Inside information...

Medicamundi allows healthcare professionals and the industry to share inside information on the latest technological developments and their medical applications. Over the last fifty years, Medicamundi has been among the first to present many of the extraordinary developments in healthcare technology in general, and medical imaging in particular. As a result, the Medicamundi archives provide an outstanding record of half a century of development.

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Clinical research:
• A tradition of innovation
• Advances in cardiac imaging
• Ultrasound-triggered drug release
• Myocardial perfusion imaging
• Computer-based decision support
• Novel imaging techniques
Dear Friends,

I have great pleasure in introducing this issue of Medicamundi, dedicated to clinical research. The leading article provides an overview of more than a century of research into X-ray technology conducted by Philips and its associated companies, resulting in innovations that have had far-reaching implications for modern clinical practice.

The tradition of innovation continues today, with the development of new modalities and techniques for prognosis, diagnosis and treatment.

In the developed countries, coronary artery disease continues to be the leading cause of death, often in individuals with no prior symptoms. Multidetector CT coronary angiography offers a non-invasive method for early detection, with quantification and characterization of plaque on the Brillance Workspace. Even modestly obese patients can be examined, using the powerful new Brillance SCT scanner.

Ultrasound also has a role in treatment, with targeted ultrasound-triggered drug delivery using temperature- and pressure-sensitive agents.

Myocardial perfusion imaging with radioactive tracers is an additional aid to identifying patients at risk of myocardial infarction. This issue of Medicamundi presents a comparison of single photon emission computed tomography (SPECT) and positron emission tomography (PET), and assesses the use of combined PET-CT and SPECT-CT scanner units.

Ongoing research includes investigation into the application of computer-based decision support systems to help distinguish Alzheimer’s disease from other less frequent dementing illnesses, and the use of confocal microscopy and microCT to image angiogenesis, which is a fundamental step in the transition of tumors from a dormant state to malignancy. In addition, we present clinical research into optical brain imaging using an experimental Diffuse Optical Tomography (DOT) system.

I hope that you will find this glimpse into the new and developing technologies that are expected to play an increasing role in prognosis, diagnosis and treatment in the not-too-distant future both interesting and informative.

Kevin Haydon
Executive Vice President & Chief Executive Officer
Philips Healthcare Global Sales & Service International

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Although not all criteria will be appropriate for every article, the article should cover all of the following points:

• the type of healthcare institution
• the clinical problems to be solved
• the type of equipment used
• the examination parameters
• the results obtained, with good-quality illustrations.

Printed images demand a higher resolution than electronic displays. Please read the previous section on Electronic submission.

The article should proceed smoothly from start to conclusion, without digression. As it is an article rather than a scientific report, the sections should be short, but not be numbered.

The article should not exceed 2500 words, and should be accompanied by an abstract of not more than 100 words.

Please note that it is not always possible to include all articles submitted. Sometimes, a selection has to be made! The decision to publish is the responsibility of the Executive Board of Medicamundi, who will review all submitted articles.

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Correction  
In the article *Evaluation of a Recently Developed 56" Monitor in CV Interventions* by M.M. Drost (Medicamundi 53/3 pages 25-28) Figure 2 was incorrectly attributed to BCVI Miami. The correct attribution is Fondation Rothschild Paris. We apologize for the error.
Clinical applications

The art of medical imaging: Philips and the evolution of medical X-ray technology

J.A.M. Hofman  Former Marketing Director, Universal RF Systems, Philips Healthcare

The history of Philips’ involvement in X-ray technology begins with the history of two companies: Philips, in Eindhoven, the Netherlands, and C.H.F. Müller in Hamburg, Germany. Together, these two companies played a major role in the development of X-ray technology.

Because it would be impossible to deal with every new development within the context of a single article, we have selected a series of milestones, illustrated by typical products from each era.

Philips
In 1891 Gerard Philips, backed by his father, founded a company in Eindhoven for the manufacture of incandescent light bulbs. In 1895, Gerard’s brother Anton also joined the company to support the commercial activities.

During World War I, when it became increasingly difficult for physicians in many European countries to have their defective X-ray tubes repaired or replaced, since most of these tubes were produced by German-based companies, Dutch physicians made an urgent request to Philips, asking the company if they could repair their X-ray tubes. Because Philips had the necessary expertise in glass and vacuum technology, the company complied with the request, and so the Philips Research Laboratory (founded in 1914), took on the repair of these tubes.

While they were repairing X-ray tubes, the laboratory began acquiring knowledge of X-rays, and in 1919 the laboratory started producing small series of X-ray tubes to their own design.

C.H.F. Müller
In 1864, Carl Heinrich Florenz Müller, who was then 19 years old, began a small glass blowing facility in Hamburg, Germany, where he produced mainly artistic glass products, including wine glasses and “Venetian” goblets. Later, he decided to use his know-how and experience in glass production for other glass products, and he began to produce Geissler, Hittorf and Crookes gas discharge tubes, as well as incandescent light bulbs.

Shortly after Röntgen’s announcement of the discovery of the new X-rays in January 1896, Müller began to play a prominent role in this area.

On April 17th, 1927, C.H.F. Müller became part of the Philips company, but the name would continue until 1986.

1895 - 1954

1895 W.C. Röntgen discovers X-rays
The German physicist, Wilhelm Conrad Röntgen, was among many scientists experimenting with gas discharge tubes in order to investigate the nature of electricity and the mysterious cathode rays.
On November 8, 1895, he discovered that a screen coated with barium platinocyanide fluoresced when a nearby gas discharge tube was activated, even though the tube was fully covered with black cardboard. Because he could think of no explanation for this effect, he decided to investigate the cause of this phenomenon, and began a number of very systematic experiments. Several weeks later, on December 28, 1895, Röntgen presented an initial communication to the Physical Medical Society in Würzburg with the title, “Über eine neue Art von Strahlen” (“On a New Kind of Rays”). In the document’s 17 chapters, he provided a complete explanation of the newly discovered rays.

Nearly buried among other explanations were the words, “Hält man die Hand zwischen den Entladungsapparat und den Schirm, so sieht man die dunkleren Schatten der Handknochen in dem nur wenig dunklen Schattenbild der Hand” (If one places one’s hand between the discharge tube and the screen, one can see the dark shadows of the bones against the lighter shadows of the hand). This single description of an experiment with a hand would later have an incredible influence on the development of the new rays for medical applications.

Shortly after Röntgen’s first publication, Professor B. Walter and J. Classen at the National Physics Laboratory in Hamburg reproduced Röntgen’s experiment using a cathode ray tube which had been supplied by C.H.F. Müller.

The sharpness of the images was far from optimal. This was due to the geometrical distortion caused by the divergent cathode rays and the movement distortion caused by the long exposure time that was necessary because of the low X-ray yield of the tube. To improve this, Walter contacted Müller very early on, and this was the beginning of a very long and fruitful collaboration between them.

1896 C.H.F. Müller’s first X-ray tube
By March 1896, Müller had already manufactured an X-ray tube for Professor Walter that had a bowl-shaped aluminum cathode. The cathode rays converged into one point on the glass wall, which resulted in a much sharper image. However, the localized heat load on the glass built up tremendously, which shattered a number of tubes. The next logical step, taken shortly thereafter, was to place a platinum anticathode in the tube and focus the cathode rays on this. Because this increased the amount of radiation, it was possible to reduce the exposure time, resulting in less movement blurring. Using the anticathode also reduced the heat load on the glass, and the tube was further improved by making it spherical instead of cylindrical, and adding pipe-shaped protrusions on both of its sides for the electrodes.

1899 First patent on water-cooled anode
To meet the demand for a higher radiation intensity, Walter introduced the idea of cooling the anti-cathode with water. In 1899, this idea
was patented by Müller and in the same year, the first water cooled X-ray tubes were manufactured that could produce about 15 to 20 mA. Because of the higher radiation output, these tubes became known by the name “Müller-Rapidröhre” and they made the Müller company famous around the world.

1901 Gold medal for first X-ray tube
Müller became even more widely known when, in 1901, the British Röntgen Society awarded his tube the gold medal for the best X-ray tube (out of the 28 tubes that were tested).

Fairly soon after the discovery of X-rays, Müller decided to focus solely on manufacturing X-ray tubes. In January 1904 he ended his business activities due to poor health. Because of the many experiments he had carried out with radiation, Müller, like many others, had sustained a great deal of radiation exposure and died as a result of this on November 24, 1912. Before that, in 1909, Dr. Max Liebermann had taken over the management and ownership of the “Spezialfabrik für Röntgenröhren” (Special factory for X-ray tubes).

As X-rays became more widely used, the demand for X-ray tubes also increased. By November 1911 the company had already produced their 100,000th X-ray tube.

The early X-ray tubes were all ion tubes. A major problem with these tubes was that the intensity (current) and penetration (voltage) of these tubes could not be independently controlled. The current in the tube, which resulted from the voltage generating the gas discharge, was very dependent on the gas pressure. However, this gas pressure decreased over time because the glass wall absorbed the gas ions released by the discharge. Thus an increasingly higher voltage was needed to initiate the discharge, resulting in a hardening of the radiation.

1914 The high vacuum tube with heated anode
The solution to these drawbacks was presented by W. D. Coolidge, who worked in the United States at the General Electric research laboratory. In 1913, Coolidge made the first high-vacuum X-ray tube with a directly heated cathode. In this tube, the electron current that was necessary for generating the radiation came from thermionic emission and not from gas ionization. This made it possible to control the voltage and the tube current independently by varying the current through the filament of the cathode. By using direct heating, much higher currents could be achieved. This meant that the radiation output of the tube was about 10 times higher than that of the ion tubes.

1919 Philips begins manufacture of X-ray tubes
Drawing on the experience gained in the repair of X-ray tubes during World War I, the Philips Research Laboratory began the small-scale
In December 1923, this shielded X-ray tube was demonstrated for the first time at a meeting of the British Institute of Radiology in London. In 1925, at the first International Congress of Radiology in London, the tube was displayed under the name Metalix, and was enthusiastically received by participants. Initially, the metal canister was intended to form one pole of the high voltage system, at ground potential but, due to the lack of suitable generators, a new version was designed with symmetrical anode and cathode voltage.

The new version opened the way for a successful introduction of the Metalix. At the second International X-ray Congress in Stockholm in July 1928, participants saw devices with a Metalix tube on just about every display booth.

1925 The Philips Metalix tube

Two problems with early X-ray devices were the emission of undesired radiation in all directions and the hazard of exposed high-voltage cables. Both of these problems were solved by Professor A. Bouwers of the Philips Research Laboratory, who constructed a cylindrical X-ray tube comprising a grounded metal (a ferrochrome alloy) canister with a glass window on one side. A lead layer covering the metal canister ensured that the X-rays could only leave the tube via the special glass window. This protected the patient and physician against the hazardous radiation that was not directly used to create the image. The design also made the X-ray tube smaller than a conventional spherical tube.

In December 1923, this shielded X-ray tube was demonstrated for the first time at a meeting of the British Institute of Radiology in London. In 1925, at the first International Congress of Radiology in London, the tube was displayed under the name Metalix, and was enthusiastically received by participants. Initially, the metal canister was intended to form one pole of the high voltage system, at ground potential but, due to the lack of suitable generators, a new version was designed with symmetrical anode and cathode voltage.

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The heat of the red-hot anode could be dissipated through the hard glass envelope and then be transported via the oil and the housing to the outside. This completely improved Rotalix tube, called the Rotalix O 75 was introduced in 1946, and would become the standard type of X-ray tube for many years to come.

1931 Simplicity and safety
Professor Bouwers, the inventor of the Rotalix tube, had a clear vision of how X-ray technology should be developed. In a 1931 publication titled “New Possibilities in Radiology” in Archives d’Electricité Medical, he began by saying, “Simplicity and safety are the two principal features considered when designing the new series of X-ray apparatus which is herein described.”

Simplicity of operation enables the radiologist to concentrate on his case and to deal with medical questions only, while effective radiation shielding and electrical insulation improve safety for both patient and operator.

“Simplicity and safety” continues to be the leitmotif of Philips Healthcare.

1929 Rotalix Metalix: the first X-ray tube with a rotating anode
As a result of its shielding against unwanted radiation and its high voltage, the introduction of the Metalix tube gave an enormous boost to the development of X-ray equipment that were much more patient and user-friendly. It enabled the expansion of applications into the examination of fast-moving organs, such as the heart, lungs, and stomach. To produce images that were sufficiently sharp and rich in contrast, the focal spot had to have a high specific loadability, and this became a limiting factor.

Professor Bouwers and his team investigated the problem and realized that the specific loadability could be significantly improved by using a rotating anode in which the heat load could be spread over a larger, ring-shaped area. This resulted in the first X-ray tube with a rotating anode, the Rotalix tube, which Philips introduced in 1929.

The anode of the Rotalix was originally made of a cylindrical copper block with a disc encased with spiral-shaped tungsten. Later, this was replaced by a large anode disc of sintered tungsten, and the metal casing around the area holding the anode and cathode was replaced with a hard glass envelope. This all-glass tube, surrounded by oil, was enclosed in a metal housing. The heat of the red-hot anode could be dissipated through the hard glass envelope and then be transported via the oil and the housing to the outside. This completely improved Rotalix tube, called the Rotalix O 75 was introduced in 1946, and would become the standard type of X-ray tube for many years to come.

1924 Super D: the first generator with falling load
In the early days, the X-ray tube was powered by a Ruhmkorff induction coil, and later with the advent of mains electricity, by a transformer. However, the alternating current was potentially damaging, so it had to be converted into direct current before connecting it to the tube. At first rotating mechanical rectifiers were used, but
different possibilities to increase the brightness of the X-ray images.

In January 1951, Philips Research Laboratory presented a 5″ medical image intensifier that increased the brightness of the image about 400 times, with the expectation to improve that to about 1500 times.

1952 Philips starts deliveries of the 5″ X-ray image intensifier

In Europe, Philips introduced the 5″ image intensifier in 1952, just a few months before Westinghouse introduced their own image intensifier in America. Initially, the radiologist had to look directly at the small output screen, which often meant an awkward and uncomfortable position. However, viewing became more comfortable at the end of the 1950s, when a television camera was connected to the output screen of the image intensifier. This allowed several people to look at the X-ray image on the monitor at the same time no matter how the image intensifier was positioned. This breakthrough opened the way for the development of different systems for different clinical applications – the idea that Bouwers had first talked about in 1934.

1955-1974

1955 The BV 20

By the 1950’s, medical practitioners were already using X-ray technology to support surgery, in particular orthopedic procedures, with the X-ray tube attached to various kinds of stands.
To improve the ease of viewing, clinicians used a fluoroscope. But because the brightness of these fluoroscopes was not very high, the X-ray intensity was increased to improve image visibility. As a result, the system exposed both the patient and the surgeon to unnecessary radiation.

These problems made the operating room the ideal application area for the image intensifier, and L. Vökel, a product manager at C.H.F. Müller, together with L. Diethelm, a professor at the University of Kiel, developed the first X-ray system optimized for surgery applications. It consisted of a movable C-arm with an X-ray tube at one end and a 5” image intensifier at the other. This was the first of the surgical C-arm systems that soon became standard equipment in the surgical suite.

The new device was referred to as the BV 20 (BV stood for Bildverstärker, the German for image intensifier, and 20 stood for 20 mA). In 1954, Philips introduced the BV 20 at the German X-ray Congress in Wiesbaden and a year later the first commercial deliveries began. The BV 20 remained the market leader until the 1960’s.

1957 First image intensifier/TV chain
In February 1957, Philips’ first X-ray television image was shown on a Closed Circuit Television (CCTV) system coupled to an image intensifier. The ELA product division of Philips marketed the CCTV system, which comprised a camera, a control unit with a video amplifier, and a monitor. Shortly afterwards, Philips started clinical application evaluation of the image intensifier-television combination. It quickly became apparent that using the television camera provided an enormous improvement for the radiologist and his staff. Because the X-ray image could now be shown on the monitor, the radiologist had much more freedom of movement with the X-ray system. An other advantage was that several people could look at the X-ray image at the same time.

1958 First remote-controlled system
The original idea for the remote-controlled systems came from Professor A. Jutras, from Hotel Dieu Hospital in Montreal, Canada. Professor Jutras felt that the efficiency of radiological examinations could be greatly improved by making optimal use of the newest technologies, including the image intensifier, television, and cineradiography. To further explore this, Jutras and his colleagues made an educational trip to Europe in 1957, and visited Philips. There they discussed whether it would be possible to adapt a new Philips tilting table, known as the Ring Stand, to create a remote-controlled system with all the features Professor Jutras envisioned.

Remote control would enable the radiologist to work behind a lead glass screen, away from the potentially damaging X-rays.

Philips rose to the challenge, and in 1958, the first adapted Ring stand was used in Montreal. It was equipped with two 5” image intensifiers, one of which was coupled to a TV camera and the other of which was coupled to a 16-mm cine film camera.
Remote controlled systems offered more positioning flexibility for different applications such as linear tomography and enlargement techniques. In 1966, Philips introduced the Diagnost 100, with a height adjustable table and a tabletop that could be moved longitudinally and transversally, and was also equipped with a compression cone. The X-ray detector consisted of a 9” image intensifier with a television chain and a serial changer.

Building on the experience gained with the Diagnost 100, Philips developed a new remote-controlled system with an integrated modular control desk for both the stand and the generator. This system, known as the Diagnost 120, was introduced in 1973.

1959 The Super Rotalix (SRO) tube

The expansion of specialized medical applications requiring lengthy imaging sessions demanded increasingly heavy tube loads. These could only be achieved by increasing the rotation speed and diameter of the rotating anode. However, the inertia of a massive tungsten anode made this difficult to achieve. Consequently, the massive tungsten anode disc was replaced by one with a composite molybdenum substrate, which has a high melting point but a low relative density, with a layer of tungsten on it. By doing this, engineers could increase the size of the anode disc to 90 mm and triple the rotational speed to 9000 rotations per minute. With the same focal spot size, the output increased by about 70%. Philips brought this new tube, called the Super Rotalix (SRO), to the market in 1959. It is still one of the workhorses currently used for universal fluoroscopy and bucky systems.

1961 The Plumbicon TV camera tube

The vidicon camera tube was compact and efficient, but was subject to comet-tail and trailing artifacts. After years of experimenting, Philips succeeded in developing a new camera tube using lead monoxide as the sensitive layer. This tube, known as the Plumbicon, was presented to the broadcast industry in 1961. The Plumbicon, which had good dynamics, a high level of sensitivity, and better contrast than the vidicon, was therefore also introduced in X-ray television cameras in 1962. It soon became the standard camera tube in image intensifier TV systems.

1969 Cesium iodide phosphors

At the World Congress in Tokyo in 1969, Philips announced a major improvement in input screen of the image intensifier. Until this time, manufacturers had used zinc cadmium sulfide as the detection material, but the new input screen used cesium iodide (CsI). The crystalline structure of CsI made it possible to construct an input screen of fine crystal rods, each of which acted as a miniature light guide, so that less light was scattered and the contrast of small details was improved significantly. Because CsI also had better X-ray absorption, the X-ray quantum noise in the image could be reduced.

1969 The 6” image intensifier with TV and fiber optics

In addition to the improvements in the input screen and electron optics, the new image intensifiers were provided with a fiber optic output window that could be coupled directly to the camera tube, without an intervening lens system. The result was a further improvement in image quality and a lighter, more compact assembly.

1973 The Super Rotalix Metal (SRM) X-ray tube

New techniques demanded even higher output from the X-ray tube. After improvements in the
anode design, the limiting factor had now become the glass envelope. Constant bombardment with electrons and ions, as well as the deposition of metal particles from both electrodes, changed the insulation characteristics of the envelope and, hence, the high voltage stability of the tube.

The only option was to use another material for the tube envelope. The step that Philips took then was actually to do what Bouwers first did in 1925, using a grounded metal housing for the area around the anode and cathode. The X-rays could leave the tube via a beryllium window added to the metal housing. The Super Rotalix Metal (SRM), a tube with an envelope made of a combination of metal and glass, with a higher loadability than the existing SRO tubes, was introduced in 1973.

1973 The Angio Diagnost table
Examinations of the heart require a wide range of X-ray projections around the patient. To achieve this, the patient should, ideally, be floating in space to allow access from any angle. The nearest practical solution to this problem was the Angio Diagnost, which had a floating tabletop supported by a single narrow column at one end. This innovative design is still the standard table for cardiovascular examinations.
1979 The Super Rotalix Ceramic (SRC) X-ray tube
The demand for increased output from the X-ray tube continued unabated. The limited heat capacity became an increasingly serious problem, particularly in cardiac examinations, because of the long fluoroscopy times and the series of acquisitions that were made in quick succession. Even with the introduction of a metal tube envelope, the existing tube technology and dimensions allowed very little scope for increasing the maximum X-ray output, heat capacity, and lifetime of the tube.

In 1979, Philips introduced an X-ray tube with a radically different design: the Super Rotalix Ceramic (SRC). Unlike the SRM tube, which had an envelope made mostly of metal and some hard glass, the SRC tube envelope was made completely of metal, with ceramic insulators, which allowed a very compact design. The new tube had a large anode diameter of 120 mm with bearings at both sides of the anode. The SRC tube provided an X-ray source with a much higher loadability for continual use and in large series of acquisitions, which greatly reduced the long waiting times between series.

1975-1990

1975 The Poly Diagnost C cardiovascular system
Because the heart is approximately an ellipsoid, standard frontal and lateral projections are not adequate for visualizing the cardiac anatomy. Ideally, cardiac examinations require an imaging system that provides a virtually unlimited choice of projections. This was achieved in 1975 with the introduction of the Poly Diagnost C, a stand that consisted of a hinged parallelogram that could rotate around a horizontal axis.

For many years the Poly Diagnost C would be the standard in X-ray systems for cardiac applications. In addition to the flexible positioning, part of its success was due to the Optimus M 200 generator that used secondary switching with tetrode tubes to produce the short exposure times that were important for cardiology.

1977 The 14” image intensifier
The image intensifier had only one drawback when compared with the fluorescent screen, and that was the smaller field size. To overcome this problem, Philips decided to develop an image intensifier with a large 14” input screen. The new image intensifier had switchable input fields of 14”, 10”, and 6”, as well as a greatly improved electron optical system, and a fiber optic output screen. Instead of glass, which would need to have been thick and heavy, the tube envelope was made of a nickel-iron alloy with very high magnetic permeability. This also reduced the influence of the ambient magnetic field on the electron optics. The input screen consisted of a thin membrane of titanium that had very low X-ray absorption. The new image intensifier was presented at the ICR in Rio de Janeiro in 1977.

1980 DSA
Digital subtraction angiography (DSA) was one of the most important advances in X-ray technology. It enabled real-time subtraction of X-ray images and paved the way for many new interventional procedures.

