MANAGEMENT OF PATIENTS WITH NON-ISCHAEMIC CARDIOMYOPATHY

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The term ''cardiomyopathy'' refers to specific diseases affecting the myocardium which generally lead to clinical manifestations of heart failure, including exercise intolerance, dyspnoea, and fluid retention. The causes of cardiomyopathy can be broadly divided into two categories, ischaemic and non-ischaemic. In ischaemic cardiomyopathy, ventricular dysfunction is a consequence of myocardial ischaemia and infarction related to coronary arteriosclerosis, while there are many potential causes of non-ischaemic cardiomyopathy (NICM), including haemodynamic pathology, infection, immunologic abnormalities, toxic injury, or genetic factors. Determining the prevalence of NICM is made difficult by the heterogeneity in definitions and diagnostic criteria, selection bias in populations studied, and geographic variation. Many epidemiological and clinical studies simply classify patients as having NICM if heart failure is present but there is no clinical or electrocardiographic evidence of coronary disease. In addition, there are clear differences in population characteristics between community-based studies versus analyses of populations from referral centres. Finally, there appears to be geographic variation in the prevalence of specific aetiologies of NICM. Estimates of the prevalence of NICM range from 2–15% in community or hospital settings, and up to 50% in large clinical trials.[1]

Although the causes of NICM are many and varied, they generally culminate in a final common pathway of myocardial injury leading to ventricular dysfunction and clinical heart failure. In many cases of NICM a specific aetiology is never identified, or if one is, then frequently no aetiology-specific treatment is available; thus, treatment of NICM frequently includes standard management for systolic heart failure. While a minority of cardiomyopathies manifest with preserved systolic function, this article specifically reviews management of NICM manifesting with left ventricular (LV) systolic dysfunction.

AETIOLOGY

Many types of NICM are not treatable with specific therapies beyond those used for heart failure in general. A significant proportion of patients with NICM have idiopathic dilated cardiomyopathy, the cause of which has not been established and which is likely to be multifactorial, potentially including occult viral myocarditis, abnormalities of the immune system, or genetic factors. Occasionally, occurrence of a viral illness preceding onset of heart failure symptoms is recalled, or there may be a family history of NICM. Acute myocarditis involves myocardial inflammation associated with a wide range of infections and systemic diseases, with symptoms ranging from subclinical to fulminant cardiogenic shock. Peripartum cardiomyopathy is likely to be an immune-mediated development of cardiomyopathy occurring late in pregnancy or shortly after delivery.

However, initial evaluation of the patient with NICM should include identifying an aetiology if possible, as some types of NICM may require specific treatment. These types include metabolic disorders, some systemic autoimmune disorders, some toxic injuries, and tachycardia-induced (fig 1). Systemic autoimmune diseases most frequently associated with NICM include sarcoidosis and amyloidosis cardiomyopathy. NICM may also occur as a consequence of metabolic disease, most notably thyroid disorders. Both hypothyroidism and hyperthyroidism can cause abnormalities in myocardial contractility leading to NICM, and in addition, hyperthyroidism may cause cardiac dysfunction secondary to persistent tachycardia or tachyarrhythmia.

Giant cell myocarditis is a little understood disease characterised by fulminant myocarditis with multinucleated giant cells on histologic examination of the myocardium, frequently refractory ventricular arrhythmias, occurrence in young to middle-aged adults, and a rapidly fatal course. Although no specific treatment for giant cell myocarditis is available, these patients may benefit from urgent mechanical circulatory assistance or cardiac transplantation.

