



SPECIAL ARTICLE: EUROPEAN NSJ ALMANAC 2011

## Almanac 2011: Cardiomyopathies. The national society journals present selected research that has driven recent advances in clinical cardiology\*

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### Introduction

Cardiomyopathies are myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease, sufficient to cause the observed myocardial abnormality. They are classified into a number of morphological and functional phenotypes that can be caused by genetic and non-genetic mechanisms. A few key themes have been dominant in 2010 to 2011, foremost of which are the use (and interpretation) of increasingly sophisticated genetic analyses and the use of new non-invasive imaging techniques to study clinical phenotypes. There were few advances in treatment reported and it remains clear that there is a need for properly conducted randomised trials in all forms of cardiomyopathy.

### Hypertrophic cardiomyopathy (HCM)

HCM is defined by the presence of myocardial hypertrophy unexplained by loading conditions. It is a genetic disorder predominantly caused by mutations in sarcomere protein genes, but other genetic diseases, including metabolic

disorders such as Anderson-Fabry disease, account for a substantial minority of cases.<sup>1</sup>

The literature over the past year illustrates the continued importance of conventional diagnostic tools such as electrocardiogram (ECG) and echocardiography in the diagnosis of HCM, but various refinements using different technical approaches, such as deformation imaging and 3D echo, were reported. Perhaps the most important advance has been the use of cardiac MRI. Two aspects were prominent: the ability of cardiomagnetic resonance (CMR) to detect myocardial segments 'invisible' to echocardiography (eg, posterior septum and apex) and probably more importantly, the ability to image myocardial scar using gadolinium enhancement. Numerous papers have examined the pattern and distribution of scar and its relation to clinical presentation and prognosis.<sup>2-4</sup> Most data suggest that the presence of scar is predictive of heart failure rather than sudden cardiac death, but larger unbiased cohort studies are required. Methods to detect diffuse fibrosis are likely to be even more important as this probably develops at an early stage of the disease and represents an important therapeutic target.<sup>5,6</sup>

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## Management

Many patients with HCM experience premature death or have decades of poor health. The current state-of-the-art in the management of each patient with HCM focuses on three aspects of the disease: identification of individuals who are at increased risk of sudden cardiac death and thus might benefit from implantable cardioverter-defibrillator (ICD) treatment; relief of left ventricular (LV) outflow tract obstruction and palliation of limiting symptoms caused by systolic or diastolic dysfunction. In all three areas, treatments remain suboptimal, particularly in the prevention of progressive heart failure. Potential benefits of presymptomatic diagnoses in affected family members, largely justified on the basis of sudden death prevention, is also an emerging theme in many papers.<sup>7,8</sup>

## Relief of LV outflow obstruction

Several meta-analyses comparing the results of septal myectomy with septal alcohol ablation have been published.<sup>9-12</sup> In general, these studies show that alcohol septal ablation is associated with broadly similar mortality rates and improvements in functional status to those reported for surgical treatment, albeit with a higher risk of permanent pacemaker implantation and greater postintervention outflow tract gradient. Some series have shown an excess of deaths after alcohol ablation, resulting in cautionary comments about the safety of this procedure.<sup>10</sup> The search for alternative treatments for outflow tract obstruction also continues with reports of radiofrequency ablation of the septum and reappraisal of dual chamber atrioventricular sequential pacing.<sup>13-15</sup> In the absence of a randomised comparison, the controversies about the relative strengths and weaknesses of each of these treatments will continue. Currently, invasive treatment of LV outflow obstruction is recommended only in patients with drug-refractory symptoms.

## Sudden cardiac death

In contemporary practice, a small number of clinical risk markers are used in aggregate to predict the probability of sudden cardiac death and the need for ICDs.<sup>16,17</sup> While remaining valid, current approaches have important limitations. In particular, many patients receiving ICDs for primary prevention never require device intervention, are exposed to risks of device-related complications and remain at risk of premature death from thromboembolic stroke and progressive heart failure.<sup>18</sup> In addition, while the genetic causes of HCM in children are similar to those in adults,<sup>19</sup> conventional risk prediction algorithms may not apply to paediatric populations.<sup>20</sup> Further data on risk prediction and randomised trials of interventions that might prevent disease progression are clearly necessary.