Although analog subtraction techniques had been known for some time, they were difficult and cumbersome to use. The story of real-time subtraction really begins in 1976, when Dr. C. Mistretta and his colleagues at the University of Wisconsin, developed an experimental digital subtraction device. In September 1979, a refined...
The advantages of such a system were clear. The development machine was replaced by an electronically controlled reader. Because the dynamic range of the phosphor plate (about 1:40,000) was much larger than film, the X-ray exposure became much less critical, and the fast processing meant that the waiting times for patients would become much shorter.

To introduce the digital radiography system in clinical practice, Philips and Fuji entered into an agreement in which Philips would develop the workstation and the necessary hardware, while Fuji would supply the phosphor plates, the scanning system, and the read-out electronic. Philips introduced the system under the name Philips Computed Radiography (PCR) at the RSNA in 1985, and began the first deliveries in 1986.

1987 DCI

With the advent of DSA, cardiologists became eager to employ the new technology in cardiac applications. However, there were problems in applying the subtraction principle to the moving heart.

To address this problem, Philips engineers began developing a system that was optimized for cardiac applications. The starting points were a 512^2 image matrix, as well as real-time acquisition, processing, and storage of 50 to 60 images per second, but no subtraction function. At first, the new system, known as the DCI (Digital Cardiac Imaging) had about the same functionality as film systems. The big difference was that cardiologists now had their images immediately available, which was of critical importance for the interventions they were performing. Cardiologists immediately saw that this was exactly what they needed, a dedicated system for their applications, that...
universal fluoroscopy systems. The project started in 1987. During this project, close attention was paid to image quality to make sure that the wide variety of images routinely acquired on the universal fluoroscopy systems would have the best possible image quality. Both the technical and clinical aspects were addressed.

At the General Infirmary in Leeds, England, the clinical utility of digital spot imaging was explored and its image settings were optimized. Dr. A.R. Cowen in the Medical Physics Department at Leeds University, together with F. Clarke, carried out a wide range of comparison experiments on various test models over a long period.

In 1988, Philips introduced Digital Spot film Imaging (DSI) at RSNA, and began worldwide deliveries in 1989.

1989 Maximus Rotalix Ceramic (MRC)

In 1989, Philips became the first company to introduce an X-ray tube that replaced the existing ball bearings with a spiral groove bearing using a liquid-metal alloy as a lubricant. This design substantially reduced the noise produced by the tube, increased the lifetime and heat dissipation, and improved the current conduction.

This new bearing, combined with the technology of the SRC tube, produced the compact new MRC tube featuring a noiselessly rotating anode that could be switched on in the morning and switched off in the evening, and that had a very long lifetime. The excellent heat dissipation of the bearings via the liquid metal lubricant gave the tube three times more cooling capacity than the SRM tube during a cine examination. The introduction of this tube would have an enormous impact on performance and ease of use, particularly for cardiology and vascular systems.

This digital image standardization stimulated the development of the Picture Archiving and Communication System (PACS), a system that enabled digital images to be distributed and archived. Philips began its PACS activities around 1985, when the American government decided to implement a complete digital distribution and archiving system in two hospitals.

One of the first practical PACS was CommView, the result of a cooperation between Philips and AT&T. After the necessary adaptations and improvements, CommView was brought to market worldwide. In the Netherlands, Philips carried out an extensive application research project with the Academic Hospital at the University of Utrecht. This research, which lasted from 1987 to 1989, provided much worthwhile information for further PACS development.

1988 DSI

The advantages of digital image acquisition and processing were so clear that Philips quickly began to think about replacing the analog spot film camera with a digital equivalent in the universal fluoroscopy systems. The project started in 1987. During this project, close attention was paid to image quality to make sure that the wide variety of images routinely acquired on the universal fluoroscopy systems would have the best possible image quality. Both the technical and clinical aspects were addressed.

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1991 XTV 8 X-ray TV camera
Until the beginning of the 1980s, X-ray TV chains used adapted commercial TV pick up tubes operating with a 50 or 60 Hz television standard. However, in 1986, the broadcast industry introduced the first broadcast television camera with CCD sensors, followed within a few years by the first consumer camcorders.

Because this new image sensor had many advantages compared to the existing camera pick-up tube, Philips began to research possible applications for X-ray systems early on. However, an image sensor used in medical applications had different requirements from those used in broadcast and consumer applications.

In October 1990, the first CCD camera for X-ray applications, the XTV 8, was delivered from the factory mounted on a 9” image intensifier. The image quality was outstanding. There was no geometric distortion, the entire image had uniform sharpness, and there were no blooming effects. The XTV8 chain was first applied to the mobile surgical C-arm systems.

1992 Rotational Angiography
In conventional X-ray imaging, a three-dimensional object is represented as a two-dimensional image, which frequently limits the spatial insight for users. This could be improved by making two separate projections at right angles to each other, but is still not ideal. In 1992, Philips introduced Rotational Angiography (RA), in which a complete series of projections was acquired at a rate of at least 7.5 images per second, while the C-arm made a continuous rotation over 180°. When these images were viewed in a loop, they gave a three-dimensional impression of the object. Besides saving a great deal of time, RA also greatly reduced the usage of contrast medium and patient dose.

1993 Thoravision digital chest system
Since the 1970’s researchers of the Philips Research Laboratories in Aachen, Germany, were experimenting with methods to read out a latent image stored in a selenium plate, after radiation with X-rays. At the end of the 1980’s this was realized by applying a 500 µm thick layer of selenium to a rotating drum. After the exposure, a set of electrical probes was used to read out the X-ray image. This principle was incorporated in the Thoravision, the first completely digital thorax system, which was presented in September 1993 at the European Congress of Radiology in Vienna and later at the RSNA in Chicago.

1995 Grid Controlled Fluoroscopy
In order to reduce the X-ray dose in universal fluoroscopy systems, pulsed fluoroscopy was introduced, based on the observation that the image content is not very dynamic for most examinations performed on fluoroscopy systems, so the temporal resolution of the image is of secondary importance. However, although the theory was correct, these pulsed fluoroscopy systems (which used kV switching), could not generate a truly rectangular pulse, due to capacitance effects in the generator and cables, so that undesirable soft radiation was produced during the rise and fall of the pulse. Moreover to achieve good stable image quality, the minimal
1998 3D Rotational Angiography

Rotational angiography, in which a complete series of projections was acquired on a conventional angiography system while the C-arm made a continuous rotation over 180° around the patient, had the potential to create a 3D data set. However, this potential could not be realized because it was not possible to perform the scan during the few seconds of the contrast injection, while longer injection times were regarded as impractical because the arterial and venous phases would then be superimposed.

However, phantom studies in which contrast agent was applied over the whole seven-second rotation period produced superb results, and clinicians were persuaded to inject contrast medium during the entire rotation period. By using a large viewing window, because of the high contrast, the overlap of the arterial and venous phase disappeared.

3D-RA was introduced at the RSNA in 1998 and the first deliveries took place in the second half of 1999. Some 60 systems were supplied in the first six months. The research into 3D imaging now began in earnest and would lead to more interesting technological and clinical results.

1999 The static flat panel detector

In the early 1990’s, work began on the development of a flat panel detector to replace the image intensifier. A flat panel would be less bulky than the image intensifier, and would offer several technical advantages. For example, it would have a higher dynamic range, able to differentiate a larger range of grayscale values to provide clearer images with better contrast. In addition, there would be no distortion due to ambient magnetic fields, and no pincushion distortion, because the convex image intensifier input screen would be replaced by a truly flat detector panel.

Pulse frequency was limited and would not reduce X-ray dose significantly.

This problem was solved by using a grid-controlled X-ray tube that could create a rectangular X-ray pulse. A new regulator controlled the high-voltage, current, and time during the pulse, rather than after the pulse as was normal. This made it possible to use very low pulse frequencies, even with dynamic images. The combination of short pulse length and a higher dose per pulse produced much better fluoroscopy images with an integral lower dose, depending on the chosen pulse frequency. This new technique, referred to as Grid Controlled Fluoroscopy, was demonstrated for the first time at the RSNA in 1995.

Research at Philips Research Laboratories and at the X-ray predevelopment group of Philips in Best resulted in several successful prototypes, but it soon became clear that the investment required to develop a commercial product was far beyond what one company could afford. Accordingly, Philips became stakeholder in a joint venture with Thomson and Siemens under the name “Trixell”. This company would not only deliver detectors to Philips, Siemens, and Thomson, but would also sell detectors to third-party X-ray companies. By selling to third parties, the output of the factory could be increased, and as with semiconductors, the yield of the production process could be more
quickly increased, which would reduce the cost price of the product.

For technical reasons, the first detector was a flat static detector (FSXD) for radiography with an image matrix of 3000 x 3000 pixels and a spatial resolution of 3 lp/mm.

Philips used this detector for the first time in the Digital Diagnost, a high-end bucky system that was brought to market in 1999.

2001-2010

2002 The dynamic flat panel detector
After the successful introduction of the static flat panel detector at the turn of the century, small flat dynamic detectors for cardiac applications were introduced and, later, large flat detectors for vascular and multifunctional fluoroscopy systems. Combining 3D RA with a flat dynamic detector made it easier to perform simple CT-like scans with a conventional X-ray system. These developments are expected to play a major role in the future.

2005 The XperCT
Interventional radiologists had long been confronted with the problem of obtaining a three-dimensional view of the internal structures. 3D-RA made this possible for high-contrast structures, but these views do not show any soft tissue. These could be obtained via a CT system or MRI system, but this meant moving the patient back and forth between the angio system and the other imaging modality, which was time-consuming, often impractical, and not real time. Integrating an X-ray system with a CT system or MRI system was realized, but was not an optimal economic solution. Eventually,
During these procedures, an electrophysiologist uses X-ray and many other medical devices, including monitors, electrophysiology recorders, ultrasound scanners, and ablation and navigation equipment.

To meet the increasing demand for EP procedures, and to provide an integrated package of equipment, Philips began the Electrophysiology Business Program as part of its Cardiovascular Business Unit.

The first step in this direction was made with EP Cockpit, a total solution that became available in 2007. It consisted of a ceiling-suspended equipment rack that could hold all bedside equipment used during the EP procedure, displays to show the information from all of the EP imaging and information sources, and two keyboards to control the system. Connecting the system to an Xcelera PACS made it possible to grab images and archive them. EP Cockpit was delivered for the examination room and the control room, and significantly improved the EP working environment.

During an EP procedure, the electrophysiologist has to apply ablation to very specific electrical connections in the heart. The procedure requires very accurate navigation to be carried out successfully. For this reason, the second EP product that Philips made available was EP Navigator: a navigational tool that used automatic segmentation software to make the left atrium visible in a previously acquired 3D image. This image then serves as a map to navigate the catheter in the patient’s heart using the overlaid live fluoroscopy image.

Philips decided not to integrate the CT scanner with the X-ray system, but to design an X-ray system that would use 3D-RA technology to generate CT-like images itself.

Philips brought this new feature to the market in 2005 as XperCT.

In addition to XperCT, the company also developed Dynamic 3D Roadmapping to further improve interventions. During navigation, the orientation of the three-dimensional image is automatically changed to match the projection direction, which provides tremendous support in real-time catheter navigation or when placing a coil.

In 2007, Philips introduced XperGuide to support percutaneous interventions. Based on XperCT images, XperGuide plans a trajectory that the needle must follow to reach the correct position.

2007 EP Cockpit
Because of the increasing number of older people in the population, the number of heart attacks as a result of irregular heart rhythms in the heart’s electrical system is also rising. This trend, as well as new technologies and treatment methods, has also led to an increase in the number of diagnostic and therapeutic electrophysiology procedures.
Quo vadis?
In 2010, 115 years after their discovery, X-rays are still the most frequently applied technology for medical imaging. As we have seen, a great deal has changed over the years – in technology as well as in applications. For a long time, the X-ray system was a very technical device that was made up of separate components. Today, these are well-designed systems with the newest technologies, largely automated functionality, and very intuitive and user-friendly controls. Sense and Simplicity, as Albert Bouwers already saw it in 1934, is now a reality.

Over the years, diagnostic examinations, which were once very diverse, have become increasingly limited to the most basic ones. At the same time, the number and diversity of interventions have increased significantly. This trend will continue in the coming years. If we look at the way in which X-ray technology has adapted itself to both threats and opportunities in the past, we can be confident that there are still many exciting developments to come.

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Non-invasive quantification and characterization of coronary plaque: the role of multidetector CT

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Investigations and research

Coronary artery disease

Coronary artery disease (CAD) remains the leading cause of death in the United States and most developed countries, and is an increasing cause of worldwide mortality [1, 2, 3]. Tragically, 50 - 60% of the deaths attributed to CAD occur in individuals who were asymptomatic prior to an acute coronary event [2]. Considering that the prevalence of CAD exceeds 13 million individuals in the United States alone [2], the need for earlier detection of atherosclerotic lesions and concomitant treatment is paramount.

Coronary atherosclerosis, the cause of most CAD, was once believed to be a disease of the lumen whereby plaque was thought to first appear within the lumen and then to develop inward to eventually cause clinically significant, flow-limiting stenoses. However, through autopsy research, it was found that arteries outwardly remodel as plaque accumulates within the vessel wall to a point where the plaque area reaches 40% of the total vessel cross sectional area [4]. At this point, the wall can no longer outwardly remodel and the lumen begins to shrink. Invasive coronary angiography (CAG) is able to show such luminal narrowing; however, CAG is not able to visualize the atherosclerotic lesion itself, and a stenosis is visible only after a period of substantial disease progression [5]. Consequently, patients may have plaque development for many decades before it is visible on CAG [6], reflecting the fact that a stenosis actually represents only the “tip of the iceberg” of CAD.

Intravascular ultrasound (IVUS) has emerged as the gold standard for imaging atherosclerosis in vivo [7]. IVUS is a catheter-based technique that provides a series of cross-sectional images of the vessel, enabling simultaneous visualization and assessment of the lumen, vessel wall, and atherosclerotic plaque.

Skejby Sygehus

Skejby Sygehus (Figure 1) is a state-of-the-art university hospital where extensive research and education is carried out, and it is one of the most modern and well-equipped hospitals in Europe. It serves as a basic hospital for Aarhus City, a regional hospital for Aarhus County and the West-Danish regions, and as a national hospital for specific diseases, including coronary artery disease.

This article presents early experience obtained at the hospital with CT plaque imaging using the Philips Brilliance 64-channel scanner and the Brilliance Workspace workstation with Comprehensive Cardiac Analysis (CCA) Version 4.0. All images were analyzed using CT Plaque Analysis, part of the CCA package.

Coronary artery disease

Coronary artery disease (CAD) remains the leading cause of death in the United States and...
Despite these advantages, IVUS is an invasive procedure limited to the presence of favorable anatomy, and provides a limited arterial assessment since not all vessels are catheterized. Like CAG, the invasive nature of IVUS limits its application to symptomatic individuals, thus precluding early disease detection. In addition, IVUS has difficulty in imaging heavily calcified lesions due to their high acoustic impedance, and is limited to larger caliber vessels with low tortuosity.

Technological advances in cardiac multidetector computed tomography (MDCT) throughout the past decade have provided clinicians with a non-invasive way to comprehensively evaluate the coronary arteries. Coronary CT angiography (CCTA) has been shown to have a very high negative predictive value in ruling out clinically significant stenoses [8-12]. In addition, CCTA allows the morphologic assessment and characterization of atherosclerotic lesions, and vascular remodeling. This additional information may provide knowledge regarding the presence of so-called vulnerable plaques [13-16] and the likelihood of future coronary events, which cannot be obtained from the luminal narrowing and potential reduction of flow as demonstrated by CAG [17-19].

**CT acquisition**

Contrast-enhanced, ECG-gated spiral retrospective cardiac CT scans are performed at our institution using a 64-channel scanner (Brilliance 64, Philips Healthcare, Cleveland, Ohio, USA). A dedicated cardiac gating algorithm was used that identified the same physiological phases of the cardiac cycle while taking into account the non-linear changes in the individual cardiac states with the heart rate variations during the CT acquisition [20, 21].

A cardiac adaptive multi-cycle (or multi-segment) reconstruction technique was used that combined data from consecutive cardiac cycles, significantly improving temporal resolution [22]. MDCT images are reconstructed at multiple phases using axial planes, multiplanar reconstructions, and maximum intensity projections at 0.67 – 1.0 mm slice thickness and 0.33 – 0.45 increment.

**CT image analysis**

All image analyses were performed using an advanced cardiac CT application (Comprehensive Cardiac Analysis (CCA), Version 4.0, Philips Healthcare, Cleveland, Ohio, USA) on a dedicated CT workstation (Brilliance Workspace, Philips Healthcare). CCA provides no-click coronary segmentation which enables automatic extraction and visualization of the entire coronary tree. Each artery and subsequent side branches can be selected for analysis. A quick measurement of the luminal stenosis in both diameter and area is available using Coronary Analysis where the vessel and lumen contours are calculated and displayed.

A new feature of CCA in v 4.0 is CT Plaque Analysis, which provides the ability to quantify and characterize coronary arterial plaque composition from the CT exam. Once the coronary arteries have been identified and centerlines automatically detected, the application then performs a complete coronary plaque assessment using a simplified workflow with detection of findings along the vessel wall performed via a single-click algorithm. It provides measurements for the lumen, vessel, wall and plaque that comply with the standard IVUS measurements while also providing a remodeling index for each finding. The total plaque volumes are calculated both on a per-segment and per-vessel basis.

CT Plaque Analysis provides two methods to interrogate the plaque findings: either via Threshold, where plaque content is based on simple thresholding, or by a novel Gaussian mixture model technique [23]. The latter technique assumes that the detected plaque volume contains one or more different components, each of which could be represented by a Gaussian distribution with a certain mean and standard deviation. Each of these distributions is then combined linearly to model the whole plaque. The relative compositions are determined by the ratio of their distributions within the plaque. Measurements for each finding, vessel and entire coronary tree are available and can be saved and exported in various formats.

**Case Studies**

**Case 1**

A 56-year-old male presented at the emergency room with chest pain and no prior medical history besides hypertension.

The electrocardiogram (ECG) showed ST-depression in leads II, III, aVF, V4-V5 with no ST elevation. The blood samples showed elevated cardiac biomarkers. A non-ST-elevation myocardial infarction (NSTEMI) was diagnosed, and the patient was scheduled for invasive coronary angiography (CAG).
Prior to the CAG, the patient underwent a contrast-enhanced (Iomerone, 80 cc at 6 cc/sec) cardiac CT scan as part of a research project. The ECG-gated spiral retrospective scan parameters were a collimation of 64 x 0.625 mm, pitch of 0.2, gantry rotation time of 0.42 sec, tube voltage 120 kV, and tube current of 1000 mAs. The scan, completed in 7 sec and covering a length of 80.9 mm, was only intended to image the proximal part of the heart as part of a research protocol. Using a k value of 0.014 for a chest CT, the effective radiation dose was 6.6 mSv.

The CT scan showed abnormal coronary anatomy with the left circumflex (Cx) originating from the right coronary artery (RCA) (Figure 2). It also showed several minor calcifications and diffuse atherosclerosis but no segmental stenosis. These findings were confirmed by both CAG and intravascular ultrasound (IVUS).

The curved multiplanar reconstruction (cMPR) showed a plaque in the most proximal part of the RCA with a minor calcification and a large non-calcified area (Figure 3). This was confirmed by CT Plaque Analysis, which revealed a 3.8 mm long, mainly non-calcified plaque. The threshold between calcified and non-calcified tissue was set at 120 HU [24]. The mean HU in the plaque was 50.2; the total plaque volume was 42.7 mm³, and the maximum plaque burden on the cross-sectional images was 54% (Figure 4).

CT and IVUS findings along with percent difference are shown in Table 1. In the proximal part of the RCA, the plaque was identified and virtual histology (VH) confirmed the presence of a mainly non-calcified plaque. By means of IVUS-VH (Volcano Corporation, San Diego, CA, USA), the plaque was classified as a fibroatheroma [25] with necrotic core and fibrous tissue accounting for more than 90% of the plaque volume. Total plaque volume reviewed by IVUS was 48.6 mm³, and the maximum plaque burden on the cross-sectional frames was 66.9% (Figure 5a and b).

Plaque findings by means of CT Plaque Analysis were in agreement with the content findings with a difference of 4 %, which is within the 93 – 97 % accuracy of IVUS-VH and ex vivo histology validation [26]. The differences in maximum burden, volume and length are attributed to the small size of the plaque.

<table>
<thead>
<tr>
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<th>CT plaque analysis</th>
<th>IVUS-VH</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max burden</td>
<td>54%</td>
<td>66.9%</td>
<td>12.9</td>
</tr>
<tr>
<td>Volume</td>
<td>42.7 mm³</td>
<td>48.6 mm³</td>
<td>12.1</td>
</tr>
<tr>
<td>Content</td>
<td>14% Calcified, 86% Non-calcified</td>
<td>10% Calcified, 90% Non-calcified</td>
<td>4.0</td>
</tr>
<tr>
<td>Length</td>
<td>3.8 mm</td>
<td>3.3 mm</td>
<td>15.2</td>
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</table>
Percutaneous coronary intervention (PCI) was not performed since no significant stenosis was present. Instead, standard medical treatment was initiated (aspirin, clopidogrel, ACE-inhibitors, oral beta-blockers and statins). When the patient was re-examined after one month, he was asymptomatic.

**Case 2**

A 59-year-old man was hospitalized due to several attacks of severe chest pain over a three-week period. He had no prior medical history besides hypercholesterolemia.

The patient presented with a normal ECG and normal biomarkers, but he was submitted to a sub-acute CAG due to the severe and sustained chest pain. CAG found diffuse atherosclerosis in all main vessels. In particular, a stenosis in the LAD and the first diagonal branch (D1) distal to the bifurcation was observed. Furthermore, significant stenoses were detected at the Cx/first obtuse marginal (OM) bifurcation (Figure 6) and in the RCA just distal to the crux (Figure 7). IVUS was performed in the Cx and RCA.

Prior to the CAG, the patient underwent a contrast-enhanced (Omnipaque 350, 75 cc at 6 cc/sec) cardiac CT scan as part of a research project. The spiral retrospective scan parameters were 64 x 0.625 mm collimation, 0.2 pitch, 0.42 sec gantry rotation time, 120 kV tube voltage, and tube current of 800 mAs. An ECG-triggered dose modulation protocol (DoseRight Cardiac, Philips Healthcare, Cleveland, Ohio, USA) was applied to reduce radiation dose during systole. The scan covered a length of 132.8 mm in just under 10 sec for an effective dose of 8.7 mSv. The CT findings were consistent with the CAG, revealing severe atherosclerosis with multiple non-calcified plaques in all main vessels.

