CARDIOMYOPATHY

Diagnosis and management of dilated cardiomyopathy

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Dilated cardiomyopathy is a heart muscle disorder defined by the presence of a dilated and poorly functioning left ventricle in the absence of abnormal loading conditions (hypertension, valve disease) or ischaemic heart disease sufficient to cause global systolic impairment. A large number of cardiac and systemic diseases can cause systolic impairment and left ventricular dilatation, but in the majority of patients no identifiable cause is found—hence the term “idiopathic” dilated cardiomyopathy (IDC). There are experimental and clinical data in animals and humans suggesting that genetic, viral, and immune factors contribute to the pathophysiology of IDC.

Diagnosis

Clinical presentation

The first presentation of IDC may be with systemic embolism or sudden death, but patients more typically present with signs and symptoms of pulmonary congestion and/or low cardiac output, often on a background of exertional symptoms and fatigue for many months or years before their diagnosis. Inter-current illness or the development of arrhythmia, in particular atrial fibrillation, may precipitate acute decompensation in such individuals. Increasingly, IDC is diagnosed incidentally in asymptomatic individuals during routine medical screening or family evaluation of patients with established diagnosis.

A careful family history facilitates diagnosis of inherited causes of IDC by characterising the family phenotype, and also defines the scope of family screening.¹ At least 25% of patients have evidence for familial disease with predominantly autosomal dominant inheritance. Clinically, familial disease is defined by the presence of two or more affected individuals in a single family and should also be suspected in all patients with IDC and a family history of premature cardiac death or conduction system disease. A further 20% of relatives have isolated left ventricular enlargement that can progress to IDC in a minority of cases. Dilated cardiomyopathy can occur in a number of X linked diseases such as Becker's and Duchenne's muscular dystrophies and X linked IDC. It may also occur in patients with mitochondrial DNA mutations and inherited metabolic disorders. Thus when taking a

Causes of dilated cardiomyopathy

Young

- Myocarditis (infective/toxic/immune)
- Carnitine deficiency
- Selenium deficiency
- Anomalous coronary arteries
- Arteriovenous malformations
- Kawasaki disease
- Endocardial fibroelastosis
- Non-compacted myocardium
- Calcium deficiency
- Familial IDC
- Barth syndrome

Adolescent/adults

- Familial IDC
- X linked
- Alcohol
- Myocarditis (infective/toxic/immune)
- Tachycardiomyopathy
- Mitochondrial
- Arrhythmogenic right ventricular cardiomyopathy
- Eosinophilic (Churg Strauss syndrome)
- Drugs—anthracyclines
- Peripartum
- Endocrine
- Nutritional—thiamine, carnitine deficiency, hypophosphataemia, hypocalcaemia

family history, specific attention should be given to a history of muscular dystrophy, features of mitochondrial disease (for example, familial diabetes, deafness, epilepsy, maternal inheritance), and signs and symptoms of other inherited metabolic diseases. Inborn errors of metabolism usually present in infancy and childhood, but some may present in adulthood, in particular haemochromatosis. Nutritional deficiencies and endocrine abnormalities may produce heart failure, and a complete drug history is essential, both in relation to the administration of cardiotoxic drugs such as anthracyclines and with respect to the use of illegal substances. Cocaine abuse, in particular, can produce a chronic IDC picture as well as an acute cardiomyopathy. Exposure to HIV and other infectious agents such as hepatitis C may be relevant in some patients.

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Electrocardiography

The ECG in patients with IDC may be remarkably normal, but abnormalities ranging from isolated T wave changes to septal Q waves in patients with extensive left ventricular fibrosis, prolongation of atrioventricular (AV) conduction, and bundle branch block may be observed. Sinus tachycardia and supraventricular arrhythmias are common, in particular atrial fibrillation. Approximately 20–30% of patients have non-sustained ventricular tachycardia and a small number present with sustained ventricular tachycardia.

