History and evolution of pacing and devices

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Received 14 November 2021
Accepted 23 February 2022

To cite: Haydock P, Camm AJ. *Heart* 2022;**108**:794–799.

ABSTRACT

Cardiac implanted electronic devices are commonplace in the modern practice of cardiology. This article reviews the history of the development of these technologies, with particular reference to the role played by UK physicians and members of the British Cardiovascular Society. Key breakthroughs in the treatment of heart block, ventricular arrhythmia and heart failure are presented in their historical and contemporary context so that the reader might look back on the incredible progress and achievements of the last 100 years and also look forward to what may be achieved in the coming decades.

INTRODUCTION

The modern practice of cardiac rhythm management represents the constant evolution of clinical, cardiac electrophysiology, which has its origins among the founders of the Cardiac Club, now the British Cardiovascular Society (BCS).

The electrical activity of the human heart was first recorded by Augustus Waller, chief of physiology at St Mary's Hospital, London in 1887. Waller's ECG Train, part of the BCS Archive, was a valuable laboratory tool but Willem Einthoven's string galvanometer proved a more effective clinical apparatus. Sir Thomas Lewis, chair of the first meeting of the Cardiac Club, corresponded with Einthoven and pioneered the use of the ECG in clinical practice—an early example of the benefits of international collaboration, which have been fundamental to the development of clinical cardiology over the last 100 years.

In 1908, Lewis, with Arthur MacNalty, reported the occurrence of complete heart block in a patient, demonstrating independent sinus and ventricular rhythms using James Mackenzie's polygraph as well as Einthoven's ECG[1] (figure 1). These observations complemented the contemporary work of fellow Club member John Hay, who first described second-degree heart block, and performed the first necropsy demonstrating changes in the atrioventricular (AV) bundle of a patient in whom heart block had been recorded during life.[2] This work laid the foundation upon which generations of clinical scientists, physiologists and electrical engineers have built the modern specialty of cardiac electrophysiology, and on which multinational corporations have been founded to develop new technologies in the interests of patients across the globe.

THE DEVELOPMENT OF CARDIAC PACING

Establishing the clinical problem

Building on the work of Mackenzie and Lewis, John Parkinson—first president of the BCS and chair of the first European Congress of Cardiology—proposed a more rigorous definition of the Stokes-Adams syndrome in 1941. This was based on the occurrence of ventricular standstill associated with normal function of the auricles on the ECG at the time of symptoms.[3] At the time, the prognosis of nearly all cases was terminal and was a primary driver for the development of pacing technologies.

Developing the technology for implanted cardiac devices

In 1951 at Harvard, Paul Zoll developed an external system to pace the heart comprising an ECG combined with a pulse generator attached to a pair of electrodes applied to the patient's chest.[4]

The fledgling specialty of cardiac pacing subsequently developed through the 1950s due to the enthusiasm of a disparate group of early adopters in the UK, continental Europe and the USA. Key among these was Aubrey Leatham, who established a cardiac unit at St George's Hospital, London at the beginning of the decade. Leatham had been trained by Paul Wood at the National Heart Hospital, having been invited there by Sir John Parkinson, and was one of the new breed of 'cardiologists' emerging as specialists at that time.[5]

The St George's Cardiac Unit made an unparalleled contribution to the advancement of the fields of cardiology and cardiac surgery through the triumvirate of cardiologist Aubrey Leatham, surgeon John Parker and pathologist Michael Davies, who was awarded his MD in 1968 for his work on the pathology of complete heart block. His research was published in the British Heart Journal in 1969—an inspiration to the subsequent cohorts of early career clinical scientists who have received the award given in his name by the BCS.[6]

In the early 1950s, the St George's unit pioneered pacing in the UK via an external, battery-powered stimulator built by bioengineer Geoffrey Davies for Aubrey Leatham and implanted via thoracotomy performed by Harold Siddons (figure 2). Leatham was aware of Zoll's external pacing system but recognised that fixed rate pacing might stimulate the heart at a time of spontaneous depolarisation and risk inducing ventricular fibrillation. He therefore worked with Davies to design and manufacture an apparatus to detect and be suppressed by the spontaneous rhythm of the heart—the earliest example of a 'demand pacemaker' (figure 3).[7]

