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NIKOS - A SYSTEM FOR NON-INVASIVE EXAMINATION OF CORONARY ARTERIES BY MEANS OF DSA WITH SYNCHROTRON RADIATION

II. IN-VIVO INVESTIGATIONS

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ABSTRACT

For routine investigations a non-invasive method of coronary angiography without using a catheter is necessary. When introducing the contrast medium into a peripheral vein, due to dilution in the central circulation it is not possible to get sufficiently good images of the anatomical situation with conventional radiologic equipment. These difficulties can be overcome with digital subtraction angiography (DSA) in energy-subtraction-mode at the K-absorption-edge of iodine (33.17 keV). Today only synchrotron radiation offers enough intensity for this method. The system NIKOS was developed for DSA in energy-subtraction-mode. Main parts of the system are a two beam double crystal monochromator, a scanning device, a two line photodiode detector with large dynamic range and a computer system for data acquisition and image processing. With this arrangement in-vivo investigations of 8 dogs were carried out. The resulting images show, that it should be possible to visualize human coronary arteries down to 1 mm diameter when 10-20 ml contrast medium is rapidly injected into the brachial vein. The necessary extensions of NIKOS for these investigations are under construction.

CONTENTS

1.0 INTRODUCTION

The reason for an acute myocardial infarction almost always is an acute thrombotic occlusion of a coronary artery at the site of a preexistent stenosis. When coronary artery stenoses are detected prior to a myocardial infarction, interventions such as a by-pass-operation or a percutaneous transluminal coronary artery dilatation could salvage the myocardium.

Because selective coronary angiography carries a significant risk to the patient with respect to mortality (0.07 to 0.23%) and morbidity (1.2 to 2.2%), for routine investigations a non-invasive method of coronary angiography without using a catheter would be preferable. During such a procedure the contrast medium is introduced into a peripheral vein. Before entering the coronary arteries it is diluted in the central circulation system. Hence, compared to the intracoronary application, the iodine concentration is much lower and overlap with left heart chambers occurs. With conventional radiologic equipment it is not possible to get sufficiently good images of the anatomical situation.

During the last years, digital subtraction angiography (DSA) has become a powerful method for non-invasive investigations [1]. However, DSA in time-subtraction-mode, normally used in clinical routine, is not acceptable for the heart, if arteries of at least 1 mm diameter are to be imaged. Even more complex systems that take the two images at equivalent phases of the heart cycle (ECG - trigger) are limited to several millimeter resolution due to the nonperiodic motion of the heart [2].

These difficulties can be overcome with a different mode of DSA - the energy-subtraction-mode. In this mode the two images for subtraction are produced in the presence of iodine using two different quasi-monochromatic energies. At present, only synchrotron radiation offers enough intensity in such a small bandwidth for this method. Experiments on coronary angiography by means of DSA in energy-subtraction-mode with synchrotron radiation are carried out at Stanford [3], Tsukuba [4], Novosibirsk [5] and Hamburg [6].

At HASYLAB in Hamburg we have developed the system NIKOS for this purpose. This system, as well as in-vivo investigations of dogs with NIKOS, are described in detail.

2.0 FUNDAMENTAL CONSIDERATIONS

The two images for subtraction are taken simultaneously in the presence of iodine using the two different energies E_1 and E_2 respectively. These lie below and above the K-absorption-edge of iodine at 33.17 keV (Figure 1).

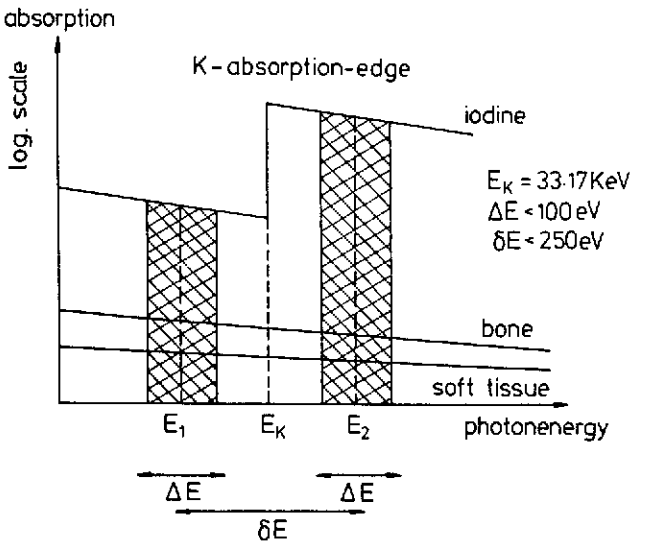

Figure 1. Energy dependence of the absorption coefficients (schematical) of contrast material, soft tissue, and bone around the K-edge of iodine.