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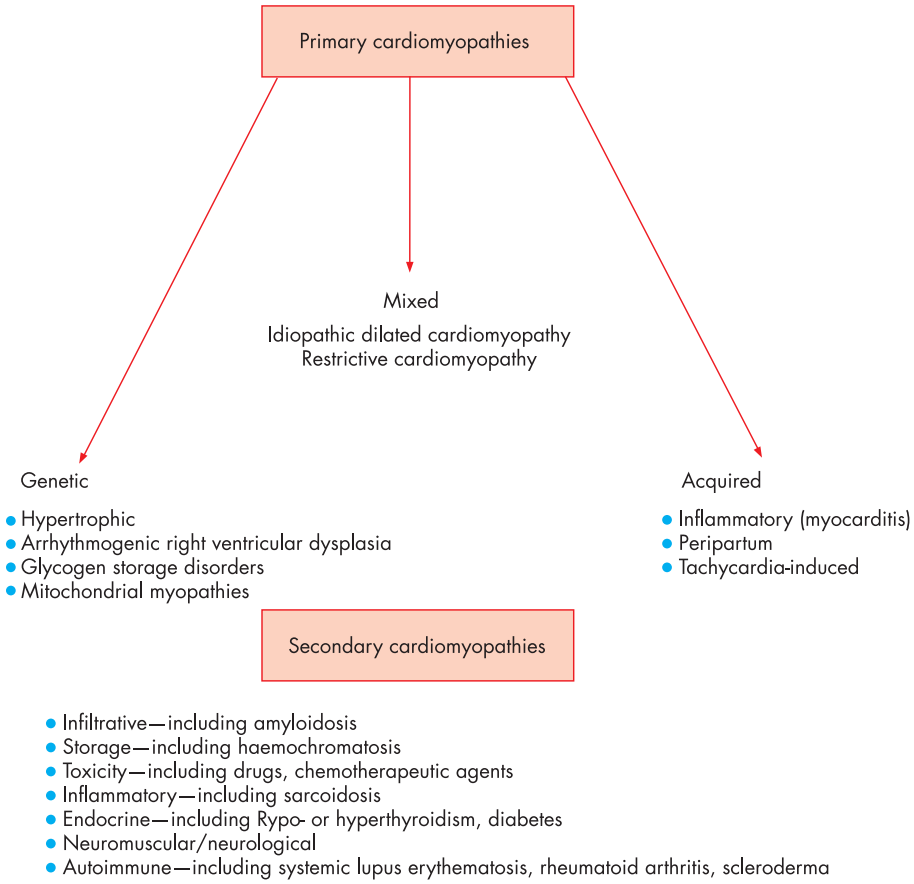

Figure 1 Classification of cardiomyopathies. Adapted from Maron BJ, Towbin JA, Thiene G, *et al*. Contemporary definitions and classification of the cardiomyopathies. *Circulation* 2006;**113**:1807–16.

Drugs or toxins causing NICM include certain chemotherapeutic agents, alcohol, and stimulant drugs such as cocaine and amphetamines. The anthracycline chemotherapeutic agents doxorubicin and daunorubicin, the related agent mitoxantrone, and the monoclonal antibody trastuzumab may cause cardiomyopathy, primarily through the generation of free radicals, which cause cell membrane damage. Alcohol, cocaine, and amphetamines cause direct toxic damage to myocardium, and in addition, stimulant drugs may cause myocardial injury through pronounced vasoconstriction and tachycardia in response to excess catecholamines. There is no specific treatment for chemotherapy-induced cardiomyopathy, but cessation of the offending agent in other types of drug-induced NICM is vital to potential myocardial recovery.

Tachycardia-induced cardiomyopathy results from structural and cellular myocardial dysfunction due to chronic tachycardia, which is usually supraventricular, although in some cases ventricular tachycardias may be involved. The primary treatment for tachycardia-mediated cardiomyopathy is slowing or elimination of the culprit arrhythmia, which generally results in normalisation of myocardial structure and function in weeks to months.

EVALUATION AND PROGNOSIS

After establishing the diagnosis of NICM, the goals of initial and ongoing evaluation include assessing disease severity, current state of compensation, and prognosis. Initial evaluation of the patient with NICM typically includes routine blood chemistry, an electrocardiogram (ECG), and an echocardiogram. Particular areas of interest in blood tests include evidence of neurohormonal activation (hyponatraemia), volume overload (hepatic congestion), or contraction alkalosis related either to poor perfusion or actual intravascular volume depletion. The ECG may demonstrate atrial fibrillation or interventricular conduction delay, both of which would affect treatment strategies. Echocardiography provides information about ventricular size and function, valvular anatomy and function, diastolic properties, and other possible findings such as pericardial effusion or intracardiac thrombus.

