Seeing the heart; the success story of cardiac imaging

On 29 January 1896 a large audience at the Würzburg Physical Medical Society attended a lecture and a demonstration of a new kind of ray produced by electrical discharges from an induction coil through a Hittorf–Crookes tube. The demonstrator was Wilhelm Konrad Röntgen (1845–1923), professor of physics, who, a few months earlier, had discovered in his modest laboratory in Elberfeld, that these unknown and invisible rays (he called them ‘X-rays’) caused a paper coated with barium platinocyanide to glow with a mysterious light. He had also observed that when he held his hand before it, the shadow of his bones was cast on the paper. He published his discovery on 28 December 1895 in a paper ‘Eine Neue Art von Strahlen’[1] in the Annals of the Society and the news rapidly spread over the civilized world.

During this public demonstration, an image of the hand of the famous anatomist F. Von Kölliker (1817–1905) was visualized, who unhesitatingly suggested that the rays be called Röntgen-rays rather than X-rays. This demonstration was the only formal lecture presented by W. K. Röntgen — he even declined to give a lecture on the occasion of his election as the first Nobel prize laureate in Physics in 1901. Doctors immediately realized the diagnostic possibilities of the X-rays — as an unprecedented method of viewing organs within the body! Imaging had entered medicine and cardiology!

Modern cardiac imaging aims to provide comprehensive evaluation of (patho)anatomy, (patho)physiology, prognosis and management, and includes a variety of methods using many different energy forms: X-rays, ultrasound, radioactivity and magnetic resonance. The 50th anniversary of the European Society of Cardiology offers a timely opportunity to reflect on the many European contributions and the early pioneers who, by a combination of observation, receptiveness and serendipity, made remarkable discoveries resulting in the amazing imaging technologies we use today — the success story of cardiac imaging!

X-ray imaging

After Röntgen’s presentations, doctors immediately realized the diagnostic possibilities of the X-ray — as a method of seeing inside the body. No other discovery has ever been so rapidly introduced into medicine as diagnostic radiology! Indeed, after bones, soon the shadows began to reveal organs and their abnormalities, bringing rational diagnosis into reach by visualizing the changes caused by disease.

Immediately after the publication of this sensational discovery, T. A. Alva Edison (1847–1931) started to study chemical substances that would fluoresce more brightly than barium platinocyanide and found calcium tungstate to be the best. He constructed the ‘fluoroscope’ for instantaneous visualization, and in the very year of the demonstration in Würzburg, F. H. Williams (1852–1936) began lecturing on the use of X-rays in cardiac diagnosis. He reported on the visualization of the heart as follows: ‘... the outline of the heart, as seen from the front of the body through the fluoroscope, corresponds in a general way to the outline drawn on the skin with percussion as a guide’. In those days, Corvisart’s percussion method was considered to be the reference method! He also noted that because of the constant motion of the heart and diaphragm, fluoroscopy was more valuable than radiography. In his paper ‘A method for more fully determining the outline of the heart by means of a fluoroscope together with other uses of this instrument in medicine’[2], he laid the basis for quantitative cardiac measurements from the chest X-ray. Orthodiagraphy, providing a permanent cheap record of the cardiac contour and size, was introduced in 1902 by F. Moritz and teleröntgenography by H. Kohler in 1905[3]. Soon, however, the fluoroscope would become responsible for many radiation complications — a sad passage in medical history!

In 1904, W. Rollins published a paper on an interesting instrument — ‘the Seheear’ — a combination of a fluorescent screen and a stethoscope. Heart sounds could be auscultated while the image of the heart was visualized — making cardiac imaging also part of the physical examination!

In 1913, W. D. Coolidge (1873–1975) invented the hot tungsten cathode X-ray tube, which was a major advance[4]. This more powerful source of X-rays permitted more detailed studies and more accurate measurements of cardiac contours (the
cardiothoracic ratio was proposed by C. S. Danzer in 1919[53] and pulsations. This resulted in the development of kymography and the beginnings of angiocardiology.

