

Treatment of end stage dilated cardiomyopathy

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Dilated cardiomyopathy continues to be a serious clinical problem with about 20 000 new patients affected in the United States each year. By definition, the cause of injury to the myocardium is unknown.¹ Consequently, treatment is purely symptomatic because it cannot be specifically directed toward aetiology. In most cases, the major symptomatic presentations of dilated cardiomyopathy, arrhythmia, embolic phenomena, and congestive heart failure, are successfully managed, at least initially, by conventional treatment. However, if myocardial injury persists or is so severe that conventional treatment does not palliate the symptoms, cardiac transplantation remains the only viable alternative. In fact, 50% of those undergoing cardiac transplantation have dilated cardiomyopathy.² In the present paper we describe the conventional management of dilated cardiomyopathy and discuss new approaches that may prolong survival and reduce morbidity.

Management of congestive heart failure

VOLUME OVERLOAD AND EXERCISE

The management of congestive heart failure in patients with dilated cardiomyopathy differs little from the management of patients with specific heart muscle diseases or other causes of left ventricular dysfunction (table 1). Volume overload owing to salt and water retention is prominent. Sodium and water restriction are appropriate and diuretics are indicated. Loop diuretics (frusemide, bumetanide, etc) are preferred. When the dose of loop diuretics is increasing and the response diminishing, the addition of a thiazide (metolazone) to the loop diuretic may be of additional benefit.³ With low cardiac output and an oedematous gut intestinal absorption may be poor. An intravenous bolus or continuous infusion of frusemide may be successful when high oral doses do not induce the desired diuretic effect.⁴ Ultrafiltration can reduce fluid overload in severe refractory congestive heart failure.⁵ Patients with symptoms and physical findings of volume overload should be treated with diuretics. Patients without evidence of volume overload, dyspnoea, or peripheral oedema do not require diuretic treatment.

Though bed rest is appropriate during the acute presentation of congestive heart failure, a programme of progressive physical activity may improve exercise tolerance and enhance functional capacity in patients with dilated cardiomyopathy. Supervised exercise training

has beneficial haemodynamic and metabolic effects.^{6,7} Anaerobic (isometric) exercise should be avoided and aerobic training encouraged.

VASODILATORS

Reduction of preload and afterload improves cardiac efficiency and ejection fraction in patients with left ventricular dysfunction. The angiotensin converting enzyme inhibitors are most widely applied for this purpose. Short term treatment with captopril, the prototype of this class of drugs, reduces systemic vascular resistance and filling pressures, increases cardiac output, and improves exercise tolerance. The haemodynamic benefit is sustained during long term treatment.⁸ Other angiotensin converting enzyme inhibitors have similar haemodynamic properties.⁹ The cooperative north Scandinavian enalapril survival study (CONSENSUS) concluded that patients with severe symptomatic limitation (New York Heart Association (NYHA) class III and class IV) and a markedly reduced ejection fraction have a significant survival benefit at one year if randomly assigned to receive enalapril plus conventional therapy compared with a control group treated with placebo plus conventional therapy.¹⁰ In the Studies of Left Ventricular Dysfunction (SOLVD) the survival of patients who were less severely ill than those studied in CONSENSUS also improved when enalapril was added to conventional treatment.¹¹ In the SOLVD prevention arm the development of congestive heart failure and instances of hospital admission with congestive heart failure were reduced (by 37% and 36% respectively) in symptom free patients with abnormal systolic function.¹² This finding emphasises the importance of angiotensin converting enzyme inhibitors.¹² Therefore, angiotensin converting enzyme inhibitors must be regarded as standard treatment for dilated cardiomyopathy. Unfortunately, it is estimated that only 25% of those with congestive heart failure in the United States receive angiotensin converting enzyme inhibitors. Alternative vasodilators may be necessary in about 20% of patients who do not tolerate the agents because of renal dysfunction, hypotension, hyperkalaemia, or cough.¹³

In the first Veterans heart failure trial (V-HEFT I) the survival of moderately symptomatic patients with abnormal systolic function was better when a combination of hydralazine and isosorbide dinitrate was given compared with prazosin or placebo.¹⁴ In the Hy-C trial, captopril alone was more efficacious than the

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Table 1 Conventional management of congestive heart failure in dilated cardiomyopathy