## Refractory symptomatic HCM

It has been hypothesised that excessive sarcomeric energy consumption is important in the pathophysiology of HCM and other heart muscle diseases. The mechanism of this energetic disturbance is not understood, but high

energy phosphate ratios are reduced in patients with mutations in sarcomere proteins and little or no hypertrophy, suggesting that energy deficiency is a fundamental characteristic of the HCM phenotype. As disturbance of fatty acid metabolism is one of the key drivers of inefficient energy use in the failing heart,<sup>21</sup> perhexiline, an inhibitor of mitochondrial fatty acid uptake, was used to treat exertional symptoms in a randomised placebo-controlled trial. Perhexiline improved symptoms, exercise capacity and diastolic function during exercise in symptomatic patients with non-obstructive HCM, suggesting that this and similar drugs might be of use in some patients.<sup>22</sup>

## Family screening

Recently published cost-benefit analyses comparing genetic and clinical screening strategies provide an economic argument for the use of genetic testing in family screening.<sup>7,8</sup> However, the published models are based on the assumption that risk-prediction algorithms developed and validated in populations at relatively high risk (largely comprising proband patients) apply equally to cohorts at lower baseline risk (Moons et al., unpublished data). In addition, confounders such as family size, disease penetrance, genetic variants of uncertain significance and the relatively high frequency of compound heterozygosity are largely unaccounted for in current cost-efficacy models. Prospective evaluation of different screening strategies is necessary.

## Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic heart muscle disease characterised histologically by cardiomyocyte loss and replacement by fibrous or fibrofatty tissue, and clinically by arrhythmia, sudden cardiac death and heart failure. In many people, the disease is caused by mutations in genes that encode components of the intercalated disc of cardiomyocytes.<sup>23</sup> Clinically, ARVC is difficult to diagnose, requiring integration of data from family members, genetic testing, electrocardiography and imaging techniques.<sup>24</sup> The major management problems in ARVC are prevention of sudden cardiac death and treatment of symptomatic arrhythmia and heart failure.

## Aetiology

Systematic family studies have shown that ARVC is inherited in up to 50% of cases as an autosomal dominant trait with incomplete penetrance and variable clinical expression. To date, most studies have shown that the majority of familial cases are caused by heterozygous mutations in genes encoding desmosomal proteins, but other genes have been implicated including transforming growth factor  $\beta$ 3 and transmembrane protein 43 (TMEM43), a cytoplasmic membrane protein.<sup>23,25</sup> Over the past year, further evidence of genetic heterogeneity has been demonstrated by the discovery of pathogenic mutations in desmin, an intermediate filament protein, and titin.<sup>26-28</sup> In addition,

studies continue to report complex genetic status in many patients with multiple variants in different desmosomal genes.<sup>29</sup> The presence of multiple mutations appears to increase the severity of the clinical phenotype, but also poses a challenge for the interpretation of genetic testing, particularly with regard to variants that may occur in normal populations which do not cause disease in themselves, but might conceivably alter disease susceptibility in the presence of other genetic or environmental factors.

