Predicting Prognosis in Dilated Cardiomyopathy

Michael Arad MD and Dov Freimark MD

Heart Failure Service and Leviev Heart Center, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: dilated cardiomyopathy (DCM), remodeling, prognosis

IMAJ 2012; 14: 687-689

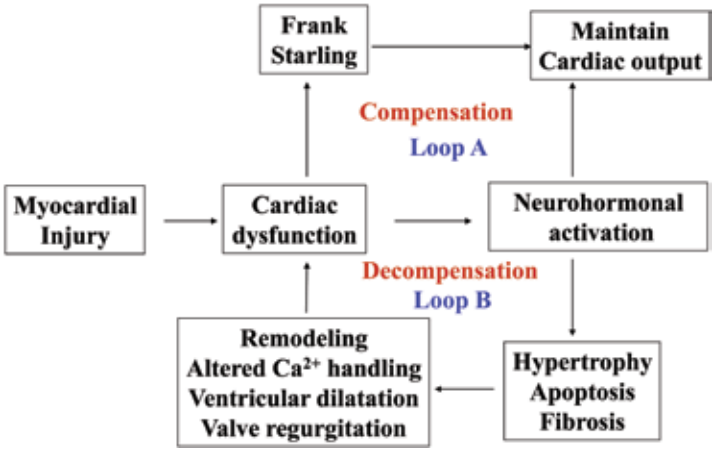
Dilated cardiomyopathy is a primary disease of the myocardium defined by the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease), or coronary artery disease sufficient to cause global systolic impairment [1]. The term "idiopathic" assumes ruling out identifiable and potentially treatable causes such as hypo- or hyperthyroidism, tachyarrhythmia, alcohol abuse, dietary deficiency, or association with a systemic illness. Once a single mechanism to explain cardiomyopathy cannot be established, the condition can be described as "idiopathic." In real live, extensive clinical investigation combined with endomyocardial biopsy failed to identify the specific cause of cardiomyopathy in 50% of patients referred to the Heart Failure Clinic [2].

In our opinion, DCM, with the possible exception of familial cardiomyopathy, is a multifactorial disorder constituting a final common pathway of several injury mechanisms. These mechanisms often coexist to either initiate or aggravate the disease process. This complex etiology led to a simplified approach used in everyday clinical practice to classify cardiomyopathy with reduced ventricular function as either ischemic or non-ischemic. Patients with non-ischemic cardiomyopathy are often referred to a specialized clinic to isolate the factors contributing to the disease and to tailor the therapy. While the general heart failure therapy does not differ between different etiologies, certain patients with DCM improve, others remain clinically stable for many years, while some deteriorate and require assist device or heart transplantation [3,4]. Most remarkably, some of the hearts undergo reverse remodeling to resume a normal geometry and function. Therefore, the ability to appreciate individual prognosis has manifold personal and clinical implications.

The primary cause of myocardial injury may be either persistent or transient. The development of cardiomyopathy requires the coexistence of myocardial dysfunction with a remodeling process that is mediated by wall stress and neurohumoral factors [Figure 1]. This process perpetuates independently of the initial injury but is badly affected if the primary process goes unabated. The schematic diagram [Figure 1] defines the targets of therapy in dilated cardiomyopathy: hemodynamic factors and congestion (loop A) and neurohumoral activation (loop B). However, it is the ability to intervene with the primary cause(s) of injury before irreversible damage develops that ultimately defines the prognosis.

Gene mutations account for a substantial minority of DCM cases (~30%), but these individuals may present with either familial or sporadic disease [5].

Figure 1. A trigger of myocardial injury evokes contractile dysfunction which is compensated through The Frank Starling mechanism and neurohumoral activation (Loop A). This essential biological response restores cardiac output at the expense of congestion, increased wall stress and higher energy requirements. In case of an ongoing injury process or when permanent myocardial damage results in persistent cardiac dysfunction, wall stress and neurohumoral mediators initiate the remodeling process (Loop B). This sequence leads to structural and functional decompensation, resulting in heart failure due to dilated cardiomyopathy.