- Sodium and water restriction
- Diuretics
- Digoxin
- Angiotensin converting enzyme inhibition if tolerated

Table 2 Positive inotropic agents in the management of dilated cardiomyopathy

- Digitalis glycosides
- Intravenous β adrenergic agonists (dobutamine and dopamine)
- Phosphodiesterase inhibitors (amrinone, milrinone)
- Quinolinones (flosequinan, vesnarinone, OPC18790)

hydralazine/isosorbide dinitrate combination.¹⁵ The V-HEFT II study confirmed that mortality was lower in patients treated with enalapril than in those randomised to hydralazine/isosorbide dinitrate.¹⁶ None the less, this combination remains a useful alternative in those who are intolerant of angiotensin converting enzyme inhibitors.

The fluorinated quinolinone, flosequinan, has vasodilatory and inotropic properties.¹⁷ In FACET, patients treated with intermediate doses of flosequinan (100 mg *v* placebo) in addition to ACE inhibitors exercise tolerance increased and quality of life improved.¹⁸ Unfortunately, preliminary unpublished analysis of the PROFILE study demonstrated enhanced mortality at this dose: this suggests a greater inotropic effect than previously recognised. The effect of low dose (≤ 75 mg day) flosequinan on mortality remains unclear.

Calcium channel blockade was shown to be of benefit when diltiazem was added to conventional treatment in patients with dilated cardiomyopathy and mild to moderate congestive heart failure.¹⁹ However, diltiazem's known negative inotropic properties have deterred intensive clinical investigation. Calcium channel blockade with a less negatively inotropic agent, amlodipine, showed improved exercise tolerance in this subgroup.²⁰ Before calcium channel blockade can be regarded as adjunctive therapy in dilated cardiomyopathy, multicentre trials, which are underway, must show a beneficial effect.

INOTROPES (TABLE 2)

Digitalis glycosides are the historical cornerstone of treatment for congestive heart failure. Accurate doses have replaced the tea brewed with the foxglove leaves by Withering in 1785, but the mechanism of the beneficial effect has come into question and randomised withdrawal studies have only recently shown its efficacy. Although digitalis glycosides block sodium/potassium ATPase and increase intracellular calcium through passive sodium/calcium exchange, they also modify cardiac sympathetic activity, which suggests that they have a modulating effect on baroreceptor reflexes.²¹ Not enough is known about this effect to attribute any beneficial effect to modulation of neural activity. The efficacy of digoxin has been questioned. However, the randomised assessment of digoxin and inhibitors of angiotensin converting enzyme (RADIANCE) study showed clinical deterioration in patients with chronic congestive heart failure and sinus rhythm when they are randomly withdrawn from treatment with digitalis glycosides.²² In those randomised to long term oral digoxin the beneficial effect was retained. Consequently, the debate regarding the efficacy of this age-old treatment has become less intense. Only its effect on mortality remains in question and awaits the completion of a trial sponsored by the National Institutes of Health.

The selective β adrenergic agonist, dobutamine, is effective for the short-term manage-

ment of congestive heart failure or exacerbations of chronic heart failure when given as an intravenous infusion to doses of 10 $\mu\text{g}/\text{kg}/\text{min}$.²³ Attempts to develop oral β adrenergic agonists for the long-term treatment of heart failure have been frustrated by the rapid development of tolerance,²⁴ which presumably is associated with down regulation of β adrenergic receptors. In patients with severe congestive heart failure, the beneficial effect of brief (three to four day) infusions of dobutamine may be sustained.²⁵ This observation served as the rationale for intermittent infusions of dobutamine in ambulatory patients. Many protocols for intermittent infusion have been proposed and there is no consensus on the duration of infusion and interval between infusions.²⁶ Additionally, the technological advances in the design of infusion pumps allow patients to be maintained on continuous intravenous dobutamine as outpatients. Such treatment is usually reserved for patients awaiting cardiac transplantation.²⁷ Despite the apparent acceptance of this approach, randomised prospective trials designed to document efficacy have not been completed.

