incidence of pro-arrhythmia in the milrinone-treated patients compared with the placebo group. Pro-arrhythmia was defined as a 3- to 10-fold increase in the frequency of ventricular premature beats per hour between the baseline and the randomized phase, or a 10-fold increase in repetitive forms of ventricular arrhythmia per hour, or both. Pro-arrhythmia was observed in nine (18%) patients receiving milrinone as compared with two (4%) patients not receiving milrinone. However, pro-arrhythmia did not adversely affect clinical outcome\(^\text{13}\).

Importantly, in view of previous findings with the parent compound amrinone, none of the multicentre controlled or uncontrolled trials of milrinone has shown an increased frequency of gastrointestinal disorders, abnormal liver-function tests or thrombocytopenia.

**Survival**

Symptomatic improvement in patients with heart failure is an important goal of therapy, particularly in the more severe grades of heart failure. However, the ultimate goal of therapy in all patients with heart failure is, in addition to symptomatic improvement, to enhance survival. The management of heart failure in recent years has been influenced by the recent reports that the ACE inhibitor enalapril has been demonstrated in the Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS)\(^\text{18}\) to improve survival. Similarly, in the Veterans Administration co-operative study (V-HeFT), the combination of nitrates and hydralazine was shown to improve survival\(^\text{19}\). In order to establish a major therapeutic role, phosphodiesterase inhibitor drugs like milrinone must be shown not only to produce symptomatic improvement, but also to have a beneficial effect on survival.

Experimentally induced congestive heart failure (e.g. by coronary artery ligation in rats) has served as a model for evaluating the effects of milrinone on survival. Milrinone, like enalapril and captorpril, has been shown to prolong survival in this rat model of congestive heart failure\(^\text{20,21}\).

No formal controlled clinical mortality/survival study has yet been performed with milrinone. Similarly, open milrinone therapy has not been evaluated over a sufficiently long period of time to produce meaningful estimates of its effect on survival. In this randomized, controlled 3-month trial of milrinone, no clear difference in survival was apparent between patients receiving the drug and those on placebo.

**Future studies**

The role of phosphodiesterase inhibitors such as milrinone in the therapeutic management of heart
**Therapeutic achievements of phosphodiesterase inhibitors**

**Future studies: Mild heart failure (NYHA class II or III)**

![Diagram](https://example.com/diagram.png)

- **DIURETIC**
- **ACE**
- **DIGOXIN**
- **MILRINONE**


**Figure 3** Future studies: mild heart failure (NYHA class II or III). Sample size 3000–4500 to demonstrate a 25% reduction in mortality; monitor exercise-tolerance time and quality-of-life indices.

Failure requires further comparative evaluation with established agents. This is particularly important since the publication of the V-HeFT trial and the CONSENSUS trial results\(^{18,20}\). In patients with mild heart failure, in whom symptomatic improvement may be modest, comparative trials are urgently needed to assess the influence of therapy with drugs such as milrinone on survival. A large-scale multicentre trial of patients with NYHA class II or III heart failure who are already receiving a diuretic is required. Patients would be randomly allocated to three separate treatment groups (Fig. 3), and would receive either an ACE inhibitor such as enalapril, or digoxin, or milrinone. In order to demonstrate a 25% reduction in mortality between these groups in such a study, it would be necessary to recruit between 3000 and 4500 patients. Such a study should also monitor changes in quality-of-life indices and exercise tolerance.

Because ACE inhibitors have been shown in the CONSENSUS trial to not only improve symptomatic status, but also survival, treatment with an ACE inhibitor and a diuretic is likely to become the treatment of choice in patients with NYHA class III or IV heart failure. In patients with heart failure it has been clearly demonstrated that haemodynamic improvement is more significant with milrinone than with captopril and that limb blood flow is increased by milrinone but not changed by the ACE inhibitor captopril. The addition of milrinone to captopril therapy increases limb blood flow beneficially\(^{16}\). This suggests that symptomatic improvements with combined therapy might well be enhanced. A large-scale comparative trial in NYHA class III or IV patients is, therefore, desirable in which patients receiving both a diuretic and an ACE inhibitor will be randomly allocated to receive milrinone or placebo therapy (see Fig. 4). Again the outcome of such trials

**Moderate/severe heart failure (NYHA III or IV)**

![Diagram](https://example.com/diagram.png)

- **ACEI + DIURETIC**
- **PLACEBO**
- **MILRINONE**

Monitor survival

- **ETT**
- Quality-of-life indices

**Figure 4** Future studies: moderate/severe heart failure (NYHA class III or IV). Monitor survival, exercise-tolerance time and quality-of-life indices.
using survival, quality-of-life indices and exercise-tolerance time should be assessed.

Finally, it would be attractive, in view of the results of the V-HeFT study to compare, on a multicentre basis, patients already receiving digoxin and diuretics who would in addition receive therapy with either isosorbide + hydralazine, or an ACE inhibitor, or milrinone.

Conclusion

The phosphodiesterase inhibitor milrinone has been shown to produce clear improvements in systolic and diastolic function following both intravenous and oral administration. This is achieved without a significant increase in myocardial oxygen consumption, because the associated vasodilator action offsets any tendency for an increase in oxygen consumption to be produced by the increase in contractility. In placebo-controlled, double-blind studies, milrinone has been shown to increase exercise tolerance and to improve total body oxygen consumption. Side-effects are relatively infrequent, although a modest incidence of headache and palpitations in patients receiving milrinone is observed. Ventricular tachyarrhythmias were not significantly increased in placebo-controlled studies of milrinone therapy, but a modest pro-arrhythmic effect may occur. Experimentally, milrinone prolongs survival in a rat heart failure model, but no clinical evidence of prolonged survival following milrinone is currently available. Future large-scale studies of survival and symptomatic response to milrinone are required in patients already receiving a diuretic and an ACE inhibitor.

References