Year 1958 marked the start of a decade in which permanent pacing moved into mainstream clinical practice. Åke Senning at the Karolinska University Hospital, Sweden, implanted a device designed by Rune Elmqvist involving epicardial wires attached to a rechargeable generator in the abdominal wall—the first device truly worthy of the title permanent pacemaker.[8]

Senning and Elmqvist published their case report at the same time William Chardack and Andrew Gage reported the implant of a self-contained, internally powered artificial pacemaker designed

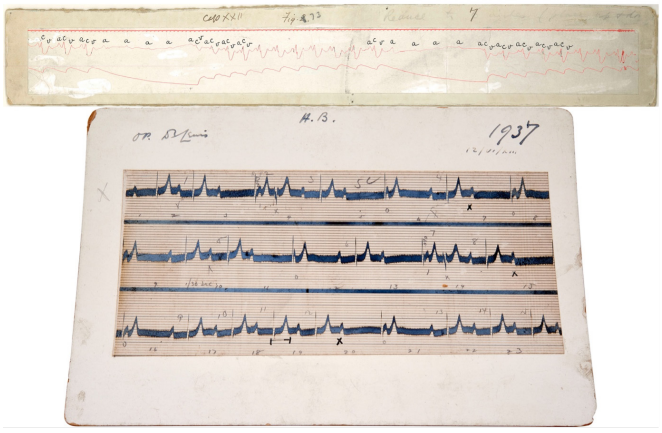

Figure 1 Recordings made by Thomas Lewis. Upper: ink polygraph demonstrating two episodes of 'ventricular standstill'. Lower: ECG demonstrating heart block. (With permission of the British Cardiovascular Society Archive).

by engineer Wilson Greatbatch.[9] In the UK, in the same year, Birmingham surgeon Leon Abrams implanted a device developed with Ray Lightwood and the Lucas battery company. This comprised a subcutaneous coil attached to epicardial leads, over which was strapped an induction coil attached to a battery-powered, external pulse generator with a patient-controlled variable rate function (figure 4). The patient who received this first implant following ventricular septal defect (VSD) repair and consequent complete heart block eventually died 3 years later of an unrelated malignancy.[10] The Lucas-Abrams pacemaker was widely used in the early 1960s, with one unit being implanted by a young Peter Sleight in Oxford in 1964. The ability of patients to increase their heart rate manually was an advantage when physical activity was required but a steady hand was required for battery changes to prevent prolonged asystole.

Future BCS and British Pacing and Electrophysiology Group president Edgar Sowton took simultaneous degrees in physics and medicine from Cambridge and was awarded the Horton-Smith prize for the best doctoral thesis at the university for his work on cardiac pacing. His UK training was primarily at St George's where, in 1961, Leatham, with Harold Siddons and O'Neal Humphries, implanted the first indwelling pacemaker in the UK (figures 5 and 6).

Figure 2 Components of the first pacemaker developed by Geoffrey Davies and Aubrey Leatham.

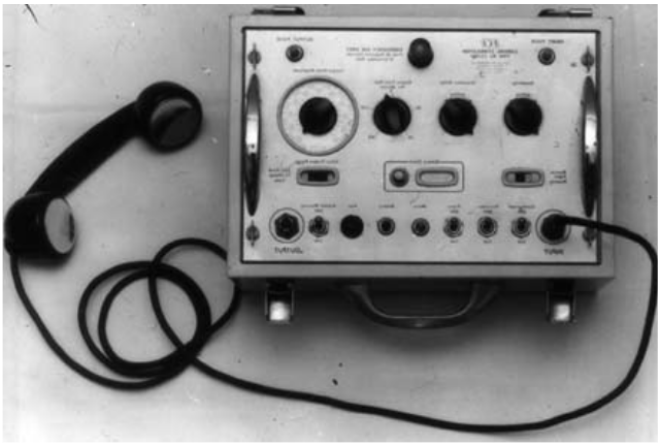

Figure 3 Geoffrey Davies' external 'demand' pacemaker.