The difference in iodine contrast which is essential for DSA is caused by the abrupt change of the iodine absorption coefficient at the K-edge (factor 6). Using radiation with a small energy bandwidth the two energies can be selected very close to the iodine K-edge and hence both soft tissue and bone contrast are suppressed in the subtracted images.

A system suited for the imaging of coronary arteries with non-invasive DSA in energy-subtraction-mode should fulfill the following conditions:

2.1 MEDICAL CONSTRAINTS

Contrast medium: Iodine.

Concentration and mass density of iodine in coronary arteries: Intravenous application of iodine into a brachial vein (10 ml contrast medium with a concentration of 370 mg/ml iodine injected within 1 sec) results in an iodine concentration of 10 mg/ml in the coronary arteries corresponding to 1 mg/cm^2 in arteries of 1 mm diameter.

Spatial resolution: Arteries down to 1 mm diameter should be visible leading to a matrix size of 256×256 pixels with 0.5 mm pitch.

Time resolution: The two images must be taken within the same heart cycle at a phase of minimum motion of the heart (typically within 200 ms) in order to avoid motion artifacts and strong image distortions. In a line scan system this leads to a readout time of 1 ms per line.

Delay between the two images: Due to the large speed of the coronary arteries during heart motion (up to 6 cm/s in the 30°RAO projection) the corresponding pixels in the two images should be taken within at most 4 ms.

Radiation dose: The skin dose per investigation should be less than 5 rem.

2.2 PHYSICAL CONSTRAINTS

K-absorption-edge of iodine: at 33.17 keV.

Absorption length in soft tissue: 2.1 cm.

Monochromatic beams: The bandwidth of the two monochromatic beams must be less than 100 eV each, the energy separation of the beams less than 250 eV.

Signals: Under the conditions stated above a 1 mm coronary artery gives a signal of 3% in the subtracted image.

Signal-to-noise ratio (SNR) in the subtracted image: at least 3.

Noise: Aiming at this SNR, X-ray quantum noise has to be limited to 1%. Electronical noise should add not more than 10% to the quantum noise.

Flux: The 1%-noise requirement leads to a minimum flux of 1.4×10^4 detected photons per pixel at each energy. Assuming the time requirements mentioned above and transmission through 20 cm of soft tissue this corresponds to an intensity in front of the patient of about 5×10^{10} photons/(mm^2 s).

3.0 COMPONENTS OF NIKOS

NIKOS consists of five main elements: a two beam double crystal monochromator, a scanning device, a two line photodiode detector, a computer system for data acquisition and image processing and a neat little storage ring (Figure 2).

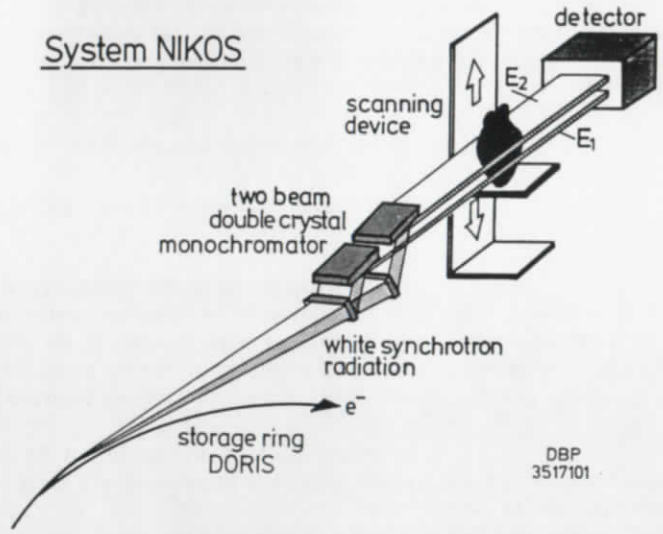

Figure 2. Components of NIKOS

These components are described in detail as they were used for in-vivo investigations of dogs. The necessary changes and extensions for investigations of patients are mentioned. They are under construction as well as the new beam line with higher X-rays intensity. Until now all investigations have been performed at the topography station at HASYLAB. This station is at a distance of 34 m from the source and receives synchrotron radiation from a bending magnet of the electron storage ring DORIS. During most of the investigations DORIS was run with electron energies between 5.0 and 5.3 GeV and 20-40 mA current. Under these conditions the incident photon flux at 33 keV is about 4×10^8 photons/(mm^2 eV s). The maximum horizontal beam aperture is 50 mm.