Echocardiography

An echocardiogram is essential for the diagnosis of IDC (fig 1). In patients with poor echo windows other imaging modalities such as radionuclide scans and magnetic resonance may be useful. Recently suggested echocardiographic criteria for IDC are shown in the adjacent box. When making the diagnosis of IDC it is important to take into account sex and body size. The most widely applied criteria in family studies are based on the Henry formulae, with a left ventricular cavity dimension of $> 112\%$ of predicted normal values used to define left ventricular enlargement and a shortening fraction of $< 25\%$ defining abnormal systolic function. These criteria have some limitations, in particular the use of only short axis dimensions and a relatively low specificity in young patients, but they are practical and reproducible. Recent European guidelines have suggested that when screening family members a more conservative cut off of $> 117\%$ of predicted values (2 SD plus 5%) should be used in order to increase specificity.¹

Exercise testing

Symptom limited upright exercise testing is of considerable value when assessing functional limitation in patients with IDC, particularly when combined with respiratory gas analysis. Metabolic exercise testing provides an objective measure of exercise capacity, facilitates assessment of disease progression, helps assess prognosis, and is useful in selecting patients for cardiac transplantation. Metabolic exercise testing may also provide diagnostic information in patients with left ventricular impairment caused by primary metabolic abnormalities such as mitochondrial disease, by detecting severe acidaemia.

Viral serology

In children and adults with acute myocarditis, viral culture and serology may be useful in establishing a diagnosis of viral myocarditis by demonstrating rising titres of neutralising antibodies, or virus specific IgM class antibodies to enteroviruses indicative of recent infection. In adults with IDC the relation between viral infection and disease is more uncertain. Many studies purporting to demonstrate a positive association between viral infection and IDC are very small, and have failed to control for cross contamination with laboratory controls.² The source of disease and control populations is also important as the most commonly impli-

Diagnostic criteria for IDC

Ejection fraction < 0.45 and/or a fractional shortening of $< 25\%$, and a left ventricular end diastolic dimension of $> 112\%$ predicted value corrected for age and body surface area.

Exclusion criteria:

- Absence of systemic hypertension ($> 160/100$ mm Hg)
- Coronary artery disease ($> 50\%$ in one or more major branches)
- Chronic excess alcohol (> 40 g/day female, > 80 g/day male for more than five years after six month abstinence)
- Systemic disease known to cause IDC
- Pericardial diseases
- Congenital heart disease
- Cor pulmonale

Key

The criteria for left ventricular enlargement are based on data of Henry *et al* (*Circulation* 1980;62:1054–61). A value of $> 112\%$ of predicted represents 2 SDs from the mean corrected for body surface area and age given by the formula:

$$(45.3 \times (\text{body surface area})^{1/3} - (0.03 \times \text{age}) - 7.2) \pm 12\%.$$

Mestroni *et al* have suggested a more conservative cut off of $> 117\%$ (2 SDs + 5%) in order to increase specificity for family studies.¹ However, a value of 112% is probably just as predictive of disease if systolic function is also abnormal.

cated enterovirus, coxsackie B, is ubiquitous in most communities and causes small subclinical epidemics. At present, the detection of viral antibodies in patients with stable chronic IDC has little impact on management, but viral studies may become more important in the future if current trials suggest a role for immunosuppressive/modulatory treatments in IDC.

Endomyocardial biopsy

Although endomyocardial biopsy can be used to diagnose a wide range of myocardial diseases, most are rare causes of IDC and can often be diagnosed by other means. Even the detection of an inflammatory cardiomyopathy is of limited use, given the uncertainties and inconsistencies surrounding its diagnosis using conventional light microscope criteria. Endomyocardial biopsy may be of use in selected patients—for example, those with suspected cardiac haemochromatosis and other infiltrative or malignant diseases—but in general it should be confined to carefully conducted clinical trials. A number of immunohistological studies have already demonstrated increased numbers of T cells and increased expression of endothelial and interstitial MHC (major histo-

Figure 2: Myocardial section from a patient with IDC stained for the intercellular adhesion molecule 1 (ICAM-1) (green) and factor VIII (red). Dual staining in yellow indicates the presence of endothelial ICAM activity, indicative of chronic low grade inflammation. Reproduced with permission from Professor Michael Davies.