Other luminaries in the history of cardiac pacing practised their art at St George's and the National Heart Hospital. As well as Sowton, Alan Harris, Kanu Chatterjee, Richard Sutton and Tony Rickards were present as endocardial pacing via the transvenous route became established as an alternative approach to the more invasive thoracotomy technique in the late 1960s.

In 1968, 10 years after the first pacemaker implant, Richard Sutton presented the 5-year follow-up data for the first 53 patients undergoing permanent pacing at the St George's unit to the European Congress of Cardiology. Complication rates were high but over 50% of patients remained alive—a remarkable figure given that survival in heart block could generally be measured in days up until the late 1950s.[11]

Establishing permanent pacing in routine clinical practice

The potential scale of the problem of AV block in the general population, and the implications for provision of permanent pacing, was highlighted at the start of the 1970s by David Shaw in his paper with Dennis Eraut on the prevalence and morbidity of heart block in Devon.[12]

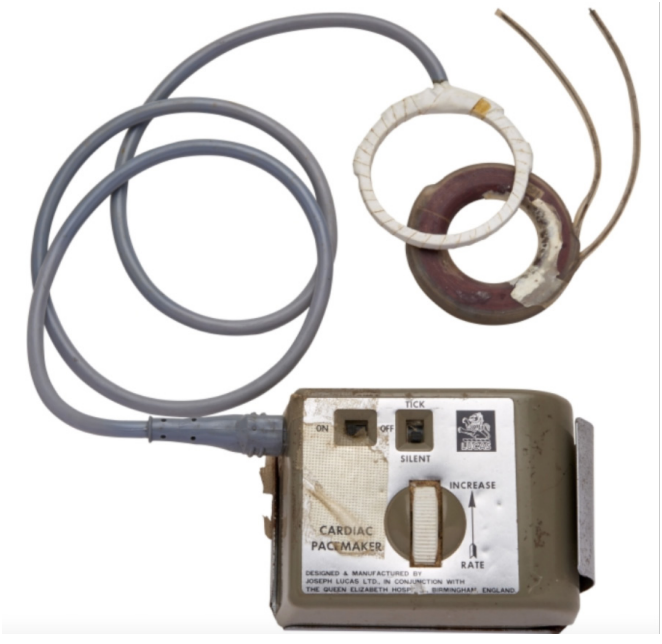

Figure 4 The Lucas-Abrams pacemaker (courtesy of the British Cardiovascular Society Collection).

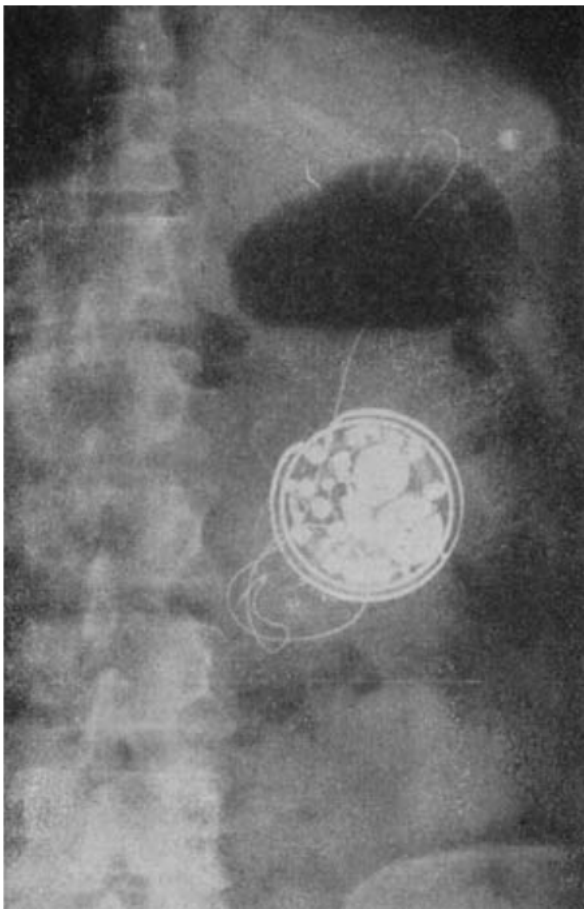

Figure 5 X-ray of the first implanted pacemaker at St George's Hospital, 1961.