3.1 THE TWO BEAM DOUBLE CRYSTAL MONOCHROMATOR

The incident white synchrotron radiation beam is split into two monochromatic output beams by two Ge(111)-crystals. The first crystal reflects (Bragg case) a beam with the energy E_1 from the lower part of the beam, the second reflects a beam with the energy E_2 from the upper part. The germanium plates are 60 mm wide and 80 mm long each. The Bragg angles for reflection are 3.29° (E_1) and 3.26° (E_2) respectively. The bandwidth of the two monochromatic X-ray beams is about 75 eV each, the energy separation of the beams is 300 eV. Each crystal is followed by a second Ge(111)-crystal that reflects the monochromatic beams back to the horizontal direction. The parallel setting of the two crystals within a few seconds of arc is controlled by a piezoceramic. We chose two independent crystals per beam to be able to minimize the fraction of higher harmonics (99 keV, 132 keV) and the contamination by unwanted reflections in the monochromatic beams. The center distance between the two 0.5 mm high X-ray beams in front of the investigated dogs was 2 mm, the beam width 45 mm. The flux at that point was 1.4×10^9 photons/(mm^2 s).

During the experiments a different version of the monochromator with only one crystal per monochromatic beam was tested, too. In this case the monochromator itself was easier to handle and its reflected intensity was more stable. On the other hand adjustment of the complete system was difficult because the monochromatic beams were not parallel to the incident white synchrotron radiation beam. Also the larger portion of higher harmonics did not allow complete subtraction of the bones in the images due to beam hardening effects when bones and iodine structures are superposed.

For these reasons we will keep to the double crystal version of the monochromator. It is planned to exchange the two first crystals by thin Laue case crystals (reflecting netplanes perpendicular to the surface) instead (Figure 3).
This has the advantage, that the monochromator is vertically focusing and less sensitive to vertical beam oscillations.

3.2 THE SCANNING DEVICE

To avoid artifacts in the subtracted image, a very uniform motion of the scanning device is required. In addition it has to be able to carry a heavy load. We use a mechanically driven table (Uhing, Kiel, FRG). Its central part is a hardened and polished driving shaft which rotates at constant speed. The moving table is clamped to this shaft by pairs of ball bearings.

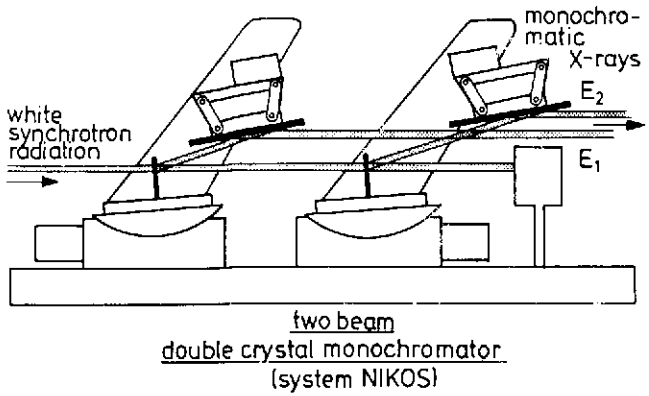

Figure 3. Schematic beam geometry of the monochromator (final version with Laue- and Bragg-crystals).

When the orientation of their axis of rotation is inclined with respect to the shaft the ball bearings start to move along the shaft. The speed is controlled by the angle which can be changed by an external steering shaft. Thus the motion of the table can be varied continuously although the driving motor rotates at constant speed.

This scanning device can carry 100 kg net load and move 40 cm with a speed of up to 60 cm/s. The actual position of the table during the scan is recorded by a train of electric pulses which are generated in an incremental linear transducer (Heidenhain LIDA 19). The scanning device is started ECG-triggered by the computer.