### Diagnostic criteria

As in other heart muscle diseases, current diagnostic paradigms for ARVC represent the latest iteration of a scientific and clinical narrative that began with the study of severe cases presenting with sudden cardiac death or ventricular arrhythmia. Pathological examination of postmortem specimens from these advanced forms of the disease were used to establish histological hallmarks of the disease—namely, fibrofatty replacement, aneurysm formation and right ventricular dilatation. Thereafter, standard clinical tools such as ECG, ventriculography, echocardiography and latterly cardiac MRI have been used to diagnose ever more subtle manifestations of this histological phenotype. Recognition that the disease is a familial trait caused by mutations in genes that code for proteins of the intercalated disc, has added to this complexity.<sup>30</sup> A rationalisation of these different aspects of the disease formed the basis for modified diagnostic criteria published simultaneously in *Circulation* and the *European Heart Journal* in 2010.<sup>24</sup> This important paper has already defined future clinical and scientific enquiry, and evidence from families suggests that the sensitivity and specificity of the criteria have improved.<sup>31,32</sup> Nevertheless, the greater emphasis on quantification and genotyping is already posing significant diagnostic and management challenges. For example, athletic training alone may result in a phenotype that fulfils criteria in the absence of genetic evidence for the disease<sup>33</sup> and ECG criteria may also show considerable variability with time.<sup>34</sup>

### Prevention of sudden death

In spite of the reputation of ARVC as a major cause of sudden cardiac death, prospective data on the risk of sudden death in unselected populations and its prevention are surprisingly few. Current AHA/ACC/ESC 2006 guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend ICD implantation in patients with ARVC who have documented sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and who are receiving optimal medical treatment with reasonable expectation of survival with a good functional status for more than 1 year. Recommendations in patients without these features are necessarily more speculative. Retrospective analyses have identified a number of possible predictors of adverse outcome in probands, including early age of onset of symptoms, participation in competitive sports, a malignant family history, severe right ventricular dilatation, LV involvement, syncope, episodes of ventricular arrhythmias and increased QRS dispersion on 12-lead

ECG. In 2010, Corrado and colleagues published a study on 106 consecutive patients with ARVC who received an ICD based on one or more arrhythmic risk factors, such as syncope, non-sustained VT, familial sudden death and inducibility at programmed ventricular stimulation.<sup>35</sup> During follow-up, 24% of patients had appropriate ICD interventions, 17 of which (16%) were for VF or ventricular flutter. All patients survived to 48 months. Syncope was the most important predictor of ICD intervention but programmed ventricular stimulation had a low accuracy for predicting ICD treatment. These data add to current advice for ICD implantation in symptomatic patients, but the issue of primary prevention in asymptomatic patients remains a question for the future.

### Dilated cardiomyopathy (DCM)

DCM, when defined as LV dilatation and systolic impairment in the absence of previous myocardial infarction, is one of the commonest heart muscle diseases in developed countries.

Over the past year, research emphasising the importance of genetics in the aetiology of inherited and apparently acquired forms of DCM has been a prominent feature. Tissue characterisation imaging with CMR is another notable feature of recent DCM research, with studies suggesting that it provides additional diagnostic and prognostic information. Patient management continues to consist largely of standard symptomatic and prognostic heart failure treatments, but recent work has begun to identify the importance of aetiology in determining management.

### Aetiology

The difficulty in distinguishing between inherited and acquired cases of DCM remains a major challenge as the profile of clinical findings rarely helps to identify aetiology. In cases of sporadic disease (ie, in the absence of affected family members), circumstantial evidence may suggest the causative cardiac injury is inflammatory, toxic, load or heart rate dependent, or due to metabolic abnormalities. However, recently published data suggest that genetic susceptibility is often underestimated in apparently sporadic disease. In the past, animal data have demonstrated the importance of host genetic factors in determining susceptibility to cardiomyotropic viral pathogens;<sup>36</sup> in 2010, an association between myocarditis and common gene variants was reported for the first time in humans<sup>37</sup> In peripartum cardiomyopathy, studies demonstrated an association of a chromosomal locus with peripartum DCM<sup>38</sup> and the presence of undiagnosed DCM in first-degree family members (3 of 10) of women diagnosed with peripartum DCM.<sup>39</sup>

Recent genetic studies have also challenged previously accepted concepts of disease pathogenesis.<sup>40-54</sup> A study of 100 unrelated patients with idiopathic DCM<sup>41</sup> identified desmosomal gene sequence variants (some previously associated with ARVC) in 18 patients, five of which were classified as pathogenic. In limited co-segregation studies in two of the pedigrees, no mutant gene carriers fulfilled diagnostic criteria for either ARVC or DCM, but frequent

ventricular ectopy and/or myopathic patterns of late gadolinium enhancement (LGE) were detected in some mutation carriers with normal echocardiograms. These findings illustrate the frequency of genetic variants in patients with DCM and the heterogeneous and often subtle manifestations of disease in relatives who carry the same variant.

