

Conclusion

Cardiovascular medicine has changed so dramatically over 50 years that it is impossible to predict the future. The specialty has been dominated by the disease burden of coronary disease. The current revascularisation techniques have improved the well-being of many thousands of sufferers, nevertheless CABG and angioplasty are rather blunt instruments with which to counter a progressive disease. Although more can now be done to prevent progression of atherosclerosis, our powers are still limited. Vastly more is now known about the pathogenesis of coronary disease, at both cellular and molecular levels, but as yet this knowledge has had no direct impact on clinical practice. I am sure it will.

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CURRENT KEY DEVELOPMENTS

Grown up congenital heart (GUCH) disease: a half century of change

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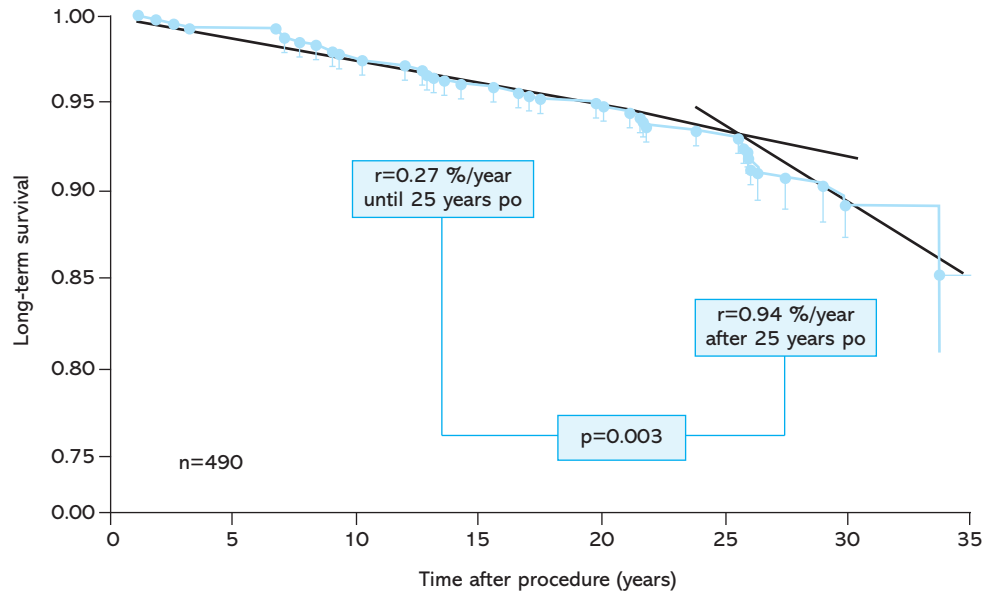
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The incidence of all levels of congenital heart disease (CHD) remains at 7–12/1,000 live births. Despite intrauterine recognition of fetal CHD, very few lesions are now considered incompatible with life. The numbers of adults with CHD now significantly exceeds the paediatric population. The 18-year survival for a child born with complex CHD in the 1960s was 10% whereas a child born with the same complex disease in the 1980s had a 50% 18-year survival. Now 90% survive into adolescence and beyond; the recent Department of Health report has estimated the total number (England and Wales) of grown up congenital heart disease (GUCH) patients in 2000 as 133,190 rising to 158,990 by 2010.¹ The better palliated and natural history of these patients has important implications for long-term care and training of cardiologists in the management of both the natural and unnatural (operated) history of CHD.² Coarctation of the aorta was first repaired in 1945 and frequently patients were discharged as ‘cured’. It is now clear, however, that late complications relating to the type of surgical intervention (namely restenosis with end-to-end anastomosis, aneurysm formation with Dacron patch) require continued surveillance. Moreover some patients are prone to premature coronary artery disease, persistent upper limb hypertension (despite relief of the coarctation) and ascending aortic dilatation – probably related to the bicuspid aortic valve present in at least 50%.³ As a result of the natural and palliated sequelae, late survival is still significantly compromised.⁴

Long-term survival of tetralogy of Fallot (ToF) is already known to be excellent (Fig 1) but many will need further surgery to the right ventricular (RV) outflow tract (RVOT) for free pulmonary regurgitation or RVOT aneurysms (both of which complications are likely to have occurred as a result of the original surgical technique) as well as other interventions (eg implantable cardioverter defibrillator implantation or aortic root surgery). The revolutionary technique of percutaneous pulmonary valve replacement introduced by Phillip Bonhoeffer over the last five years has allowed selected patients to avoid further sternotomies with subsequent improvement in RV function.⁵