Ejection fraction and functional capacity are frequently used markers of disease severity, while assessment of symptoms and volume status by physical and laboratory examination yield indications of clinical compensation. Many analyses have been performed to identify prognostic indicators in heart failure. In general, patients with NICM have a better prognosis that those with ischaemic cardiomyopathy. Factors associated with poorer prognosis include resting tachycardia, low blood pressure, poor functional status, hyponatraemia, presence of interventricular conduction delay, lower ejection fraction, restrictive LV filling pattern by Doppler echocardiography (fig 2), and presence of a third heart sound.[2 3]

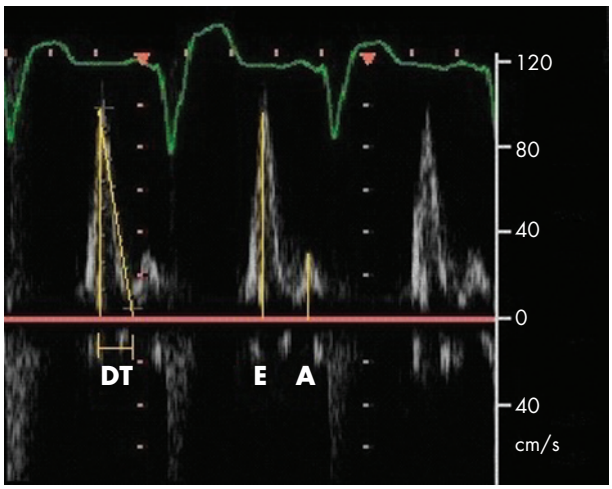

Figure 2 Example of restrictive mitral inflow pattern by Doppler echocardiography in a 61-year-old man with non-ischaemic cardiomyopathy with New York Heart Association class IV symptoms, who underwent cardiac transplantation three months later. E/A ratio = 3.1; deceleration time (DT) = 130 ms.

In select cases, further evaluation with right heart catheterisation, exercise testing or endomyocardial biopsy may be useful. Right heart catheterisation can clarify volume status in cases when it is difficult to determine by usual non-invasive means and when empiric medical treatment is limited by factors such as renal insufficiency or hypotension. It is also helpful in severe end stage cases where assessment of filling pressures and pulmonary hypertension is necessary in the course of evaluation for cardiac transplantation. Exercise testing modalities include the six-minute walk test or cardiopulmonary exercise test. In addition to formally quantifying functional capacity, cardiopulmonary exercise testing can also help distinguish between other, non-cardiac causes of functional limitation and assist with risk stratification for cardiac transplantation listing. Current practice varies widely between institutions with regard to use of endomyocardial biopsy as part of routine evaluation of NICM, but it is most useful in assisting with diagnosis of infiltrative myocardial diseases such as amyloid or giant cell myocarditis. Otherwise, in general, endomyocardial biopsy for NICM has a low diagnostic yield, likely related to heterogenous disease involvement and small sampling size.[4]

PHARMACOLOGIC TREATMENT

In the absence of patient intolerance or contraindications, treatment with angiotensin-converting enzyme (ACE) inhibitors and β-blockers is indicated for all patients with LV systolic dysfunction, regardless of the presence or severity of symptoms and aetiology of heart failure. Both agents independently reduce mortality and morbidity in patients with LV systolic dysfunction, and ACE inhibitors also delay the onset of heart failure symptoms in patients with asymptomatic LV systolic dysfunction. ACE inhibitors provide direct haemodynamic benefit by afterload reduction through peripheral vasodilation, and in addition have beneficial neurohormonal effects and reduce maladaptive left ventricular remodelling. In the setting of a failing heart, compensatory adrenergic activation occurs, although this is associated with deleterious consequences such as increased myocardial oxygen demand, cardiac fibrosis, and adverse ventricular remodelling. β-blockers ameliorate or reverse these pathologic responses to sympathetic activation. Agents with additional α-blocking properties (such as carvedilol) also provide afterload reduction through vasodilation.

One study observed occurrence of fewer hospitalisations in patients treated with higher versus low doses of ACE inhibitors,[5] but no significant neurohormonal or mortality differences have been demonstrated. On the other hand, with β-blocker treatment there does appear to be a dose-related benefit on morbidity and mortality in heart failure. In general mortality is reduced by about 30% across the board for the majority of trials.[6] Both β1-selective agents (bisoprolol, metoprolol succinate) and non-selective β1- and β2-antagonists (carvedilol) have been shown to reduce morbidity and mortality in heart failure. The Carvedilol Or Metoprolol European Trial (COMET) compared carvedilol to short-acting metoprolol (metoprolol tartrate), and found superior survival with carvedilol; however, no large, prospective, randomised, head-to-head comparison of carvedilol to metoprolol succinate has been performed.[7]