Despite the sub-occlusion in segment two of the LAD, CCA with CT Plaque Analysis was able to segment the artery as demonstrated in the volume rendered and cMPR images (Figures 8, 9). Further analysis by CT Plaque Analysis revealed a primarily non-calcified plaque (11% calcified and 89% non-calcified) with a mean HU of 39.4 and a total plaque volume of 62.8 mm³ (Figure 10).
In the RCA a non-calcified plaque was visible just distal to the bifurcation (Figure 11). The vessel was segmented and CT Plaque Analysis demonstrated a non-calcified plaque. The mean HU was 57.7, the maximum plaque burden 79%, the plaque length 7.3 mm, and the total plaque volume 66.6 mm$^3$. The corresponding IVUS-VH image showed a fibroatheroma consisting of mainly fibrous and fibro-fatty tissue. In this case, the maximum plaque burden was 76.1%, the plaque length 7.4 mm, and the total plaque volume was 58.1 mm$^3$ (Figure 12a and b).

The findings for the two different imaging modalities are shown in Table 2. There is good agreement between the two modalities, with the exception of the plaque volume, which was slightly higher in the IVUS-VH analysis.
agreement in maximum burden and plaque length. The volume difference in plaque is within the range of up to 18% difference in cross-sectional area measurements that can be found with different IVUS imaging catheters. [27]. The percentage difference in content findings can be attributed to the inherent underestimation in calcium by IVUS due to inadequate penetration of calcium by the IVUS transducer signal and the overestimation of CT in instances of blooming due to calcification.

The patient was treated with stent implantation in the LAD segment one and two and in the Cx obtuse marginal branch while PCI with balloon angioplasty was performed in D1. When the patient was re-examined after three months, he was asymptomatic and able to play tennis as he did before.

**Discussion**

The Philips CT Plaque Analysis, with its simplified workflow, provides physicians with plaque information, including the location, morphology, and composition. As the case studies demonstrate, CT-based plaque indices agree with the findings of CAG and IVUS with virtual histology. This type of information could potentially be useful in risk stratifying patients with sub-clinical cardiovascular disease and may guide preventive treatment. However, the clinical value of these new tools will have to be confirmed by randomized trials proving a prognostic value of such early risk stratification. Consequently, they must still be regarded as experimental at this stage.

In addition, these tools may enable the evaluation of different therapeutic strategies to prevent the further development of sub-clinical disease. For research purposes, CT Plaque Analysis provides an excellent way to standardize the evaluation of different plaque types. The expected further technical development of this application will likely allow for an even more precise plaque characterization. With the advent of the next generation of scanners, such as the Brilliance iCT (Philips Healthcare) with improvements in speed, tube power, and coverage along with dose reduction technologies, there are opportunities to further investigate plaque characterization in a wider range of patient cohorts.

**Conclusion**

Philips CT Plaque Analysis may help in further understanding the morphology and the underlying composition of significant and non-significant atherosclerotic lesions. These lesions can be interrogated to provide additional information on the entire disease state of the patient, and may guide further prevention and treatment options, which will hopefully prevent future adverse cardiovascular events.

<table>
<thead>
<tr>
<th>CT plaque analysis</th>
<th>IVUS-VH</th>
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<tr>
<td>Max burden</td>
<td>79%</td>
<td>76.1%</td>
</tr>
<tr>
<td>Volume</td>
<td>66.6 mm³</td>
<td>58.1 mm³</td>
</tr>
<tr>
<td>Content</td>
<td>15% Calcified, 85% Non-calcified</td>
<td>3% Calcified, 97% Non-calcified</td>
</tr>
<tr>
<td>Length</td>
<td>7.3 mm</td>
<td>7.4 mm</td>
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</table>

Table 2. Results of CT Plaque Analysis and IVUS-VH for the RCA plaque.

**References**


The prevalence of obesity is increasing rapidly in the industrialized world and in the United States in particular [1]. For adults, a body mass index (BMI) of more than 25 is considered “overweight”, with a BMI of more than 30 classifying them as “obese”. The most rapidly growing sections of the obese population are in those with a BMI of more than 40, classified as severely and morbidly obese [2].

Obesity is not only a risk factor for multiple pulmonary and cardiovascular conditions, with morbidly obese adults having the highest cardiovascular mortality risk [3], but also complicates the treatment of otherwise unrelated conditions. A recent advisory from the American Heart Association has dealt with the evaluation and management of severely obese patients [2]. Coronary artery disease (CAD), heart failure, systemic hypertension and pulmonary hypertension, associated with sleep apnea and obesity-related hypoventilation, are just a few of the related conditions commonly present in obese patients.

In addition, a specific cardiomyopathy of obesity has also been described [4]. A high incidence of CAD events was reported in women with BMI of more than 35 in the Women’s Health Initiative Observational Study (11.6% had prior myocardial infarction, angina pectoris or revascularization) [5] and these findings were related to the increasing prevalence of type 2 diabetes mellitus and systemic hypertension associated with increasing BMI.

In addition to their weight posing logistical challenges [6], the body habitus of the morbidly obese severely limits the signal-to-noise ratio (SNR), which prevents reliable diagnostic imaging. In cardiac catheterization laboratories, image quality is limited by the power of the X-ray generators. Invasive coronary angiography in the extremely obese may be compromised both by poor image quality as well as by the technical difficulty of access, requiring special attention to the entry site to maintain a low complication rate [7].

Non-invasive imaging modalities such as current generation echocardiography, multi-detector computed tomography (MDCT), nuclear medicine and magnetic resonance imaging are preferred for evaluation of patients with morbid obesity.
scanners face similar challenges [8], with pharmacological functional and perfusion tests performing poorly in ruling out coronary artery disease in morbidly obese patients [7]. Lastly, because of the limited exercise capacity of these patients, exercise stress is often not possible.

At the Lady Davis Carmel Medical Center in Haifa, Israel, we have had prior experience in the cardiovascular care of challenging patient cohorts. We were among the first to use the Philips’ Brilliance 40 MDCT scanner in a patient cohort with implanted coronary stents [9] and the Brilliance 64 in the Emergency Department [10, 11]. We have also had recent experience with invasive coronary angiography in moderately obese patients [12].

Currently, with over 12 months experience with the use of the Brilliance iCT scanner, we have now turned our attention to tackling the challenge of non-invasive imaging of morbidly obese patients. Investigations have studied risks of bariatric surgical procedures and proposed ways to improve decision making for the treatment of obesity [13]. We are now increasingly using the Brilliance iCT for coronary assessment in this patient category, and in the pre-procedural assessment of patients prior to bariatric surgical intervention.

In the following sections, we present our experiences with cardiovascular MDCT imaging of morbidly obese patients using the Brilliance iCT scanner. All post-processed images shown were generated via Comprehensive Cardiac Analysis (CCA) on the Philips Brilliance Workspace CT workstation.

The Brilliance iCT

With a longitudinal coverage of 8 cm and the medical industry’s fastest rotation time of 0.27 seconds (resulting in a standard temporal resolution of 135 msec), the Brilliance iCT has significantly reduced the breath hold and acquisition times in chest CT angiography (CTA) scans [14]. At the same time it shows the capability of accommodating a wider range of heart rates for coronary CTA applications with contrast optimization [15, 16].

The detector system is equipped with a 2D antiscatter grid (ClearRay Collimator) as shown in Figure 2a. This reduces the scatter radiation, thereby improving the Hounsfield Unit (HU) uniformity and contrast resolution over a larger z-axis coverage. Other innovations include radiation dose saving technologies across the entire imaging chain. For instance, low-dose prospectively-gated axial scans (“Step & Shoot Cardiac”) using the Brilliance iCT have been successfully applied for not only coronary and aorta applications [14, 15] but also as an ultra-low dose option in the imaging of infant/pediatric population to assess congenital defects [16].

Additionally, a dynamic z-collimator (“Eclipse DoseRight Collimator”) and an adaptive z-collimator offer significant radiation dose savings in helical and axial modes of scans respectively, by reducing z-overscanning at the ends of the acquisitions [17]. Lastly, in contrast to other commercially available scanners, the Brilliance iCT has a 120 kW tube (iMRC).
The availability of high instantaneous power from the tube and generator system now provides us with the capability to image morbidly obese patients. At the same time, dose management tools (“DoseRight Cardiac”) are available that enable radiation dose savings of approximately 40% depending on the heart rate during the acquisition. Typical acquisition parameters are:

- \(128 \times 0.625 \text{ mm collimation}\)
- \(0.27-0.33 \text{ seconds rotation time}\)
- \(120-140 \text{ kVp}\)
- \(900-1500 \text{ mAs}\)
- \(0.16-0.18 \text{ pitch}\)
- \(0.8-1.0 \text{ mm reconstructed slice thickness}\).

(Figure 2b) and generator system, providing the high instantaneous power needed for the short duration cardiac scans, thus making it easier to image obese and morbidly obese patients [18].

**Imaging morbidly obese patients**

**Retrospectively-gated helical coronary CTA**

With this commonly used protocol, the entire cardiac anatomy of interest (12 cm) can now be covered in 5 seconds or less using the Brilliance iCT. Optimizing temporal resolution via advanced adaptive multi-slice reconstruction algorithms [19] and using a variable delay algorithm to capture the same physiological phase during the acquisition [20, 21] provides high-quality imaging of coronary artery segments.

(Figure 3a) A “Surview” image from an ultra low-dose scan, providing a two-dimensional overview of the anatomy that is used to plan the diagnostic three-dimensional CTA scan.

(Figure 3b) Normal left anterior descending artery.

(Figure 3c) Tortuous but normal right coronary artery.

(Figure 3d) Normal right coronary artery.

(Figure 3e) A three-dimensional maximum intensity projection (MIP) image showing an overview of the coronary arteries and their side branches.

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(Figure 3. Retrospectively-gated helical coronary CTA of a 60-year-old morbidly obese female patient (BMI ≈ 40). The patient had a history of hypertension and hypercholesterolemia with symptoms of atypical chest pain. Curved reformatted images show no significant disease.)
Automatic bolus tracking (BolusPro) is employed in all patients, with a region of interest (ROI) placed in the descending aorta. Scans are triggered when the contrast enhancement reaches a pre-set threshold (for example, 150 HU). 80-100 cc of non-ionic contrast is injected at 5-7 cc/sec, with the volume adjusted depending on the length of the scan.

If the resting heart rate is greater than 65 bpm, beta blockers are administered in order to stabilize and reduce the heart rate (provided that there is no contraindication for the use of beta blockers). All patients are given sublingual nitroglycerin to dilate the coronary arteries, thereby improving arterial definition and resolution.

Figure 3 shows the coronary arteries of a 60-year-old woman referred for bariatric surgery who suffered from atypical chest pain and had a history of hypertension and hypercholesterolemia. Her weight was 106 kg and height 163 cm (BMI ≈ 40). The CT acquisition was performed using a volume of 90 cc of contrast (Ultravist 370, Bayer Schering Pharma AG) injected at 7 cc/sec.

The average heart rate during the acquisition was 73 ± 2 bpm. An acquisition length of 14 cm was covered in six seconds. The image quality was diagnostic and sufficient to exclude any significant CAD and the study obviated the need for any further coronary investigation prior to surgery.

**Low-dose prospectively-gated coronary CTA**

One approach to mitigate the risk of radiation dose is to use prospectively-gated axial acquisition (“Step & Shoot Cardiac”), where the X-rays are only emitted during the quiescent cardiac phase (for example, ventricular diastasis).

This approach has been shown to reduce radiation dose by 80% compared with the standard retrospectively-gated helical approach [22]. While recent literature has shown the success of this approach at lower heart rates [22, 23], preliminary experience with the Brilliance iCT has shown promise of it being applicable over an expanded range of heart rates with diagnostic image quality [15].

Typical Step & Shoot Cardiac acquisition parameters are:

- 128 x 0.625 mm collimation
- 0.27-0.33 sec rotation time (with the option of the slower rotation time for obese patients)
- 120-140 kVp
- 160-300 mAs (with the higher mAs applicable at the slower rotation time for obese patients)
- 0.8-1.0 mm reconstructed slice thickness

Automatic bolus tracking is employed as described earlier.

Figure 4 shows the right coronary artery of a 48-year-old female who had a history of stable angina pectoris, but was hospitalized acutely due to increasingly severe chest pain. She was obese (height 170 cm, weight 105 kg, BMI ≈ 36) and had a history of hypertension, hypercholesterolemia and a family history of CAD. She had a treadmill stress test shortly before hospitalization that showed exercise-induced ischemic changes on the electrocardiogram.

The CT acquisition (Figure 4a, b) was performed using a prospectively-gated (“Step & Shoot Cardiac”) protocol with a volume of 90 cc of contrast (Omnipaque 350, GE Healthcare) injected at 7 cc/sec. The average heart rate during the acquisition was 48 ± 0.6 bpm. Using a k value of 0.014 applicable to chest CT, the estimated effective radiation dose was 6.4 mSv, much lower than that attainable in such patients using the conventional retrospectively-gated protocol.

The image shows a tight proximal narrowing of the right coronary artery with predominantly non-calcified plaque with a localized spot of calcification and positive remodeling of the coronary artery. These three features have been described as markers of elevated risk when assessed by CT angiography or intravascular ultrasound imaging [24-26].

The speed and coverage of the Brilliance iCT has thus expanded the use of cardiovascular applications, accommodating not only a wider range of heart rates [15] but also a diverse patient population, such as pediatric patients with congenital anomalies [16]. Extending this further, we have now shown that by appropriately harnessing the power of the tube and generator system it is possible to perform high-quality cardiovascular imaging of obese and morbidly obese patients who have previously presented challenges for reliable diagnostic assessment of their underlying symptoms.
Conclusion

With the increasing prevalence of obesity, diabetes mellitus and hypertension and their co-morbidities, the need for assessment of the coronary arteries in obese patients is on the rise. We have defined a protocol to harness the power of the iCT scanner to this end and the results show that imaging of the coronary arteries utilizing the high output of this novel scanner makes scanning of the coronary arteries in the very obese a clinically useful reality.

Prospective data-driven studies are currently under way, investigating the diagnostic image quality of coronary arteries, such as the percentage of assessable coronary segments in this challenging cohort of patients.
References


Pediatric cardiology with the iE33 echocardiography system

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The Children’s Heart Centre Linz was created in 1995 with the cooperation of the Department of Pediatric Cardiology of the Maternity and Children’s Hospital of Linz (Figure 1) and the Department of Cardiac surgery of the General Hospital of Linz.

The department of Pediatric Cardiology is part of the Gespag Organization (Öö Gesundheits- und Spitals-AG), which is Austria’s largest hospital group with 11 hospitals at 14 locations, comprising eight general hospitals and three specialist hospitals.

Established in 1993, the Pediatric Cardiology Department is one of Austria’s leading and best-equipped clinics for pediatric cardiology, with its own modern cath lab and MRI installation. In October 2006, the department was the first in Austria to be equipped with the Philips iE33 echocardiography system (Figure 2). This system represents a new generation of ultrasound equipment for echocardiography, with live high-definition 3D imaging and on-cart data analysis tools.

Pediatric echocardiography

Echocardiography has become the primary imaging modality for the diagnosis and assessment of congenital and acquired heart disease in infants, children, and adolescents. Currently, some 6,000 to 7,000 echocardiographic exams are performed annually in the Department, 4,000 of which are in outpatients.

The principal advantages of echocardiography are that it is noninvasive, and is capable of providing detailed morphological, hemodynamic and physiologic information.

Pediatric echocardiography may be indicated for a number of conditions, including:

- Congenital heart disease
- Acquired heart disease
- Arrhythmias
- Transplants
- Noncardiac disease.

Congenital heart disease

The term “congenital heart disease” covers a wide spectrum of anomalies, including intracardiac left-to-right or right-to-left shunts, obstructive lesions, regurgitant lesions, conotruncal anomalies, coronary artery anomalies, functionally univentricular hearts, and other complex lesions, including abnormal laterality (heterotaxy/isomerism).

Congenital heart disease can manifest itself by a variety of symptoms and signs, but echocardiography may also be indicated by a family history of inherited heart disease or abnormalities on other tests such as electrocardiography.

Acquired heart disease

Echocardiography may also be indicated for the evaluation of acquired heart diseases in children, including infective endocarditis, rheumatic fever, myocarditis, pericarditis, and exposure to cardiotoxic drugs.
Doppler allows precise quantification of flow velocities and gradients.

The new X7-2 transducer was used to acquire 3D loops in real-time, offering the possibility of storing a complete dataset for post-processing. ECG triggering is, of course, not possible in fetal echocardiography, but the “estimate fetal heart rate” option overcomes this problem and allows triggered acquisition of several heart cycles, thus improving image quality.

**Technical requirements**

The minimum requirements for pediatric echocardiography are facilities for M-mode, 2D imaging, color flow mapping, and spectral Doppler studies, including pulsed wave and continuous wave capabilities. The electrocardiogram should be displayed simultaneously with the image, and there should be an indication of range or depth.

Measurement facilities should be available for distances, areas, blood flow velocities, time intervals, and peak and mean gradients from spectral Doppler studies.

There should also be adequate provision for the transmission and storage of moving images.

**Examination protocol**

In the conventional echocardiographic examination, a large number of 2D images are acquired in multiple orthogonal imaging planes, supplemented by Doppler and color Doppler information. Particular attention is paid to acquiring the subxiphoid (or substernal), suprasternal notch, and parasternal views.

This is a time-consuming procedure, and can be particularly difficult in the case of uncooperative patients.

**The Philips iE33 echocardiography system**

With the Philips iE33 “intelligent” echocardiography system (Figure 2), acquisition is very much faster than with the conventional examination protocol. The images are acquired as a complete 3D data set in a single sweep. Free navigation through the 3D data set allows any plane through the heart to be visualized, and the images are precisely reproducible.

The ability to perform a complete acquisition in a few seconds, rather than a quarter of an hour, allows much faster diagnosis, which is of great importance in pediatric applications.
Case 1.

Color tissue Doppler and strain of a fifteen year old boy with dilated cardiomyopathy following a viral myocarditis. The ejection fraction is less than 50%. There is asynchronicity due to the lack of septal contraction. (Figure 3)

Case 2.

1½ year-old-girl with Down’s Syndrome. Status post repair of a complete AV septal defect at the age of 4 months. Now there is significant AV valve regurgitation. 2D color doppler shows the jet, but the origin is unclear. 3D color Doppler shows that there are multiple origins between the leaflets. Figure 4a shows the heart in diastole, with normal tricuspid valve inflow (shown in red). Figure 4b shows the heart in systole, with the tricuspid valve closed. 3D color Doppler shows tricuspid regurgitation with separate origins.

Figure 4. Severe tricuspid regurgitation.

Figure 4a. Heart in diastole, with normal tricuspid valve inflow (red).

Figure 4b. Heart in systole, with the tricuspid valve closed. 3D color Doppler shows tricuspid regurgitation with separate origins.
The Philips iE33 system was installed in our department in October 2006, and has integrated CardioCare software, TomTech QLAB and X47. The system is used to examine children of 2 kg and over. It provides high-quality 2D image quality, high-quality 3D images of the valves, powerful 2D and 3D measurement of cardiac function and anatomy, and live 3D imaging of the moving heart.

S5-1 transducer helps to ensure accurate detection of the endocardial border. Global LV volume curves and regional waveforms can be used to identify and measure LV regional timing.

3DQ allows quantification to be performed in both 2D and 3D images. Segmental analysis is possible in the left ventricle. Tissue Doppler is used with a high frame rate of 5 ms per frame. This is very important, and allows early detection of diastrophy.

3DQ segment analysis in neonates is excellent. The system yields exquisite 3D images, covering every aspect of cardiac morphology and function. However, the images require a certain degree of familiarization. There is a fairly steep learning curve, so some doctors continue to use the 2D images, because they are familiar with them. Nevertheless, 3D imaging is rapidly gaining acceptance because it provides results in a few seconds, rather than quarter of an hour, allows much faster diagnosis.

Electrophysiology
The 3D ultrasound images provide the necessary spatial information for placing resynchronization electrodes, even in the abnormal or incomplete heart. Positioning of electrodes is notoriously difficult. In very small children the electrode is positioned in the left ventricle. In larger children, the left ventricular lead is passed into the coronary sinus and into the back of the left ventricle, as in adult patients.

The high-quality imaging helps to ensure accurate positioning, even in children with severe cardiac abnormalities.

Ergonomics
An added benefit of the Philips iE33 system is its unique ergonomic design that adjusts to the individual user. It is a known fact that some 80% of sonographers have experienced work-related pain, resulting in reduced patient throughput and increased workers compensation claims. The iE33 system has been designed to address these challenges with independent height adjustment of the monitor and control panel, and the full range of viewing distances, meeting the SDMS (US Society of Diagnostic Medical Sonography) Industry Standards.

In addition, the iE33 has voice command, one-button automated optimization controls for quick and consistent image acquisition between users of varying skill levels, and a simpler, easy-to-use interface.

The images display astonishingly crisp and clear anatomic and physiological details.

The morphological information provided by the iE33 system is excellent.

New transducers
The Philips iE33’s new line of transducers includes the X7-2 transducer, combining xMATRIX and PureWave crystal technology. PureWave is an entirely new class of piezoelectric material whose properties provide greater transmission efficiency than conventional transducers. The resulting 2D and color flow images display astonishingly crisp and clear anatomic and physiological details which help enhance diagnostic confidence, even on the most technically challenging patients.

Clinical application
The morphological information provided by the iE33 system is excellent. The full 3D data set requires extensive postprocessing, but can provide any required 2D image. There is free navigation though the data set, and the images are precisely reproducible, saving a great deal of examination time. This is important for small, uncooperative children.

The full data set provides the pre- and post-interventional information needed for Amplatz closure, both pre- and post-interventional.

Quantification
The ability to quantify is becoming more and more important. The Philips iE33 system has fully integrated QLAB 2D and 3D cardiac quantification software for measurements such as left ventricle (LV) volume and ejection fraction. The software uses three-dimensional border detection to provide rapid access to ventricular volumes of the whole heart, with waveforms that show the function of up to 17 different segments of the heart simultaneously. The enhanced image quality obtained with the
Case 3.

Fetal echo at 29 weeks gestation: Fetus with a large rhabdomyoma. 2D clearly shows the tumor (Figure 5a), and color Doppler demonstrates flow around this tumor (Figure 5b). 3D provides additional information regarding 3-dimensional extension, tumor volume and its relation to the AV valves (Figure 5c).

Conclusion

In spite of some initial reluctance, physicians were agreeably surprised by the high quality of the 3D images.

Free navigation through the 3D data set allows any plane through the heart to be visualized, and the images are precisely reproducible.

The ability to perform a complete acquisition in a few seconds, rather than quarter of an hour, allows much faster diagnosis, which is of great importance in pediatric applications.

Fully integrated QLAB 2D and 3D cardiac quantification software provides fast and accurate measurements, including left ventricle (LV) volume and ejection fraction calculations.
The local delivery of therapeutic molecules mediated by ultrasound is a novel approach to addressing unmet clinical needs by providing a minimally-invasive platform for targeted delivery of pharmaceuticals [1]. It enables high concentrations of drugs to be deposited under image guidance to specific locations in the body. It can, therefore, be a preferred treatment option for non-systemic diseases. This produces more constant and controlled drug concentration profiles with favorable pharmacokinetics.