Transposition of the great arteries was palliated by the atrial repairs of Mustard and Senning in the mid-1960s. This has permitted good survival for at least 30–40 years but the systemic RV leads to heart failure. Baffle obstructions and leaks are now dealt with percutaneously but considerable morbidity occurs with

Fig 1. Palliated survival after first repair of tetralogy of Fallot. po = post operation.



intra-atrial re-entry tachycardias.⁶ These difficulties led to the development of the arterial switch in which the great vessels are transposed and the coronary arteries are reimplanted. As ever in palliated CHD, late complications of subpulmonary obstruction, neo-aortic regurgitation and ostial coronary stenoses need knowledgeable follow up.

It is still not clear whether angiotensin converting enzyme inhibitors have as much effect in failing systemic right ventricles as has been demonstrated in acquired left ventricular failure, but device therapy in the form of cardiac resynchronisation therapy in some conditions such as congenital corrected transposition of great arteries has been promising.⁷ Late sudden cardiac death in many types of complex CHD remains difficult to predict. Implantable cardioverter defibrillators may often require ingenious vascular access – it is possible that subcutaneous leads may be an alternative approach. Arrhythmias continue to be a main cause of acute admission especially in Fontan-type circulations – either they herald new haemodynamic compromise (requiring conversion to total cavopulmonary connection) or specialist three-dimensional electroanatomic (CARTO) mapping systems to allow ablation. Pulmonary hypertension, secondary to a

reversed shunt (Eisenmenger), now shows encouraging response to phosphodiesterase inhibitors, prostanoids and endothelin-receptor antagonists. It is an exciting development since treatment previously had mainly been supportive and reactive. The question remains as to how to retard disease progression and the ways to combine these, and other newer, agents most effectively.

Knowledge of the genetic basis of CHD is growing.⁸ The most common chromosome deletion (22q11) accounts for 20–30% of all CHD (estimated incidence around 1 in 4,000 live births (Table 1).⁹ It is incompletely penetrant, and has an expansive phenotype, key features of which are encapsulated by the acronym CATCH 22 (cardiac outflow tract defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcaemia, and deletion of chromosome 22q11).¹⁰ It has a 50% inheritance risk and is thus of relevance when counselling for pregnancy.

Mutations in the coding region of NKX2.5 have been seen in 8–19% of familial ASDs and nearly all genotype positive individuals develop heart block.¹¹ This bradyarrhythmia is often severe, appears to be progressive, and may not manifest until later in life but allows closer follow up of affected patients once the genetic basis is known.¹² Additional cardiac abnormalities – ventricular septal defects (VSD), ToF and pulmonary stenosis for example – have been discovered repeatedly in familial clusters of ASD that have identical homeodomain-coding errors of the gene.^{9,10,11,12} It remains impossible to predict the exact form of CHD from the location or nature of a given NKX2.5 mutation but is one of the many challenges ahead in care of the CHD patient.

Table 1. Cardiovascular findings in the 22q11 deletion syndrome.

Cardiac diagnosis	Percentage of total (%)
Normal	20–25
Tetralogy of Fallot	22–35
Interrupted aortic arch	15–19
Ventricular septal defect	13–18
Truncus arteriosus	7–12
Vascular ring	5
Isolated aortic arch anomalies	5
Other	10–15

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Contemporary percutaneous coronary intervention – 30 years in the making

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The birth of angioplasty goes back to the pioneering work of Dotter and Judkins who in 1964 published the outcomes using solid plastic tubes to increase the luminal area of peripheral vessels.¹ However, the true visionary and initiator of modern day percutaneous treatment for obstructive coronary disease was Andrea Gruntzig. In 1976 Gruntzig presented animal work in which he used a balloon catheter to dilate arterial stenosis. Studies in human peripheral arteries were performed in 1974,² and the first coronary intervention on a conscious patient was performed in 1977. The stenosis was in the left anterior descending artery, and the excellent outcome achieved held for many years. It is fascinating to read Gruntzig's original paper since he predicted difficulties with heavy calcification and tortuosity that even today present a challenge to angioplasty.³ The procedure spread rapidly with early publication of databases from the National Heart, Lung, and Blood Institute. The first balloon angioplasty in the UK was undertaken in the early 1980s although there is debate whether this was at the Royal Brompton Hospital or the London Chest Hospital. Either way the 1980s saw a rapid expansion with crossover in numerical terms from coronary artery bypass graft surgery (CABG) to angioplasty occurring as early as 1998 in the USA. There were, however, a number of problems that needed resolution.

