

Cardiology

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CARDIAC DEVICES: PAST, PRESENT AND FUTURE

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The evolution of implantable cardiac rhythm devices has been rapid over the past half century and is accelerating. We now have pacemakers which can stimulate the atria, right and left ventricles to prevent bradycardia and restore efficient synchronisation of cardiac contraction. We also have devices which can detect and automatically deliver rapid pacing or defibrillation shocks to terminate life-threatening tachycardias. The future holds new technologies that will allow us to more accurately tailor our treatments to our patients in order to allow more people to benefit and to improve long-term outcomes for device recipients. Our challenge is not only to develop better technology, but also to deliver our evidence-based treatments to all those who require them. To do this we must improve the identification of device indications in our patients through public and medical education. We also need to work with the manufacturers and NHS bodies to ensure that we are able to maintain uniform national funding within the NHS by accurately targeting these cost-effective treatments and auditing our performance against our peers in the UK and around the world.

CARDIOMYOPATHIES: THE EXPANDING ROLE OF GENE TESTING

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The first systematic characterisation of the cardiomyopathies occurred in the second half of the 20th century in association with the development of cardiac catheterisation and non-invasive imaging modalities. The earliest systematic reports noted the familial basis of hypertrophic cardiomyopathy (HCM) with autosomal dominant inheritance and the potential to identify disease causing genes. Recognition that dilated cardiomyopathy was familial and potentially genetic was not until the 1990s when systematic studies of families were performed. HCM penetrance within a family ranges from 30–100% and is usually 80–90%. In contrast, penetrance of autosomal dominant dilated cardiomyopathy is 30–50% and expression is age related throughout the decades rather than during adolescence and the early adult years.

Arrhythmogenic right ventricular cardiomyopathy which was not recognised clinically until the 1980s is also an autosomal dominant condition with low penetrance (30–50%) and age related expression (similar to dilated cardiomyopathy) into the middle and later decades.

These conditions are associated with the development of heart failure and its complications, stroke and premature sudden death. Identification of individuals at risk of disease development is therefore important. Prior to the genetic era, serial evaluation with non-invasive testing (mainly ECG and echo) was advocated. The potential for a gene test to identify the disease causing mutation in the proband and enable cascade screening of relatives has been recognised, but remains to be fully realised. Genetic testing requires sequencing, recognition of which variants are modifiers or disease causing, and then delivery of the information to patients and their families. The major road block to clinical mutation analysis to date has been the logistics of sequencing. Development of next generation sequencing is ongoing but realistically will enable rapid and cost effective platforms to be developed. It will also present the new challenge of determining which of multiple variants identified are relevant to disease development in a particular family. This will be the next challenge, which is already being addressed systematically by major groups worldwide. Clinical mutation analysis is rapidly emerging as an essential part of clinical management of the cardiomyopathies, as well as other forms of inherited arrhythmia. International guidelines for all of the inherited cardiovascular conditions have recently been published and several European countries have adopted ambitious national programmes, while others have taken a more cautious approach and are effectively rationing mutation analysis until proof of clinical efficacy is better established.

Next generation sequencing has thrown up a number of new realities, perhaps one of the most important of which is the fact that variants associated with the disease are much more common than previously recognised. Arrhythmogenic right ventricular cardiomyopathy is caused by mutations in desmosomal genes; almost all of the major groups publishing in this arena have found that there are two or more probable disease causing variants in 10 to 15% of their families. This led to a systematic evaluation of desmosomal variants in a large control population which revealed 16% of 'normal individuals' carried a potential disease causing variant! Systematic evaluation of disease

populations for multiple variants, not simply those associated with the particular condition, reveals that multiple variants in individual patients are common, e.g. a patient with hypertrophic cardiomyopathy may have a beta myosin heavy chain mutation and may also carry a sodium channel mutation. At this point it is unclear to what extent additional variants influence disease expression and contribute to disease complications such as sudden death. The current state of play with respect to clinical mutation analysis can be likened to the transition era from the horse and buggy to the automobile. The future is clear, but the time frame uncertain. Ultimately (probably soon) clinical mutation analysis will play an important role in the management of inherited cardiomyopathies.