**Angiocardiography**

To make angiocardiology of the heart possible, the feasibility of human cardiac catheterization had to be demonstrated. In 1929 W. Forssman (1904–1979) introduced ‘... a well oiled 65 cm long ureteral catheter’ into his antecubital vein to reach the right atrium. Soon thereafter he performed the first cardiac angiogram on himself using 20 cc of 25% sodium iodide[60]. Forssman shared the Nobel Prize for Medicine with A. Cournard and D. Richards in 1956. In the early 1930s, practical methods for angiocardiology were further developed, paralleling the early phases of cardiac surgery. The first successful use of intravenous angiocardiology, as a diagnostic method, was reported in 1937 by A. Castellanos and co-workers in Cuba, demonstrating congenital malformations[7]. They also introduced the first automatic injection apparatus and biplane angiocardiology.

It was a coincidence that Louis Lumière (1864–1948) and his brother Auguste invented cinematography (for which E. J. Marey had laid the basis) in the same year that Röntgen discovered X-rays! X-rays, cinematography and the intracardiac catheter merged into a powerful diagnostic modality when W. H. Stewart and co-workers made the first cine-angiogram in 1939[59]. Subsequently, many systems were developed for rapidly changing cassettes and roll-films for continuous film X-ray exposures.

The modern era of cardiac X-ray imaging began after the Second World War. Electronic and computer developments resulted in the image intensifier in 1952, which was a critical tool for analysing internal cardiac anatomy and the performing of selective coronary arteriography[9]. The image intensifier considerably decreased X-ray exposure to both the patient and the operator.

**Computed tomography (CT)**

The principle of CT evolved from the work of the Austrian mathematician J. Radon. He showed, in 1917, that the image of a three-dimensional object could be reconstructed from an infinite number of two-dimensional projections of the object[10].

A. M. Cormack of South Africa demonstrated in 1964 that the attenuation coefficients of a slice of an object could be reconstructed from a series of angular projections, and derived a mathematical theory for image reconstruction[11].

G. Hounsfield of EMI Limited tested these mathematical solutions and constructed the first clinical CT, which was installed in the Atkinson Morley Hospital in London in 1971 for brain scanning[12]. This instrument revolutionized radiological imaging because of its wide dynamic range, permitting the display of the entire spectrum of tissue densities. In 1979, Cormack and Hounsfield received the Nobel Prize for Physiology.

The potential role of CT in the diagnosis of cardiovascular disease was realized after differences in X-ray attenuation of normal and infarcted myocardium were demonstrated. This spurred on research into the use of CT in the diagnosis of cardiac disease. Subsequent major advances have been the dramatic increase in the speed of scanning and image reconstruction and improved image quality as a result of faster and more sophisticated computers. At the Mayo Clinic, dynamic volume scanning was achieved in 1975 with the dynamic spatial reconstructor which is based on multiple X-ray sources and multiplex detectors for scanning the heart using the mathematical principles of CT[13].

**Electron beam computed tomography**

Fast computed tomography, or electron beam tomography of the heart, was introduced by D. Boyd and co-workers in 1979 at Imatron[14]. Contrary to the conventional CT scanner, this instrument has no moving parts and can acquire an image in as little as 50 ms, obviating the need for ECG-gating. By successively steering a small focal spot size electron beam at four tungsten target rings, to produce a moving fan beam of X-rays of 180° about the patient, with a 180° ring of detectors above the patient, the heart can be imaged virtually free of motion artifacts.

**Ultrasound imaging**

Cardiac ultrasound is the most important advance in diagnostic cardiology since the discovery of X-rays by W. K. Röntgen. Its development closely paralleled advances in electronic and computer technology.

The existence of ultrasound was recognized by L. Spallanzani (1729–1799). He demonstrated that bats who are blind navigate by means of echo-reflection using inaudible sound. In 1880, Jacques and Pierre Curie discovered the piezo-electric effect, a peculiar phenomenon observed in certain...
quartz crystals, which were the basis of early ultrasound systems and were later replaced by ferroelectric materials.