The first of these was restenosis, which in the early/middle 1990s was an all encompassing term around pathological changes that resulted clinically in the need for a repeat procedure. With balloon angioplasty this occurred in 35% of cases. Restenosis was presumed the consequence of scar tissue that formed within the vessel wall as a result of response to injury mechanisms, which then encroached on the lumen and induced recurrent ischaemia. While local drug delivery with balloons was being (unsuccessfully) tested in an attempt to reduce scar tissue a number of solutions to various problems came together at the same time. Acute vessel closure was another issue. When a balloon is inflated in any artery, the vessel wall, and particularly the intimal layer becomes disrupted – indeed this is partly how balloon angioplasty works. In the late 1980s/early 1990s acute closure of ballooned vessels led to many patients requiring emergency coronary artery bypass surgery to prevent myocardial infarction/death.

The development of the stent (a fine metal mesh) to create a scaffold which prevents the disrupted flap from obstructing the lumen was a critical breakthrough. The first stent was deployed by Puel and Sigwart in Toulouse in 1986 but it took developments over a number of years, particularly by Palmaz and Schatz to devise a user-friendly/patient-friendly device. As stent use accelerated to 90% throughout the 1990s with the development of conformable alloy laser cut designs, and the need for emergency

surgery plummeted and is now rarely required (<0.5%). It was also observed that with increased stent use the incidence of restenosis/need for a repeat procedure also fell from 35% with balloon alone to 15–20% with stenting. Understanding of the causes of luminal re-narrowing now had to take account of the apparent benefits of stenting. The use of intravascular ultrasound (echo imaging within the artery) helped – recurrence after balloon angioplasty it would seem in fact comprised three components: re-coil of the vessel wall, late negative re-modelling (normally a vessel gets larger as atheroma develops, but as a result of adventitial injury, ballooned vessels become inappropriately smaller over time), and the response-to-injury scar. Stents clearly dealt with the recoil and the negative re-modelling leaving only the problematic scar tissue. The BENESTENT and STRESS studies and the pioneering work, by Serruys in Europe and by groups led by Leon in the USA, confirmed the clinical benefits of stenting on restenosis, and need for repeat procedures fell.^{4,5}

The residual problem of the 15%+ restenosis rates with bare metal stenting remained however. Meanwhile it became clear that stenting carried with it a risk of thrombus formation and pivotal studies comparing anti-thrombotics (such as warfarin) with anti-platelet medication demonstrated the need for pre-procedural and post-procedural treatment with dual anti-platelet therapy (aspirin for life and thienopyridines such as clopidogrel for one month). Clot after stenting was ‘platelet-centric’.

The penultimate development in percutaneous intervention was drug-eluting stents. Throughout the 1990s, studies were published on the loading and elution from stents of tiny amounts but locally delivered high concentration of drugs.⁶ Rapid expansion of the concept of drug-eluting stents and research developments by many groups led to pivotal clinical trials.^{7–9} Over 10,000 patients have been included in the numerous randomised trials and real-life registries. Use of drug-eluting, scar-inhibiting stents reduces the chance of clinical recurrence by 80% (from 15%+ to around 5–7%) especially in those patients at greatest risk of recurrence (small vessel diameters, long lesions and diabetics). Such indications were approved by the National Institute for Health and Clinical Excellence in 2003 and again recently (2008). Concerns regarding the small chance of excess stent thrombosis beyond the timeframe for bare metal stent anti-platelet therapy are currently under review. A large number of studies appear to show that although there may be an excess of 0.3% stent thrombosis per annum, overall mortality (cardiac) may in fact be improved with drug-eluting stents by up to 3% over two to three years. Clopidogrel is currently continued for 12 months.

The ratio of stenting/CABG in the UK currently stands at 3:1 but is higher worldwide (as much as 8:1 in parts of Europe). The impact of stenting on those previously considered ‘surgical cases’ (multi-vessel disease/ left main stem disease) is also under review through registry, but more importantly upcoming trials such as the SYNTAX study.