Angiotensin II type 1 receptor antagonists (angiotensin receptor blockers, or ARBs) were developed to completely block the effects of angiotensin II, which because of alternative production pathways is not completely eliminated by ACE inhibitor treatment. Angiotensin II has been implicated in promoting several adverse processes, including vasoconstriction and myocardial fibrosis. With regards to morbidity and mortality benefits, ARBs appear to be a reasonable substitute for ACE inhibitors for the treatment of LV systolic dysfunction in patients intolerant of ACE inhibitors.[8] The addition of the ARB candesartan to standard heart failure treatment, including ACE inhibitor, was shown in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial to reduce the risk of cardiovascular death and heart failure hospitalisation: 483 (38%) of the candesartan group experienced the combined end point, versus 538 (42%) of the placebo group ($p = 0.011$) who experienced the combined end point.[9] While patients may be intolerant of ACE inhibitors because of cough related to increased bradykinin concentrations, occurrence of cough is generally significantly less with ARBs, although, as with ACE inhibitors, hyperkalaemia and renal insufficiency can also occur with ARB treatment.

For patients unable to take ACE inhibitor or ARB because of reasons other than hypotension (such as renal insufficiency or hyperkalaemia), a suitable alternative vasodilating regimen is the hydralazine/nitrate combination, which also improves survival in patients with LV systolic dysfunction compared to placebo, although to a lesser degree than ACE inhibitor or ARB.[10] In addition, the recent African American Heart Failure Trial (A-HeFT) demonstrated that the addition of hydralazine and isosorbide dinitrate to standard heart failure treatment in blacks with severe heart failure (New York Heart Association (NYHA) functional class III or IV) resulted in a 43% reduction in all-cause mortality versus placebo (6.2% vs 10.2%, respectively).[11]

Aldosterone is not completely suppressed, even with chronic ACE inhibitor treatment, and causes sodium retention,

potassium wasting, myocardial fibrosis, and endothelial dysfunction. In the Randomized Aldactone Evaluation Study (RALES), patients with severe heart failure (NYHA class III or IV, LV ejection fraction ⩽35%) who were already on ACE inhibitor and diuretic randomised to treatment with spironolactone had a 30% reduction in mortality versus placebo (46% mortality for placebo vs 35% for spironolactone group, $p<0.001$).[12] The selective antagonist eplerenone can be used instead if the patient develops bothersome gynaecomastia with spironolactone, although eplerenone currently has only been proven to improve outcomes in patients with LV dysfunction after acute myocardial infarction.

Other pharmaceutical agents with less definitive effects on survival but with effect on morbidity are also used in the treatment of NICM. Diuretics are used frequently for management of volume overload, although careful dose titration should be employed to minimise side effects of electrolyte imbalances, hypotension, and renal insufficiency.

For heart failure patients in sinus rhythm, treatment with digoxin improves morbidity, including reducing all-cause and heart failure hospitalisations, but no definitive survival benefit has been shown.[13]

The role of calcium channel blockers in the setting of NICM is limited to control of other conditions, such as hypertension, not adequately managed with other agents with more robust survival benefits such as ACE inhibitors or β-blockers. Second-generation agents (amlodipine, felodipine, isradipine, nicardipine) are more selective for vasodilation than early generation agents, and thus avoid the problem of negative inotropy leading to reactive sympathetic activation. Amlodipine is the only agent that has been studied in a large randomised control trial of heart failure patients, and it was found to have a neutral—but not negative—effect on survival.[14] Amiodarone is an antiarrhythmic agent that importantly, unlike other antiarrhythmics, does not appear to increase mortality in patients with LV dysfunction.[15]

Amiodarone is not indicated for first-line primary prevention of sudden death or for reduction of mortality in patients with LV dysfunction; however, amiodarone is the treatment of choice in patients who are not candidates for an implantable cardioverter-defibrillator (ICD). In addition, amiodarone may be a useful adjunctive treatment to reduce the frequency of ICD discharges in patients with recurrent ventricular tachyarrhythmias.

Although there is clear evidence for chronic anticoagulation for conditions not uncommonly encountered in heart failure patients, such as atrial fibrillation, intracardiac thrombus, or history of thromboembolism, there are currently no definitive data supporting chronic anticoagulation or antiplatelet therapy solely for treatment of low ejection fraction.