Figure 6 Her Majesty Queen Elizabeth II visiting St George's Hospital and discussing the pacemaker with Aubrey Leatham and a patient (courtesy of Richard Sutton).

Advances in manufacturing processes and principally the development of lithium-based battery technology were critical steps which increased the use of pacemakers in the UK and around the world. Polyurethane insulated leads and the development of both passive and then active fixation mechanisms improved implant success and reduced lead failure and displacement issues. In the latter part of the decade, there was much interest in developing physiological pacing, with the initial development of VDD pacing and then subsequently true sequential AV pacing systems comprising a lead in both the right atrium and the right ventricle.[13]

David Shaw continued to inform the scale of those who might benefit from such technologies, publishing the results of his 8-year, county-wide survey of heart block and sinoatrial disorder in the British Heart Journal.[14] He continued to publish data from this population into the early years of the 21st century supporting the prescription of pacing for Mobitz II[15] and Mobitz I heart block.[16]

As the 1980s arrived, Tony Rickards developed the world's first rate-responsive pacemaker having studied the effects of both exercise, atrial pacing and fixed ventricular pacing on the QT interval. His elegant paper with John Norman describes the experimental studies leading to the development of this system to allow physiological responses to exercise in patients with standard unipolar pacing leads according to the 'Stimulus-T interval'.[17] This work allowed for the expansion of pacing therapy into the arena of chronotropic incompetence, although the technology has been superseded by accelerometers detecting motion or impedance monitoring to assess minute ventilation.

Richard Sutton's group published on the use of AV pacing in the treatment of carotid sinus hypersensitivity in the British Heart Journal in 1982[18] and continued to research the utility of pacing in both cardio-inhibitory and neurogenic syncope following on from establishing the role of the tilt-table in assessing patients.[19] This group was also interested in the potential benefits of 'physiological' pacing,[20] which remained a hot topic throughout the 1980s and 1990s. A study from Richard Charles' group in Liverpool examined the temporal trends of pacemaker mode prescription in their centre over the 10 years from 1984 to 1994 and was published in *Heart* in 1996. These data demonstrated an increasing use of dual-chamber pacing in general, but a lower likelihood of elderly patients receiving physiological pacing.[21] Subsequent, pivotal data to inform pacemaker prescription were provided by the results of the UKPACE Study in 2005, led by William Toff and John Camm. These data—demonstrating no significant mortality benefit for dual versus single-chamber pacing in patients >70 years over a median follow-up of 4.6 years—represent an important contribution from a collaborative UK cardiology community to the modern practice of pacing.[22]

IMPLANTED DEFIBRILLATORS

That defibrillation to allow resuscitation was a realistic possibility outside of the cardiac operating theatre became recognised in the late 1950s and the early technology of external defibrillators is well reviewed by Roy Shephard in the British Heart Journal in 1960.[23]

In 1964, Frank Pantridge was involved in the successful resuscitation of a collapsed patient just outside of the Royal Victoria Hospital, Belfast. This event led on to the development of portable, battery-powered defibrillators and 'mobile intensive care units' to improve survival post-cardiac arrest—'The Pantridge Plan'—enthusiastically adopted in the USA and Ireland, but only implemented in a few UK centres until a statutory mandate to employ it throughout the National Health Service (NHS) in 1990.