### Advanced cardiac imaging and myocardial characterisation

Tissue characterisation, CMR's unique contribution to non-invasive imaging, can differentiate normal myocardium from oedematous, fibrotic and infiltrated myocardium and can detect fatty change. In specific clinical situations, the profile, spatial distribution and temporal characteristics of tissue abnormalities, can differentiate between causes of cardiac damage.<sup>55-57</sup> Myocardial LGE after myocardial infarction is typically subendocardial; in non-ischaemic DCM, LGE is detected in at least one-third of cases<sup>58-60</sup> and is typically mid-wall or subepicardial, but neither the presence of LGE or its localisation are specific for any particular aetiology.<sup>41,61,62</sup> However, recently published work suggests that the presence of LGE may be a marker of disease severity and is prognostically important in some settings.<sup>58-60,63-65</sup> Management strategies that incorporate LGE findings have not been formulated or assessed.

CMR in the diagnosis of myocarditis, in particular with respect to acute and chronic abnormalities in tissue characteristics and their relation to disease progression to DCM and to the development of heart failure.<sup>56,57,66</sup>

Larger studies are now needed to validate CMR diagnostic criteria for myocarditis in a variety of clinical settings (eg, in a cohort with idiopathic DCM), and to establish whether CMR findings have prognostic value.

### Treatment

Guidelines for pharmacological and device therapies in heart failure make little reference to aetiology-specific management. In considering indications for device therapy (both ICD and cardiac resynchronisation therapy), major national guidelines suggest slightly different criteria for non-ischaemic than for ischaemic heart failure that recognise the greater likelihood that, on average, non-ischaemic DCM may have a better prognosis.<sup>67-69</sup>

Recent work by Millat et al. identifies some of the hazards in assuming homogeneity among patients with DCM.<sup>45</sup> They demonstrated that nearly 10% of unrelated patients with DCM had mutations in LAMIN A/C, a cause of DCM associated with particularly high risks of ventricular arrhythmias and progressive conduction disease.<sup>70</sup> Similar complications are also common in the cardiomyopathy associated with myotonic dystrophy.<sup>71-72</sup>

More conventional imaging findings may also be important in refining device therapy.<sup>73-75</sup> Recent publications describe the prognostic importance of functional mitral regurgitation, a feature of DCM related to LV geometry, contractility and dyssynchrony.<sup>76,77</sup> Rossi et al. demonstrate, in non-ischaemic DCM, that functional mitral

regurgitation is associated with doubling of a combined end point of all-cause mortality hospitalisation and worsening heart failure.<sup>74</sup>

### Genetics

Many of the inherited cardiac conditions for which a genetic cause was first detected were highly penetrant monogenic diseases with a readily detectable cardiac phenotype amenable to discovery approaches such as genetic linkage. In suitably sized pedigrees with highly penetrant disease, linkage analysis can provide statistical associations between a genetic locus/mutation with a disease phenotype (ie, a statistically robust co-segregation expressed as a logarithmic or LOD score). This classic genetic technique continues to deliver new genetic findings in hereditary heart muscle disease.<sup>78,79</sup>

More restricted candidate approaches in mutation detection have predominated in recent research; advantages include lower costs and an ability to study small families or individuals with low penetrance disease. Candidate genes are selected for a number of reasons that include membership in a gene group already associated with disease (eg, sarcomeric or desmosomal genes), an understanding that the gene's function may be important in the development of the phenotype (eg, genes involved in hypertrophic signalling) and particular features identified in the disease state (eg, differences in myocardial gene expression profiles between affected and normal subjects).