Intravenous infusions used to treat NICM may include positive inotropic agents (adrenergic agonists, phosphodiesterase inhibitors, and dopaminergic agonists) or the recombinant human B-type natriuretic peptide, nesiritide. Continuous infusion of positive inotropic agents is indicated for short-term treatment of cardiogenic shock, while more prolonged treatment may be necessary as a bridge to cardiac transplantation, or as chronic treatment in end-stage heart failure. Although haemodynamics and cardiac output are improved, intravenous inotropes likely increase mortality in many cases. Intermittent outpatient infusion of inotropes has not been definitively shown to improve morbidity or mortality, while oral inotropic agents have been associated with increased mortality. Nesiritide has venous, arterial, and coronary vasodilatory properties, without direct inotropic effects. Several short term trials (mostly <48 hours treatment duration) demonstrated favourable haemodynamic effects, including increased cardiac index and reduced pulmonary capillary wedge pressure, in patients treated for acutely decompensated heart failure.[16] However, the long term effect of nesiritide on morbidity and mortality has not been established, and in fact recent analyses have suggested increased risk of mortality.[17]

Table 1 summarises both the medical and device therapies for NICM.

Table 1 Summary of medical and device therapy for NICM

Functional status	Medical treatment	Device therapy
Asymptomatic (NYHA class I)	ACE inhibitor (if intolerant, consider ARB or hydralazine/isosorbide dinitrate) β-blocker Diuretic as needed	ICD for: Haemodynamically significant ventricular arrhythmia Resuscitated cardiac arrest EF ⩽35%
Symptoms with moderate activity (NYHA class II)	As above Diuretic probably needed Digoxin if symptomatic Consider amlodipine if additional vasodilation needed	As above
Symptoms with mild activity (NYHA class III)	As above Spironolactone Diuretic Digoxin If black, hydralazine/isosorbide dinitrate	As above If IVCD or dyssynchrony consider or CRT
Symptoms at rest (NYHA class IV)	As above Consider chronic inotrope infusion, ventricular assist device, cardiac transplantation	As above If IVCD or dyssynchrony consider or CRT

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT, cardiac resynchronisation therapy; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; IVCD, interventricular conduction delay; NICM, non-ischaemic cardiomyopathy; NYHA, New York Heart Association.

DEVICE THERAPY

Both ventricular tachyarrhythmias and bradyarrhythmias have been found to be the terminal rhythm in patients with NICM and sudden cardiac death. Assessing risk for sudden cardiac death is an ongoing area of intense study, as no non-invasive or invasive modality has proven to be sensitive or specific enough. Currently there is no established role for routine electrophysiology study for risk assessment in NICM patients. While an ICD is indicated for any patient with haemodynamically significant ventricular arrhythmias or resuscitated cardiac arrest (secondary prevention) regardless of the presence or absence of coronary disease or LV dysfunction, recent trials also suggest that prophylactic implantation of ICDs for primary prevention of sudden death in patients with NICM with LV ejection fraction ⩽35% appear to reduce mortality.[18]

Interventricular conduction delay may occur in up to one third of all patients with heart failure, and is thought to result

from regional heterogeneity in ventricular electrical activation, which in turn leads to asynchronous ventricular contraction and worsened mitral regurgitation. Patients with low ejection fraction (⩽35%), interventricular conduction delay (QRS >120 ms), and severe symptoms (NYHA class III or IV) despite optimal medical treatment for heart failure would likely benefit from implantation of a biventricular pacemaker, also called cardiac resynchronisation therapy (CRT). CRT improves short- and intermediate-term quality of life and also measures cardiac performance parameters such as cardiac index, severity of mitral regurgitation, LV volume, and six-minute walk test duration. More recently, CRT has been shown to improve survival as well, an effect that was evident in both ischaemic and non-ischaemic subgroups.[19] However, as many as 20–30% of patients meeting current criteria do not improve with CRT, and there is ongoing research into refining selection criteria, with particular interest currently focused on the use of echocardiographic tissue Doppler assessment of ventricular dyssynchrony.[20]

SURGICAL THERAPY

While there is an established role for surgical ventricular remodelling with ischaemic cardiomyopathy, earlier enthusiasm for such in NICM (Batista procedure) has waned due to the high incidence of surgical failures. Current surgical options for treatment of NICM include mitral valve annuloplasty, cardiac support devices, mechanical circulatory support devices, and cardiac transplantation. Mitral regurgitation occurs frequently in the setting of LV dysfunction and is frequently related to progressive LV dilation and secondary distortion of the mitral apparatus. Mitral valve annuloplasty improves intermediate-term outcomes such as symptoms and functional status, but long-term effects on survival have not been prospectively studied. One type of cardiac support device currently being studied is a mesh that is surgically wrapped around the heart to provide support during diastole and theoretically reduce myocardial transmural stress and progressive LV dilation.