From the early 1970s, a decade-long process of research and development by Michel Mirowski and his collaborators Morton Mower and Arthur Moss in Baltimore culminated in the implanted cardioverter defibrillator (ICD).[24] Contemporaneously, Pantridge developed the automated external defibrillator—an idea of which Mirowski was not convinced but one which has undoubtedly resulted in the implant of many subsequent secondary prevention ICDs.[25]

Technological advancements in ICD therapy closely mirror those of pacing, with the first devices requiring sternotomy and screw-in sensing leads combined with epicardial patches to deliver asynchronous, monophasic shocks. Work in the early 1980s allowed for synchronous shock delivery for cardioversion of ventricular tachycardia and in 1985, after around 500 implants, the Food and Drug Administration approved the ICD for general use.[13] In the UK, the first ICD was implanted in April 1984 by Alan Yates in a 49-year-old woman referred by Edgar Sowton.

The technology continued to advance, both in terms of software and hardware, and by 1996 all devices were recognisable as the transvenous systems in common use today, with the capability of not just cardioversion/defibrillation, but also antitachycardia pacing.

CARDIAC RESYNCHRONISATION THERAPY

In 1971, Derek Gibson and colleagues published data demonstrating the positive haemodynamic effects of simultaneous pacing of both ventricles in six patients following aortic valve replacement with Starr-Edwards' prostheses.[26] These data built on prior observations regarding the haemodynamic effects of both atrial and ventricular pacing. It took some time for interest in AV pacing in drug-resistant dilated cardiomyopathy to gain some traction, but in 1994 Serge Cazeau and colleagues published their seminal case report of a 54-year-old man managed for recalcitrant heart failure with pacing of all four cardiac chambers in the context of an ECG demonstrating a QRS duration of 200 ms—the birth of cardiac resynchronisation therapy (CRT).[27] Subsequent study, including in many UK centres, demonstrated the acute haemodynamic benefits of sequential biventricular pacing and apparent beneficial effects on heart failure symptoms in small case series. Development of left ventricular lead implant techniques via the coronary sinus, such that an epicardial approach was no longer required, allowed for more widespread use of the technology and led on to large-scale clinical trials of CRT-P and CRT-D to establish their clinical utility in heart failure with reduced ejection fraction (HFrEF).

CONTEMPORARY IMPLANTED DEVICES AND THE MODERN MANAGEMENT OF HEART FAILURE

Developments in pacing and implanted defibrillators have largely related to improvements in lead design and battery technology. In recent years, cloud-based technologies have facilitated remote monitoring of not only pacing parameters but a host of physiological information to potentially inform patient management—from diurnal heart rate variability, to activity levels and measures of thoracic impedance. Device monitoring has evolved rapidly and contemporary platforms integrate seamlessly with smartphone apps for relay of data to cardiac rhythm management departments, reducing the requirements for hospital visits. Such data can be harnessed by heart failure multidisciplinary teams (MDTs) and embedded into clinical practice to support patient self-management and prompt clinical review in situations of apparent, impending decompensation. Pathways to support the use of remote monitoring in this manner need to be carefully developed according to the individual heart failure service and implanted devices need to be considered as complementary to and synergistic with optimal heart failure medical management, including decongestion with diuretics alongside inhibition of the renin–angiotensin–aldosterone system, the sympathetic system and the sodium-glucose co-transporter-2 (SGLT2i).[28]

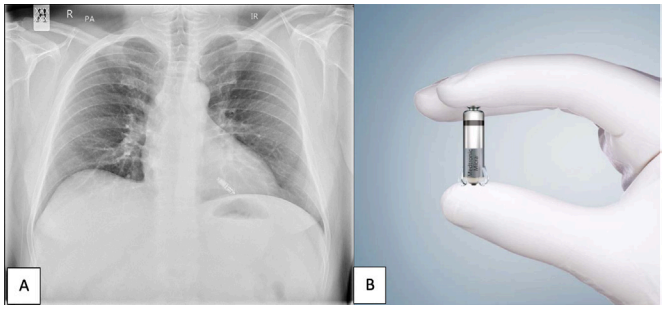

Figure 7 Example of a leadless pacemaker—Medtronic Micra. (A) Chest X-ray demonstrating implanted device appearance. (B) Device ex-corporo.