Recommended tests in adult patients with IDC

- Erythrocyte sedimentation rate (ESR)
- Creatine kinase (CK)
- Viral serology (if acute presentation)
- Renal function
- Liver function tests/calcium
- Serum ferritin/iron/transferrin
- Thyroid function tests

Only in specific indications:

- Coronary angiography
- Blood
 - autoantibodies
 - carnitine
 - lactate/pyruvate
 - selenium
 - pyruvate
 - acylcarnitine profile
 - drug screen
 - red cell transketolase (beri beri)
 - infective screen (HIV/hepatitis C, enteroviruses)
- Urine
 - organic acid/amino acids
- Skeletal muscle biopsy
- Endomyocardial biopsy

compatibility complex) antigens and cell adhesion molecules in IDC hearts, consistent with previous observations of immune activity in IDC (fig 2).³ As our understanding of the clinical significance of immunohistochemical markers improves, it is likely that endomyocardial biopsy will become more important in guiding immunomodulatory treatment.

Figure 1: Parasternal long axis (A) and apical four chamber (B) cross sectional (two dimensional) echocardiograms in a 23 year old patient with IDC.

Treatment

Specific treatments are not available for most patients with IDC. Therefore, the primary aims of treatment are to control symptoms and to prevent disease progression and complications such as progressive heart failure, sudden death, and thromboembolism. Diuretics remain central to the management of congestive symptoms, but they should not be used as monotherapy as they exacerbate neurohumoral activation and may contribute to disease progression unless administered concomitantly with neurohumoral antagonists.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS
Activation of the renin-angiotensin-aldosterone system (RAAS) is central to the pathophysiology of heart failure of whatever underlying aetiology. For this reason, angiotensin converting enzyme (ACE) inhibitors are the mainstays of treatment in patients with IDC, irrespective of the severity of heart failure.⁴ ACE inhibitors improve dyspnoea and exercise tolerance, reduce hospitalisation rates, and reduce cardiovascular mortality. They also

prevent or slow disease progression in asymptomatic patients. A substantial proportion of patients who are given ACE inhibitors fail to reach the target doses reported in randomised studies. Recent evidence from the ATLAS study⁵ suggests that maximum recommended doses of lisinopril (32.5–35 mg) are as well tolerated as low doses (2.5–5 mg), and are associated with a 12% greater reduction in the combined risk of death or hospitalisation. Although the comparative benefit of intermediate doses is still uncertain, it seems prudent to try to achieve recommended target doses in most patients.

Significant side effects are uncommon during ACE inhibitor treatment, the most frequent being hypotension, cough, and deterioration of renal function. Mild impairment of renal function (creatinine up to 265 $\mu\text{mol/l}$) in the absence of renal artery stenosis is not, however, an absolute contraindication for ACE inhibition. Similarly, a resting systolic pressure of 80–90 mm Hg during treatment is acceptable in the absence of postural symptoms. When side effects are problematic, the first step is to consider reducing the dose of other medications. In particular, diuretic doses can often be reduced in patients who no longer have congestive symptoms. When ACE inhibitors have to be discontinued, hydralazine–nitrate combination can be useful in treating congestive symptoms.

ANGIOTENSIN II RECEPTOR ANTAGONISTS

Angiotensin II (AII) receptor antagonists have recently attracted much interest and controversy with regard to their place in the heart failure therapeutic armoury. AII receptor antagonists have haemodynamic effects broadly similar to those of ACE inhibitors, but may be slightly better tolerated and at least theoretically overcome the “escape” of angiotensin system blockade observed in some patients on ACE inhibitors. However, unlike ACE inhibitors, AII receptor antagonists do not inhibit bradykinin metabolism and thus lack a potentially beneficial vasodilatory effect. The ELITE-1 study⁶ suggested that losartan may have a greater effect on mortality than captopril in elderly patients with mild to moderate heart failure. Preliminary data from the follow up to this study have failed to demonstrate a superior effect of losartan over captopril, but the study was not powered to detect equivalence between the two drugs. The recent RESOLVD study⁷ has suggested that combination treatment with an ACE inhibitor and an AII antagonist may be more beneficial in reducing neurohumoral activation and in preventing ventricular remodelling than either drug alone. A number of trials (VALHEFT, CHARM) are currently addressing these and other issues regarding AII receptor treatment.

