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Heart failure in dilated non-ischaemic cardiomyopathy

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Heart failure (HF) is the prevailing cause of morbidity and mortality in patients with dilated non-ischaemic cardiomyopathy (DCM) and DCM is one of several causes of HF, with several distinct epidemiological and clinical features which may have important implications for its management and prognosis. This article reviews cardiovascular monitoring of specific characteristics of HF in DCM. DCM is defined as ventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions or significant coronary artery disease, the predominant phenotypes of being HFmrEF or HFrEF. DCM accounts for ∼40% of all cardiomyopathies but its true prevalence among patients with HFrEF is difficult to ascertain with certainty.

Compared with patients with other HF aetiologies, individuals with DCM tend to be younger, more likely male and less likely to have associated comorbidities. A genetic aetiology of DCM is deemed responsible for ∼40% of cases. Confirmation of a specific genetic background is clinically relevant (e.g. Duchene or Backer muscular dystrophies, lamin A/C mutation), because those patients may be at a high risk of progressive left ventricular dysfunction or conduction system disease and sudden death, prompting early prophylaxis with an implantable cardioverter defibrillator. However, in most instances, HF in DCM has a multifactorial aetiology, with multiple factors needing to be systematically evaluated and/or monitored, since correction of reversible causes or (e.g. tachycardia-induced cardiomyopathy, alcohol intoxication, iron-overload, cancer therapies etc.) or targeting specific pathophysiological causes could lead to an improvement in clinical status.

The treatment of DCM encompasses HF-related pharmacological and device therapies, and aetiology-specific treatments. At present, options for aetiology-related therapies are limited, and their effectiveness mostly requires confirmation from larger scale randomized trials. Whether outcomes of patients with HF in DCM differ from those with other HF aetiologies is unresolved. DCM is attributable for >40% of patients receiving mechanical circulatory support for advanced HF and it is the leading indication for heart transplantation. More aetiology-specific information is needed both in the evaluation and treatment of dilated cardiomyopathy.

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Introduction

Heart failure (HF) is the prevailing cause of morbidity and mortality in patients with dilated non-ischaemic cardiomyopathy (DCM).[1] In comparison with other aetiologies, HF in DCM has distinct epidemiological and clinical features with important implications for the management and prognosis. Hence, this review will focus on cardiovascular monitoring of specific characteristics of HF in DCM.

Dilated non-ischaemic cardiomyopathy is defined as ventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions or significant coronary artery disease.[2,3] Consequently, the predominant phenotypes of HF in DCM are either HF with midrange ejection fraction, or HF with reduced ejection fraction (HFrEF). The prevalence of DCM is ~36 patients per 100 000 population and it accounts for ~40% of all cardiomyopathies. The true prevalence of DCM among patients with HFrEF is difficult to ascertain because few studies have characterized HF aetiology beyond ischaemic or non-ischaemic. Recent data from a large northern European observational study suggests that DCM is the cause of HF in 7.9% of unselected patients admitted to hospital for HF.[4] In the PARADIGM-HF trial, enrolling only patients with ejection fraction <35-40%, DCM was the specified aetiology in 19% of all HFrEF patients, and in 47% of those with non-ischaemic HFrEF.[5] Significant geographical variations have been noted in epidemiology, with non-ischaemic DCM being the leading cause of HFrEF in Asia Pacific Region (28%), followed by Latin America (21%), whereas in Europe and North America DCM accounts for ~14% of HFrEF patients.[5,6]

Monitoring of aetiology of heart failure in dilated non-ischaemic cardiomyopathy

Compared with patients with other HF aetiologies, individuals with DCM tend to be approximately 5–10 years younger at diagnosis and more likely to be male (70–78%).[5] Owing to their younger age, they are less likely to have associated comorbidities, including hypertension, diabetes, atrial fibrillation, or stroke.[5] Despite an overall lower burden of comorbidities, several important features increase the complexity of HF in DCM. The aetiology of DCM is often multifactorial. Although, genetic factors are deemed responsible for ~40% of cases,[1] monogenetic forms of DCM are rare in clinical practice. Nevertheless, confirmation of specific genetic background is clinically relevant (e.g. Duchene or Backer muscular dystrophies, lamin A/C mutation), because those patients may be at a high risk of progressive left ventricular dysfunction or conduction system disease and sudden death, prompting early prophylaxis with an implantable-cardioverter defibrillator.[7,8] However, in most instances, HF in DCM results from an interplay between familial predisposition and direct myocardial damage caused by infectious, immune-mediated, or toxic agents, as well as endocrine and metabolic abnormalities. These factors need to be systematically evaluated or monitored, since correction of reversible causes or (e.g. tachycardia-induced cardiomyopathy, alcohol intoxication, iron-overload, cancer therapies etc.) or targeting specific pathophysiology could lead to an improvement in clinical status and reverse left ventricular remodelling (i.e. improvement in left ventricular systolic function).