3.3 THE TWO LINE PHOTODIODE DETECTOR

The general design of the detector is shown in Figure 4.

It consists of a phosphor screen, an image-intensifier and a photodiode array, all these components being coupled by means of special fibre optics. The two X-ray beams generated by the monochromator are converted to visible light by means of a phosphor layer. This layer consists of two rows of Gd_2O_2S:Tb powder, one for each X-ray beam with a center distance of 2 mm. The dimension of each row is 63×0.5 mm² thus constituting 126 pixels 0.5×0.5 mm² each.

The optical light output of each phosphor pixel is transferred to an image intensifier by means of a glass fibre bundle. This bundle consists of 27 sin-

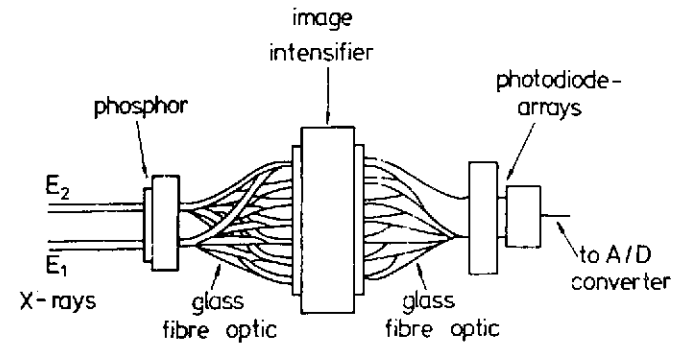

Figure 4. The two line photodiode detector

gle glass fibres of 85 μm diameter glued together to a quadratic cross section of 0.5×0.5 mm² at the phosphor side and a circular cross section of 0.7 mm diameter at the image intensifier side.

A small fraction of each of the two monochromatic beams is stopped by two monitor phosphors to detect the beam intensity in front of the patient. They are coupled to the image intensifier by two additional fibre bundles thus also monitoring the gain of the image intensifier.

To enhance the light level of the phosphor screen to the needed intensity level at the photodiode, an image intensifier is required. We chose a double stage proximity focused image intensifier (Proxitronic Proxifier BV 2543 MX 35) having zero distortion and a gain factor of 120. To get minimum crosstalk the 256 incoming fibre bundles are distributed over the whole active input area (25 mm diameter) with a center to center spacing of 1.3 mm.

A second set of 256 glass fibre bundles is positioned at the output face of the image intensifier to collect the intensified input signals. In this way every bundle of the second set just carries the information from one phosphor pixel. Whereas the input cross-section of these second bundles again is circular (0.7 mm diameter) their output end is formed to give a cross-section of 0.1×2.5 mm² to match the photodiode sizes.

The photodiode array is a Reticon RL 1024 SF chip consisting of 1024 photodiodes each having a 0.025×2.5 mm² input area. The second fibre bundles precisely packed side by side to form a single line are coupled to the Reticon chip. In this way every pixel of the phosphor screen is coupled to four photodiodes.

A modified Reticon standard evaluation circuit is used for electronic readout. The internal readout trigger was replaced by an external one, which is generated by the linear transducer of the scanning device every 0.5 mm of translation. The clock frequency was increased to enable readout times of 2 ms per line. The output signals were amplified to an appropriate level for the following 12 bit, 0.5 MHz ADC (Datel ADC-817).

A new detector with two phosphor screen lines 127×0.5 mm² each is under construction. The readout electronic is completely redesigned to enable readout times of 1 ms per line.

3.4 THE COMPUTER SYSTEM

Two computers connected via PADAC are installed (Figure 5).