β BLOCKERS

In spite of ACE inhibitor treatment, mortality continues to be high in patients with heart failure. This is perhaps not surprising given that ACE inhibitors act on only one aspect of the neurohumoral cascade (RAAS) that contrib-

utes to progressive left ventricular dysfunction. It has been recognised for some time that excess sympathetic activity contributes to the clinical syndrome of heart failure, but it was only recently that use of β blockers in heart failure patients gained widespread acceptance. Three recent multicentre placebo controlled studies, the US carvedilol studies,⁸ CIBIS II (bisoprolol),⁹ and MERIT-HF (metoprolol),¹⁰ have demonstrated substantial reductions in sudden death and death from progressive heart failure in patients with predominantly New York Heart Association (NYHA) class II and III symptoms treated with β blockers. In CIBIS II and MERIT-HF, but not the US carvedilol study, subgroup analysis suggested a greater effect in patients with ischaemic heart failure compared to “non-ischaemic” heart failure. Nevertheless, when taken together with earlier studies, these data suggest that it is advisable to consider β blockers in IDC patients with mild to moderate symptoms in spite of maximal treatment with ACE inhibitors. Patients should not be started on β blockers if they have signs or symptoms of decompensated heart failure, and initial doses should be low (carvedilol 3.125 mg twice daily, bisoprolol 1.25 mg once daily, metoprolol SR 12.5 mg once daily). Doses should be increased gradually every 2–4 weeks, monitoring closely for hypotension, bradycardia or worsening heart failure until the target dose is achieved or side effects occur.

SPIRONOLACTONE

High plasma concentrations of aldosterone are frequent in patients with moderate to severe heart failure and contribute to sodium retention, potassium loss, sympathetic activation, myocardial fibrosis, and baroreceptor dysfunction. ACE inhibition usually results in only a transient decrease in aldosterone concentrations, probably because a major source of aldosterone is reduced hepatic clearance rather than angiotensin dependent adrenal secretion. The recent RALES study¹¹ has shown that the addition of 25 mg of spironolactone to conventional treatment in patients with an ejection fraction < 35% and a history of NYHA class IV heart failure is associated with a 30% reduction in the overall risk of death. Hospitalisation rates for cardiac causes and functional status also improved, and serious hyperkalaemia was infrequent in patients with a serum creatinine < 221 $\mu\text{mol/l}$. The drug should be considered in all patients presenting with moderate to severe heart failure symptoms.

Novel potential pharmacological treatments

NATRIURETIC PEPTIDES

Atrial natriuretic peptide (ANP) is released from atrial myocytes in response to stretch, and induces diuresis, naturesis, vasodilatation, and suppression of the renin–angiotensin system. Circulating concentrations of ANP are increased in congestive cardiac failure and correlate with NYHA functional class and prognos-

sis. Both ANP and brain natriuretic peptide are potent vasodilators and diuretics, but clinical trials have shown that tolerance frequently develops during intravenous ANP administration. This problem may be overcome by the development of drugs that inhibit neutral endopeptidase, the enzyme responsible for breakdown of natriuretic peptides.