The first suggestion that submerged objects could be located by echo-reflection probably came after the Titanic disaster in 1912. During World War I, P. Langevin (1872–1946) conceived the idea in 1917 of using a piezo-electric quartz crystal as both transmitter and receiver, and this ultimately led to the development of sonar which was completed with the invention of the cathode ray tube and extensively used in World War II for ship navigation and remote submarine detection. Interestingly, the Austrian K. T. Dussik was the first to apply ultrasound in medical diagnosis in 1941[15]. He tried to outline the ventricles of the brain using echo-transmission, a principle similar to X-ray imaging. Dussik can be regarded as the ‘father of diagnostic ultrasound’. He also considered the use of echo-reflection, but discontinued this idea after being ridiculed. In 1950, the German W. D. Keidel, also using an echo-transmission technique, performed the first cardiac examinations in an attempt to measure cardiac output[16]. This ‘sonocardiometric’ technique was later used by R. F. Rushmer in his classic cardiovascular experiments in conscious animals.

The first experiments using ultrasonic echo-reflection to examine the heart were initiated by I. Edler and C. H. Hertz in Lund, Sweden[17]. These investigators were largely stimulated by their surgical colleagues who wanted more accurate diagnosis before surgery, cardiac catheterization still being in its infancy at that time. They produced the first echocardiograms of the heart in 1953. An industrial pulse-echo ultrasonic scanner, used to find cracks in metal and which they borrowed from a shipyard in Malmö, was implemented. This industrial reflectoscope was only available during weekends. Fortuitously, this instrument had the wavelength and other physical characteristics appropriate for visualizing the heart, and is yet another story indicating that scientific discoveries are often based on chance rather than design. Edler and Hertz identified many of the structures of the heart. C. H. Hertz also devised the ink-jet recorder, producing a strip chart recording of the echoes originating from a selected structure (time-motion of M-mode recording) and the simultaneous recording of ECG. In the late 1960s, the fibreoptic recorder, a spin-off from space technology, was introduced allowing the M-mode recording of all structures along the ultrasound beam: this constituted the definitive breakthrough in echocardiography.

Today, M-mode echocardiography remains an important part of a complete cardiac ultrasound examination because of its high temporal resolution, which allows accurate analysis of fast moving structures.

In 1968, R. Gramiak and P. M. Shah[18] described constant echocardiography, an accidental observation during indocyanine green injections for cardiac output measurement. The technique is presently being refined for myocardial perfusion studies.

Two-dimensional echocardiography

In the 1960s, great progress was made in the development of real-time two-dimensional echocardiography. In fact, it was the combination of sonar technology with advanced radar circuitry which improved ultrasonic instrument performance and the prospect of two-dimensional echocardiography. After the early pioneering work of J. J. Wild and J. M. Reid[19] and D. H. Howry and W. R. Bliss[20] in the early 1950s, both European and Japanese investigators introduced real-time two-dimensional instruments based on different principles. The practical use of these instruments, however, was limited because of the large footprint of the bulky transducers. Indeed, the small precordial acoustic windows to the heart dictate the use of a small transducer. In 1968, J. Somer[21] constructed the first electronic phased-array scanner based on the wavefront theory formulated in the 17th century by C. Huygens, and sonar technology, but the advantages of two-dimensional echocardiography over M-mode echocardiography were yet to be realized. J. Griffith and W. Henry[22] introduced the mechanical sector-scanner in 1974, in the same year that F. L. Thurstone and O. T. von Ramm[23] constructed their electronic phased-array scanner similar to the instrument developed by J. Somer. This instrument marked the beginning of the revolutionary impact of ultrasound on clinical cardiology. Today, phased-array scanners are the most widely available tomographic imaging instruments with a tremendous impact on cardiac diagnosis.

Since the early 1970s numerous investigators have explored the feasibility of three-dimensional echocardiography. Recently, new computer technologies have enabled the development of volume-rendered data which display tissue information possible[24,25] even in real-time[26]. In the coming years this modality will further strengthen the diagnostic capabilities of cardiac ultrasound.