Management of non-ischaemic cardiomyopathy (NICM): key points

- Angiotensin-converting enzyme inhibitors and β-blockers are indicated for treatment of all systolic dysfunction, regardless of presence or absence of, or severity of, symptoms
- For additional mortality and morbidity benefit, patients with severe symptomatic heart failure (New York Heart Association functional class III or IV) should be treated with spironolactone, barring contraindications such as hyperkalaemia or renal insufficiency; black patients with severe symptomatic heart failure should in addition be treated with hydralazine and isosorbide dinitrate
- Patients with NICM with left ventricular ejection fraction ⩽35% on medical treatment benefit from an implantable cardioverter-defibrillator for primary prevention of sudden cardiac death
- Patients with interventricular conduction delay or other evidence of ventricular dyssynchrony, and low ejection fraction would likely obtain functional and survival benefit from cardiac resynchronisation therapy, although current selection criteria are not perfect as up to a third of candidates do not improve

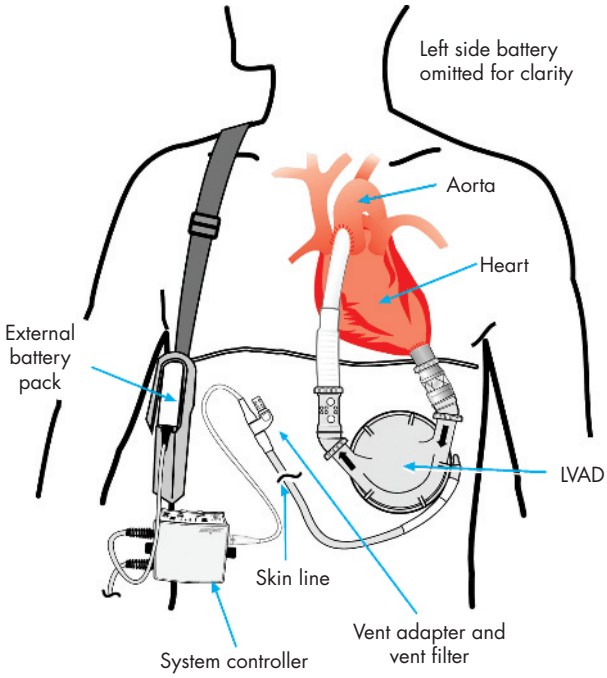

Figure 3 Example of a left ventricular assist device (LVAD). Adapted from an illustration supplied by Thoratec Corporation.

For patients with refractory end-stage heart failure, mechanical circulatory support and cardiac transplantation remain options that are potentially life-saving. The left ventricular assist device (LVAD) is currently the most commonly used mechanical circulatory assist device (fig 3). The device unloads the left ventricle by a cannula in the LV apex and returns blood to the systemic circulation by a cannula in the ascending aorta. LVADs are most often used as a temporising bridge to cardiac transplantation, while a small proportion of LVADs are used to assist recovery of severe cardiogenic shock or for support of patients who are not candidates for cardiac transplantation (''destination therapy''). Cardiac transplantation remains the ''gold standard'' for treatment of end-stage heart failure, although notable limitations still exist. Many patients die while awaiting transplantation due to the shortage of available donor organs. Disadvantages of transplantation include risk of allograft rejection; need for lifelong immunosuppression with associated medication side effects and risks for infection and neoplasm; and frequent development of transplant vasculopathy, the accelerated intimal hyperplasia affecting allograft coronary arteries.

CONCLUSION

NICM is a widely prevalent disease characterised by myocardial dysfunction resulting from a variety of causes, some of which have yet to be fully defined. Despite the wide range of potential aetiologies, the common result is ventricular dysfunction that can be treated with standard pharmacologic and device therapy for heart failure. Continued study of specific mechanisms underlying NICM and risk stratification once the disease is

present will provide the foundation for more targeted and improved treatments.

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