CYTOKINE ANTAGONISTS

Tumour necrosis factor α (TNF α) or cachectin is a proinflammatory cytokine released from activated macrophages, T cells, and failing myocardium. It circulates at high concentrations in patients with congestive cardiac failure and in experimental models causes pulmonary oedema, cardiomyopathy, cachexia, and reduced peripheral blood flow. Raised plasma concentrations of TNF α and other proinflammatory cytokines such as interleukin 6 have been interpreted as epiphenomena of heart failure, but it is increasingly thought that cytokines may promote heart failure progression. The experience with TNF α antagonists in heart failure is limited, but there are intriguing data on pentoxifylline, a xanthine derivative that suppresses TNF α production,¹² and etanercept, a soluble P75 tumour necrosis factor receptor that binds irreversibly with TNF α .¹³ Etanercept is currently being evaluated in two large multicentre studies (RENAISSANCE and RECOVER).

Endothelins are another family of locally acting peptides with profound vasoconstrictor effects found in high plasma concentrations in patients with heart failure. Experimental data using the endothelin antagonist bosentan have shown favourable haemodynamic effects in heart failure patients, although the drug is associated with dose related hepatic dysfunction, prompting the investigation of more selective endothelin antagonists.

ANTICOAGULANTS

Although the annual risk of thromboembolism in patients with IDC is relatively low, many patients are young and are exposed to an appreciable cumulative risk of systemic embolisation. At present there are no trial data to guide anticoagulant treatment in IDC, but warfarin is advised in patients with a history of thromboembolism or evidence of intracardiac thrombus. Patients with more than moderate ventricular dilatation and moderate to severe systolic dysfunction should also be advised to take warfarin.

Management of arrhythmia in IDC

There are substantial limitations to most currently available antiarrhythmic drugs in IDC, in particular their negative inotropic and proarrhythmic effects. Evidence from studies showing increased mortality in patients with advanced heart failure treated with class I agents suggest that these drugs should not be used to prevent arrhythmias of any origin in IDC except in an emergency. Two large scale

trials have evaluated amiodarone in IDC, but only one, GESICA,¹⁴ has demonstrated an improvement in overall prognosis. The second study, CHF-STAT,¹⁵ did not demonstrate an improvement in overall survival, but there was a non-significant trend towards improved survival in patients with "non-ischaemic" cardiomyopathy. Dofetilide,¹⁶ a more recently developed class III agent, has a neutral effect on overall survival but does reduce the incidence of atrial fibrillation. These data suggest that class III agents can be safely used to treat or prevent symptomatic supraventricular arrhythmias in IDC, but they cannot be recommended for sudden death prophylaxis. There are as yet no large scale randomised data of implantable cardioverter defibrillator (ICD) treatment in IDC, but it is reasonable to consider ICDs in patients with sustained haemodynamically unstable ventricular tachycardia/fibrillation. The role of ICDs in patients without symptomatic ventricular arrhythmia will hopefully be answered by ongoing trials (for example, SCD-HEFT).

Non-pharmacological treatment of advanced heart failure

Heterotopic heart transplantation is still the cornerstone of advanced heart failure management in patients with intractable heart failure symptoms and end stage disease. However, transplantation remains limited by the scarcity of suitable organs and the development of graft vasculopathy. In response to this dilemma several novel approaches are being evaluated.

PARTIAL LEFT VENTRICULECTOMY ("BATISTA" PROCEDURE)

Partial left ventriculectomy is based on the hypothesis that as wall tension is related to left ventricular diameter (Laplace's law), reducing the left ventricular size by excision of a portion of its circumference should reduce wall stress and improve ventricular haemodynamics. In the best centres results from this intervention were initially remarkably good given the nature of the procedure. It is clear, however, that even with careful patient selection many patients survive only with the benefit of left ventricular assist devices and subsequent transplantation.¹⁷ Late sudden death is also described in a proportion of survivors. The difficulties associated with patient selection and subsequent postoperative care suggest that, at best, this form of treatment will be confined to a very small number of experienced centres.

LEFT VENTRICULAR ASSIST DEVICES

Left ventricular assist devices (LVADs) have recently received approval from the US Food and Drug Administration for use in patients with end stage heart failure as a bridge to cardiac transplantation. Experience in patients with IDC suggests that LVAD treatment can result in an apparent improvement in left ventricular function that may persist when the device is removed. However, there are as yet no

reliable markers that distinguish the minority of patients that sustain useful recovery from the majority that deteriorate following explantation of the device. Technical advances in LVAD design now raise the possibility of using these devices as an alternative to transplantation in patients who are not transplant candidates. This mode of treatment is currently being evaluated in the REMATCH study,¹⁸ which if positive will have substantial clinical and resource implications for centres managing advanced heart failure.