Although the idea of transoesophageal echocardiography to circumvent chest wall problems dates back to the early 1970s, its clinical application was started by anaesthetists with an M-mode system introduced by L. Frazin et al. in 1976[27]. The Japanese engineer K. Hisanaga and co-workers[28]
first reported transoesophageal two-dimensional imaging with a mechanical scanning system 1 year later. The mono- and biplane electronic phased-array probes developed by J. Souquet in 1982 and his multiprobe probe in 1985 represented the definitive clinical breakthrough of transoesophageal echocardiography\cite{29,30}.

**Doppler echocardiography**

The Austrian C. A. Doppler (1803–1853) worked out the mathematical relationship between the frequency shift of the light of stars and the relative motion of the sound source and the observer, a theory tested in practice for sound in 1845 by C. H. D. Buyt Ballot (1817–1890) in Utrecht.

Investigation of blood flow velocity using Doppler frequency shifts to measure motion of cardiac structures and later of the velocity of red blood cells started with the work of S. Satomura and his colleagues in 1957\cite{31}. The pulsed-wave Doppler technique was almost simultaneously introduced by P. N. T. Wells\cite{32}, P. A. Peronneau et al.\cite{33} and D. W. Baker\cite{34}. The method allowed depth selection for blood flow velocity interrogation, but the major step forward for its clinical acceptance was its combination with imaging: the duplex scanner, reported by F. E. Barber et al. in 1974\cite{35}. This development ultimately led to the integration of pulsed-wave Doppler with two-dimensional phased-array systems and allowed blood flow to be studied at selected regions within the image plane. The Bernoulli equation is now the cornerstone for Doppler assessment of cardiac haemodynamics and was published by the Dutch born D. Bernoulli (1700–1782) in his treatise ‘Hydrodynamica’ in 1738. He formulated the relationship of the pressure drop across the inlet of an obstruction in a flow channel to the flow rate through it. J. Holen et al.\cite{36} showed in 1977 that the Bernoulli equation could be applied to estimate the pressure drop across a stenotic orifice from the jet flow velocity. In 1978, the Swiss born M. A. Brandestini et al.\cite{37} produced a 128 channel digital multigate Doppler instrument allowing imaging of cardiac structures and blood flow in colour and in real-time. Based on similar principles, in 1982 C. Kasai et al.\cite{38} constructed the revolutionary colour Doppler flow imaging system based on autocorrelation detection, to provide a non-invasive ‘angiogram’ of normal and abnormal blood flow on a ‘beat-to-beat’ basis. At present, M-mode, two-dimensional, pulsed-wave, continuous-wave and colour Doppler flow are all combined in one diagnosto console and represent the most comprehensive cardiac diagnostic modality by providing integrated structural, functional and haemodynamic information. A modern echo/Doppler laboratory can nowadays be appropriately referred to as the ‘non-invasive imaging and haemodynamic laboratory’.

Because of its versatility of application in a wide variety of health care environments, echo/Doppler techniques will continue to grow along with advances in digital techniques and miniaturization.

**Intracardiac intracoronary ultrasound**

As early as 1960, T. Ciezynski\cite{39} mounted a single element transducer on a catheter to obtain intracoronary echocardiograms and 3 years later, R. Omoto\cite{40} obtained intracoronary two-dimensional images with a slowly rotating single-element transducer mounted at a catheter-tip. Two years later, N. Bom et al.\cite{41} described a real-time intracoronary scanner using an electronically phased circular array of 32 elements at the tip of a 9F catheter. These developments were discontinued because of limitations in miniaturization and the striking improvements in precordial image quality making intracardiac imaging unnecessary. The rapid progress in interventional cardiology renewed the interest in imaging devices, allowing circumferential imaging of the arterial wall under the endothelial surface. Both mechanical single-element and multi-element electronic systems are now increasingly used.

**Nuclear imaging**

Within a few months of Röntgen describing his X-rays, H. Becquerel discovered radioactivity\cite{42}. In a relatively short period thereafter, E. Rutherford and his colleagues in Cambridge and the Curies in Paris made important contributions and described the types of radioactivity and both the means and unity of measurement. Thus, the basis of nuclear medicine was laid early, but contrary to X-ray imaging, the development of radionuclide imaging was relatively slow.