Finally, percutaneous coronary intervention (PCI) is likely to become the treatment that supersedes thrombolysis for acute myocardial infarction. Pivotal comparisons by Grines, O’Neill and Stone show improved outcomes for those treated with primary

(P)PCI.¹¹ Many hospital systems in the UK are now developing strategies to implement PPCI, not least since historically most patients present to hospitals without PCI facilities. Randomised trials comparing PPCI with pre-hospital lysis are underway.

Summary

Angioplasty has come a long way in 30 years. It is now the dominant therapy for obstructive coronary disease and becoming so for acute myocardial infarction and for the majority of patients it is a simple, quick procedure with same- or next-day discharge with negligible morbidity. Many of the developments have been led by pioneers conducting independent large randomised trials, but there are issues still to resolve and there are new exciting developments such as bioabsorbable stents and stereotaxis in the wings. Many have a lot to be grateful for when we reflect on the insights and pioneering work of Andreas Gruntzig.

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Non-invasive cardiac imaging

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Coronary artery disease (CAD) is the leading cause of mortality in men and women in the developed world.¹ Establishing the diagnosis, extent and severity of CAD and determining the potential risk for future cardiovascular events are crucial to improve the morbidity and mortality associated with coronary heart disease. The value of a number of commonly used non-invasive cardiac imaging techniques is now firmly established and research continues to develop both new techniques and applications of nuclear cardiology, echocardiography (ECHO), computed tomography (CT), including multidetector and dual source imaging techniques, and cardiac magnetic resonance imaging (MRI).² Current guidelines provide advice regarding the choice and use of imaging modalities but it is becoming increasingly challenging for physicians including cardiologists to ensure that patients receive the most appropriate imaging to guide management.³⁻⁵

Myocardial perfusion imaging using nuclear techniques offers a powerful prediction of the risk of cardiac death or myocardial infarction, or the need for revascularisation. A normal perfusion

scan during stress (with either adenosine or dobutamine) is associated with an excellent outcome and a cardiac event rate of less than 1% per annum.⁶ Similar information may be obtained using MRI but the optimum imaging sequence is yet to be defined and technological advances and increased field strengths together with a relative paucity of expertise in this area all combine to restrict the use of such imaging to a few, and largely research active, sites.^{7,8} The new technologies being applied to CT offer the potential to assess the presence and extents of coronary disease, assess plaque character and also the impact of such CAD on myocardial perfusion.^{9,10} The limiting factors at the present time include the radiation dose and the need for iodinated contrast but improvements are being made rapidly.^{5,11,13}

Two-dimensional ECHO provides excellent images of the heart and great vessels in the majority of patients who have a suitable acoustic window. Of all the currently available non-invasive techniques it is both the most versatile and the most readily available. Stress ECHO with exercise or dobutamine is used to assess left ventricular systolic and diastolic function, valvular heart disease, the extent of infarction and stress-induced ischaemic left ventricular dysfunction.¹⁴ Stress ECHO has good diagnostic accuracy for detecting or excluding significant CAD which is enhanced by the application of deformation imaging using tissue Doppler and speckle tracking to define in more detail myocardial wall motion abnormalities (Fig 1).¹⁵ Three-dimensional ECHO imaging is increasingly being used to assess valve lesions, and the overall use of ECHO continues to