DCM = dilated cardiomyopathy

In others there is a gene polymorphism conferring a predisposition to develop DCM following an appropriate trigger [6]. The prognosis of familial cardiomyopathy is largely dependent on the disease gene but in general may be worse because of its predetermined and irreversible nature [7]. Yet, even these patients may, at least temporarily, respond to beta blocker or angiotensin-converting enzyme inhibitors [8,9].

Myocardial inflammation constitutes another major subgroup of patients who often remain undiagnosed if endomyocardial biopsies are not routinely performed [3,10]. In patients with acute myocarditis manifest as acute febrile illness, troponin/creatine kinase elevation and various degrees of myocardial dysfunction, complete recovery is rather the rule [10,11]. Those who present with heart failure of recent onset may demonstrate a subacute or chronic inflammatory process in the myocardium in the absence of myocyte necrosis. According to the World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies, biopsy is considered to be inflamed by immunohistochemical detection of focal or diffuse mononuclear infiltrates (CD3+T lymphocytes and CD68+macrophages) with > 14 cells/mm^2, in addition to enhanced expression of HLA class II molecules. Molecular biological detection of cardiotropic viruses can be performed by nested PCR/real time-PCR. In situ hybridization techniques allow the identification of cell types replicating viral genomes as shown for PVB19 and enterovirus [10,12,13]. Ongoing inflammation adversely affects the remodeling process and numerous intervention trials have targeted the viral infection or the inflammation itself. While there is a consensus over the detrimental impact of mononuclear infiltrate and HLA expression, investigators disagree over the role of viral persistence in the myocardium [13,14]. At present there is no definite proof of benefit of a specific treatment for inflammatory cardiomyopathy. Performing a routine biopsy in DCM may become a standard policy if the results of immunosuppressive (TIMIC) and immunoadsorption single-center trials are confirmed in a large-scale study [10,15].

In their landmark study, Felker et al. [2] investigated the etiology and prognosis of cardiomyopathy subtypes. They reported a good long-term outcome in women with pripartum cardiomyopathy but a poor prognosis associated with chemotherapy-induced cardiomyopathy. Contemporary data indicate that this grim outcome may improve with close monitoring of antracycline dosage and left ventricular ejection fraction and with early medical intervention [16]. Grunig and co-authors [7] identified low LVEF, LVEDP (left ventricular end-diastolic pressure) above 15 mmHg, age over 54 years, and left bundle branch block as predictors of adverse outcome. Marburg investigators found that LVEDD (left ventricular end-diastolic diameter), New York Heart Association class and LVEF, as well as beta blocker and statin use independently predict death or heart transplantation [17]. LVEF > 30% and the absence of non-sustained ventricular tachycardia on Holter monitoring predict arrhythmia-free survival. In the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy) registry of recent-onset DCM, lower LVEDD and higher systolic blood pressure were associated with improved LVEF at 6 months, whereas black race and higher NYHA class at presentation adversely affect prognosis [3]. Delayed gadolinium enhancement on magnetic resonance imaging predicts total, cardiac and arrhythmic mortality. These findings are valid in biopsy-proven myocarditis [12] as well as in a non-selected DCM cohort [18]. Because only about one-third of DCM patients have delayed gadolinium enhancement, an MRI may be useful to identify the high risk patients who are prone to arrhythmia and are less likely to respond to conventional therapy.

In the current issue of IMAJ, Parakh and co-workers [19] report on clinical predictors of prognosis in a cohort of 171 idiopathic DCM patients. Inflammatory cardiomyopathy was excluded by endomyocardial biopsy. A comprehensive series of clinical, laboratory, electrocardiograph, echo-Doppler and hemodynamic parameters were included in the analysis, with a notable exception of B-natriuretic peptide and VO_2max. Lower age, lower NYHA class at presentation and higher LVEF emerged as independent predictors of event-free survival. A model based on these three simple clinical predictors correctly classified 71% of patients into Long-Term Survivors (median 6.4 years) versus Non-Long-Term-Survivors (median 1.8 years). Regretfully, only ~ 50% of patients had an adequate follow-up to enter the model under this classification. The predictive power of the model was highly significant but had an area under a receiver-operator curve of only 0.75. The authors should be applauded for their critical approach, acknowledging the limitations of predicting prognosis in DCM by standard clinical predictors. Nevertheless, these findings are important.