In the last decade, miniaturisation has allowed for the development of entirely leadless pacing systems[29] (figure 7), therefore potentially reducing device-related infection. These systems are now mirroring the progress of their historical forerunners in developing as dual chamber[30] and biventricular systems.[31]

As implanted device technologies have expanded in their potential, scope and complexity, it has been increasingly clear that an appropriate evidence base for their use in different clinical situations is fundamental to the modern practice of cardiology.

The evidence base for the use of ICD, not only in survivors of cardiac arrest, but as primary prevention devices in patients with HFrEF, accumulated over the decade following the publication of MADIT-1 in 1996.[32] Current UK and international guidelines continue to have these key trials at their heart, particularly SCDHeFT[33] and MADIT-2.[34] Important work published in 2004 by the DINAMIT investigators, including John Hampton in the UK, continues to influence practice in demonstrating a lack of net benefit for ICD therapy within 40 days of acute myocardial infarction.[35]

ICDs are now commonplace, and the development of entirely subcutaneous systems has provided patients with the potential for life-saving therapy, without fear of catastrophic intracardiac infection—proven effective in the PRAETORIAN trial, which included key UK principal investigators Pier Lambiase and Elijah Behr.[36]

Questions remain regarding appropriate device prescription, particularly in non-ischaemic cardiomyopathy and hypertrophic cardiomyopathy. The DANISH trial has demonstrated the potential equipoise in ICD prescription for patients without ischaemia[37] and recent developments in heart failure medical therapy—particularly the effect on mortality related to the use

of angiotensin receptor antagonism+neprilysin inhibition[38] and SGLT2i[39 40] —have also changed the prognostic trajectory of patients with heart failure when compared with the era of SCDHeFT and MADIT-2. Many now question the indication for primary prevention ICD in optimally managed patients with HFrEF in 2022 and this is undoubtedly an area which requires further study. A key hope for the future is to be able to offer a more detailed, individualised risk assessment for patients when considering ICD therapy.[37] An individualised patient data network analysis of implanted cardiac devices from 13 randomised trials, published by Beth Woods and colleagues in *Heart* 2015, gives some insight to this area,[41] and there is much contemporary interest in the use of cardiac MRI, particularly to quantify scar burden as a marker of sudden cardiac death with several trials on the horizon.[42]

The evidence base for the use of CRT has been built on an understanding of its physiological effects to allow recruitment of suitable patients with electrical evidence of dyssynchrony to large-scale clinical trials. UK cardiologists have been fundamental to establishing resynchronisation as a cornerstone of heart failure management in appropriate patients with the publication of the CARE-HF trial by John Cleland and colleagues in 2005—the first large-scale randomised trial to compare the effects of CRT-P versus optimal medical therapy on mortality and hospitalisation in heart failure.[43] Subsequent data have expanded the indication for CRT to include use in patients with only mildly symptomatic heart failure and current European consensus is to recommend CRT earlier in the treatment pathway for heart failure, where electrical dyssynchrony is clearly present. Data to support this approach are provided by subgroup analysis of the long-term follow-up data from CARE-HF.[44] Concerns regarding the efficacy of CRT in atrial fibrillation remain a reality of clinical practice, despite reassuring evidence from single-centre studies such as that from Francisco Leyva's group in Birmingham published in *Heart* in 2008.[45] The recent publication of APAF-CRT has demonstrated a survival advantage for AV node ablation and CRT and may expand this indication in a complex patient group going forward.[46] Such data emphasise the need for close collaboration between electrophysiologists and heart failure specialists, with regular MDT meetings being key to contemporary practice in both fields. Predicting individual patient response to CRT remains a challenge for future research and the use of 'big data' may hold some promise in understanding this, although the number of variables in a single individual makes this challenging to meaningfully study in a large-scale randomised trial.