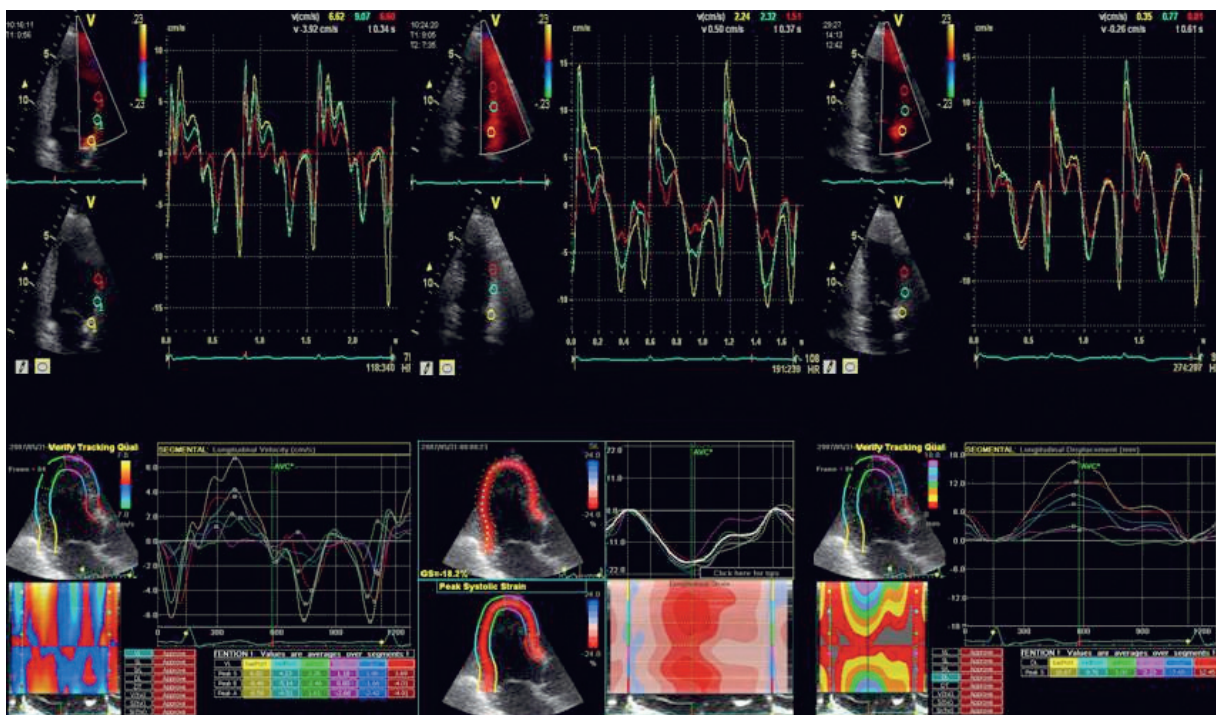


Fig 1. Echocardiographic images analysed using tissue Doppler imaging (top panel) and speckle tracking (lower panel). The tissue Doppler traces illustrate an increase in myocardial systolic velocity during dobutamine stress and confirm the presence of viably myocardium in the lateral wall of the left ventricle. The lower panel illustrates the use of speckle-tracking algorithms to identify unique patterns of echocardiographic pixel intensity that are tracked throughout the cardiac cycle. The angular displacement of these pixels can be plotted over time and averaged to provide a measurement of both degree and direction of rotational motion for each myocardial segment. The images illustrate longitudinal velocity, systolic strain and longitudinal displacement respectively.

expand. In addition there is an increasing requirement to assess ventricular dyssynchrony using the above techniques to identify patients who will benefit from cardiac resynchronisation therapy. The development of all of these techniques, however, is dependant on state of the art equipment including new transducers with pre-processing facilities, capacity for very rapid acquisition of digital images at high frame rates and appropriate workstations to facilitate subsequent analysis. Software advances and upgrades are required regularly together with experienced personnel with time to devote to the required analysis which is far more time consuming than the initial acquisition of images.

Currently few departments will be able to embrace the new technology without significant investment in both staff and equipment, and a radical change in working practice to ensure the appropriate and targeted use of these novel imaging techniques.¹⁶ Cardiologists specialising in imaging must lead multi-disciplinary team meetings and guide their interventional and other colleagues to ensure that non-invasive imaging is used optimally. Increasing collaboration with radiologists with an interest in cardiac imaging will be required and a curriculum for a final year training programme for specialist registrar's training in cardiology or radiology will shortly be approved.

There is an increasing body of data confirming that patients who present with symptoms suggestive of CAD can be accurately diagnosed and their risks stratified using appropriate non-invasive imaging techniques. Investment will enable a holistic approach that will ensure continued improvement in the prognosis of patients with coronary heart disease.