The Hungarian born G. de Hevesy (1885–1966) working with Rutherford was the first to use radiotracing using $^{212}$Pb in a gastronomy experiment in order to prove his suspicion that his landlady was recycling the remains of the Sunday meat pie into meals later in the week\cite{43}. As early as 1926, H. Blumgart developed a radiotracer technique to measure blood flow velocity which is the forerunner of dynamic tracer studies\cite{44}. De Hevesy introduced the red cell blood volume measurement and the
followed by the electronic gamma camera in 1952, Edwards and the based on the pioneering work of Kuhl and used today. Which is still the basis of the scintillation camera.

It was the introduction of technetium-99m which spurred on the growth of nuclear medicine because of its ideal properties for gamma camera imaging, its short half-life and the possibility of producing it in a hospital radiopharmacy. There are now radiopharmaceuticals labelled with 99mTc for almost every application in nuclear medicine.

However, the clinical application of nuclear imaging required both counting and detection of radioactive emissions. Modern counting equipment dates back to 1908 when H. Geiger made his electron counting tube, the precursor of the 1928 Geiger counter. The major breakthrough in radioisotope emission detection was the development of the scintillation scanner by B. Cassen in Los Angeles in 1949, an instrument rapidly followed by de Hevesy using cyclotron-produced radioisotopes and techniques that he had described many years before — he should therefore be considered the ‘father of nuclear medicine’.

Diagnostic nuclear imaging techniques can be divided into four general groups, depending on localization, dilution, flow or diffusion, and biochemical and metabolic properties. Most of these basic principles were first demonstrated by de Hevesy using cyclotron-produced radioisotopes and techniques that he had described many years before — he should therefore be considered the ‘father of nuclear medicine’.

Positron emission tomography (PET) is an advanced nuclear imaging technique which has evolved into an important research tool. Although Wren et al. laid the foundation of PET in 1951, it was Sweet and Brownell of Massachusetts General Hospital who conceived the idea of positron imaging which relies on the annihilation radiation emitted at 180° when positrons and electrons meet.

They published details of their positron scanner and a brain image as early as 1953. However, it was not until the late 1960s before the first true positron camera was constructed and using coincidence counting that the first tomographic images of the heart of a dog were produced. Positron scanners were improved by using multiple crystal detectors arranged in a ring or twin Anger cameras in opposition. These designs are still the basis for most modern PET imaging systems. PET uses biological substrates which are labelled with positron emitting tracers and allows studies of myocardial blood flow, metabolism and pharmacological agents to be made. Currently, PET has a clinical role in defining myocardial viability in patients with ischaemic left ventricular dysfunction who may benefit from revascularization rather than transplantation. It allows the sympathetic nervous system to be studied as regards the development of a number of cardiac disorders by receptor imaging. Although PET was developed before SPECT, it is less accessible because it requires direct access to a cyclotron to produce the short-lived positron emitting tracers and a radiopharmaceutical laboratory, which is not required for SPECT. Miniaturization and simplification of the cyclotron operation has increased the number of hospital-based baby cyclotrons, however.
Magnetic resonance imaging

F. Bloch et al.\textsuperscript{[60]} at Stanford and E. Purcell et al.\textsuperscript{[61]} at Harvard in 1946 published a paper on the nuclear magnetic resonance (NMR) phenomenon in bulk matter for which they received the Nobel Prize in Physics in 1952. Initial interest in the NMR phenomenon focused on the chemical shift — a small but specific change in resonant frequency of a particular nucleus in different chemical compounds. This resulted in the development of NMR spectroscopy. Initially, the major limitation to NMR spectroscopy in intact living systems was the small bore of the superconducting magnets. In the early 1980s, the Oxford Instrument Company started to produce superconducting magnets with increasing bores and extremely uniform and intense magnetic fields allowing the whole human body to be studied.