When approaching a DCM patient the clinician should consider the general clinical rules generated from cohort studies and pay meticulous attention to individual characteristics. The annual mortality rate in non-ischemic DCM patients is currently 5% or even lower [20], and nearly 50% may improve with modern therapy [3]. We believe that unless progressive heart failure or ventricular arrhythmia dictates otherwise, the inability to accurately predict

PCR = polymerase chain reaction

LVEF = left ventricular ejection fraction
LVEDD = left ventricular end-diastolic diameter
NYHA = New York Heart Association

prognosis warrants a careful wait-and-see approach. Once optimal medical therapy is instituted, the patient will have a "window of opportunity" to improve before committing to invasive procedures such as implantable cardioverter defibrillator or device implant, valve surgery, among others.

Corresponding author:
Dr. M. Arad
Heart Failure Service and Leviev Heart Center, Sheba Medical Center, Tel Hashomer 52621, Israel
email: michael.arad@sheba.health.gov.il

References

1. Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008; 29: 270-6.
2. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000; 342: 1077-84.
3. McNamara DM, Starling RC, Cooper LT, et al. Clinical and demographic predictors of outcomes in recent onset dilated cardiomyopathy. *J Am Coll Cardiol* 2011; 58: 1112-18.
4. Pieske B. Reverse remodeling in heart failure – fact or fiction? *Eur Heart J* 2004; 6 (Suppl D): D66-78.
5. Jefferies JL, Towbin JA. Dilated cardiomyopathy. *Lancet* 2010; 375: 752-6.
6. Dhandapany PS, Sadayappan S, Xue Y, et al. A common MYBPC3 (cardiac myosin binding protein C) variant associated with cardiomyopathies in South Asia. *Nat Genet* 2009; 41 (2): 187-91.
7. Grunig E, Benza A, Merelesa D, et al. Prognostic value of serial cardiac assessment and familial screening in patients with dilated cardiomyopathy. *Eur J Heart Fail* 2003; 5: 55-62.
8. Duboc, D, Meune, C, Lerebours G, Devaux JY, Vaksmann G, Bécane HM. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol* 2005; 45: 855-7.
9. Yeoh T, Hayward C, Benson V, et al. A randomised, placebo-controlled trial of carvedilol in early familial dilated cardiomyopathy. *Heart Lung Circ* 2011; 20: 566-73.
10. Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. *J Am Coll Cardiol* 2012; 59: 779-92.
11. McCarthy RE, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med* 2000; 342: 690-5.
12. Grün, S, Schumm J, Greulich S, et al. Long-term follow-up of biopsy-proven viral myocarditis. Predictors of mortality and incomplete recovery. *J Am Coll Cardiol* 2012; 59: 1604-15.
13. Kindermann I, Kindermann M, Kandolf R, et al. Predictors of outcome in patients with suspected myocarditis. *Circulation* 2008; 118: 639-48.
14. Kühl U, Pauschinger M, Schwimmbeck PL, et al. Interferon-ß treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction. *Circulation* 2003; 107: 2793-8.
15. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J* 2009; 30: 1995-2002.
16. Cardinale D, Colombo A, Lamantia G. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *Am Coll Cardiol* 2010; 55: 213-20.
17. Grimm W, Christ M, Bach J, Müller HH, Maisch B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg Cardiomyopathy Study. *Circulation* 2003; 108: 2883-91.
18. Assomull RG, Prasad SK, Lyne J, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol* 2006; 48: 1977-85.
19. Parakh K, Kittleson MM, Heidecker B, et al. The variable natural history of idiopathic dilated cardiomyopathy. *IMAJ Isr Med Assoc J* 2012; 14: 666-71.
20. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with non-ischemic dilated cardiomyopathy. *N Engl J Med* 2004; 350: 2151-8.