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Management of cardiac arrhythmia

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Over the last two decades the management of cardiac arrhythmias has moved on from a largely diagnostic and investigative pursuit, founded on hope and empiricism, in which treatments were often ineffective and potentially dangerous^{1,2} to develop into a major sub-speciality of cardiology providing definitive cures to many patients. Effective treatment certainly looked some way off when drugs, shown to be effective in the suppression of arrhythmias, were also seen to increase mortality.¹ The major advances have in fact relied on newer interventional approaches based on the targeted ablation of arrhythmia substrates and an increasing use of implanted devices.^{3,4} Conversely no important new antiarrhythmic drugs have been developed during this time.⁵ The delivery of effective but rapidly evolving invasive treatments has required adaptable teams that can quickly acquire, assimilate and deliver specialised services. In response to these challenges national societies have organised themselves effectively over a short space of time providing training and other support to develop the necessary manpower.⁶ The patient populations that may potentially benefit from specialist care are also increasing. These groups are wide-ranging encompassing bereaved families in whom there is a requirement to define more tightly the risk of sudden cardiac death (SCD) to those individuals caught up in an epidemic of atrial fibrillation (AF) a group that includes older patients that have a high prevalence of chronic heart failure.⁷

Established treatment options

Key decisions regarding management for many patients are relatively straightforward. For example, pacemakers have for over 50 years relieved patients of symptoms of bradycardia and are highly cost effective. Although some relatively minor questions remain regarding the location and number of endocardial leads pacemakers for bradycardia should be regarded as an established option.⁸ Similarly radiofrequency ablation is now undoubtedly the treatment of choice for most individuals presenting with narrow complex tachycardia, atrial flutter and normal heart ventricular tachycardia.³ Ablation is safe, well tolerated and effective usually providing a cure with a single procedure so it is unacceptable for patients to be maintained unnecessarily on chronic prophylactic drug therapy and they should be referred for specialist treatment.³ Contrasting with the substantial consensus in these various conditions aspects of the management of AF and SCD are still the subjects of debate regarding best practice.

Catheter ablation of atrial fibrillation

Atrial fibrillation is a major cause of morbidity and mortality.⁷ The possibility that AF could be cured was first shown using the

surgical Maze procedure⁹ and although initial attempts to reproduce these findings using catheter-based ablation techniques were disappointing it now seems that most patients can be cured without the need for surgery.¹⁰ Critical observations were made in Bordeaux, France, where the pulmonary veins were found to be the source of arrhythmia triggering in most patients with paroxysmal AF.¹¹ Many studies have subsequently shown that when these veins are isolated most patients are relieved of their arrhythmia.^{10,12} The techniques required for such left atrial ablation, while fundamentally safe, are occasionally associated with severe complications.¹⁰ Accordingly, techniques continue to evolve and the selection, targeting and delivery of particular ablation strategies needs further definition and will rely on emerging results of both preclinical and clinical research.^{5,10,13} The extension of these catheter-based ablation approaches to patients with more persistent patterns of AF is now clearly possible with significant implications for strategic service expansion.¹² The extent to which patients with AF will be offered ablation and the organisation of care delivery pathways will remain the subject of debate informed by ongoing research.

Sudden cardiac death

The second large area needing resolution is the risk stratification and management of patients at potential risk of SCD. Antiarrhythmic drugs including amiodarone offer no protection against SCD for most patients and while transvenous implantable cardioverter defibrillators (ICDs) are clearly effective at saving lives they have rather poor specificity with the possibility of inappropriate shocks and lead problems increasingly recognised.^{4,14} One major concern is the inability to identify patients that will most benefit from ICDs and a clearer definition of SCD predisposition phenotypes is required. The current indications for ICDs for primary prevention are based on the left ventricular ejection fraction⁴ and more direct electrophysiological measurements may provide a means of better targeting devices.¹⁵ There are clear genetic influences predisposing to SCD and these extend to acquired coronary and structural heart disease¹⁶ and it is hoped that the definition of genotype-phenotype relationships in monogenic SCD syndromes (eg long-QT and Brugada syndromes, catecholaminergic polymorphic ventricular tachycardia) will provide the means to resolve arrhythmogenic mechanisms that will be more generally applicable.¹⁷⁻¹⁹

Summary

Cardiac arrhythmia management has advanced substantially and many patients are now being offered curative treatment. There is still much to do and therefore substantial research opportunities. Technical advances with better imaging and mapping datasets,²⁰ improved ablation catheters and new devices to protect against SCD are all on the horizon. The genetic contribution to arrhythmias is now firmly established and preclinical functional studies¹⁷⁻¹⁹ will lead to more detailed phenotyping of patients leading to more rational targeting of drugs, catheter ablation and devices.