With the advancement in imaging techniques, local drug delivery can now be applied in the human body with an unprecedented spatial and temporal resolution. Apart from delivering drugs to the desired location, another advantage of using ultrasound is the increase of cellular uptake through an effect called sonoporation, which gives the method an additional advantage over needle- or catheter-based procedures.

Ultrasound for therapy is preferably highly focused, in order to expose a well-defined area, while steering of the ultrasound beam should be flexible and fast to allow for the controlled exposure of a region of interest with a potentially complex shape.

Two types of ultrasound-mediated delivery systems can be distinguished: pressure-mediated delivery and temperature-mediated delivery.

Pressure-mediated delivery is performed using microbubbles, currently clinically applied as ultrasound contrast agents, that react to short ultrasound pulses by oscillation or bubble destruction [2]. As this is a fast process and the microbubbles and their destruction can be conveniently imaged using ultrasound, ultrasound imaging is the preferred modality for guiding the drug delivery.

In the case of temperature-mediated delivery, in which ultrasound is applied for a sufficient amount of time to establish a local temperature increase, magnetic resonance imaging (MRI) is the most appropriate modality for image guidance, as it offers the possibility of therapy planning as well as monitoring of the local temperature distribution during the drug delivery procedure [3]. The first application of high intensity focused ultrasound (HIFU) in combination with MRI was in the ablation of uterine fibroids, which gives an excellent starting point for temperature monitoring during HIFU treatment.

In this overview we present recent developments in ultrasound-triggered, image-guided drug delivery with a focus on pressure- and temperature-sensitive drug delivery vehicles. For temperature-induced delivery we present material systems, where drug and imaging agent are both encapsulated in temperature-sensitive carriers that allow the monitoring of temperature-sensitive delivery vehicles using MRI and disintegrate upon temperature increase.

For pressure-sensitive microbubble agents we discuss the options of drug delivery with either co-injected drugs or drugs incorporated into the microbubble carrier, and focus on the induced permeability increase of cells. Finally an outlook on potential applications is given, ranging from the improvement in small-molecule drug delivery to gene-silencing using small interference RNA as a new therapeutic drug format.

Temperature-triggered, MRI-guided drug delivery

During ultrasound energy deposition, the actual tissue temperature is difficult to predict. Physiological processes may modify local heat conduction and energy absorption. Blood flow may increase during temperature increase and thus change heat conduction. Unlike ablation treatments, the exposure to an elevated temperature for drug delivery using ultrasound should remain well below the damage threshold. In order to improve the therapeutic efficiency and the safety of the intervention, real-time
Temperature-sensitive liposomes release the encapsulated molecules at their phase transition temperature ($T_m$), where the lipid membrane displays a transition from a gel to a liquid crystalline phase.

Studies with doxorubicin-loaded temperature-sensitive liposomes in combination with an externally applied regional temperature increase clearly showed the improved efficacy of temperature-induced drug delivery [14, 15]. Instead of relying on liposomal accumulation in the tumor, mild hyperthermia was applied during the first hour after injection of the temperature-sensitive liposomal formulation of doxorubicin. As a result, doxorubicin was rapidly released in the microvasculature of the tumor and subsequently taken up by the tumor cells.

In future applications, the incorporation of MRI contrast agents into temperature-sensitive drug vehicles will not only offer the possibility of guiding and controlling the temperature in the lesion, but can also be used to visualize and quantify the drug delivery process. However, MRI contrast agents have an effect on the relaxation phenomena, which are also temperature-dependent, and therefore complicate the quantification and reliability for monitoring the drug release. Some compromise must be made between sensitivity to co-release of such contrast agents and sensitivity to temperature change. Promising contrast agents to allow for temperature mapping and simultaneous following of the release are $^1$H CEST (Chemical Exchange Saturation Transfer) [13] and $^{19}$F MR contrast agents.

**Temperature-sensitive liposomes**

A drug delivery technology that has advanced to clinical trials for MRI-guided, temperature-induced drug delivery is based on temperature-sensitive liposomes. Liposomes consist of a lipid bilayer encapsulating an aqueous interior containing the active molecules. The temperature-sensitive liposomes release the encapsulated molecules at their phase transition temperature ($T_m$), where the lipid membrane displays a transition from a gel to a liquid crystalline phase.

Studies with doxorubicin-loaded temperature-sensitive liposomes in combination with an externally applied regional temperature increase clearly showed the improved efficacy of temperature-induced drug delivery [14, 15]. Instead of relying on liposomal accumulation in the tumor, mild hyperthermia was applied during the first hour after injection of the temperature-sensitive liposomal formulation of doxorubicin. As a result, doxorubicin was rapidly released in the microvasculature of the tumor and subsequently taken up by the tumor cells.

The co-encapsulation of hydrophilic drugs and MRI contrast agents is shown diagrammatically in Figure 1. Temperature-sensitive liposomal $^1$H CEST and $^{19}$F MR contrast agents have been explored as a potential carrier system for MRI guided drug delivery in combination with local...
Microbubbles consist of gas encapsulated in a phospholipid, protein (albumin) or polymer shell.

Pressure-mediated delivery implies an extension of the current application of microbubbles.

At temperatures below the $T_m$ of the temperature-sensitive liposomal contrast agent, the chemical shift agent remains intraliposomal and the CEST effect is obtained, whereas the intensity of the simultaneously measured $^{19}$F NMR signal is negligible. Upon reaching the $T_m$, the CEST effect disappears, due to the release of the chemical shift agent. Simultaneously, the $^{19}$F MRI probe is freed from the influence of the paramagnetic shift agent, causing an appearance of a $^{19}$F MRI signal. The combined CEST and $^{19}$F MR temperature-sensitive liposomal contrast agent provides CEST MR based contrast enhancement, to localize the liposomes before release, while the $^{19}$F MR signal can potentially be used to quantify the local release of drugs with MRI.

压力介导的输送意味着扩展了当前应用的微泡。

在它们的内腔中，温度敏感的脂质体包含两种化学位移剂（用于$^1H$化学交换饱和转移（CEST）检测）以及具有高氟化剂的$^{19}$F检测）。它们被封装在气泡中提供一个气腔池，可以在水性内核中实现1H磁共振信号。温度敏感的脂质体在特定的时间内，在指定的部位位置测量$^{19}$F NMR信号是微不足道的。当温度达到$T_m$时，CEST效应消失，由于化学位移剂的释放。同时，$^{19}$F MRI探针被从参数磁性位移剂的影响中解放出来，出现一个$^{19}$F MRI信号。结合了CEST和$^{19}$F MR温度敏感的脂质体提供了基于CEST MR的对比增强，局部化脂质体之前释放，并且$^{19}$F MR信号可能被用于量化局部释放用于MRI的药物。

压力敏感系统

超声敏感系统

一种超声设备可用于超声触发的超声成像引导的治疗，通常包含一个双探头组合，包括一个聚焦探头和一个成像探头。聚焦探头用于提供预设的强度，以在特定的位置精确地定义时间。超声波的频率范围大约在1-2 MHz，带有大约1-2 mm的径向和6-10 mm的长度。成像探头用于获得一个更宽的视野，围绕目标区域并且，例如，跟随微泡的流入。结合使用声学参数，如频率、压力和脉冲长度，可以独立地设置对于治疗和成像超声波探头。

压力介导的输送意味着扩展了当前应用的微泡。这些微泡由气体封装在磷脂，蛋白质（血清蛋白）或聚合物壳内。

微泡与壳中的脂质和血清蛋白通常是分开的。它们在临床中已经被使用。它们是很容易与药物结合的，因为它们有薄壳，但药物被封装在壳中时会很容易释放。

聚合物壳的微泡很容易准备具有更大的尺寸分布。这避免了肺部的显著积累。由于氟化气体的使用，聚合物壳的微泡可以被用于肺部的治疗。

超声胃泡的特别有效在透壁血流时被暴露于超声时[19, 20]。这允许材料的持续释放。超声可以在没有损伤的条件下，例如，可以通过超声波通透使得细胞膜破裂，而不会在肺部积累。这些类型可以被用于治疗基因[21]。在肿瘤中，通过增加药物的传递，提高了基因递送的效率。在心血管领域，超声波可以用于判断内膜异常。

超声敏感的系统

超声敏感的系统

一种超声装置适合于超声触发的超声成像引导的治疗，优选的组合包括一个聚焦探头和一个成像探头。聚焦探头用于提供预设强度，以在特定的位置精确地定义时间。超声的频率范围大约在1-2 MHz，具有接近1-2 mm的径向和6-10 mm的长度。成像探头用于获得一个更宽的视野，围绕目标区域和，例如，跟随微泡的流入。成像的组合允许声学参数，如频率、压力和脉冲长度，被独立地设置，以用于治疗和成像超声波探头。

超声敏感的系统

超声敏感的系统

一个适合于超声触发的超声成像引导的治疗系统，优选的组合包括一个聚焦探头和一个成像探头。聚焦探头用于提供预设强度，以在特定的位置精确地定义时间。超声的频率范围大约在1-2 MHz，具有接近1-2 mm的径向和6-10 mm的长度。成像探头用于获得一个更宽的视野，围绕目标区域和，例如，跟随微泡的流入。成像的组合允许声学参数，如频率、压力和脉冲长度，被独立地设置，以用于治疗和成像超声波探头。

压力介导的输送意味着扩展了当前应用的微泡。这些微泡由气体封装在磷脂，蛋白质（血清蛋白）或聚合物壳内。

微泡与壳中的脂质和血清蛋白通常是分开的。它们在临床中已经被使用。它们是很容易与药物结合的，因为它们有薄壳，但药物被封装在壳中时会很容易释放。
This indentation results in signals visible on an ultrasound scanner. The ultrafast camera has been used to investigate sonoporation as well. Van Wamel et al. [33] presented results that demonstrate that (endothelial) cell membranes follow the oscillations of adjacent microbubbles. The amplitude of the oscillations is on the micrometer scale and the time scale is in microseconds, so the movements in the cell membrane are very fast, in the order of m/s. The displacement of the cell caused by the expansion and compression of the bubbles around the cell has an amplitude of 2 μm, indicated by arrows in Figure 3. This leads to an enhanced uptake of a marker dye as shown in Figure 4 (right frame). This shows the propidium iodide uptake recorded 15 seconds after the ultrasound has been switched off. Only cells with bubbles in close proximity showed uptake. After three minutes, no propidium iodide was present in the cell, indicating that the cell was still viable. This experiment clearly demonstrates that it is not necessary to induce large pores into membranes to change the porosity, and conditions exist at which cell membrane becomes only temporarily porous.

In recent work, the importance of changes in calcium channels and the need for ATP in the membrane because of ultrasound and microbubbles has been highlighted [34, 35].
Established therapies. By depositing a larger dose at the region of interest, the efficacy of cancer therapy can be improved. Novel therapeutic formats, using DNA-based gene therapy or gene silencing by therapeutic siRNAs, need specific mechanisms to enter the cell, currently often by the use of viral vector. With sonoporation, a different way of entering the cell is introduced, avoiding potential adverse reactions and complex delivery systems such as viruses. Here ultrasound-mediated delivery becomes a true enabling application.

For chemotherapy, dose reduction and thereby the increase of the therapeutic window is the differentiating advantage. While for small-molecule drugs entry to the cells can be achieved passively, nucleic acids require an uptake mechanism. Here, ultrasound can also be used as the trigger.

Specific attention needs to be paid to the choice of drug and its formulation. Small-molecule drugs, such as doxorubicin and paclitaxel, are well-established therapies. By depositing a larger dose at the region of interest, the efficacy of cancer therapy can be improved. Novel therapeutic formats, using DNA-based gene therapy or gene silencing by therapeutic siRNAs, need specific mechanisms to enter the cell, currently often by the use of viral vector. With sonoporation, a different way of entering the cell is introduced, avoiding potential adverse reactions and complex delivery systems such as viruses. Here ultrasound-mediated delivery becomes a true enabling application.

Summary and conclusions

The first application of HIFU/MRI was in the ablation of uterine fibroids, which gives an excellent starting point for temperature monitoring during HIFU treatment. Further clinical trials are running for delivery of doxorubicin using temperature-sensitive liposomes (Thermodox™, Celsion). New options to improve image-guided drug delivery will need new imaging technology, material development and an expansion of the knowledge on mechanisms of uptake of drugs into cells, especially for high molecular weight therapeutics. These complex questions are currently addressed in public-private consortia such as the European Framework 7 project “Sonodrugs”.

Specific attention needs to be paid to the choice of drug and its formulation. Small-molecule drugs, such as doxorubicin and paclitaxel, are well-established therapies. By depositing a larger dose at the region of interest, the efficacy of cancer therapy can be improved. Novel therapeutic formats, using DNA-based gene therapy or gene silencing by therapeutic siRNAs, need specific mechanisms to enter the cell, currently often by the use of viral vector. With sonoporation, a different way of entering the cell is introduced, avoiding potential adverse reactions and complex delivery systems such as viruses. Here ultrasound-mediated delivery becomes a true enabling application.

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The specific combination of ultrasound, delivery and contrast vehicles, imaging technology and the medical application will finally determine the future development of image-guided, ultrasound-triggered drug delivery.

References


The introduction of single photon emission computed tomography (SPECT) considerably improved diagnostic accuracy and allowed better estimation of infarct size and/or ischemic burden. Subsequent development of several technetium-99m tracers, notably Tc-99m sestamibi and Tc-99m tetrofosmin, further improved image quality. The addition of ECG-gating to image acquisition brought still another dimension of left ventricular functional information to further refine perfusion pattern interpretation, particularly in differentiating true perfusion defects from soft tissue attenuation artifacts. Significant software contributions have allowed standardization and quantification of these perfusion and function parameters. These software programs have allowed standardized estimates of regional perfusion and ventricular contractility compared to normal databases as well as reproducible calculations of left ventricular volumes and ejection fractions [1].

With all these enhancements, SPECT myocardial perfusion imaging has been well validated over the years and has become widely accepted for its incremental diagnostic and prognostic value in clinical decision making. Nonetheless, development has slowed and no major improvements have occurred in the last 15-20 years. Also, true absolute quantification of important physiologic parameters such as myocardial blood flow has remained elusive. PET Positron emission tomography (PET) has emerged as a similar radiopharmaceutical tomographic imaging technique to SPECT, but with important and unique characteristics. It has inherently higher image resolution and is capable of providing accurate physiologic measurements. Pioneering work in demonstrating the myocardial perfusion imaging capabilities of...
PET [2] did not result in immediate widespread use of PET, primarily due to the limited availability of equipment and PET radiopharmaceuticals. However, with the parallel evolution of PET as a powerful diagnostic tool in oncology, PET has entered into the diagnostic imaging mainstream. The availability of rubidium-82 via onsite strontium-rubidium radiopharmaceutical generators has also allowed myocardial perfusion imaging with PET to expand, since this PET tracer is available upon demand.

**Comparison of PET and SPECT**

For cardiology applications, PET offers improved image resolution when compared with SPECT [3], enhancing detection of abnormalities in regional myocardial perfusion. This has been well established over the years, but more recent developments of iterative image reconstruction methods, time-of-flight PET acquisition, and PET quantitative software packages have further advanced accuracy. Direct comparisons of myocardial perfusion with PET and SPECT have documented the superiority of PET, especially in large patients and those with equivocal previous SPECT results [4].

In an ongoing comparison series, we have performed both Tc-99m sestamibi SPECT and Rb-82 PET on the same day in a group of patients undergoing a single pharmacologic stress protocol with dipyridamole infusion (Figure 1) [5]. This minimizes the variables inherent in most comparative studies and has demonstrated the superiority of PET with CT-based attenuation correction. The additional quantitative capabilities of PET for measurement of blood flow at rest and with vasodilator stress can add important physiologic information for clinical assessment, even when regional perfusion images appear not to demonstrate obvious ischemia or scar [6,7].

**Combination with CT**

A recent boost in acceptance of PET has resulted from incorporation of transmission tomography (CT) with PET as a combined PET-CT scanner unit. Originally conceived as an improvement for acquiring body density attenuation maps for attenuation correction of PET images, current generation units combine the state-of-the-art technologies of both PET and CT into units that have full capabilities for both modalities. Most notably, the fusion of physiologic PET images with the anatomic image information from CT (Figure 2) offers a powerful tool for disease assessment [8]. However, it also introduces new complexity in ensuring proper initial patient positioning, proper indexing of scan data sets by the imaging equipment, and minimization of both intrascan and interscan patient motion [9]. This assumes special importance when the imaging is used as a basis for planning intervention.

Attenuation correction has long been employed for PET utilizing external radiopharmaceutical sources. It appears that the combination with CT provides more reliable and faster attenuation correction and can also provide good comparative anatomic information, even when CT is typically used in a low-dose non-contrast mode.

Having state-of-the-art CT integral to PET adds further CT capabilities for calcium scoring and high resolution angiography if desired [10]. There is great interest currently in assessing the optimal combination of PET and CT imaging information that will provide the best “one-stop” evaluation of any individual patient. Multiple combinations of the two modalities can be customized to gain the desired clinical data at the lowest feasible radiation burden and cost for each patient.

These recent advances in PET-CT for cardiology have begun to translate back to single-photon tomography (SPECT) as well. Considered by
Figure 3. Tc-99m sestamibi SPECT-CT in a large male patient with a low clinical likelihood of coronary disease.

Figure 3a. Uncorrected short axis images demonstrate inferior diaphragm attenuation artifact.

Figure 3b. Uncorrected long axis images also show inferior diaphragm attenuation artifact.

Figure 3c,d. Corresponding attenuation-corrected images are normal.

Figure 4. Inferobasal infarct in a 63-year-old male patient.

Figure 4a. Tc-99m SPECT images showing a pattern of inferobasal infarct, but no ischemia.

Figure 4b. Rb-82 PET images showing a small inferobasal infarct, but with additional ischemia along the majority of the inferolateral segment.
many users to have gone through a period of developmental stagnation, SPECT technology is now benefiting from combination with CT into SPECT-CT scanner units to take advantage of the valuable integration of physiology and anatomy to improve diagnostic accuracy. CT-based attenuation corrected SPECT images appear to demonstrate similar incremental improvement in image quality and lesion conspicuity to that of PET-CT (Figure 3) [11].

**Case study**

A 63-year-old male patient presented with prior history of myocardial infarction and bypass surgery five years previously. Tc-99m SPECT images show a pattern of basal inferior infarct without ischemia (Figure 4a). Rb-82 PET images show a small inferobasal infarct but with additional ischemia along the majority of the inferolateral segment (Figure 4b). Coronary angiography demonstrated a patent LIMA graft to the LAD, patent vein graft to the RCA, and diffuse CMX stenosis, amounting to 100% distally.

**The future**

Even the near future of PET-CT and SPECT-CT cardiac imaging is difficult to foresee, especially with external forces of healthcare reform and economic regulation looming large. It is becoming clear that these new combination modalities are improving the detection and prognostic assessment of coronary artery disease in ever more quantitative fashion. As new radiopharmaceutical developments push us beyond simple detection of artery stenosis and more toward the earlier detection of atherosclerotic plaque and the very molecular basis of coronary vascular and myocardial function, these combined modality imaging technologies will be indispensable tools for the advancement of these discoveries.

**References**


Alzheimer’s disease (AD) accounts for the majority of dementia cases within USA and worldwide and its incidence increases with age. Its prevalence is estimated to be 5.3 million of cases in the USA [1] and over 25 million cases worldwide. The disease progresses within 12-18 years from an insidious onset dominated by short-term memory deficit to severe brain dysfunction rendering subjects mute and non-ambulatory. Currently, there is no specific diagnostic test to distinguish AD from other less frequent dementing illnesses. Furthermore, there is no test to accurately predict development of AD in older patients with isolated memory dysfunction but otherwise functioning well within their social environment, a condition dubbed mild cognitive impairment (MCI).

The progressive cognitive deficit clearly separates AD patients from the mild decline in cognitive functions associated with normal aging. Mild cognitive impairment is a clinical state, sometimes prodromal to fully symptomatic AD, where cognitive deficit can be delineated by psychometric testing. AD pathogenesis is associated with progressive accumulation of a toxic and hydrophobic Aβ peptide in the brain, which starts a number of years prior to the onset of clinical symptoms (Figure 1). This preclinical stage of the disease is dubbed the “brain AD stage”. Progressive accumulation of Aβ in the brain results in a number of secondary pathological processes including neurofibrillary degeneration, inflammation, synaptic loss, and neuronal dropout, whose severity correlates with clinical symptoms of the disease.

Making a diagnosis of AD is based on clinical experience and skill of an evaluating neurologist whose diagnostic accuracy can be further improved by complex, expensive and time consuming psychometric testing. Thus, current challenges concerning the diagnostic process of AD include:

- Providing reliable diagnosis of incipient AD in patients with MCI (or even in cognitively normal) within a defined time period of 3-5 years. This process should also reliably dismiss patients with subjective memory complaints.
- Improving differential diagnosis of AD vs other forms of dementia.
- Providing clinicians who are not experts in AD with tools enabling diagnostic conclusions with similar accuracy to dementia experts.

Figure 1. Evolution of Alzheimer’s disease. AD is characterized by progressive cognitive deficit which clearly separates AD patients from the mild decline in cognitive functions associated with normal aging. Mild cognitive impairment is a clinical state, sometimes prodromal to fully symptomatic AD, where cognitive deficit can be delineated by psychometric testing. AD pathogenesis is associated with progressive accumulation of a toxic and hydrophobic Aβ peptide in the brain, which starts a number of years prior to the onset of clinical symptoms (yellow dotted line). This preclinical stage of the disease is dubbed the “brain AD stage”. Progressive accumulation of Aβ in the brain results in a number of secondary pathological processes including neurofibrillary degeneration, inflammation, synaptic loss, and neuronal dropout, whose severity correlates with clinical symptoms of the disease (magenta dashed line).
A number of studies based on longitudinal designs have shown progressive changes in mesial temporal lobe atrophy on structural imaging and in CSF levels of β-amyloid peptide (Aβ), tau protein, and phosphorylated tau (P-tau) as subjects advance from a state of being cognitively normal to age, to MCI, and then to AD. Although these markers show statistically significant differences between AD and control groups, but due to substantial intergroup overlap, neither marker alone attains sufficient specificity and sensitivity to clearly separate among normal, MCI and AD subjects when subjected to cross-sectional analysis.

Functional imaging in form of Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) can be used to help confirming AD diagnosis and differentiate AD from other forms of dementia based on brain hypometabolism patterns, but this remains underutilized in clinical practice.