Recently published work presenting associations between new candidate genes and heart muscle disease may be considered in at least three categories: descriptions of relative frequencies of genetic abnormalities in genes known to cause a specific disease;<sup>18,43,45,48</sup> searches for sequence variants in genes associated with one heart muscle disease in another (cross-over or overlapping phenotypes)<sup>28,41,42,46-49,52,80</sup> and discovery of sequence variants in new candidates not previously associated with any cardiac disease.<sup>81,82</sup>

Until recently, largely empirical evidence has been used to support candidate gene choice but selection methods influence the pre-test probability that variants in the target gene are disease causing. More quantitative techniques for the identification of candidate genes have recently been described.<sup>83-85</sup>

Villard and colleagues performed genome-wide association studies on pooled DNA samples obtained from patients with apparently sporadic idiopathic DCM.<sup>83</sup> Two single nuclear polymorphisms on chromosomes 1p36 and 10q26 were significantly associated with DCM. An interpretation of these data is that these loci contain genes that play an important, but not causal, role in the development of sporadic DCM. However, several mutations in one of the candidate genes (BAG3, chromosome 10 locus) were identified in patients with familial DCM; several of these mutations co-segregated with the familial phenotype. It must be noted that it was unlikely that this study was designed to identify candidate genetic causes of DCM; in any case, none of the loci containing any of the many known DCM genes were identified.

Remarkably, another methodological first for cardiomyopathy also identified BAG3 as a cause of DCM. In the

proband and in three affected family members of a multigenerational pedigree with autosomal dominant DCM, Norton et al. performed both whole exon sequencing and a genome-wide assessment of copy number variation (CNV).<sup>84</sup> After exome sequencing, none of the genetic variants identified in the proband co-segregated with the disease. The high-density genome-wide CNV assay (said to have single-exon resolution) detected a deletion encompassing exon 4 of BAG3 that co-segregated with disease. As mutation detection strategies reliant only on sequencing coding regions of the genome will fail to detect CNVs caused by large deletions or insertions, future CNV studies may yet tell us that large deletions in genes already associated with cardiomyopathies are an important cause of these diseases.

Finally, using a more basic and inclusive approach to identifying candidate genes, Neely and colleagues assessed the effects of cardiac-specific 'knock-down' (with RNA-i) of more than 7000 genes in *Drosophila* reared under conditions of cardiac stress.<sup>85</sup> The authors identified nearly 500 evolutionarily conserved genes and pathways likely to have critical and conserved roles in the cardiovascular system. Their findings identify many targets for future candidate gene studies; for example, altered cardiac repolarisation is associated with a common polymorphism in the human isoform of a gene associated with a DCM phenotype in *Drosophila*.

## New technology

The term next-generation sequencing (NGS) refers to a number of technologies that provide massively parallel, high throughput DNA sequencing. Technological advances in the preparation of DNA before sequencing (enriching and labelling, for example), in sequencing chemistry and in bioinformatics will result in reduced costs and improvements in automation, accuracy and coverage. Recently published reviews describe NGS in more detail, and specifically with reference to inherited heart disease.<sup>86,87</sup>

As the inherited heart muscle diseases have striking allelic and locus heterogeneity (multiple mutations in many different genes), NGS will enable a step-change in both research and diagnostic applications of DNA sequencing. The first few reports of NGS being used to detect mutations in these conditions were published in 2010 and 2011.<sup>84,88-90</sup>

## Summary

As we approach the end of 2011 it is clear that the next few years are going to be dominated by the application of new high throughput genetic screening techniques, capable of screening the entire exome or indeed genome. Understanding the data generated by these techniques will require new and equally sophisticated analysis of large and complex datasets, using a systems biology approach with deeper phenotyping and advanced modelling techniques that have the flexibility for continuous update, refinement with discovery of new knowledge. Exciting new developments that may also transform cardiomyopathy research include those of infrastructure and organisation (multi-centre collaborations) and spin-offs from the

field of regenerative medicine research. For clinical researchers that translate this information to the clinic the focus will however remain the same; namely improvement of quality and quantity of life.

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