The concept of magnetic resonance (MR) imaging was described in 1971 by R. Damadian\textsuperscript{[62]}, and P. Lauterbur\textsuperscript{[63]} published the first two-dimensional MR images of a heterogeneous object in 1973. However, their initial work met with great scepticism. In 1977, Damadian et al.\textsuperscript{[64]} published the first horizontal image through the human thorax but the acquisition time was too long to image the heart. Shortly thereafter, Lauterbur obtained an MR image of the heart but the quality was still suboptimal. ECG gating derived from nuclear cardiology allowed the first good quality cardiac images of the heart to be generated in 1983. Images obtained with MRI resemble those of CT — organs are distinguished by their contrast on a grey scale. The underlying principles of image formation are different, however. In CT, contrast depends on differences in X-ray attenuation, whereas in MRI it depends on tissue behaviour when placed in an external magnetic field and exposed to radiofrequency radiation. The wide range of tissue contrast provides the potential for myocardial tissue characterization. Recent advances include the development of intravenous contrast agents (gadolinium) and faster imaging (MR angiography). The major advantages of MRI are that contrary to ultrasound, the images are not degraded by overlying bony structures, that there is a high natural contrast between flowing blood and soft tissue, the wide field of view, and that cross-sections of the heart can be obtained in any arbitrary orientation.

Conclusion

Progress in cardiology has often followed new technologies, especially when they provide better insights into disease processes and allow new pathophysiological and clinical questions to be addressed and answered. Cardiac imaging has fulfilled these goals and has contributed enormously to our understanding of cardiac disease. As a consequence, progress in patient management has closely followed progress in imaging modalities and currently, every patient with suspected or known cardiac disease undergoes one or more imaging procedures as part of his/her initial clinical work-up. Most often the results are crucial in establishing the diagnosis and severity of the cardiac disorder. Subsequently, imaging is repeatedly performed at variable intervals during the course of the disease for testing treatment efficacy and for prognostication.

In the past 30 years developments in computer technology and changes in clinical objectives have resulted in enormous progress in cardiovascular imaging techniques and these advances will continue to accelerate. It is difficult to predict what will be possible in the near future but undoubtedly our reliance on imaging techniques for the diagnosis of cardiovascular disease and patient management will continue.

We now increasingly use non-invasive tomographical techniques because they give us extensive information about the heart. Tomographic imaging allows three-dimensional reconstruction and presently used display modalities will gradually be replaced with dynamic, three-dimensional representations or even holography. It will then be easier to diagnose, with more certainty, complex cardiac disorders.

Standardized quantitative analysis of cardiac function, coronary artery anatomy, perfusion, and metabolism of the myocardium will be analysed online and available in a standardized digital format (DICOM 3.0) accessible through fast networks online all over the world (teleconsulting). Telecommunication will revolutionize the practice of cardiology. However, with the increasing complexity of these advanced imaging techniques and analysis, the number of indications, their pre-clinical uses for screening, and need for specific training programmes and certification will grow.

The ideal cardiovascular imaging technique would provide the cardiologist with integrated information on structure function, myocardial characteristics, perfusion and metabolism. Potentially, magnetic resonance imaging offers all this and will probably become the one-stop non-invasive diagnostic test of cardiology, particularly also when diagnostic images of the coronary arteries will be obtained. The threshold for performing a coronary arteriogram will then become similar to that of an electrocardiogram. Echocardiography is the most versatile tomographic imaging technique and gives information on
structure, function, haemodynamics, and perfusion. It has become, because of its non-invasiveness and large availability, the diagnostic ‘working horse’ of clinical cardiology. There is no doubt that it will be further developed into a standard diagnostic instrument that will find its way into primary care for use by non-specialists. Currently, hand-held devices with excellent imaging, including colour flow mapping, are being tested and have the potential of significantly expanding the clinical utility of imaging. Such devices will become an integral part of our physical examination just like the stethoscope, and used at the bedside, emergency room, office practice or anywhere.

Clinical cardiac imaging research must be directed towards identifying those cardiac conditions in which a specific imaging technique provides the optimal information needed for patient management. Indeed, the real value of any imaging technique is intimately dependent on our intellectual contributions: how, when, and in what clinical situation will it have maximal clinical impact.

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References