Data to support the routine use of remote monitoring via cardiac implanted electronic devices (CIED) to influence clinical outcomes of patients with heart failure remain sparse. The largest trial of this approach—REM-HF, led by John Morgan and Martin Cowie—did not demonstrate any impact in terms of reduction in mortality or unplanned hospitalisation, but did demonstrate increased healthcare resource utilisation.[47] Current UK health policy is increasingly focused on the utility of remote monitoring and the use of digital tools to enhance healthcare, and data from Fozia Ahmed and colleagues in Manchester are supportive of the utility of such an approach.[48] Careful assessment of the overall impact of such technologies is needed if they are to be used in routine clinical practice.

One device has been shown to have a striking effect in reducing heart failure hospitalisation in patients with New York Heart Association class III symptoms—the CardioMems implanted pulmonary artery pressure monitoring system.[49] Deployed via a modified right heart catheterisation technique, this system (figure 8) is fixed in a branch pulmonary artery and allows for daily pressure measurements via wireless telemetry. These data are transmitted for trend review by the clinical team and allow for early adjustment of diuretic therapy prior to the onset of clinical decompensation. Combined UK experience from multiple centres has been recently published and the system has been approved for routine clinical use in the NHS in 2021.[50]

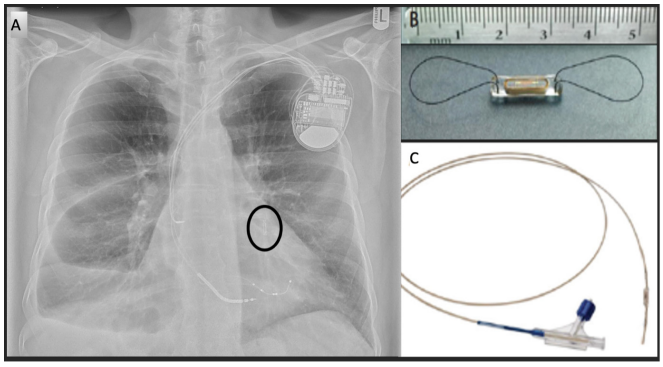

Figure 8 CardioMems device. (A) Chest X-ray demonstrating device appearance (circled)—CRT-D also in situ. (B) Device with scale. (C) Delivery system. CRT, cardiac resynchronisation therapy.

As data and clinical experience have accumulated, technology has continued to advance and such synergy has allowed for effective day-case implantation of complex devices, without the need for mandatory defibrillation threshold testing. UK centres have pioneered this approach and complex device day-case procedures are now commonplace with good data for both safety and cost-effectiveness.[51]

British cardiologists and the BCS have played a key part in the development of CIED since the inception of the Cardiac Club 100 years ago. The history of pacing and other implanted devices mirrors the story of the development of modern cardiology practice in the UK and throughout the world—from enthusiastic early adopters, driven by scientific inquisitiveness and a passion for new technology, to national and international collaboration establishing large-scale clinical trials to answer fundamental questions.

The next 100 years of development in this field will be defined by this tradition and are likely to involve the development of precise, individualised patient management based on the interaction between genotype and phenotype to allow for specific, appropriate device prescription. Such prescriptions may well include His-bundle and conducting system pacing—currently the remit of enthusiasts in single centres, but imminently to be studied in a large-scale clinical trial led by Zachary Whinnett from Imperial College. Remote monitoring systems have been rapidly embraced, accelerated in part by the COVID-19 pandemic, and their role in long-term management of patients will undoubtedly continue—likely assisted by further developments of artificial intelligence and machine learning. Ongoing miniaturisation, leadless devices, chemo-sensor development and advances in battery technology are the likely developments over the next decade and BCS members remain active in research in all of these areas.

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Contributors PH prepared the manuscript with the assistance of JC.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JC is an advisor to Medtronic, Boston Scientific and Abbott Medical and chairs a Data and Safety Monitoring Board for Biotronik. PH has acted as an advisor to Boston Scientific and Abbott Medical.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study does not involve human participants.

Provenance and peer review Commissioned; internally peer reviewed.

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