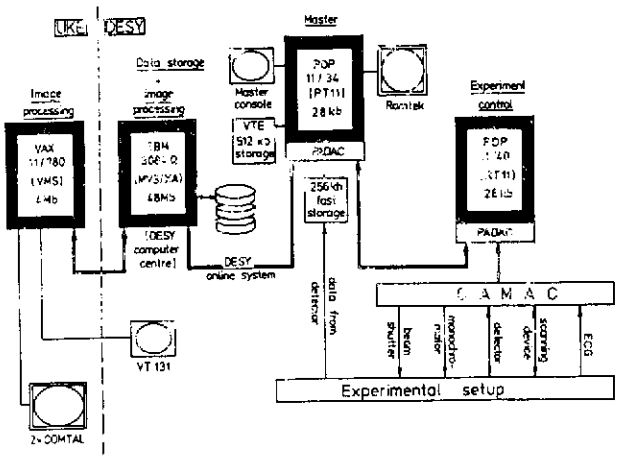

Figure 5. The NIKOS computer system

From a PDP 11/34 (Master) experiment control, data acquisition, data storage and image processing are coordinated. The programs use the PROFI image processing system [7].

A PDP 11/40 is used for the control of the complete experimental set-up (via CAMAC). It

reads the ECG for triggering the start of the scan;

starts, controls and stops the scanning device;

enables the detector for readout;

sets the monochromator to correct energies;

controls the beam shutter to minimize the radiation dose during the in-vivo investigations.

The incoming data are first stored in a fast storage. The data can be stored with a rate of 2×10^6 pixel/s (1 pixel corresponds to 12 bit). After finishing the scan the data are transferred via the DESY-online-system to the DESY computer center (IBM 3084Q) for image processing and long time storage. The processed images can be presented at the experimental site with a graphic display system (Ramtek) connected to the PDP 11/34.

The complete system is also connected to the central computer of the Dept. of Computer Science in Medicine, University Hospital, Hamburg. In this way the image processing facilities of this department are available for NIKOS, too.

4.0 IN VIVO INVESTIGATIONS

4.1 DATA ACQUISITION

During the last year 8 dogs were investigated. Their weight was between 10 and 23 kg, the soft tissue to be penetrated 12-15 cm. During the investigation they were positioned in a polyester tub which could be turned around a horizontal and vertical axis perpendicular to the beam. 5 dogs were positioned on the belly, 3 on the back. The dogs were anaesthetized for about 3 hours. The ECG-unit for supervision of the dogs was connected to the computer.

The contrast medium (Urografin 76%) was applicated via a heated tube and a catheter. The catheter was positioned in the aorta (1 dog), in the right atrium (3 dogs), in the vena cava inferior (1 dog) or in the vena cava superior (3 dogs). 6-10 ml contrast medium were applicated within 1.0-1.5 seconds. This results in about 16mg/ml of iodine in the aorta, if the contrast medium was applicated into the venous system.

The scanning device ran with a velocity of 16-20 cm/s, related to the thickness of the dogs. The exposure time per line was 2.5 ms, the readout time was 2 ms per line. For a typical velocity of 20 cm/s one scan (two images with energies E_1 and E_2 respectively) was finished within 575 ms. With one injection of contrast medium up to 4 scans with a delay of 3-4 seconds were taken.

The skin dose per scan was measured to be 100-450 mrem depending on the version of the monochromator and scan velocity. A realistic value for the final version of the monochromator is 200 mrem per scan.

4.2 IMAGE PROCESSING

In the unprocessed data there is a total noise of about 60%, most of it being fixed pattern noise. Because a contrast of 3% has to be made visible with a SNR of at least 3 the subsequent image processing must be executed very carefully. The following corrections to the images are carried out:

The dark current of the detector is subtracted. The values are measured before the scan starts.

The afterglow from line to line was measured to be 7.0% for the next line. Appropriate corrections to the data are made.

The single lines are corrected for instabilities in the motion of the scanning device. For this purpose a clock with high frequency is read at every readout of a line.

The horizontal crosstalk from pixel to pixel due to the image intensifier, the glass fibre optics, the Reticon chip and the electronics was measured for each pixel of the detector. The measurement showed a crosstalk of about 5%. The values of each pixel are corrected by deconvolution of the corresponding matrix.

The two images (E_1 and E_2) are shifted appropriate to the vertical distance of the two lines in the detector.

The images are corrected for beam fluctuations which can reach 10%. The phosphor monitors described above supply the necessary information.

The fixed pattern noise of the detector due to differences in the sensitivity of the single photodiodes and the phosphor screen is measured in every scan by using 25 lines of the scan for imaging a reference aluminium plate of 15 mm thickness.