The phosphodiesterase inhibitor amrinone was developed as a positive inotropic agent for short-term intravenous infusions.²⁸ The phosphodiesterase inhibitors are effective inotropes with vasodilating properties. The effect is most pronounced when combined with β adrenergic agonists.²⁹ These additive effects are often helpful in patients awaiting cardiac transplantation.³⁰ Because long-term treatment with amrinone is associated with thrombocytopenia, the analogue milrinone was developed. Milrinone can be given either by mouth or intravenously. The acute haemodynamic effects of milrinone and amrinone are similar. However, in the prospective randomised milrinone survival evaluation (PROMISE) trial cardiovascular mortality was 34% higher in those on long-term oral treatment.³¹ Consequently, clinical research on long-term oral administration of the phosphodiesterase inhibitors essentially has been suspended. Therefore, the digitalis glycosides are the only oral positive inotropic agents available for use in patients with chronic congestive heart failure.

NEW TREATMENTS

Vesnarinone/OPC18790

Vesnarinone (OPC8212), an orally active quinolinone, has recently been developed for the treatment of congestive heart failure.³² Although it has mild inhibitory effects on phosphodiesterase III, vesnarinone also delays outward and inward potassium currents and opens sodium channels, prolonging the action potential and slowing heart rate. The mechanism of action is not dissimilar to that of the antiarrhythmic agent sotalolol. In a randomised prospective trial of more than 500 patients with symptomatic congestive heart failure and ejection fraction $<30\%$, an intermediate dose of vesnarinone (60 mg/day) reduced all cause morbidity and mortality by more than 50%

and quality of life improved significantly.³³ The high dose arm (120 mg) increased mortality. Neutropenia occurred in 2.5% of the patients receiving the agent. This drug is currently under continued phase III clinical trials. An intravenous analogue, OPC18790, is entering clinical trials.

β Blockers

The adverse effect of neurohormonal activation is underscored by the efficacy of β adrenergic blockade in the treatment of congestive heart failure. The metoprolol in dilated cardiomyopathy (MDC) trial showed a reduction in cardiovascular morbidity and improved ejection fraction in more than 300 patients with dilated cardiomyopathy and congestive heart failure.³⁴ Although tolerance to β adrenergic blockade is quite good overall, the dose titration phase can exacerbate congestive heart failure in some patients and so delay the achievement of the maximum targeted dose. Some new β blockers have vasodilating properties that improve tolerance and reduce the difficulty with dose titration. Vasodilation by bucindolol is mediated by a nitrile-like component, and carvedilol has weak α blocking properties.³⁵ Compared with metoprolol, short-term treatment with carvedilol increased the cardiac index, decreased systemic vascular resistance, and decreased filling pressures—a reflection of the vasodilator effect. Long-term treatment with bucindolol produced a sustained increase in ejection fraction.³⁶

The mechanism of action of β blockade is unknown. Initially, it was thought that up regulation of the β receptor that resulted from long-term treatment with metoprolol was the major mechanism of action.³⁷ However, clinical and haemodynamic improvement was detected with carvedilol treatment in the absence of up regulation of these receptors.³⁸ Perhaps the major mechanism of action is simply blockade of the receptors and a reduction of the adverse effects of catecholamines on the failing human heart.

Vesnarinone and β blockade may prove to be major additions to the treatment of dilated cardiomyopathy. Additionally, if the definitive clinical trials show survival similar to the improvement reported in the preliminary studies, the outcome with this approach in patients with NYHA class III symptoms will be comparable to cardiac transplantation.

Anticoagulation

Patients with dilated cardiomyopathy are susceptible to thromboembolic phenomena, because of poor peripheral perfusion and low flow, and to the formation of mural thrombi, particularly when the ejection fraction is <30%.³⁹ The likelihood of an embolic episode is approximately 30% over a two year follow up in patients with a low ejection fraction and decompensated congestive heart failure. Therefore, it is logical to consider long-term oral anticoagulant treatment in these patients. However, regulation of anticoagulant treatment may be particularly difficult because the

patients who are most likely to benefit, those with poorly controlled congestive heart failure, have hepatic congestion and subsequent autoanticoagulation. Recently, the broad based recommendation for chronic anticoagulant treatment in patients with dilated cardiomyopathy has been questioned because no prospective clinical trials showing its efficacy and defining its morbidity have been completed. Therefore, long-term oral anticoagulation is commonplace but not of proven benefit.

Antiarrhythmic treatment

Ventricular arrhythmias are common in patients with dilated cardiomyopathy. In fact, over 70% of these patients have non-sustained ventricular tachycardia during ambulatory monitoring.⁴⁰ The arrhythmias may be inducible in the electrophysiology laboratory but a correlation between ventricular arrhythmias and sudden death in dilated cardiomyopathy has never been confirmed.⁴¹ Decompensated congestive heart failure itself is commonly associated with ventricular arrhythmias.