MULTISITE VENTRICULAR PACING

Many patients with advanced IDC have abnormal left ventricular activation that in turn results in prolonged and incoordinate ventricular relaxation. In some patients ventricular conduction delay is also associated with prolongation of atrioventricular conduction, resulting in a loss of atrioventricular synchrony and a predisposition to prolonged functional mitral regurgitation. Dual chamber pacing has been advocated as a method for restoring AV synchrony and improving left ventricular coordination in patients with severe congestive heart failure. Although initially favourable haemodynamic results using conventional right ventricular pacing were not confirmed by later studies, there has been a more consistent response in studies that have used biventricular pacing, the outcome depending critically on the native QRS duration and the paced AV delay.¹⁹ Patients should be considered for biventricular pacing if they have QRS duration greater than 150 ms, PR interval prolongation, and symptoms refractory to conventional medical treatment.

Immunomodulation/immunosuppression

While there is considerable evidence to suggest that autoimmunity plays a significant role in the pathophysiology of IDC, there has been little evidence to suggest that immunosuppressive treatment is of any benefit. This lack of response is, perhaps, not that surprising given the limitations of criteria used to select patients for treatment in immunosuppressive studies and the heterogeneity of the underlying aetiology of the condition. Immunosuppression is also a rather indiscriminate weapon, as it may suppress potentially beneficial immune responses such as neutralising antibody production in patients with chronic viral myocarditis. New approaches to the diagnosis of chronic myocarditis and the treatment of inflammatory cardiomyopathy should improve this situation. There are already interesting preliminary data suggesting that high dose immunoglobulin²⁰ and immunoadsorption may result in short term improvement in left ventricular performance in patients with dilated and peripartum cardiomyopathy.

Trial acronyms

ATLAS: Assessment of Treatment with Lisinopril And Survival
CHARM: Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CHF-STAT: Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy
CIBIS: Cardiac Insufficiency Bisoprolol Study
ELITE: Evaluation of Losartan in the Elderly study
GESICA: Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina
MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Heart Failure
RALES: Randomized Aldactone Evaluation Study
RECOVER: Research into Etanercept: Cytokine Antagonism in Ventricular Dysfunction
REMATCH: Randomized Evaluation of Mechanical Assistance Therapy as an Alternative in Congestive Heart Failure
RENAISSANCE: Randomized Enbrel North American Strategy to study Antagonism of Cytokines
RESOLVD: Randomized Evaluation of Strategies for Left Ventricular Dysfunction
SCD-HEFT: Sudden Cardiac Death in Heart Failure Trial
VALHEFT: Valsartan Heart Failure Trial

The future

IDC is a disease of diverse causes and pathophysiology. Among the many challenges facing clinicians treating patients with the disorder are the detection of early disease, the identification of the predominant mechanism of left ventricular dysfunction, and the development of treatments that target the initiating mechanism of disease. Nevertheless, there have been major advances in our understanding of the genetic and immunological basis of IDC, and recent advances in the pharmacotherapy of heart failure have substantially improved the outlook for many patients. The rapid pace of current research and the development of new treatments for the management of both early and late disease augur well for the future.

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- In this study, 674 patients with class II–IV heart failure were randomised in a double blind fashion to either amiodarone or placebo. Amiodarone was associated with an improvement in ejection fraction, and a significant reduction in the composite end point of hospitalisation and cardiac death in patients with non-ischaemic heart failure. Compared to GESICA, many more patients in this study were withdrawn from treatment because of side effects. The difference in outcome may be explained by many factors including inclusion criteria, sex differences, prevalence of non-sustained ventricular tachycardia, and the aetiology and severity of heart failure.
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website
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Additional references
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