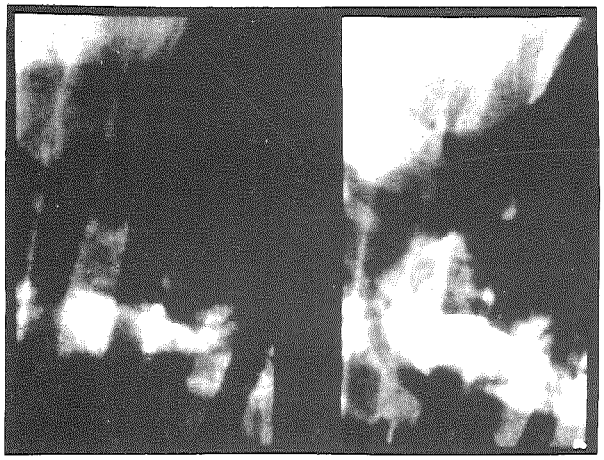

Figure 6. Images with energy E_1 and E_2 respectively of a scan (23 seconds after intravenous injection of 7 ml Urografin 76%).

In Figure 6 two exemplary resulting corrected images of one scan are shown.

4.3 SUBTRACTION IMAGE

The two images shown in Figure 6 are subtracted logarithmically. After separate normalisation of the columns and of the lines and after stretching of the grey values the subtraction image (Figure 7) clearly shows the anatomical situation of the heart. The lungs are free of contrast medium, left heart and aorta are filled. The diameter of the aorta is 16 mm. Also the right coronary artery (1 mm diameter) is visible.

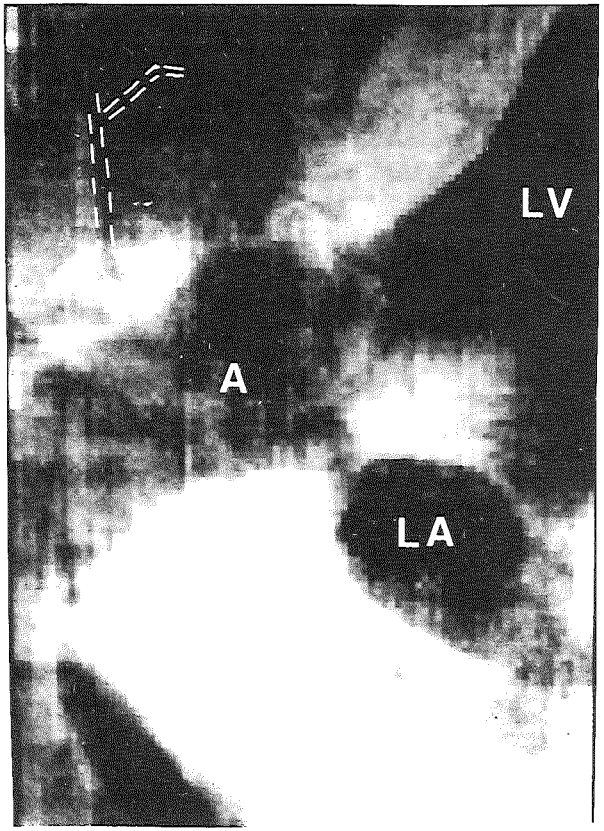

Figure 7. Subtraction image of the two images in figure 6 (A = aorta, LA = left atrium, LV = ventricle).

In this projection the left coronary arteries (LAD and Cx) are superposed by the left atrium and left ventricle.

Therefore in the next future algorithms for histogram equilization and edge enhancement will be tested to improve the images. Also corrections for saturation effects of the photodiodes and the electronic circuits and for beam hardening effects are on the way.

5.0 CONSIDERATIONS FOR INVESTIGATIONS OF PATIENTS

5.1 SUPERPOSITION OF IODINE STRUCTURES

Even if edge enhancement algorithms are used for improvement of images it should be difficult to figure out coronary arteries (CA) with good quality if they are superposed by iodine structures of the heart chambers. Therefore it is useful to find out projection angles for the investigation of patients where the CAs are projected free from the chambers.

After rapid bolus injection of contrast medium into the vena cava the right heart and the lungs are free of iodine at the time left atrium (LA), left ventricle (LV), aorta (A) and CAs contain iodine. Therefore we studied 20 human hearts, excised in toto at autopsy, with LA, LV, ascending A and CAs filled with contrast material. The hearts were mounted in a cardanic suspension and examined under X-ray control. Most parts of CAs in the same projection were seen in the 40° RAO and 20° caudocranial (CC) position (Figure 8).