Several studies have also indicated that FDG-PET in conjunction with structural imaging can also be helpful in predicting incipient AD in MCI patients, but these approaches are not available for clinical use. Recent advances in Aβ targeted imaging ligands have made it possible to demonstrate brain Aβ accumulation in living subjects by PET. The most widely used ligand is 11C labeled Pittsburgh compound B (PIB), whose use has been thus far limited to research studies. Studies utilizing PIB have demonstrated the presence of Aβ in brains of AD patients and in some of MCI patients but also in brains of many cognitively normal subjects, which finding is consistent with previous autopsy data showing Aβ deposition to precede neurodegeneration and cognitive decline.

Thus, Aβ targeting ligands can detect accumulation of Aβ in the brain, but do not provide insight into the actual temporal relationship between brain Aβ deposition and onset of cognitive decline, and does not rule out co-existence of other forms of dementia pathology. In the absence of a specific disease diagnostic marker, ways to improve diagnostic accuracy can be sought through developing tools to enhance analysis of available markers and through development of the decision support system for dementia diagnosis, which would be based on concomitant analysis of several biomarkers. Such a system could derive a statistical probability of diagnosis based on built-in normative values for particular biomarkers and marker combinations. Its application would allow for accurate earlier diagnosis, and improved differential diagnosis of AD from other dementias.

Alzheimer’s disease is classified either as familial or sporadic. The familial form accounts for about 1% of all cases and is characterized by the onset before age of 60–65 years. Disease pathogenesis in the familial form is triggered by a mutation in one of the AD specific genes. The sporadic form, which accounts for prevailing majority of cases, starts after age of 60–65, and its incidence closely correlates with advancing age. Insidious onset and slow progression of short-term memory and learning dysfunction, followed by deficits in other cognitive domains makes a pattern of clinical presentation, which is classical for early stage of AD. The full clinical course of the disease from early signs of memory disturbances until its end-stage when patients become mute and non-ambulatory, and eventually succumb to a systemic infection may take 12 to 18 years.

The principles of clinical diagnosis of AD are based on demonstrating evidence of dementia during an interview with deficits involving memory and at least one other area of cognition [2]. The magnitude of cognitive deficit should be documented by a Mini-Mental State Examination (MMSE) or Alzheimer’s Disease Assessment Scale – Cognitive part (ADAS-Cog). Further diagnostic requirements include evidence of a progressive nature of decline involving memory and other cognitive functions, no disturbances of consciousness, onset between age of 40 and 90 years, and absence of systemic disorders or other brain diseases that could account for the deficits and progression [2,3]. There is no diagnostic test allowing for screening or confirming diagnosis of AD. Fulfilling the aforementioned criteria permits diagnosis of probable AD, which is the highest level of confidences clinically attainable. An atypical pattern of cognitive deficit and/or the presence of other atypical symptoms or diagnostic findings (e.g. vascular lesions) reduce the diagnostic confidence to the level of possible AD.

Definitive diagnosis of AD can be made only by demonstration of AD pathology upon autopsy in the absence of other significant brain pathologies. A caveat in making a postmortem AD diagnosis lies in the requirement of documenting a history of progressive dementia as it has been well established that some patients may carry a substantial burden of AD pathology in the brain without signs of cognitive deficits [4,5].

Diagnostic dilemmas concerning AD are even more challenging during the incipient stage of the disease when a clinical picture of the disease has not yet fully emerged. A clinical term, mild cognitive impairment (MCI), has been coined.
The pathogenesis of AD is initiated by an accumulation of a toxic and insoluble Aβ peptide in the brain. Critical challenges include an ability to correctly differentiate AD from other dementias.

Pathogenesis of Alzheimer’s Disease

The pathogenesis of AD is initiated by an accumulation of a toxic and insoluble Aβ peptide in the brain which predates other lesions, neuronal loss and symptoms of dementia [7,8]. Aβ is a hydrophobic 39–43 amino acid peptide derived from cleavage of a larger, synaptic transmembrane protein, the amyloid precursor protein (APP) [9]. Accumulation of Aβ in the brain is an effect of a mismatch between its rate of production and brain clearance and is exacerbated by its inherently low solubility and its natural propensity to self-aggregate into toxic oligomers and insoluble fibrils [10]. Rare cases of familial AD, with onset before age 60–65 years, are related to mutations in the APP sequence which, depending on the location, can cause one of the following: an increase in total Aβ production, an Aβ mutant which is highly toxic and more prone to self-aggregation, or an increased production of more toxic and aggregation prone Aβ1-42 at the expense of less fibrillogenic Aβ1-40. Mutations in presenilins (PS) 1 and 2 genes also result in increased Aβ1-42 to Aβ1-40 ratio. The causes of Aβ accumulation in the more prevalent sporadic AD cases are less well understood. It is believed that a combination of inherited predispositions and acquired factors plays a role in developing a mismatch between Aβ production and its clearance.

The strongest and thus far the only identified genetic factor modulating the risk for late-onset sporadic AD is the inheritance of an apolipoprotein E (apoE) type, which in humans occurs in three isoforms E2, E3, and E4. A great wealth of scientific evidence exists that apoE in an isoform-specific manner interacts with Aβ, as an Aβ binding protein, what promotes Aβ sequestration in the brain and self-aggregation [11]. Multiple studies carried out in ethnically various populations, have repeatedly concluded that inheritance of the apoE4 allele increases the risk of developing AD and lowers its age of presentation in an allele-dose dependent manner. ApoE4 heterozygotes have 2-4 times increased disease risk and 5-7 years earlier age of onset, whereas homozygotes have 8-12 times increased risk and age of onset on average 10-12 year earlier, than non apoE4 carriers [12,13]. It has also been shown that E4 in allele-dose-dependent manner correlated with the burden of Aβ deposits both in AD patients and in older cognitively intact subjects [14]. Since inheritance of apoE isoforms only modulates disease predisposition, apoE genotyping has no prognostic value in diagnostic assessment. Furthermore, the apoE genotype does not influence the rate of cognitive decline in already established AD [15].

The increased Aβ level in the brain and its accumulation in form of oligomers, plaques, and vascular deposits takes place for a number of years prior to the occurrence of the first
memory. At present diagnostic accuracy relies mainly on the experience of the examining physician who has to dissect whether the severity of symptoms classifies the patient as AD, MCI, or the memory performance appropriate to age i.e. the patient is healthy. Depression and excessive somatization of memory problems frequently make it difficult to separate MCI from normal aging. The diagnostic process of AD requires differentiating AD from other forms of dementia, which in the absence of disease-specific tests relies again on the expertise of the evaluating neurologist. A diagnosis scheme derived from the chief complaint of memory loss is shown in Figure 2.

Clinical assessment of patients with memory complaints and dementia is focused on exploring episodic memory function. Episodic memory refers to acquisition of new data and facts in a context of an environment in which the acquisition took place (an episode). A significant amount of time spent by a dementia expert during evaluation of a patient with amnestic memory symptoms. It is believed that longstanding Aβ toxicity results in a spectrum of secondary neuropathological changes, which include down regulation of neurotransmitter receptors, dysfunction of synapses and neurofibrillary pathology. The former include intraneuronal accumulation of paired helical filaments composed of excessively phosphorylated tau protein (P-tau) which are located both in neuronal bodies and in neurites. Neurofibrillary pathology contributes directly to the loss of substantial numbers of neurons in the AD brain [16]. Both Aβ deposition and neurofibrillary pathology are associated with chronic inflammatory reaction of microglia, which further exacerbates the loss of synapses, the pruning of neurites and the loss of neurons. The pattern and progression rate of cognitive symptoms in AD closely correlate with the magnitude of synaptic loss, neuronal dropout, and neurofibrillary degeneration in specific regions of the brain. Structures of the mesial temporal lobe (including the hippocampus and the entorhinal cortex) which are pivotal for formation of new memories and learning are affected the earliest and the most severely, followed by areas of the association cortex in temporal, parietal, and frontal lobes. Primary motor and visual cortical areas bear no synaptic or neuronal loss until very advanced stages of the disease. Our understanding of the sequential development of AD pathology and its relationship to the occurrence of cognitive deficit has been underpinned by studies of the natural course of AD pathology in subjects with Down syndrome, who due to triplication of the chromosome 21 APP gene invariably develop AD lesions. It was shown that widespread Aβ deposits precede development of neurofibrillary pathology by 15 to 20 years [17,18,19], which in turn precede the onset of cognitive decline (defined as loss of adaptive skills in Down subjects) by another 15 to 20 years [20,21].

A limited number of neuropathological data characterizing the MCI stage are available. Reports confirm the presence of widespread plaques in the neocortex [5] and indicate development of neurofibrillary pathology in the mesial temporal lobe structures [22] (Braak and Braak, 1991) with associated neuronal dropout exceeding 30% in the entorhinal cortex [23].

Evaluation of memory dysfunction and psychometric testing

Complaints about memory are among the most frequent problems reported to a neurologist by patients who uses it as a synonym for a broad spectrum of cognitive problems rather than specifically for a dysfunction of an episodic memory. At present diagnostic accuracy relies mainly on the experience of the examining physician who has to dissect whether the severity of symptoms classifies the patient as AD, MCI, or the memory performance appropriate to age i.e. the patient is healthy. Depression and excessive somatization of memory problems frequently make it difficult to separate MCI from normal aging. The diagnostic process of AD requires differentiating AD from other forms of dementia, which in the absence of disease-specific tests relies again on the expertise of the evaluating neurologist.
MCI is concentrated on retrieving episodic data from a range of several days to several years preceding the date of evaluation. Questions regarding details of activities of the previous day, recent family or political events, names of medications, and names of local or state public figures and how a patient performs in the real word setting are asked. The verdict of the evaluation is based on the expert’s experience and has to include the educational background of a patient; therefore it is to some extent subjective. In a number of highly educated and highly performing patients, making an accurate diagnostic determination based on interview alone is often impossible.

Office-based evaluation usually includes brief cognitive screening tasks. The brief standardized test most frequently used in clinical practice is the Mini-Mental State Examination (MMSE), which is a crude assessment of various areas of cognition. The same applies to the “clock drawing task” which is another brief test, frequently applied for dementia screening purposes, and provides crude measures of combined executive and visuospatial functions. Both tests are useful in documenting dementia and the MMSE is also used to follow the clinical progression of the disease during its early through moderate stages. Both tests have no value in the assessment of MCI, and may yield normal results even in early stages of AD, especially in subjects with high premorbid intelligence and education level [6].

The cognitive part of the Alzheimer’s Disease Assessment Scale (ADAS-Cog) is another well-established instrument specifically developed for assessment of AD. Although it is more complex and sensitive than the MMSE, it is rarely used in clinical practice due to the extended time required for its administration. ADAS-Cog is one of the most common metrics used in clinical trials of new AD therapeutics. Cognitive deficit in MCI and dementia can be objectively demonstrated and precisely measured with the help of a standardized psychometric test battery. Psychometric testing is most frequently used in scenarios concerning patients with MCI and early dementia and in patients with atypical presentations. In the first scenario help from neuropsychological testing is sought to differentiate among normal-to-age performance, amnestic MCI, MCI due to depression, and early AD. In the latter situation, neuropsychological testing provides a characterization of the dementia profile that allows for example to determine the co-existence of AD and vascular dementia. Psychometric testing is based on a comparison of the subject’s performance against norms for a given test adjusted for age and education of the subject. This is done by converting subjects’ test scores into “Z scores” corresponding to the number of standard deviations from a mean performance of an age and education matched control group in either a negative (below average) or positive (above average) direction. Hence, the Z score value range from -2 to 2 corresponds to 95% of the area under the normal distribution curve (i.e. mean ±2 standard deviations). The psychometric testing is standardized both in the way the test should be administered and in providing validated values for the control groups, which are used for conversion of raw test scores into Z scores.

There are no specific guidelines defining which battery of psychometric tests should be used for evaluation of MCI, AD or other dementias. Examples of tests most commonly used for evaluation of memory performance include: Wechsler Logical Memory Immediate and Delayed Verbal Recall (derived from Wechsler Adult Intelligence Scale (WAIS), Hopkins Verbal Learning Test-Revised (HVLT-R) or Rey’s Auditory Verbal Learning Test Delayed recall. The general principle for all these tests is based on providing auditory information followed by verbatim response in both immediate and delayed recall fashion. Memory based on visual acquisition of information can be tested using Rey-Osterrieth Complex Figure recall. Attention and executive functions are tested using the Digit Span Test from WAIS, the Trail Making Test, or the Symbol Digit Modalities Test. Language skills are tested using Controlled Oral Word Association (COWA-FAS), animal fluency, Boston Naming Test (BNT), or American National Adult Reading Test.

Information about visuospatial processing can be derived from copying Rey-Osterrieth Complex Figure. Consistent scores of Z values less than –1 in several tests examining the same domain raise clinical suspicion whereas scores consistently below -1.5 or -2 in the same domain are considered abnormal. Tests focusing on memory performance play a pivotal role in the evaluation of amnestic MCI. Typical patients with amnestic MCI score below –1.5 to –2 on memory tests with normal or mildly abnormal performance on tests assessing other cognitive domains. When amnestic MCI progresses to fully symptomatic AD, scores on memory tests become worse and the performance on language and executive function tests become strikingly abnormal. Down sides of psychometric testing, include the long-testing time and substantial effort both on a side of the tester and the patient. Testing is expensive requiring a trained psychometrician as well as expertise from the referring clinician to validate the results.
A number of computerized test batteries have been developed to facilitate cognitive testing. Benefits of computerized testing include inherent standardization of test administration and stimulus presentation, accurate measures of response latencies, automated comparison against individuals prior performance, as well as against age and education related norms. Two approaches to computerized test batteries for cognitive testing in the aging are pursued: adaptation of already existing tests together with their validated norms to computerized versions or development of batteries using novel interfaces and subtests. Some computerized test batteries have been already validated for application in research on aging [24]. Further development of computerized neuropsychological testing can prove beneficial in improving diagnostic accuracy and accessibility in assessment of memory disorders. Development of web based batteries would also allow for wider access to affordable testing and contribute to generating universally accessible data bases of performance. A computerized environment can also enable development of novel interfaces and subtests including application of virtual reality environments for tests investigating spontaneous memory. This would allow for validated testing of spontaneously recorded facts that appears to be more natural than forced learning and retrieval of data involved in standard format of psychometric testing.

**Role of neuroimaging**

**Structural neuroimaging**

Although structural imaging, in the form of either brain CT or MRI, is recommended for every patient undergoing evaluation for memory loss or dementia [4], these modalities play only a supportive role in the diagnosis of MCI, AD, and other dementias with neurodegenerative pathogenesis. They also detect possible co-morbidities including stroke, chronic ischemic white matter changes, areas of encephalomalacia resulting from remote brain contusions, or space occupying lesions (e.g. brain tumor or abscess), whose anatomical location could account for the cognitive deficit. A typical MRI scan for an AD patient reveals generalized cortical atrophy, enlargement of the ventricular system which is secondary to the brain atrophy, and prominent shrinkage of the mesial temporal lobe structures, which can be frequently out of proportion to the degree of generalized atrophy. Since the mesial temporal lobe structures appear to be affected the earliest and to much greater extent than other brain areas, a number of studies have investigated the presence of atrophy of the hippocampus and/or the entorhinal cortex (two prominent mesial temporal lobe structures) with raw values normalized to skull volume as potential diagnostic markers of AD.

These studies have found the presence of mesial temporal lobe atrophy to have high sensitivity (above 90%), but limited specificity (below 50%) when differentiating clinically diagnosed AD from elderly normal control [25, 26]. However, it was also demonstrated that the frequency of the hippocampal atrophy in cognitively normal subjects increases with age with prevalence of about 5% at the age 65 years and 40% at the age of 80 years, whereas the prevalence of the hippocampal atrophy in both 65 and 80 year old AD patients is above 80% [27,28]. Therefore, including the age factor in assessment of hippocampal atrophy, may improve diagnostic accuracy. It has been also shown that the presence of hippocampal and entorhinal atrophy in patients with MCI can help to predict conversion from MCI to AD [29]. Furthermore, computerized quantification of the whole brain or its sub regions (particularly structures of the mesial temporal lobe) has been used for following the disease progression and for evaluating the response to disease modifying therapeutic strategies. Most commonly these methods are based on an automated procedure entailing a modification of the boundary-shift algorithm [30].

Despite widespread application of structural imaging during the initial dementia evaluation quantification of the mesial temporal lobe structures have not been standardized or validated sufficiently to warrant routine clinical use. Visual inspection of the mesial temporal lobe atrophy is still the only technique used in clinical practice to provide more information about the possible cause of memory loss. Development of validated software allowing for automated, region-specific analysis of brain atrophy could be helpful in improving diagnostic accuracy of dementia especially when analyzed together with other data (e.g. performance on neuropsychological testing) by a decision support system.

**Metabolic imaging**

Single photon emission CT (SPECT) and Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) have been used to evaluate the presence and anatomical pattern of hypometabolic areas in the brain with the aim of confirming dementia diagnosis and in differential diagnosis support. A pattern of brain hypometabolism, which is classical for fully symptomatic AD, includes symmetrical reduction in metabolism in parietal and temporal lobes,
and to a lesser extent in the frontal lobes with characteristic sparing of primary motor and sensory cortical strips and the visual cortex [31]. In fronto-temporal dementia (FTD) abnormalities primarily involve frontal and temporal lobes and tend to be asymmetric, whereas temporal-parietal-occipital pattern of abnormalities are typical for dementia with Lewy bodies (DLB). In vascular dementia (VAD), areas of hypometabolism correlate with structural vascular lesions revealed by structural imaging. Although validation of these methods generally has shown high sensitivity, relatively low specificity poses the risk of false-positive diagnoses. FDG-PET scans are routinely subjected to visual interpretation, hence a factor of inter-rater reliability is included in the overall sensitivity and specificity.

Development and wider introduction of standardized software could enable automatic detection of hypometabolic areas and their pattern of distribution that may improve diagnostic accuracy even among radiologists who are trained as brain imaging experts. An example of this approach is the Philips System CAD4D [32] which automatically detects areas of hypometabolism based on an automatic adjustment for global glucose metabolism and supports the clinical diagnostic process by providing automated analysis of the hypometabolism pattern, comparing it against encoded patterns characteristic for various dementias. Although FDG-PET serves well as a confirmatory and differential tool for AD, it shows some limitations in the MCI stage where the disease process is primarily limited to the mesial temporal lobe, where basic metabolism is lower than in other areas of the brain. Several studies have shown that reduced hippocampal metabolism can be considered a predictor of cognitive decline and conversion from normal to MCI and then to AD, but these data come exclusively from FDG-PET studies that used a manual region-of-interest sampling method guided by co-registered MRI [33]. Recently, some attempts have been made to automate the method of delineating hippocampal region-of-interests on PET and measuring hippocampal metabolism [34]. This method allows for cross-sectional differentiation of cognitively normal subjects from MCI with overall 78% accuracy.

The first such compound was a non-toxic derivative of a thioflavin, an amyloid binding histological dye, which was dubbed Pittsburgh Compound B (PIB) and labeled with 11C for PET imaging [35]. 11C-PIB shows the greatest binding to the cortex of frontal and parietal lobes that is consistent with the burden and distribution of Aß deposits usually seen on autopsy of AD subjects. 11C-PIB shows no signal in the mesial temporal lobe as this area, despite a prominent level of neural destruction, is characterized by relatively low burden of Aß deposits.

Several thousand patients have thus far been imaged using 11C-PIB and the experience with this new biomarker is growing. A positive 11C-PIB scan in the presence of clinical dementia can confirm the contribution of AD pathology to cognitive decline, but cannot rule out other forms of dementia, which may co-exist with AD. Evaluation of patients clinically diagnosed as MCI have shown diversity in PIB binding which might help to predict their clinical course and risk of conversion to AD [36]. Most studies have found that the MCI group includes subjects with no PIB binding (these are thought not to convert to AD), subjects whose intensity of PIB binding falls between negative controls and AD, (uncertain whether they will convert to AD or not) and subjects with 11C-PIB signal comparable to that of AD patients (who are believed to convert to AD relatively soon).

Whether these concepts correlating 11C-PIB binding and likelihood of developing AD are correct is being tested in a number of ongoing longitudinal studies. Evaluations of cognitively normal patients have also confirmed various degrees of 11C-PIB in about 10-20% [37,36]. These asymptomatic subjects can be identified with levels of PIB retention that are intermediate between those typically observed in normal controls and clinically diagnosed AD patients [37]. This finding is consistent with a fact previously recognized on autopsy material that cognitively normal individuals may harbor a significant amount of Aß deposits [4,5,14]. Taken together these data underscore the notion of a slow buildup of Aß in the brain preceding the onset of clinical AD. However, since longitudinal Down syndrome subject data indicate the presence of Aß deposits for longer than a decade before the onset of cognitive decline [17,18,19], other metrics beyond merely a finding of positive PIB binding have to be developed to help effectively predict incipient disease with diagnostic accuracy. These markers may include defining a specific cut off value for the PIB binding signal and/or combining positive PIB binding with other metrics.
The former approach is justified by the fact that the burden of Aβ deposition increases exponentially in preclinical disease and plateaus during the clinical phase of the disease [38,39], thus a cut-off value indicating full saturation of PIB binding can be established. The latter approach suggests combining the positive PIB binding with FDG-PET, CSF biomarkers (see below), or cognitive deficit to demonstrate when Aβ presence starts taking its damaging toll. A longitudinal study combining PIB and FDG PET in AD patients has revealed stable PIB retention after 2 years of follow-up in patients with mild Alzheimer’s disease but progressive reduction in glucose metabolism in Aβ laden cortical areas by 20% during the period of follow-up. It was also found that cortical PIB binding intensity significantly correlates with hippocampal atrophy and episodic memory dysfunction in MCI patients [40,36]. This suggests that combining biomarkers in the setting of positive PIB binding can provide a disease predictor with enhanced accuracy, although validation studies assessing the conversion rate from MCI to AD for various biomarker scenarios are needed.

Besides 11C-PIB a number of other PET ligands are being evaluated for utility in AD diagnosis. Recently, promising results of phase two clinical trials evaluating toxicity and diagnostic efficacy of 18F labeled PIB derivative dubbed GE067 (GE Health Care) [41] and another 18F labeled Aβ binding ligand AV-45 (Florpiramine, AVID Radiopharmaceuticals) [42] were reported, heralding the possible introduction of 18F labeled Aβ PET imaging to clinical practice within next couple of years. A compound called FDDNP was shown not only to bind to Aβ but also to bind to neurofibrillary tangles [43]. Although FDDNP also nonspecifically binds to the white matter it is investigated as a ligand useful for quantifying mesial temporal lobe pathology which primarily includes neurofibrillary tangles with limited presence of Aβ deposits. Therefore, it may be useful in the diagnosis of MCI.