Monitoring of specific clinical features in dilated non-ischaemic cardiomyopathy

The complexity of HF in DCM is further outlined by data indicating that the mean left ventricular ejection fraction (LVEF) at presentation tends to be lower compared to LVEF of either unselected HF patients, or patients with other non-ischaemic HFrEF aetiologies, including hypertension or valvular heart disease.[4,5] In addition, patients often present with significantly impaired functional status [the New York Heart Association (NYHA) Class III-IV][4,5] and frequently require repeated hospitalization for HF, as suggested by a study reporting that approximately two-thirds of newly-diagnosed DCM patients had at least one HF hospitalization in the previous 6 months.[9] Lower baseline LVEF, higher NYHA class, and repeated HF hospitalization, as well as older age (>60 years) and male sex, have been consistently associated with poor outcomes of HF in DCM.[10-12]

By monitoring specific clinical features, several indicators of adverse prognosis could be identified. Importantly, these features may not be present at diagnosis, but develop along the course of the disease and are amenable to treatment. This includes new-onset left bundle branch block, a sign of dyssynchronous mechanical contraction, associated with ~three-fold greater all-cause mortality,[13] which could be reduced with cardiac resynchronization therapy.[14] Also, development of severe functional mitral regurgitation confers ~two-fold greater risk of death or worsening HF in DCM.[15] Therefore, echocardiographic monitoring and surgical or interventional treatment for severe mitral regurgitation may be considered in selected patients.[16] Occurrence of atrial fibrillation, even when asymptomatic, may cause severe deterioration of functional status and increase the risk of stroke and mortality.[17] Hence efforts to detect atrial fibrillation and provide oral anticoagulation (to all patients) and catheter ablation (in selected cases), could effectively improve outcomes and quality of life in those with HF in DCM.[18]

In contrast, female sex, smaller left ventricular cavity size, and less mid-wall fibrosis on cardiac magnetic resonance may indicate individuals with a greater potential for reverse left ventricular remodelling.[9,19,20] Sustained improvement in left ventricular function is associated with ~50% lower mortality at long-term follow-up.[20]

The role of monitoring in the treatment of heart failure in dilated non-ischaemic cardiomyopathy

The treatment of DCM encompasses HF-related pharmacological and device therapies, and aetiology-specific treatment. Guideline-directed therapies of chronic HFrEF confer a consistent improvement in outcomes, regardless of aetiology.[21] Over the last two decades, a consistent reduction in hospital admissions, HF-related mortality and

the risk of sudden death has been observed with contemporary treatment.[12,22] In the treatment of acute HF, there is a suggestion that milrinone might be beneficial in patients with non-ischaemic HF unlike those with ischaemic aetiology.[23] The treatment of chronic HF in DCM should continue indefinitely, even in patients with left ventricular functional recovery, due to a high risk of relapse upon withdrawal of targeted therapies.[24]

At present, options for aetiology-related therapies are limited, and their effectiveness mostly requires confirmation from randomized trials. Available evidence indicates a beneficial role of bromocriptine (in conjunction with anticoagulation) for left ventricular functional recovery and reduction in morbidity and mortality in peripartum cardiomyopathy.[25] There is a suggestion that immunosuppression could have salutary effects for the treatment of virus-negative inflammatory DCM, giant-cell or eosinophilic myocarditis, and cardiac sarcoidosis.[26–28] Also, immunoadsorption of circulating antibodies is currently evaluated as a potential treatment in selected patients with DCM.[29]

Whether outcomes of patients with HF in DCM differ from those with other HF aetiologies is unresolved. Earlier reports have suggested worse outcomes in ischaemic compared with non-ischaemic HF, but amongst non-ischaemic aetiologies, patients with DCM had greater mortality than those with hypertensive of valvular heart disease.[4,30] Conversely, recent data indicates similar survival across different HF aetiologies, possibly owing to beneficial effects of contemporary treatment.[5] However, despite advancements in treatment, DCM often has an unfavourable course leading to advanced HF. Monitoring of HF progression is a key element in indication for a timely referral to specialized advanced HF centres. Indeed, DCM is attributable for >40% of patients receiving mechanical circulatory support for advanced HF.[31,32] Likewise, it is the leading indication for heart transplantation, accounting for 64% and 51%, respectively, of all transplantations in younger (18–39 years) and middle-aged adults (40–59 years).[33] Only after the age of 60 years, HF in DCM is preceded by ischaemic heart disease as the most frequent cause of heart transplantation. Following transplantation, patients with DCM have a favourable long-term prognosis, owing to their younger age and lower burden of comorbidities, with a median survival of 12 years post-transplantation.

Conflict of interest: Outside of this work, in the last 3 years, Professor Coats declares having received honoraria and/or lecture fees from: Astra Zeneca, Bayer, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Cardiac Dimensions, CVRx, Enopace, Faraday, Gore, Impulse Dynamics, Respicardia, Stealth Peptides, V-Wave. Others declare no Conflicts.

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