Antiarrhythmic treatment is fraught with difficulty in this group of patients because of the arrhythmogenic effects and negative inotropic properties of most antiarrhythmic agents. Antiarrhythmic agents should be avoided if possible and only used in those patients with symptomatic ventricular arrhythmia. Selected patients with recurrent, symptomatic, uniform ventricular tachycardia may be considered for an implantable cardioverter.

Cardiac transplantation

Dilated cardiomyopathy remains the most common indication for cardiac transplantation. This procedure was first used clinically over 25 years ago and its use has expanded considerably over the past two decades. Survival rates have improved to more than 80% at one year and to about 70% at five years.² The quality of life is considered excellent. In fact, the likelihood of returning to normal activities is higher than with other common forms of cardiac surgery.

Unfortunately, the morbidity of immunosuppression, the development of coronary artery disease in the allograft, and the lack of donors all limit access to this procedure by patients with congestive heart failure or adversely affect outcome. The outcome of transplantation in patients with severe (NYHA class IV) congestive heart failure is much better than with medical management, but the shortage of donors, more than any other factor, limits its wider use.

Those patients who are most likely to benefit from the procedure should be selected as recipients.⁴² Recipient selection criteria have been liberalised because of improvements in the pharmacological treatment of allograft rejection. In the United States, donor organs are allocated regionally and those recipients who are in the intensive care unit and receiving mechanical assistance or intravenous

Table 3 Approach to management of dilated cardiomyopathy

- Initiate conventional management with digoxin, diuretics, and ACE inhibitors or hydralazine/isosorbide dinitrate
- Consider β blockade or vesnarinone if symptoms persist
- Add anticoagulation for EF < 0.30, history of thromboembolic phenomena, or detection of mural thrombi
- If symptomatic at rest despite above measures, add intravenous dobutamine and/or phosphodiesterase inhibitors and consider cardiac transplantation

inotropic support (status I) have the highest priority. All other patients are in a second priority category (status II). Some contend that status I patients are not the ideal candidates for major cardiac surgery and their outcome is poorer than those who are in better physiological condition at the time of operation. Careful analyses of outcomes in status I and status II patients undergoing transplantation show no difference. However, status I recipients are much more likely to die before transplantation. Consequently, the donor allocation scheme is justified.

As the treatment of congestive heart failure improves, the outcome of patients who are NYHA class III may improve to the point where transplantation is no longer warranted. Many centres now use peak oxygen uptake (VO_2) on exercise testing as a valuable index of predicting requirement for cardiac transplantation. Only patients with a peak $\text{VO}_2 < 14$ ml/min/kg are regarded as candidates for cardiac transplantation.⁴³ Even with these stringent criteria, some patients improve and may ultimately be removed from the list. There are twice as many patients added to the waiting list in the United States each month as actually undergo transplantation. If this trend continues, patients who are NYHA class III may no longer be eligible for a donor organ because of low priority. Furthermore, there was no improvement in survival after transplantation in those patients who waited more than six months for a donor organ when compared with patients who were treated medically.⁴⁴ These data further imply that the transplantation waiting list should be dynamic and some patients may be listed for transplantation but removed because medical management is successful. The addition of successful oral therapeutic agents for heart failure such as β blockade or vesnarinone warrants a prospective randomised trial comparing transplantation with medical management in status II patients. The most effective means of assuring the equitable and timely distribution of donor hearts is to treat congestive heart failure as well as possible.

Summary

Patients should be referred for cardiac transplantation only after all other means of management of congestive heart failure have been attempted and have been unsuccessful (table 3). An adequate therapeutic trial of conventional and experimental agents including β blockade and vesnarinone should be completed and be shown to be unsuccessful before transplantation is considered in patients in NYHA class III. Prospective clinical trials need to be completed to define the role of newer therapeutic options. The scarcity of donor organs will probably preclude the use of cardiac transplantation in all patients who may benefit. Alternative methods of cardiac replacement (such as dynamic cardiomyoplasty, permanent implantable mechanical circulatory assistance, and xenografting) must be developed. These methods coupled with

better pharmacological treatment will greatly improve the outcome of patients with dilated cardiomyopathy.

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