**Blood tests and spinal fluid markers**

The Aβ level can be quantified by sandwich ELISA in plasma and in the cerebrospinal fluid (CSF) in normal subjects. The CSF of normal subjects also contains some level of tau and phosphorylated tau (P-tau) proteins. Serum Aβ levels can be markedly increased in subjects with early onset familial AD, but show no difference between sporadic AD patients and normal subjects [44]. Significant reduction in the CSF Aβ1-42 level and significant increase in the total tau and in P-tau levels (detected using antibodies against tau phosphorylated at serine in position 181 or threonin in position 231, therefore dubbed P-tau181, or P-tau231, respectively) are seen in AD subjects compared to age-matched controls. The decreased Aβ1-42 CSF level is explained by entrapment of the aggregation-prone Aβ1-42 in plaques and vascular Aβ deposits and inversely correlates with intensity of the 11C-PIB binding on PET scan [45]. Increase in the CSF tau and P-tau levels reflect development of brain neurofibrillary pathology. Multiple longitudinal studies have shown that these changes are progressive and the CSF level of Aβ1-42 decreases while levels of tau and P-tau raise as cognitively normal subjects start displaying memory complaints (normal to MCI converters). Then the changes becomes more pronounced when patients progress to fully developed dementia (MCI to AD) [46]. The differences in CSF Aβ1-42, tau and P-tau levels between AD and older, cognitively normal subjects remain unfortunately, statistical phenomena related to differences in the mean values between groups.

A large dispersion and substantial overlap of particular subjects between AD and control groups makes it impossible to establish norms allowing for clear cut separation of AD subjects from normals. For the same reasons generating a separate category for MCI subjects is also impossible. A solution to dispersion of the marker values in particular subjects is sought by combining particular metrics to create markers with increased sensitivity and specificity. Combining levels of decreasing Aβ1-42 and increasing tau in the CSF (tau/ Aβ1-42 ratio) can attain sensitivity and specificity above 85% when distinguishing AD from controls [47,48].

Measurement of P-tau in combination with Aβ1-42 appears to be even more sensitive and specific than measurement of the total tau [49]. It has also been demonstrated that reduced tau/ Aβ1-42 and P-tau/Aβ1-42 ratios may predict conversion from normal to MCI or AD, and thus help to diagnose preclinical disease. Fagan et al. [45] demonstrated that using a ratio of CSF tau to Aβ1-42 ≥1.15 or a ratio of P-tau/Aβ1 to Aβ1-42 ≥ 0.214 as cutoff values, identified 60% of cognitively normal subjects who convert to MCI or AD within less than three years. However, the remaining patients meeting the same tau/Aβ ratio criteria continued cognitively normal over the 8 year period of study follow-up, which disqualify this approach as a clinical diagnostic tool. Nevertheless, predicting onset of AD symptoms based on tau/Aβ ratio might...
be utilized in design of clinical trials testing anti-\( \beta \) compounds targeting preclinical disease with rationale to prevent or delay onset of dementia symptoms.

**Differential diagnosis of AD**

AD is routinely differentiated from other dementing illnesses based on the pattern of cognitive deficit documented during office evaluation, structural imaging and frequently with help from psychometric testing. While dementia with insidious onset, dominated by progressive short-term memory deficit and structural imaging findings limited to atrophy are classical for AD, stepwise cognitive deterioration in multiple cognitive domains associated with clinical strokes documented by structural imaging indicates multiinfarct dementia. Progressive cognitive decline, especially data retrieval, but with relatively preserved short-term episodic memory, associated with extensive white matter disease (on structural imaging) in the setting of diabetes, hypertension, and hypercholesterolemia is indicative of another form of vascular dementia called leukoariosis or Binswanger disease, which primarily affects small arteries supplying subcortical white matter.

Unlike AD, both types of vascular dementia, multiinfarct dementia and leukoariosis, are associated with symptoms other than cognitive neurological (e.g. hemiparesis, gait dysfunction) which may occur early in the course of the disease. Fronto-temporal dementia is characterized by a distinct clinical pattern with prominent dysfunction of executive functions and language contrasting with relatively spared short-term memory. To confirm this pattern, a complex neurobehavioral evaluation and/or additional psychometric testing are required. Structural imaging may show asymmetric frontal and/or temporal lobe atrophy but since these are not routinely quantified, the role of structural imaging in fronto-temporal dementia akin to its role in AD diagnosis, remains mainly focused on ruling out space occupying lesions and assessment of a burden of vascular pathology. FDG-PET can be diagnostic for fronto-temporal dementia if it shows a pattern of hypometabolism predominant to frontal and/or temporal lobes which is often asymmetric. Fronto-temporal dementia appears to affect individuals younger than those with sporadic AD which is another discriminating factor, but is within a range of patients with familial AD, hence in cases of atypical presentation genetic testing for familial AD or/ and CSF \( \alpha \beta 1-42 \), tau and P-tau testing are performed [50]. Unlike AD, in fronto-temporal dementia an increase in tau and P-tau level is not associated with lowering of \( \alpha \beta 1-42 \). Hence the \( \tau \)/\( \alpha \beta 1-42 \) ratio is relatively less affected. Another relatively frequently observed form of dementia is dementia with Lewy bodies where the leading clinical symptom is visual hallucination, symptoms of Parkinsonism, and sensitivity to neuroleptics (both in terms of rapid cognitive decline and worsening of Parkinsonism symptoms) are additional characteristic features. FDG-PET can be helpful in differential diagnosis by showing hypometabolism in parietal and occipital lobes.

**Summary and discussion**

Although no specific test for AD exists, the diagnosis and differentiation from other dementing illnesses can be made with high accuracy and confidence by a trained neurologist. The level of confidence can be further confirmed by psychometric testing, which is time and effort consuming. However, lack of readily available accurate tests limits diagnostic effectiveness made by non-specialists. Furthermore, readily available tests are needed to separate patients with subjective memory complaints from those with true MCI (currently done by psychometric testing) and to distinguish subjects who are unlikely to develop AD from those with incipient AD.

A number of studies based on longitudinal designs showed progressive changes in structural metabolic imaging and CSF biomarkers as patients progressed from a state of being cognitively normal to age to MCI and then to AD. However, none of these biomarkers alone attains sufficient specificity and sensitivity to clearly separate normals from MCI and AD when subjected to cross-sectional analysis. Furthermore, it appears that accuracy of clinical decisions derived from particular biomarkers is higher in research studies than in clinical practice. In addition certain metrics e.g. mesial temporal lobe atrophy are not available for clinical interpretation due to lack of appropriate tools like software for automated analysis of anatomical structure volume. Therefore, two major strategic directions toward improved diagnostic accuracy appear to be logical to pursue. One is to enhance quality of the data derived from currently available markers whereas the second is to develop a clinical decision support system for dementia evaluation, which would combine the diagnostic power of particular biomarkers toward improved diagnostic precision.

A successful example of a strategy augmenting the accuracy of routinely available clinical data
is the development and validation of Philips software CAD4D [32] that allows for accurate classification of an FDG-PET pattern of glucose hypometabolism enhancing diagnostic accuracy for various types of dementia. Other examples would be developing software for the assessment of mesial temporal lobe atrophy and computerizing psychometric testing. The computerized psychometric testing could provide new diagnostic capacity in dementia by exploring novel testing interfaces and virtual reality environments. The development of a decision support system for dementia diagnosis that would combine several biomarkers can be justified by a number of studies demonstrating that joint analysis of two or more biomarkers significantly improves diagnostic accuracy [51,52, 53]. Therefore, development of decision support, designed to process multidimensional data including psychometric scores, degree of brain atrophy, pattern of glucose metabolism and CSF concentration of Aβ, tau and P-tau would greatly enhance the accuracy of early AD diagnosis and differential diagnosis of dementia. Such a system would derive statistical probabilities of diagnosis based on built-in normative values for particular biomarkers, could be operational in case not all possible biomarkers data are provided (e.g. Aβ and tau CSF level are not provided), and would seek a solution in case conflicting data are present. If properly validated, such a decision support system would allow a physician who is not an expert in dementia to arrive at correct diagnosis with the accuracy demonstrated by experts. Furthermore, the system could be further developed allowing for longitudinally tracking progression of the natural course of disease. Such additional functions would allow monitoring the efficacy of prescribed treatments, and justify their modification.

References


All tissues depend on blood supply and the blood supply depends on healthy vessels. The wall of mature blood vessels such as arteries and veins has a layered structure with the innermost layer being a single layer of endothelial cells, known also as the vascular endothelium [1]. The smallest branches of the vascular tree are the capillaries. Their size is in the 5-10 µm range [1].

The wall of a capillary consists of endothelial cells wrapped in basal lamina that hold the cells together. The wall is so thin that nutrients can pass through it by diffusion and enter the surrounding tissue [1]. Waste products can diffuse back into the blood to be carried away and removed from the body. Thus, endothelial cells not only line the entire vascular system, but also control the passage of materials into and out of the bloodstream [1].

The adult vascular endothelium is normally maintained in a differentiated, quiescent state [2, 3]. During embryonic development, and in some adult physiological and pathological events, the endothelial cells become activated, thus enabling them to acquire migratory and proliferative properties. This process is angiogenesis: the formation of new blood vessels from existing vessels [4].

Formation of angiogenic vessels requires orchestrated activation of growth factors, integrins, membrane-bound proteinases and extracellular matrix (ECM) components [2, 3, 5]. These factors stimulate extracellular and intracellular signaling pathways that regulate endothelial cell branching, sprouting, lumen formation and proliferation [5].

Anti-angiogenic factors are also produced during the angiogenic process to balance the activities of pro-angiogenic molecules through tightly controlled cell death and survival functions [3, 6-8]. In pathological conditions, that balance is disrupted, ultimately leading to formation of diseased vessels.

The subtle stage of diseased vessel formation is a primary focus of study in the field of vascular biology. It is involved in many aspects of cardiovascular disease as well as growth of tumors. This review highlights the capabilities of confocal microscopy and micro computed tomography (MicroCT) in imaging vessels, particularly with reference to growth of atherosclerotic plaque.

Imaging vasa vasorum

Angiogenesis is associated with more advanced stages of human atherosclerosis [9]. Angiogenic vessels found in plaque are thought to originate from the vasa vasorum [10]. These vessels (Latin, “vessels of the vessels”) form a network that supplies the outer (tunica adventitia) layer and middle (tunica media) layer of the larger blood vessels [11]. The vasa vasorum can expand to the second order forming many angiogenic microvessels that enter the vessel wall to provide arterial blood supply to the arterial wall [12].

The development and expansion of the second order vasa vasorum correlates with atherosclerotic lesion size in hypercholesterolemic animal models and are thought to be the conduit for nutrient supplies to the plaque [13-15]. We and others have demonstrated that inhibition of neovascularization in the vasa vasorum reduces plaque progression [13, 14, 16]. In each case the inhibitor is a breakdown products of an ECM protein that does not have anti-angiogenic function in its normal configuration [17-20].

Interestingly, others have proposed that inhibition of the expanded vasa vasorum leads to plaque progression [21]. The rationale is that loss of oxygen supply from the vasa vasorum to the vessel wall would generate a hypoxic environment, a process that stimulates factors that lead to plaque development. This was supported by data which demonstrated that an occluded vasa vasorum led to atherosclerosis [22-24]. However, these studies were performed in non-diseased
animal models, which may be quite different from those with the disease.

Animal models of atherosclerosis enable examination of disease progression, while advanced imaging technology provides a means of examining the vasculature and how its changes correlate with initiation and growth of the atherosclerotic lesion. Genetically modified mice that develop plaque when fed a high fat diet are commonly used to study these effects. We present imaging techniques that have been applied to studying atherosclerosis in a genetically modified LDLR-/-ApoB48 deficient mouse, which lacks the LDL receptor and has a mutation in the ApoB48 gene such that it is non-functional [25].

The mice were fed an atherogenic diet for 14 weeks and then treated with either saline or an angiogenesis inhibitor, rPAI-123, which is a truncated plasminogen activator inhibitor-1 (PAI-1) isoform [17, 18]. Plaque size, plaque cholesterol and vessel wall measurements showed that the inhibitor has a significant effect on reducing plaque growth and, in fact, suggest that it promotes plaque regression [16]. Confocal microscopy and micro CT techniques were used to compare the vasa vasorum in the rPAI-123 treated mice with the saline treatment group [16].

Confocal microscopy
Confocal microscopy is an optical molecular imaging technique that provides reconstruction of 3D images (Z-stacks) of specific molecules that are detected when antibodies conjugated to a fluorophore bind to the target molecule. The most common application is to apply a fluorescently-labeled antibody or molecule to a tissue sample to identify the presence of the specific target molecule [26-28]. The technique can show localization of the target molecule and provide a sense of expression levels.

Quantitative data can be obtained by analysis of confocal Z-stacks with image software such as Volocity V.3.7 (Improvision, Coventry, UK). Figure 1 demonstrates application of this approach [16]. Another approach is to probe tissue for two specific target molecules using two antibodies, each specific for a different target and each conjugated to a fluorophore that excites in a different wavelength.

This approach enables identification of co-localized target molecules, as is demonstrated in Figures 2a-c and 3a-c [16]. In this case, a FITC-conjugated antibody to CD31 was used to identify endothelial cells in the adventitia and plaque of atherogenic mice treated with either rPAI-123 or saline. A second antibody specific for smooth muscle actin was conjugated to Alexa Fluor 568 (Invitrogen). This antibody binds smooth muscle cells in the vessel wall and is an indicator of vessel maturity/stability. If the two fluorophores, conjugated to their respective antibodies, co-localize, then the emitted color spectra are seen as merged (Figures 2a-c, 3a-c). Confocal microscopy plays a very important role in correlating and validating results. For example, the confocal images shown in Figures 2 and 3 were collected as Z-stacks, then thresholded to segment out the signal of the fluorophore-conjugated antibody bound to the specific target.

Blood vessels in the plaque, adventitia, and vessel wall can be visualized by alignment of confocal Z-stacks images in a 3-D volumetric image.

The resolution of the volumetric data is increased by tri-linear interpolation to yield a 0.254 µm isotropic voxel. The reconstructed Z-stacks are then manually segmented to represent the detected co-localized probes in consecutive axial slices. Contours of blood vessels going all the way through the interpolated volumes are modeled and stacked in 3-D to provide volumetric surface representation (Figures 2d-2f) and (Figures 3d-3f) [16].

Micro Computed Tomography (MicroCT)
Micro Computed Tomography is a structural imaging modality that provides differentiation of contrast-enhanced tissues or structures with high attenuation from non-enhanced soft tissues [29, 30]. Traditional MicroCT imaging applications include screening for anatomical abnormalities [10, 31-35] as well as detection and quantification of changes in live animals [36, 37] or tissue samples removed from sacrificed animals [38].

Most current in vivo MicroCT scanners have resolutions ranging from 100 to 30 µm, while ex vivo scanners have resolutions from 30 to 1 µm. Due to its high spatial resolution, MicroCT has become an important structural imaging modality for vascular applications and angiogenesis [38]. Its high-resolution 3D representation of vascular structures directly reflects the level of angiogenesis or inhibition/development of neovascularature, providing a quantitative means for assessment of tumor growth over time.

The imaging is a two-step procedure. In the first step, 2D X-ray projections of the imaged object at different orientations of the X-ray source or object are acquired by the X-ray detector. In the second step, the acquired projections are first corrected for various image artifacts and/or
Figure 1. Vasa vasorum detected with descending aorta whole mounts. Atherogenic LDLR-/-Apob48 deficient mice were treated with either (A) saline or (B) an angiogenesis inhibitor for six weeks with continued high fat diet. Following the treatment period, mice were perfused, descending aortas removed and probed for CD31 using a FITC-labeled anti-CD31. Vasa vasorum were visualized in Z-stack confocal images of descending aorta whole mounts. Figure from Drinane et al. [16].

Figure 1a. Saline.  
Figure 1b. Angiogenesis inhibitor.

Figure 2. Blood vessels of the vasa vasorum in the descending aorta (adventitia, wall and plaque) of saline treated atherogenic mice. Atherogenic mice were treated with either saline or rPAI-123, an angiogenesis inhibitor. Descending aorta cross sections were probed for smooth muscle actin (green) and Lycopersicon esculentum lectin (red) and imaged by confocal microscope. Z-stacks were acquired at a physical resolution of 2.54 μm. To visualize blood vessels in the adventitia, vessel wall and plaque, the Z-stacks were manually segmented to represent co-localized probes in consecutive axial slices. The contours obtained were modeled and stacked in 3D for volumetric surface representation. Figure from Drinane et al. [16].

Figure 2a. Cross section of descending aorta: adventitia.  
Figure 2b. Cross section of descending aorta: vessel wall.  
Figure 2c. Cross section of descending aorta: plaque.  
Figure 2d. Blood vessels in the adventitia.  
Figure 2e. Blood vessels in the vessel wall.  
Figure 2f. Blood vessels in plaque.
Figure 4. MicroCT images of second order vasa vasorum. Atherogenic mice treated with saline or an angiogenesis inhibitor, were infused with microfil. Descending aortas were removed and scanned at 6.5 microns and three-dimensional volumetric images of vasa vasorum were reconstructed from mice receiving various diets and treatment. Figure from Drinane et al. [16].

Figure 4a.
Atherogenic diet for 14 weeks (T0).

Figure 4b.
20 weeks of atherogenic diet, saline treatment during weeks 14-20.

Figure 4c.
20 weeks of atherogenic diet, rPAI-123 treatment during weeks 14-20.

Figure 4d-f.
Reconstructed images rotated to show plaque.
distortions due to sensor nonlinearity and then used to reconstruct the final volumetric data representing the scanned object in 3D.

Depending on the parameters of the imaging protocol, a scan may take from several minutes to hours. During image acquisition, X-rays emitted by the source are attenuated as they pass through the imaged object. This proportionally reduces the original intensity of the X-rays due to absorption or scatter of photons [29, 30]. Objects with low attenuation properties, like most soft tissue, allow most of the X-rays to pass through the object unabsoed and arrive at the detector on the other end.

However, if the imaged object has high attenuating properties, for example bone, fewer X-rays will have the kinetic energy to arrive at the detector. In imaging of diseased vessels with MicroCT, we are interested in the vascular structures whose attenuation properties differ very little from the surrounding soft tissue. Consequently, vascular MicroCT requires the use of contrast agents such as Fenestra, Microfil, and Bismuth. The contrast agents either circulate in the blood pool or are used to replace it.

Figure 4a-c shows an example of second order vasa vasorum detected by MicroCT [16]. The contrast agent selected for this procedure consisted of a mixture containing silicone rubber compound Microfil Blue (1 ml), Microfil Clear (3 ml), diluent (8 ml) and curing agent (0.6 ml) (Flow Tech, Inc., Carver, Massachusetts). The mixture is infused through an aortic cannula into the ascending aorta of atherogenic mice treated with saline or the anti-angiogenic protein.

Once the microfilm polymerizes, the descending aortas are removed for ex vivo microCT scanning followed by 3-D reconstruction of the scanned images. In these experiments, the scanning protocol was optimized for soft tissue imaging before the mice were scanned at a voltage and current of the X-ray tube of 52 kV and 118 mA respectively. The X-ray exposure time for a single projection was set to 1700 ms and a total of 720 projections per scan were acquired at the maximum resolution of the X-ray detector, 6.5 microns. Following the scan, three-dimensional volumetric images were reconstructed from the acquired two-dimensional projections without averaging, yielding a final voxel size of 6.5 microns and data volumes of approximately 1.5 GBs.

Differences in the density of the vasa vasorum among treatment groups are clearly visualized. The correlation between the vasa vasorum density and plaque size were made possible by rotating the MicroCT images to visualize plaque in the luminal side of the descending aorta (Figures 4 D-F) [16].

**Conclusion**

Confocal microscopy and MicroCT are two of the techniques available for imaging angiogenesis. Confocal microscopy provides targeted imaging of specific biological molecules involved in angiogenesis, while MicroCT provides high-resolution structural imaging. As such, the two techniques are complementary. They can be combined with the use of genetically modified mice to perform studies that investigate mechanisms of disease. Further challenges include the development of novel contrast agents and better imaging hardware that can bridge the gap between sensitivity and resolution that exists in the functional imaging modalities today. Another important challenge is the interpretation and processing of the acquired data.


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Investigations and research

Optical imaging of the breast: clinical research using an experimental Diffuse Optical Tomography system

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Optical imaging for breast cancer can be performed either by relying on intrinsic breast tissue contrast alone (mapping hemoglobin, water, and lipid content) or with the use of exogenous imaging agents that accumulate at the tumor site, either by targeting cancer-specific molecules or by extravasation due to leaky tumor vasculature.

The light used in optical imaging is commonly monochromatic and in the near-infrared (NIR) range, permitting imaging up to several centimeters deep in soft tissue. Different tissue components have unique scattering and absorption characteristics for each wavelength. The use of a single wavelength gives some diagnostic information on the tissue of interest, e.g. if there is high total blood content, associated with angiogenesis. By combining data from multiple wavelengths, more precise information can be obtained on relative concentrations of oxy- and deoxyhemoglobin, lipid, and water in the tissue (spectroscopic imaging). This may allow for better discrimination between malignant and benign tissue. With the use of exogenous imaging agents, such discrimination may be improved even further, especially with imaging agents specifically targeted to cancer-associated molecular changes (molecular imaging).

Although X-ray mammography reduces mortality significantly, due to earlier cancer detection [5, 6], overall sensitivity is moderate (~75%), resulting in a number of missed breast cancers [7]. In addition, the positive predictive value of X-ray mammography is relatively low and discrimination between benign and malignant lesions with further diagnostic tests is difficult, leading to a high number of unnecessary biopsies [3].

MRI has very high sensitivity (> 95%) and is clinically used as an adjunct to X-ray mammography in high risk patients [8, 9]. However, MRI generally only allows detection and classification of lesions from 5 mm upwards, and has a high false-positive rate [10].

Optical imaging is being pursued as an adjunct to the current imaging modalities due to its potential to provide biophysical and molecular information on breast tissue.

In this overview of previously published data [11-13] we shall summarize our first clinical experiences in the evaluation of an experimental Diffuse Optical Tomography (DOT) system dedicated for breast imaging. We initiated the evaluation under optimal settings in small patient groups. First, we evaluated the potential of optical breast imaging to discriminate between benign and malignant tissue. For this we used only data on intrinsic tissue contrast at four different NIR wavelengths without spectroscopic analysis. In this study we also assessed inter- and intra-observer agreement of DOT image interpretation (study 1) [11].

Optical imaging has some intrinsic advantages over other breast imaging modalities.

Optical imaging has the potential to provide biophysical and molecular information.
Secondly, we investigated the added value of spectroscopic analysis for imaging well-defined benign cysts, by combining all information from the four wavelengths (study 2) [12]. Finally, we evaluated optical breast imaging using escalating doses of a novel fluorescent non-targeted imaging agent (Omocyanine, Bayer Schering Pharma, Berlin, Germany) in patients highly suspected of breast cancer (study 3) [13].