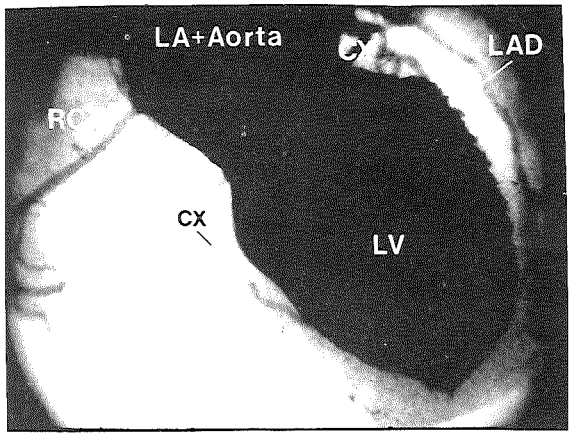

Figure 8. Projection 40° RAO and 20° CC position. Diastolic heart: LA, LV, ascending A and CAs filled with contrast material. Right CA, LAD and parts of Cx are visible.

LAD was seen in 40° RAO and -20° CC position (Figure 9).
Left main stem was only seen in 3 of 6 diastolic hearts. Cx and marginal branches were visible only in part together with LAD or right CA, depending on the coronary type. These examinations showed that it is possible to project the interesting parts of the CAs free from the iodine structures of the left heart and aorta.

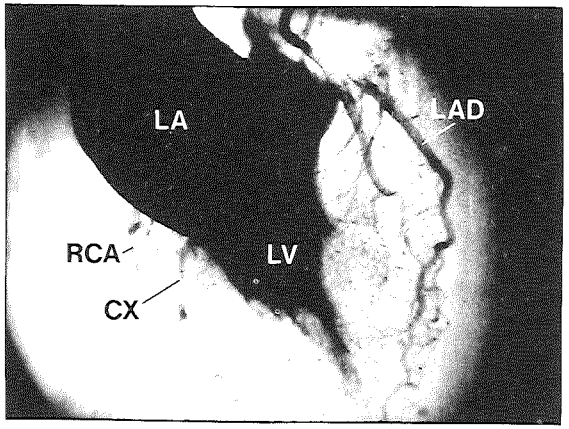

Figure 9. Projection 40° RAO and -20° CC position. Systolic heart: LA, LV, ascending A and CAs filled with contrast material. LAD and parts of RCA and Cx are visible.

5.2 RADIATION DOSE

Assuming a mass density limit of 1 mg/cm^2 of iodine, a SNR of 3 and 20 cm of soft tissue the skin dose was theoretically calculated to be 0.9 rem per scan. In the in-vivo investigations of dogs (12 cm of soft tissue) we measured 0.2 rem per scan. Assuming the same signal-to-noise ratio in the images for the investigation of patients an extrapolation gives 3.2 rem per scan. The examination of human hearts described above showed that with three scans per investigation all CAs can be figured free of superposing iodine structures. The projection angles for these three scans are so different that the skin dose of 3.2 rem is hardly increased by these three scans. So the limitation of 5 rem per investigation is not exceeded.

6.0 CONCLUSION AND OUTLOOK

The in-vivo investigations of dogs showed that with NIKOS it is possible to image vessels and coronary arteries down to 1 mm diameter after rapid intravenous injection of contrast medium containing iodine. This encourages us to prepare the investigation of patients with the system. For this purpose some components have to be changed or extended:

The scanning device has to run with 50 cm/s instead of 20 cm/s. This means, the readout time per line of the detector must be decreased from 2 ms to 1 ms. Also the width of the detector has to be increased from 6.4 to 12.8 cm. The flux in front of the patient of 1.4×10^{9} photons/(mm^2 s) is too small. Changes in the monochromator and the installation of a new wiggler beamline will enable us to get the necessary flux of 5×10^{10} photons/(mm^2 s). All these changes and extensions are under construction and will be finished in 1987.

It is planned to investigate the first patient in 1988. During the following 5 years we shall use NIKOS for validation studies against selective coronary angiography, basic research on natural history of coronary artery disease, and for studies of effects of therapeutic interventions.

6.1.1 Acknowledgement

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