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Fifty years of permanent pacemakers: chronotropic rescue to inotropic support

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The dawn of permanent pacing was heralded by Seymour Furman's demonstration in 1958 (published the following year) that an endocardial pacing electrode could be placed in the right ventricle (RV) using a transvenous approach guided by fluoroscopy.¹ The first attempt at a fully implantable endocardial pacemaker system took place in 1958; sadly, the reliability of electronic components resulted in failure of this device after a short period. In the UK, Leon Abrams took a different approach to avoid the reliability issue and developed an external device with transcutaneous induction to a surgically-implanted loop and epicardial leads.²

The need for permanent cardiac pacing in these early days was driven largely by problems of sudden death due to heart block, often after cardiac surgery for conditions such as ventricular septal defect. As such, the aim of the procedure at the time was life-saving ventricular rate support and little consideration was given to the effects of RV stimulation on left ventricular (or overall cardiac) function. As pacing became widely accepted, the more common indications became acquired high degree heart block and later sinus node disease.

The RV apex became the endocardial site of choice for most pacemakers; this site is easily accessible from a transvenous approach and provides the potential for lead stability by virtue of the muscular trabeculations in this region. Stimulating the heart from this site produces abnormal conduction and contraction patterns (similar to left bundle branch block (LBBB), resulting in a significant negative inotropic effect. This was not a new discovery; Wiggers had demonstrated the negative impact of stimulating the heart outside the intrinsic conduction pathways in 1925.³

Pacemaker lead stability and design constraints limited attempts to approach other sites in the early days and efforts were turned to enabling restoration of atrioventricular (AV) synchrony with the introduction of dual-chamber pacemakers and the ability to influence cardiac rate through sensor-driven rate response. In order to achieve dual-chamber pacing, another trabeculated site, the right atrial appendage, became the preferred atrial pacing site. Atrial pacing alone was also developed for sinus node disease; despite the attractions of using the His-Purkinje system to enable normal ventricular conduction, it has not been universally accepted due to concerns about future AV conduction problems.

The dual-chamber approach was labelled 'physiological' pacing, and certainly demonstrated benefits over ventricular pacing,^{4,5} but it soon became apparent that, despite maintaining AV synchrony and offering chronotropic response, the effects on left ventricular function of stimulating from the RV apex were

far from physiological.⁶ Indeed, over the long term, evidence began to accrue that RV apical pacing may result in clinically apparent heart failure.⁷ In addition, work with atrial-based pacing showed the detrimental effects of ignoring atrial activity in patients with sinus node disease; ventricular-based pacing was shown to increase the risk of atrial fibrillation, stroke and death.^{8,9} Efforts to identify pacing sites that would not impact in such a negative way on left ventricular function were complemented by the demonstration that, in patients with significant intraventricular conduction delay (usually LBBB) and reduced LV function, resynchronisation of ventricular function was possible using the technique of biventricular stimulation.¹⁰ As the effects of prolonged endocardial stimulation of the ventricle have become clear, the aim of cardiac pacing is no longer simply to restore chronotropic competence but also to optimise or, in the case of biventricular stimulation, to improve LV function.

Biventricular pacing (or cardiac resynchronisation therapy (CRT) as it is now known) is more challenging than 'routine' pacing for bradycardia. The most difficult aspect is accessing the LV; this is achieved via the coronary sinus and cardiac veins, allowing leads to be placed on the endocardial surface of the LV using a transvenous approach. This requires cannulation of the coronary sinus, with the lead being passed down a catheter and steered into a cardiac vein, usually on the posterolateral aspect of the LV. This is chosen as the site of latest depolarisation of the ventricle as simultaneous stimulation from here and the RV endocardium results in a shortening of QRS duration, improved LV wall synchronisation and an increase in cardiac output. Studies have shown that this works best when the patient is in sinus rhythm so that the ventricular stimulation can be timed to atrial contraction with an AV delay optimised to provide the best filling times.¹¹ Cardiac resynchronisation therapy has now been shown to be a cost-effective treatment for selected patients with heart failure, improving quality of life and reducing hospitalisation.¹²

Pacing for bradycardia remains the largest part of pacing therapy; new algorithms and sophisticated electronic hardware now enable a great deal of manipulation of the electrical activity of the heart. As we move towards the second 50 years of this

therapy, the challenges will be to meet the increasing demands of an ever-aging population, and to develop techniques to identify and access pacing sites that will optimise long-term ventricular function.^{13,14}

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