Materials and methods

Patients
A total of 48 patients (mean age 52, range 22 to 85) were recruited for the three studies between October 2006 and September 2007 from the University Medical Center Utrecht and the Diakonessenhuis Utrecht. Each study had different inclusion and exclusion criteria tailored to the research questions. Detailed criteria have been given in previous publications [11-13] but all women had to be diagnosed with a breast lesion on X-ray mammography and/or ultrasound.

Study 1 included women with BI-RADS (Breast Imaging Reporting and Data System) 2-5 lesions. Study 2 comprised women with benign cysts (BIRADS 2) and Study 3 comprised women with highly suspicious lesions (BIRADS 4-5). All study protocols were approved by the institutional ethics committees, and written informed consent was obtained from all patients.

Imaging protocols
Diffuse optical tomography (DOT) scans were performed on an experimental DOT system (Figure 1). The patient was placed in prone position on the scanner bed with one breast suspended in a size-matched cup. The scanning unit of the DOT system consists of a cup with a total of 507 optical fibers mounted on the surface. The light of four continuous-wave solid-state lasers is directed into the cup via 253 source fibers, which are interleaved with 254 detector fibers on all sides of the cup. For each scan, the cup was filled with a matching fluid that has similar optical properties to those of the average breast. This matching fluid provides a stable optical coupling between the fibers and the breast, and eliminates optical short cuts of the diffuse light around the breast.

During imaging, the breast was sequentially illuminated with continuous wave near-infrared light from all source positions. Light emanating from the breast was detected in parallel for each source position. Images were obtained at four discrete wavelengths (690, 730, 780, and 850 nm). Each breast was scanned separately. During each scan the system was operated in two modes: transmission and fluorescence mode (the last used for the study with Omocyanine).

The transmission measurements were intended to acquire information on the optical absorption and scattering properties of the breast at four wavelengths. The fluorescence measurements were performed with excitation at one wavelength (730 nm), and the emitted fluorescent signal was detected at a different wavelength (> 750 nm) while the laser light was blocked by filters in the detection path. The duration of the examination was approximately one minute per wavelength in the transmission mode, and five minutes for the fluorescence mode, making a total of nine minutes per breast.

After optical data acquisition, three-dimensional absorption images were reconstructed at each of four wavelengths (based on the Rytov-approximation [14]), as well as three-dimensional fluorescence images for the studies with Omocyanine (based on the Born approximation [15]). In the spectroscopic study of patients with cysts, optical information from the four wavelengths was combined to convert the absorption coefficients into hemoglobin, oxy-hemoglobin, water, and lipid concentrations [12]. This information was used to generate three-dimensional enhanced-water maps, with high signal intensity for high water concentration, and three-dimensional enhanced-blood maps, with high signal intensity for high blood concentration (and low signal intensity in case of blood-depletion).
MRI of the breast was performed on a 3.0T clinical MR system (3.0T Achieva, Philips Healthcare, Best, the Netherlands) using a dedicated four-element SENSE compatible phased-array bilateral breast coil (MRI devices, Würzburg, Germany). Fat-suppressed T1-weighted, T2-weighted, and dynamic T1-weighted images were acquired according to routine clinical protocols. MRI was used as a benchmark for the optical image analysis, because both MRI and DOT are tomographic imaging techniques that provide threedimensional data and in which patients are positioned in a similar way. In addition, MRI gives high-resolution anatomical information with excellent soft tissue contrast, which made it our method of choice to use for comparison with optical imaging and to derive lesion location and size.

Data analysis and study-specific methodology

Study 1. Discrimination of malignant and benign lesions
Per lesion, a region of interest (ROI) was drawn on the absorption image for all three wavelengths at the site of the lesion, derived from the axial MRI slice that showed the lesion at its maximum diameter. For comparison, an identical ROI was drawn at an exactly mirrored location on the image of the contralateral breast, where no lesion was detected by MRI.

The visibility of the lesions on DOT was assessed both quantitatively and qualitatively. Quantitative contrast values were obtained by dividing the mean absorption coefficient within an ROI by the mean absorption of the background on that specific tomographic slice, including the rest of the breast but excluding the lesion. Furthermore, all images were anonymized, placed in random order, and independently scored by two readers separately, blinded for other examinations as well as pathology results. These two readers allotted qualitative contrast scores for every ROI, on a scale from −4 to +4, where: 0 = no visibility; 1 = slight heterogeneity; 2 = moderate contrast, but less than other structures on the image; 3 = contrast comparable to that of other structures; 4 = major contrast. A minus sign was used for signals lower than the background (less absorption), and a plus sign for higher signals (more absorption).

Images were scored again after three months in a second independent reading by the two investigators. Intra- and interobserver agreements were calculated using kappa statistics and intraclass correlation coefficients. Discriminatory values for presence of malignancy were determined by Receiver Operating Characteristic (ROC) analyses. Cancer detection rates were calculated using a qualitative score of ≥2 as a cut-off.

Study 2. Spectroscopic analysis of benign cysts
The visibility of the cysts on DOT was assessed in a qualitative manner both for the absorption images and for the spectroscopic reconstruction images. When the values at the lesion site (derived from MRI) were lower than those of the surrounding tissue the cyst was considered to be visible (visibility score < -2). The physiological enhanced-water and enhanced-blood maps were evaluated and compared to MRI data in the axial plane. Maximum diameters of the cysts were estimated on the physiological maps from the full width at half maximum of the signal intensity through the center of the cyst region, and compared to the maximum diameters measured on the MR images. The Bland Altman method was used to measure the agreement of lesion size between the MRI and DOT measurements [16]. The Pearson correlation coefficient was calculated to estimate the correlation between the two methods.

Study 3. Dose-escalation of Omocyanine, a novel fluorescent imaging agent
The study protocol comprised three periods:
• a screening period to verify inclusion criteria
• an imaging period, during which the study agent was administered in a single intravenous injection (0.01, 0.02, 0.05, or 0.1 mg/kg bodyweight) and optical images were acquired at five different time points (up to 24 hours after injection)
• a follow-up period of one week to monitor adverse events.

Separate ROIs were drawn on a single optical image slice at the lesion location derived from the MRI scan for all fluorescent images over time (1, 2, 4, 8, 24 hours after injection). For comparison, a similar ROI was drawn for each time point at the mirror image lesion location of the contralateral breast, where no lesion was found on MRI. The mean fluorescence intensity was determined for all the ROIs. To calculate the lesion-to-background ratio, this value was divided by the mean fluorescence of the background, which included the rest of the breast on that slice except for the lesion and the nipple (that showed very high fluorescence intensity). The same was done for the mirror image ROI to compare the values in the ipsilateral and contralateral breast. Absorption images obtained before contrast administration were also assessed
for lesion visibility. Lesion-to-background ratios were calculated in the same way as for the fluorescence images.

To assess the pharmacokinetics of the new imaging agent in the breast, the uptake over time was compared quantitatively on the fluorescence images for the different ROIs in the ipsi- and contralateral breast, and the optimal imaging time point was estimated.

Final diagnosis
The reference standard for final diagnosis of all solid lesions was histopathology, but for the benign cysts and the healthy contralateral breast (mirror image) the reference standard was MRI. The patients diagnosed with benign cysts received a follow-up mammography and ultrasound examination after six months.

Results
Not all of the 48 patients were able to undergo the entire imaging protocol. We decided to exclude the patients that did not undergo MRI (5 patients), since we used MRI as a benchmark for all optical image analyses. Also, technical limitations of the DOT system, i.e. leakage of matching fluid from the system (6 patients) and the inability to measure lesions located close to the patient’s chest wall due to the geometry of the cup (8 patients), resulted in the exclusion of recruited patients for some of our analyses. For the fluorescent imaging agent study (Study 3), one patient had to be excluded due to renal failure detected during the screening period.

To answer our first research question on the potential to discriminate between benign and malignant tissue based on intrinsic contrast, 17 women (mean age 54, range 22 to 85) diagnosed with 18 BI-RADS 2-5 breast lesions on mammography/ultrasound were included. For the second study, using spectroscopic analysis for benign cysts imaging, we included eight women (mean age 48, range 38 – 60) diagnosed with a total of 20 cystic breast lesions. For the third study, the dose escalation of a new fluorescent imaging agent (Omocyanine), we included 11 women (mean age 54, range 23 to 81) diagnosed with a 1-5 cm BI-RADS 4-5 breast lesion on mammography.

Study 1. Discrimination of malignant and benign lesions
Here we studied a patient population with different types of breast lesions with the DOT system [11]. Under optimal settings we:
• investigated optical properties of different types of breast lesions
• assessed the potential to discriminate between benign and malignant tissue with a known lesion position
• assessed intra- and interobserver variability of the obtained results.

Of the 18 lesions included in the study, ten lesions were diagnosed as malignant by histopathology after surgery (9 invasive ductal carcinomas and 1 invasive lobular carcinoma) with a median diameter of 23.5 mm (range 13 – 54 mm). Two lesions were confirmed to be benign fibroadenomas by large core needle biopsy, with diameters of 13 and 24 mm. Six lesions were diagnosed as benign cysts by ultrasound and MRI, with a median diameter of 28.5 mm (range 20 – 40 mm). The 18 mirror image regions of the contralateral breasts appeared as normal breast tissue without lesions on DCE-MRI.

A typical example of a DOT image is shown in Figure 2. The visibility of the lesions on DOT was assessed both quantitatively and qualitatively. Quantitative scores are shown in Table 1.

Median absorption scores for malignant lesions were higher (2.15 to 3.03 across wavelengths) than those for fibroadenomas (1.30 to 1.75), cysts (0.13 to 0.23), and the contralateral normal breast (1.16 to 1.39). Qualitative visibility scores are shown in Table 2. Scores for malignant lesions were higher (with medians between 2 to 4 across wavelengths) than for fibroadenomas (0 to 2), cysts (all -4), and the contralateral normal breast (all 0).

Discriminatory values for presence of malignancy were determined by Receiver Operating Characteristic (ROC) analyses. Areas under the ROC curves (AUC) ranged from 0.92 to 0.95 for quantitative scores, and from 0.97 to 0.99 for qualitative scores (with both observers having exactly the same AUC). Cancer detection rates for the four wavelengths (690, 730, 780, and 850 nm, respectively) were 70%, 80%, 80%, and 70% for Observer 1; and 60%, 70%, 70%, and 60% for Observer 2, using a qualitative score.
<table>
<thead>
<tr>
<th>Wavelength</th>
<th>Lesion type</th>
<th>No lesion (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Malignant (n=10)</td>
<td>Fibroadenoma (n=2)</td>
</tr>
<tr>
<td>690</td>
<td>3.03 (1.91 to 3.40)</td>
<td>1.75 (1.36 to 2.14)</td>
</tr>
<tr>
<td>730</td>
<td>2.94 (1.74 to 6.31)</td>
<td>1.50 (1.01 to 1.98)</td>
</tr>
<tr>
<td>780</td>
<td>2.57 (1.54 to 3.22)</td>
<td>1.36 (1.13 to 1.58)</td>
</tr>
<tr>
<td>850</td>
<td>2.15 (1.27 to 2.55)</td>
<td>1.30 (1.24 to 1.35)</td>
</tr>
</tbody>
</table>

Table 1. Study 1. Median (range) of quantitative absorption score according to lesion presence and lesion type [11].

Qualitative visibility was scored on a scale from -4 to +4, where: 0 = no visibility; 1 = slight heterogeneity; 2 = moderate contrast, but less that other structures; 3 = contrast comparable to other structures; 4 = major contrast; a minus sign was used for signals lower, and a plus sign for signals higher than the background.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Imaging agent dose (mg/kg)</th>
<th>Lesion type</th>
<th>Lesion diameter on MRI (mm)</th>
<th>Detected by DOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>0.01</td>
<td>IDC</td>
<td>25</td>
<td>No *</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>0.01</td>
<td>ILC</td>
<td>29</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>0.01</td>
<td>IDC</td>
<td>18</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>0.02</td>
<td>IDC</td>
<td>24</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>0.02</td>
<td>IDC</td>
<td>74</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>0.02</td>
<td>IDC</td>
<td>34</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>0.05</td>
<td>IDC</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>0.05</td>
<td>FA</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>0.05</td>
<td>IDC</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>0.1</td>
<td>ILC</td>
<td>51</td>
<td>No *</td>
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<tr>
<td>11</td>
<td>55</td>
<td>0.1</td>
<td>IDC</td>
<td>13</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 3. Study 3. Overview of results per patient for optical imaging with imaging agent [13].

IDC – Invasive Ductal Carcinoma; ILC – Invasive Lobular Carcinoma; FA – Fibroadenoma;
* in these cases the lesion was located close to the patient's chest wall and physically too far above the upper optical fibers in the cup to be measured by the current DOT system.
of ≥ 2 (at least moderate contrast) as a cut-off. Between 0% and 22% false positive results were found per wavelength for both observers.

Intra- and inter-observer agreements for the qualitative scores were excellent. The intra-observer agreement was assessed with three months between the readings, and the intraclass correlation coefficient was 0.978 for Observer 1 and 0.987 for Observer 2, whereas the kappa statistic was 0.88 for both observers (combining the data from all wavelengths). With regard to interobserver agreement, the intraclass correlation coefficients varied between 0.96 and 0.98 over the four wavelengths and the kappa statistics varied between 0.77 and 0.95.

Study 2. Spectroscopic analysis of benign cysts
A total of 20 benign cysts were included in the study. Maximum lesion sizes ranged from 8 to 40 mm (median size 21 mm).

Based on the absorption images only, 6/20 (30%) benign cysts were clearly distinguishable with DOT, showing marked lower absorption compared to surrounding tissue. When the spectroscopically derived physiological enhanced-water and enhanced-blood maps were evaluated and compared to the MRI data, 13/20 (65%) benign cysts were evident on DOT. The enhanced-water and enhanced-blood maps showed high water content and low total hemoglobin content at the position of these cysts (Figure 3).

Detected lesions after spectroscopic analysis had maximum diameters of 15 mm and larger. Two cysts with diameters of 8 and 10 mm were not visible with DOT. Five cysts that were located close to the chest wall were not detected because they were outside the field of view of the current system. There was good agreement between optical size measurements and MRI (Pearson correlation coefficient 0.7; p<0.01). DOT overestimated the lesion size on average by 2.5 mm (mean difference MRI-DOT, -2.5 mm; 95% confidence interval, -6.4 to 1.3).

Study 3. Dose-escalation of Omocyanine, a novel fluorescent imaging agent
Following initial evaluations of the system without imaging agent, we tested its ability for optical imaging with contrast agent using a novel fluorescent imaging agent in a patient group highly suspected of breast cancer [13]. Eleven women (mean age 54, range 23 to 81) diagnosed with a 1 – 5 cm BI-RADS 4/5 breast lesion on mammography were included in the study.

Histopathology results showed invasive ductal carcinoma in eight patients (median lesion diameter 21 mm), invasive lobular carcinoma in two patients (median lesion diameter 40 mm), and a benign fibroadenoma (lesion diameter 15 mm) in one patient (Table 3).

In the lowest dose group (0.01 mg/kg), lesions were detected in two patients on the fluorescence DOT images. In the second dose group (0.02 mg/kg), all three lesions were detected by DOT. No lesions were detected in the two highest dose groups (0.05 and 0.1 mg/kg). In total, five of the ten malignant lesions (50%) were visualized by DOT using the fluorescent imaging agent. The locations of lesions detected with DOT showed excellent agreement with MRI. Lesion location on the optical images was reproducible over time (Figure 4). Optimal lesion-to-background signals were obtained after eight hours, ranging from 1.8 to 2.8 for the detected lesions. Non-specific fluorescent
enhancement of glandular tissue was clearly visible on all optical fluorescence images, starting after 30 minutes and still evident 24 hours later (Figure 4). The imaging agent signal evidently increased with dose. Higher concentrations were problematic for the current reconstruction algorithm. This algorithm assumed absorption by the imaging agent to be significantly lower than tissue absorption, an assumption that did not hold true for the higher doses. The absorption images obtained with DOT before the contrast administration showed higher attenuation in the lesions than in the surrounding normal parenchyma (mean lesion-to-background ratios 1.4–2.6).

No adverse events related to the study agent were observed during this study.

Discussion

In our first system evaluation studies we have shown that, based on intrinsic breast tissue contrast alone, the DOT system was able to visualize cysts and elucidate their high water and low total hemoglobin content by spectroscopic analysis, and has the potential to discriminate malignant from benign breast tissue by assessing optical properties of the tissue in a reproducible quantitative and qualitative way. Using a low dose of the fluorescent imaging agent Omocyanine, the DOT system has the potential to safely visualize malignant breast tumors in patients. During the course of these studies, we encountered several limitations of our experimental DOT system. First, the system was unable to visualize some breast lesions located close to the chest wall. These lesions were most likely physically located too far above the upper optical fibers in the cup to influence the light pathways. Advances in cup geometry are feasible and would result in improved visualization of these lesions.

Secondly, the spatial resolution of DOT is poor, resulting in a lower signal-to-noise ratio and limited detectability for small lesions. Lesion detection seems to be more difficult and size measurement less precise in the center of the cup compared to the edge of the cup, because longer light pathways decrease spatial resolution. This may be a limitation in large breasts with centrally located lesions. Optical data acquisition using slab geometry with slight breast compression could offer a solution to this problem.

Cancer detection rates in our study were between 60% and 80% for each wavelength separately, using a cut-off value of 2 (at least moderate contrast visible compared to surrounding structures).

We have to note that we used knowledge of lesion localization from MRI for the optical data interpretation, which may have resulted in limited false positive findings with consequent overestimation of the ROC analyses. The detection rates and false positive results can probably be improved when combining information of four different wavelengths in one model.

At present, our spectroscopic model works well for cysts but is still being optimized for different lesion types. However, based on current literature, the diagnostic performance of optical imaging without imaging agent is likely inadequate for clinical application [17, 18]. We think that the development of imaging agents that target specific molecular changes associated with breast cancer formation will provide the opportunity for clinical success of optical breast imaging.

With the use of target-specific imaging agents (i.e., molecular imaging), optical imaging could be a valid candidate for the early detection of breast cancer, e.g., in young women with dense breasts who are at increased risk for breast cancer and for whom X-ray mammographic screening has very limited sensitivity due to the tumor-camouflaging projection of this dense glandular tissue [7, 19]. NIR light is likely to be far less hampered by this glandular tissue. Other potential applications of this technique may be the selection of appropriate adjuvant treatment and evaluation of response to such treatment in breast cancer patients.

Important advantages of optical imaging in the molecular imaging arena are that it uses no radioactive components (unlike PET and SPECT), and that its sensitivity for probe detection is very high (possibly in the nanomolar to the 100 picomolar concentration range) as compared with MRI (micromolar to millimolar range).

As of now, however, no targeted optical imaging probe is available for clinical use. This is in contrast to PET or SPECT, where various radioligands are available, for example targeting human epidermal growth factor receptor 2 [HER2], epidermal growth factor receptor [EGFR], and carcinoembryonic antigen [CEA] [20-22]. On the other hand, optical probes are abundantly used in preclinical research settings [23-25].
Critical hurdles in the introduction of such probes for human use include molecular target identification and translation of preclinical evaluated probes to the clinical setting. In the Netherlands, efforts are being made within the Center for Translational Molecular Medicine to develop new optical molecular imaging agents for breast cancer. These agents will be evaluated in an experimental setting using both animal models and the new DOT system, aiming for eventual translation to a clinical setting (MAMMOTH project) [26].

In conclusion, we have described some first steps in the evaluation of a new experimental system for diffuse optical tomography of the breast. Further developments in system design and relevant molecular imaging agents could eventually allow for this technique to be used in routine clinical practice.

Further refinements could eventually lead to optical imaging being used in routine clinical practice.

References


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www.philips.com/medicamundi
The art of medical imaging: Philips and the evolution of medical X-ray technology
J.A.M. Hofman

Philips and its associated companies have been involved in the development of X-ray technology since the very beginning, and many significant developments were pioneered by Philips. This article presents some of the most important technological innovations over more than a century, from the first rotating anode X-ray tubes to the clinical image intensifier and the digital revolution. Each of these innovations has had far-reaching implications for clinical practice, from diagnosis to advanced interventional procedures.

Non-invasive quantification and characterization of coronary plaque: the role of multidetector CT
M.G. Dalager, H.E. Bøtker, M. Bøttcher, T.B. Ivanc, M.E. Olszewski, and K. Norrgren

Coronary artery disease (CAD) remains the leading cause of death in the developed countries, with more than half of the deaths occurring in individuals who were asymptomatic prior to an acute coronary event. Intravascular ultrasound (IVUS) is the current gold standard for imaging atherosclerotic plaque in vivo, but it is limited to the presence of favorable anatomy and only applied in symptomatic individuals. Multidetector CT angiography offers a non-invasive way method for evaluating the lumen and the vessel wall, while CT Plaque Analysis on the Brilliance Workspace enables quantification and characterization of the plaque composition within the coronary tree.

Non-invasive cardiac imaging of morbidly obese patients using the Brilliance iCT scanner

Assessment of the morbidly obese (body mass index greater than 40) patient presenting with chest pain is often challenging. Traditional imaging of the coronary arteries by invasive cardiac catheterization or contrast-enhanced cardiac CT angiography is complex, due to limitations imposed by the decreased signal-to-noise ratio, which can impair reliable diagnosis. The recently introduced Brilliance iCT scanner delivers improvements in speed, power and coverage compared with the existing generation of CT systems, thus enabling more reliable diagnostic imaging in this difficult population. The authors present their preliminary experience in cardiovascular CT imaging of morbidly obese patients with the Brilliance iCT scanner.

Pediatric cardiology with the iE33 echocardiography system
G. Tulzer

The Philips iE33 System has been in use in the Department of Pediatric Cardiology of the Children’s Heart Centre Linz since October 2006. It is used for pre- and postoperative assessment of neonates and children with congenital heart disease, for evaluation of dyssynchrony and myocardial function as well as for prenatal (fetal) echocardiography. This article describes the main features of this high-end ultrasound system, and reports on the author’s experience in the setting of a pediatric cardiology clinic.

Ultrasound-triggered image-guided therapy
C. Moonen, N. de Jong, O. Steinbach, M. Böhmer and S. Langereis

Medical imaging technologies are becoming an integral part of therapeutic interventions. One emerging application is ultrasound-triggered drug delivery, and delivery vehicles and image guidance techniques are being developed for this purpose. This article discusses advances in temperature- and pressure-sensitive agents for ultrasound-triggered, image-guided local drug release. Temperature-sensitive liposomes with incorporated drugs and MRI imaging labels are described, together with pressure-sensitive microbubbles loaded with various drugs, and specific ultrasound imaging and release characteristics. The authors conclude with an overview of the potential applications of both types of delivery vehicle for different drug formats, such as small molecules and nucleic-acid based therapeutics.

Myocardial perfusion imaging: past, present and future
J.K. O’Donnell, P. Wojtylak and P.F. Faulhaber

Myocardial perfusion imaging is an aid to identifying those patients who are at risk of myocardial infarct or death. In this article the authors present an overview of the development of myocardial perfusion imaging, beginning with planar imaging of thallium-201 uptake, and going on to the present day and beyond. Particular attention is paid to the introduction of single photon emission computed tomography (SPECT) and positron emission tomography (PET), with a comparison of their strengths and weaknesses, as well as the combination of the two techniques in PET-CT and SPECT-CT scanner units.
Toward improving the diagnosis of Alzheimer’s Disease
M.J. Sadowski, J. D. Schaffer and E. Silfen

Alzheimer’s disease (AD) accounts for the majority of dementia cases with an estimated prevalence of 5.3 million of cases in the USA and over 25 million worldwide. There is no specific diagnostic test to distinguish AD from other less frequent dementing illnesses. We present a discussion of current challenges in making dementia diagnoses, and make the case that there is an opportunity for computer-based decision support systems that are able to enhance the analysis of available biomarkers (some currently only available in research settings) and combine the evidence from multiple markers.

Imaging diseased vessels
M. Mulligan-Kehoe and L. Zagorchev

Confocal microscopy and MicroCT are two of the techniques available for imaging angiogenesis. Confocal microscopy provides targeted imaging of specific biological molecules involved in angiogenesis, while MicroCT provides high-resolution structural imaging. As such, the two techniques are complementary. They can be combined with the use of genetically modified mice to perform studies that investigate mechanisms of disease. This article presents the application of these techniques in a mouse model of atherosclerosis to distinguish between untreated diseased vessels and those that receive an angiogenesis inhibitor.

Optical imaging of the breast: clinical research using an experimental Diffuse Optical Tomography system

Optical breast imaging is a promising technique for breast cancer diagnosis and treatment due to its potential to provide biophysical and molecular information on breast tissue. Optical breast imaging can be performed either by relying on intrinsic breast tissue contrast alone (mapping blood, water, and fat content), or by using exogenous imaging agents that accumulate at the tumor site. Both of these techniques are illustrated in this overview of our clinical experiences with an experimental Diffuse Optical Tomography (DOT) system. The three clinical studies summarized in this article have been published previously.

L’art de l’imagerie médicale:
Philips et l’évolution de la technologie des rayons X
J.A.M. Hofman

Philips et ses filiales font partie des pionniers à l’origine du développement de la technologies des rayons X et de nombreux progrès en la matière ont été introduits par Philips. Cet article présente une rétrospective sur plus d’un siècle des innovations technologiques les plus importantes, des premiers tubes à rayons X à anode tournante jusqu’aux amplificateurs de luminance et à la révolution de l’imagerie numérique. Chacune de ces innovations a contribué à l’évolution profonde des pratiques cliniques, du diagnostic aux procédures avancées de radiologie interventionnelle.

Quantification et caractérisation non invasives des plaques coronariennes: le rôle de la TDM multidétecteur
M.G. Dalager, H.E. Barker, M. Battcher, T.B. Ivanc, M.E. Olaszewski et K. Norrgren

Les coronaropathies restent la cause majeure de décès dans les pays développés. Dans la moitié des cas, les victimes ne présentaient aucun signe avant-coureur d’un accident coronarien aigu.
À l’heure actuelle, l’échographie intravasculaire est la technique d’imagerie de référence pour l’acquisition d’images des plaques d’athérome in vivo ; elle connaît cependant des limites d’application en fonction des régions anatomiques et peut uniquement être employée chez des patients symptomatiques.
L’angiographie par TDM multidétecteur propose une méthode d’imagerie non invasive permettant d’évaluer la lumière et la paroi vasculaire. La fonction d’analyse de la plaque par TDM disponible sur Brilliance Workspace permet quant à elle de quantifier et de caractériser la composition des plaques dans l’arbre coronaire.

Scanner Brilliance iCT: l’imagerie cardiaque non invasive désormais applicable chez les patients atteints d’obésité morbide

La prise en charge des patients atteints d’obésité morbide (indice de masse corporelle supérieur à 40) et présentant des douleurs thoraciques s’avère souvent complexe. Les techniques d’imagerie coronarienne classique, par cathétérisme cardiaque invasif ou angiographie cardiaque par TDM avec injection de produit de contraste, sont difficiles à mettre en œuvre en raison d’un rapport signal-bruit plus faible qui peut affecter la fiabilité du diagnostic.
Le scanner Brilliance iCT commercialisé dernièrement offre des performances optimisées en termes de vitesse, de puissance et de surface d’acquisition par rapport aux systèmes TDM de la génération précédente, augmentant ainsi la fiabilité de l’imagerie diagnostique chez ces patients difficiles à examiner. Les auteurs présentent leurs conclusions preliminaires sur l’imagerie cardiovasculaire par TDM, avec le scanner Brilliance iCT, chez les patients atteints d’obésité morbide.
L'échocardiographe iE33 au service de la cardiologie pédiatrique
G. Tulzer


Traitement par ultrasons focalisés guidé par l’image
C. Moonen, N. de Jong, O. Steinbach, M. Böhmer et S. Langereis

Les technologies d’imagerie médicale revêtent une importance croissante dans le cadre des interventions thérapeutiques. L’une des applications émergentes consiste à administrer des médicaments via l’application d’ultrasons focalisés. Dans cette optique, de nouveaux modes d’administration et des techniques de guidage par l’image sont actuellement mis au point. Cet article passe en revue les progrès réalisés dans le domaine des agents thermosensibles et sensibles à la pression pour l’administration locale de médicaments par ultrasons focalisés avec guidage par l’image. Il décrit le principe de fonctionnement de liposomes thermosensibles contenant des médicaments et de marqueurs IRM qui sous forme de micro-bulles sensibles à la pression libèrent les agents thérapeutiques ainsi que l’imagerie ultrasonore spécifique et ses caractéristiques. Les auteurs concluent sur une présentation générale des applications possibles de ces deux types de modes d’administration sous diverses formes pharmaceutiques, telles que des traitements à base de micro-molécules ou d’acides nucléiques.

L'imagerie dans le cadre de la perfusion myocardique: passé, présent et futur
J.K. O’Donnell, P. Wojtylak et P.F. Faulhaber

Le recours à l’imagerie dans le cadre de la perfusion myocardique constitue un moyen d’identifier les patients présentant un risque d’infarctus du myocarde, voire de décès. Cet article présente une vue d’ensemble de l’évolution de l’imagerie dans le cadre de la perfusion myocardique, depuis les débuts de l’imagerie planaire avec la fixation du thallium 201 jusqu’aux techniques actuelles et aux innovations à venir. L’introduction de la gammatomographie (SPECT) et de la tomographie par émission de positons (TEP) fait l’objet d’une analyse plus approfondie comparant notamment leurs atouts et leurs points faibles respectifs. Une description des scanners TEP-TDM et SPECT-TDM combinant ces deux techniques est également proposée.

Maladie d’Alzheimer: une méthode diagnostique plus fiable en perspective
M.J. Sadownik, J. D. Schaffer et E. Silfen

La maladie d’Alzheimer est à l’origine de la plupart des cas de démence, avec une prévalence estimée à 5,3 millions de cas aux États-Unis et plus de 25 millions de cas dans le monde entier. Aucune épreuve diagnostique spécifique ne permet actuellement de distinguer la maladie d’Alzheimer des autres maladies moins fréquentes pouvant être à l’origine de la démence. Nous exposons les défis rencontrés actuellement en matière de diagnostic des cas de démence et nous soulignons l’utilité du recours aux systèmes informatisés d’aide à la prise de décision, ceux-ci permettant en effet de faciliter l’analyse des biomarqueurs disponibles (pour certains, à des fins de recherche uniquement) et de rassembler les données probantes issues de divers marqueurs.

L'imagerie des vaisseaux pathologiques
M. Mulligan-Kehoe et L. Zagorchev


Système expérimental de tomographie optique diffuse utilisé à des fins de recherche clinique en imagerie optique mammaire

L’imagerie optique mammaire est une technologie prometteuse dans le cadre du diagnostic et du traitement du cancer du sein. Elle permet en effet de recueillir des données biophysiques et moléculaires relatives aux tissus mammaires. L’imagerie optique mammaire peut s’appuyer sur le seul contraste intrinsèque des tissus mammaires (cartographie des concentrations tissulaires en hémoglobine, eau et graisse) ou impliquer le recours à des agents de contraste exogènes concentrés au niveau du site tumoral. Ces deux techniques sont décrites dans le passage en revue des expériences cliniques réalisées à l’aide d’un système expérimental de tomographie optique diffuse (DOT). Les trois études cliniques présentées brièvement dans cet article ont fait l’objet d’une publication antérieure.
Die Kunst der medizinischen Bildgebung: Philips und die Evolution der medizinischen Röntgentechnik
J.A.M. Hofman


Nichtinvasive Quantifizierung und Charakterisierung von Koronarplaque: die Rolle der Multidetektor-CT
M.G. Dalager, H.E. Bøker, M. Bøttcher, T.B. Ivanc, M.E. Olszewski und K. Norrgren


Nichtinvasive kardiologische Bildgebung bei krankhaft adipösen Patienten mit dem Brilliance iCT-Scanner


Der kürzlich eingeführte Brilliance iCT-Scanner bringt im Vergleich zur bestehenden Generation von CT-Systemen Fortschritte in den Bereichen Geschwindigkeit, Leistung und Abdeckung und ermöglicht somit auch bei diesen aus medizinischer Sicht komplizierten Patienten eine zuverlässigere diagnostische Bildgebung. Die Autoren präsentieren ihre vorläufigen Ergebnisse der kardiovaskulären CT-Bildgebung bei krankhaft adipösen Patienten mit dem Brilliance iCT-Scanner.

Pädiatrische Kardiologie mit den iE33 Echokardiographie-Systemen
G. Tulzer


Ultraschall-getriggerte bildgeführte Therapie
C. Moonen, N. de Jong, O. Steinbach, M. Böhmer und S. Langereis


Bildgebung der Myokardperfusion: Vergangenheit, Gegenwart, Zukunft
J.K. O'Donnell, P. Wüstlak und P.F. Faulhaber

Wege zur Verbesserung der Alzheimer-Diagnose
M.J. Sadowski, J. D. Schaffer und E. Silfen


Bildgebung von erkrankten Gefäßen
M. Mulligan-Kehoe und L. Zagorchev


Optische Mamma-Bildgebung: klinische Forschung mit einem experimentellen DOT-System (Diffuse optische Tomographie)


El arte de las imágenes médicas: Philips y la evolución de la tecnología médica de rayos X
J.A.M. Hofman

Philips y sus empresas filiales están comprometidas en el desarrollo de la tecnología de rayos X desde su mismo comienzo; de hecho, Philips ha estado a la cabeza de muchos de los avances más significativos. En este artículo se presentan algunas de las innovaciones tecnológicas más importantes desde hace más de un siglo: desde los primeros tubos de rayos X de ánodo giratorio hasta el intensificador de imágenes clínicas y la revolución digital. Cada una de estas innovaciones ha tenido una gran repercusión en la práctica clínica, desde el diagnóstico hasta los procedimientos intervencionistas avanzados.

Caracterización y cuantificación no invasiva de la placa coronaria: el papel del TAC multidetector
M.G. Dalager, H.E. Butker, M. Batchar, T.B. Ivanc, M.E. Olszewski y K. Norrgren

La coronariopatía continúa siendo la principal causa de muerte en los países desarrollados, con más de la mitad de las muertes producidas en personas asintomáticas antes de un episodio coronario agudo. Los ultrasonidos intravasculares (IVUS) son el método de referencia actual para detectar la placa arterosclerótica in vivo, pero con el inconveniente de que necesita condiciones anatómicas favorables y de que sólo se puede aplicar en personas con síntomas. La angiotomografía con multidetectores ofrece un método no invasivo para evaluar la luz y la pared vascular, mientras que el análisis tomográfico de la placa con Brilliance Workspace posibilita la caracterización y cuantificación de la composición de la placa dentro del árbol coronario.

Imágenes cardíacas no invasivas de pacientes con obesidad mórbida mediante el escáner Brilliance iCT

La valoración de pacientes con obesidad mórbida (índice de masa corporal superior a 40) que cursan con dolor torácico es con frecuencia complicada. Las técnicas convencionales de imágenes de las arterias coronarias por cateterismo cardíaco invasivo o por angiotomografía cardíaca realizada con contraste son complejas, debido a las limitaciones impuestas por la reducida relación señal/ruido, que puede afectar a la fiabilidad del diagnóstico. El escáner Brilliance iCT, introducido recientemente, presenta mejoras en velocidad, potencia y cobertura si se compara con la actual generación de TAC, con lo que se logra unas imágenes diagnósticas más fiables para esta difícil población de pacientes. Los autores exponen sus experiencias preliminares en imágenes tomográficas cardiovasculares de pacientes con obesidad mórbida con el escáner Brilliance iCT.
Hacia la mejora del diagnóstico en la enfermedad de Alzheimer
M.J. Sadowski, J. D. Schaffer y E. Silfen
La enfermedad de Alzheimer comprende la mayoría de casos de demencia con una prevalencia estimada de 5,3 millones de casos en los EE.UU. y de más de 25 millones en todo el mundo. No existe una prueba diagnóstica específica que distinga la enfermedad de Alzheimer de otras demencias menos frecuentes. Exponemos las dificultades actuales para realizar diagnósticos de demencia y proponemos que existe la posibilidad de que los sistemas computerizados de ayuda a la toma de decisiones mejoren el análisis de los biomarcadores disponibles (algunos sólo están disponibles en instituciones de investigación) y combinen las evidencias de diversos marcadores.

Imágenes de vasos coronarios afectados
M. Mulligan-Kehoe y L. Zagorchev
La microscopía confocal y la microtomografía son dos de las técnicas disponibles para visualizar la angiogénesis. La microscopía confocal ofrece imágenes de moléculas biológicas específicas implicadas en la angiogénesis, mientras que la microtomografía proporciona imágenes estructurales de alta resolución. Por tanto, son dos técnicas complementarias, que se pueden combinar con el uso de ratones modificados genéticamente para realizar estudios que investiguen los mecanismos de la enfermedad. En este artículo se presenta la aplicación de estas técnicas en un modelo de aterosclerosis en ratones para distinguir vasos afectados sin tratar de aquellos que reciben un inhibidor angiogénico.

Imágenes ópticas de la mama: investigación clínica con un sistema experimental de tomografía óptica difusa
La adquisición de imágenes ópticas de la mama es una técnica prometedora para el diagnóstico y el tratamiento del cáncer de mama por las posibilidades que ofrece en cuanto a información biofísica y molecular del tejido mamario. Esta técnica se puede realizar mediante el uso exclusivo de un contraste intrínseco en el tejido mamario (presentando sangre, agua y materia grasa), o bien con agentes exógenos para diagnóstico por imagen que se acumulan en el foco tumoral. Estas dos técnicas aparecen ilustradas en este resumen de nuestras experiencias clínicas con un sistema experimental de tomografía óptica difusa. Los tres estudios clínicos que aparecen resumidos en este artículo ya han sido publicados con anterioridad.

Cardiología pediátrica con el sistema de ecocardiografía iE33
G. Tulzer
El sistema iE33 de Philips se lleva utilizando en el Departamento de Cardiología Pediátrica del Centro de Cardiología Infantil de Linz (Austria) desde octubre de 2006. Se utiliza en la valoración pre y postoperatoria de neonatos y pacientes pediátricos con cardiopatía congénita, en la evaluación de la disincronía y la función miocárdica, así como en ecocardiografía prenatal (fetal). En este artículo se describen las principales características de este sistema de ultrasonidos de gama alta. También informa sobre la experiencia del autor en el desarrollo de una clínica de cardiología pediátrica.

Terapia guiada por imágenes y activada con ultrasonidos
C. Moonen, N. de Jong, O. Steinbach, M. Böhmer y S. Langerei
Las tecnologías de imágenes médicas se están convirtiendo en parte esencial de las intervenciones terapéuticas. Una aplicación emergente es la administración de fármacos activada con ultrasonidos, por lo que se están desarrollando para este fin formas de administración y técnicas de guiado de imágenes. En este artículo se exponen los avances en agentes sensibles a la temperatura y a la presión para la liberación local de fármacos guiada por imágenes y activada con ultrasonidos. Se describen liposomas sensibles a la temperatura con fármacos incorporados y etiquetas de imágenes de resonancia magnética, junto con microburbujas sensibles a la presión y cargadas con distintos fármacos, así como características específicas de su liberación y de las imágenes con ultrasonidos. Los autores concluyen con un resumen de las aplicaciones potenciales de ambos métodos de administración para diferentes formatos de fármacos, como pequeñas moléculas y tratamientos basados en ácidos nucleicos.

Imágenes de perfusión miocárdica: pasado, presente y futuro
J.K. O'Donnell, P. Wojtylak y P.F. Faulhaber
Las imágenes de perfusión miocárdica suponen una ayuda en la identificación de pacientes con riesgo de infarto de miocardio o de muerte. En este artículo los autores presentan una introducción al desarrollo de las imágenes de perfusión miocárdica, desde imágenes planares de la absorción del talio 201 hasta el presente y sus perspectivas futuras. Se presta especial atención a la introducción de la tomografía por emisión de fotón único (SPECT) y a la tomografía por emisión de positrones (PET), con una comparación de sus ventajas y desventajas, así como a la conjunción de ambas técnicas en unidades de escáner PET-CT y SPECT-CT.
Technology news

Veradius mobile C-arm with flat detector technology

The mobile C-arm market is expected to transition from image intensifiers towards fully digital systems with flat detectors. Philips is the first of the big three manufacturers to introduce a mobile C-arm with flat detector technology. Designed to give excellent image quality at low X-ray dose, the super-thin flat detector has several advantages over the image intensifier, offering a wider dynamic range, clearer, sharper images, and fewer distortion artifacts.

This breakthrough technology delivers the superb image quality, space and convenience needed to carry out cardiac, vascular and orthopedic surgery, as well as the most challenging minimally invasive procedures, with greater confidence.

The super-thin flat detector also improves communication in the operating room, because it is less obtrusive and so does not block eye contact between members of the operating team.

The flat detector technology eliminates the problem of pincushion distortion, ensuring constant image quality, even at the periphery of the image field. This means that it is no longer necessary to reposition the C-arm to ensure that the region of interest is in the center of the field of view. Consequently, the procedure is faster and, as fewer images are required, there is an overall saving in X-ray dose and the quantity of contrast agent needed.

An additional monitor on the C-arm stand allows the operator to position the flat detector easily and accurately, providing a further saving in X-ray dose and time.

The Veradius’ breakthrough technology delivers the superb image quality, space and convenience needed to carry out cardiac, vascular and orthopedic surgery, as well as the most challenging minimally invasive procedures, with greater confidence.
Philips CT Introduces Plaque Analysis on its “Best in KLAS” Extended Brilliance Workspace

Coronary artery disease is the leading cause of death in the industrialized world. The diagnosis and monitoring of coronary atherosclerosis are key steps in managing this devastating disease.

Philips Plaque Analysis application was built to meet these clinical needs. Building on the industry’s first, fully automatic, model-based whole-heart segmentation software, Plaque Analysis utilizes a combination of advanced knowledge-based algorithms and sophisticated editing tools to facilitate efficient, comprehensive vascular visualization, and analysis.

This comprehensive analysis includes known metrics of lesion/plaque morphology which agree with standard Intravascular Ultrasound (IVUS) measurements such as minimum lumen diameter and plaque volume, in addition to quantification and characterization of lesion/plaque composition and remodeling index.

Philips Plaque Analysis is the industry’s only application to utilize a novel Gaussian mixture model technique to calculate plaque content, while also providing the simple threshold technique option. Current research efforts utilizing Plaque Analysis are underway at clinical sites around the globe.

Iterative reconstruction enables up to 80% dose reduction in CT

The newest addition to Philips’ DoseWise suite of radiation management tools, iDose enables up to 80% reduction of X-ray dose while maintaining high image quality and fast reconstruction times. iDose is an iterative reconstruction technique designed to provide diagnostic images at lower doses in most, if not all clinical applications.

The first clinical trial of iDose was completed in 2009, involving 20 radiologists representing 14 global sites. These trials showed that iDose successfully maintained diagnostic image quality while significantly reducing dose. Also, these trials have shown that greater dose reduction is clinically acceptable when the procedure is intended to investigate anatomical information that has high contrast to noise values such as chest, CTA or orthopedic studies. “Good spatial detail with good reduction of noise. Natural appearance of the images. Helps to enhance the image quality of the low-dose acquisitions” said Dr. Nakaura, Kumamoto University while participating in the trial.
Many of the technologies and techniques that are taken for granted today were first introduced in the pages of Medicamundi. As a consequence, the Medicamundi archives represent a valuable resource for those interested in tracing the development of healthcare technology in general, and medical imaging in particular.

On this page we present a selection of recent developments, representing three of over 450 articles available on line in the Medicamundi archives. The full texts of the articles can be accessed via: [www.medical.philips.com/medicamundi](http://www.medical.philips.com/medicamundi)

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**Endovascular abdominal aortic aneurysm repair using the Veradius with flat detector**

J.A. van Herwaarden

Over the last decade, endovascular aortic aneurysm repair (EVAR) has gained increased application for the treatment of abdominal aortic aneurysms. EVAR is significantly less invasive than open surgery, and the first randomized trials support the use of EVAR in patients. Image quality plays a key role in the procedure, and the Philips Veradius with flat detector offers significant advantages. In the Veradius, a thin, flat detector replaces the conventional image intensifier. Designed to give excellent quality at low X-ray dose, the flat detector has a wider dynamic range than an image intensifier, providing clearer, sharper images, with fewer distortion artifacts.

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**Three-dimensional real-time in vivo magnetic particle imaging**

J. Borgert, B. Gleich, J. Rahmer, H. Dahnke and J. Weizenecker

Magnetic particle imaging (MPI) is a new tomographic imaging method capable of imaging the local concentration of magnetic tracer materials with high spatial and temporal resolution. Until now, only static and dynamic 2D phantom experiments with high tracer concentrations have been demonstrated. This article presents the first in vivo 3D real-time MPI scans, revealing details of a beating mouse heart using clinically approved concentrations of a commercially available MRI contrast agent. With these abilities, MPI has taken a huge step towards proving its feasibility for medical applications.

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**Throwing new light on dementia: CAD supports easier diagnosis**

R. Buchert, H. Jahn, L. Spies, F. Wenzel and S. Young

New medications are currently under development with the potential to treat the principal neurodegenerative diseases that lead to dementia. For effective treatment, the disease must be diagnosed at the earliest possible stage.

The University Medical Center Hamburg-Eppendorf and Philips Research are cooperating in the development of a computer-aided detection system based on FDG-PET and MRI data to assist specialists in making early and accurate diagnoses. If abnormalities are detected, the images are automatically compared with images in disease-specific databases that represent typical patterns of such diseases as Alzheimer’s disease, Lewy-body dementia and frontotemporal dementia.