Intravenous coronary angiography using synchrotron radiation: technical description and preliminary results

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Coronary angiography; Minimally invasive; Outpatients.

Background. **Standard coronary angiography requires an arterial access and catheters; intravenous coronary angiography may image coronary arteries noninvasively and without catheters. The aim of this study was the assessment of the diagnostic accuracy of intravenous coronary angiography validated by selective coronary angiography.**

Methods. **Seventy outpatients (80% males, mean age 62 ± 8 years) underwent both standard and intravenous coronary angiography after a previous coronary intervention. Intravenous coronary angiography was performed within 6 weeks before or after selective coronary angiography. Two different projections were used to obtain 6-8 sequences per patient. Images were taken after injection of the contrast agent into the brachial vein or into the superior vena cava. During image acquisition, patients were moved through the scanning beam on a special chair. Thereafter, images were evaluated and compared to selective coronary angiograms for the following criteria: no stenosis, subsignificant stenosis (< 70%), significant stenosis (≥ 70%), and occlusion.**

Results. **One hundred eighty-seven target vessels were analyzed. In 50 target vessels one or more stents had been implanted. Seventeen target vessels were not analyzable due to inadequate image quality. The sensitivity of intravenous coronary angiography for the detection of lesions was 80% and the specificity was 95%. The sensitivity for the detection of significant lesions in the left anterior descending coronary artery was 84% (specificity 93%), in the left circumflex coronary artery 67% (specificity 90%), in the right coronary artery 85% (specificity 97%), and in bypass grafts 85% (specificity 97%). No complications were observed.**

Conclusions. **Intravenous coronary angiography is efficacious and safe and allows quantification of lesions of the coronary arteries and of bypass vessels. Further advances in image processing are needed to improve sensitivity especially in the left circumflex coronary artery.**

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Introduction

Coronary artery disease is the primary cause of death in the western industrialized world. In 1997, 485 440 selective coronary angiographies and 138 001 percutaneous transluminal coronary angioplasties (PTCA) were performed in Germany[1]. Although the value of selective coronary angiography is beyond discussion, the associated risk of an invasive approach, the inherent costs and the necessary hospitalization have stimulated the development of novel noninvasive techniques for coronary imaging such as electron beam tomography[2-4], magnetic resonance imaging[5-8] and multislice computed tomography[9,10]. We previously developed the technique of intravenous coronary angiography using synchrotron radiation at the Deutsches Elektronensynchrotron (DESY) in Hamburg[11-15]. During the last 4 years 355 patients underwent intravenous coronary angiography, a minimally invasive technique feasible for quality imaging of the coronary arteries, coronary stents and bypass grafts without artifacts. The aim of this study was the assessment of the diagnostic accuracy of intravenous coronary angiography validated by selective coronary angiography.

Methods

Patients. Angiographic results of 70 patients (80% males, mean age 62 ± 8 years) who underwent both intravenous coronary angiography with synchrotron radiation and selective coronary angiography were analyzed. Intravenous coronary angiography was performed within 6 weeks of selective coronary angiography. All patients had a history of coronary artery disease and had been submitted to PTCA and/or coronary artery bypass surgery. Patients with unstable angina pectoris and patients with a reduced ejection fraction (< 30%) were not included in this study. The protocol of the study was approved by the ethics committee at the institutional Medical Board of the University of Hamburg. Written informed consent was obtained from each patient.

Intravenous coronary angiography using synchrotron radiation. *Dichromography.* Intravenous coronary angiography is based on the principle of dichromography[16], a technique of digital subtraction angiography operating in an energy subtraction mode. This technique allows imaging of fast moving objects such as the heart. In contrast to time subtraction, the energy dependence of X-ray absorption is used to obtain two images with a different contrast to the contrast agent (usually iodine) but an equal contrast to other tissues such as bone and soft tissue. In order to obtain a contrast different to that of iodine, the discontinuity of the absorption at the K-edge (33.17 keV) is used (Fig. 1). Accordingly, one image is taken with monochromatic X-rays delivered at an energy level below the K-edge of iodine (mask) and the other one at an energy level above the K-edge. By performing a logarithmic subtraction, an image referring primarily to the contrast agent is obtained. The mass absorption coefficient of iodine for X-rays above the K-edge is 5.5-fold higher than that below. When the energy difference between the two monochromatic X-ray beams is 300 eV the sensitivity for iodine is 10 000 times higher than that for soft tissue. This allows intravenous injection of the contrast agent for adequate imaging of the coronary arteries, despite dilution during transit by a factor of 40. The two images are acquired simultaneously when the contrast agent fills the coronary arteries. Dichromography requires monochromatic X-ray sources (bandwidth < 250 eV) of very high intensity (3×10^{11} photons/mm^2/s) only available in synchrotron laboratories at present.

System set-up. The system NIKOS (noninvasive coronary arteriography with synchrotron radiation) is installed in a beam line of the storage ring DORIS at DESY[11]. It consists of six main components: the wiggler, the monochromator, the safety system, the scanning device, the detector and the computer system (Fig. 2). These components are described in the Appendix[17-19].

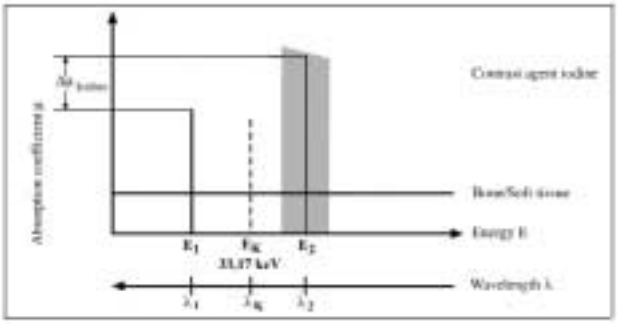


Figure 1. *Two images at energies above and below the K-absorption-edge of iodine (33.17 keV) are taken simultaneously with monochromatic X-rays. The mass absorption coefficient μ of iodine in these two images differs by a factor of 5.5 for an energy separation E_2-E_1 of 300 eV while there is practically no difference in the mass absorption coefficients of soft tissue, bone, etc. Therefore, after logarithmic subtraction of the two images the contrast of iodine is increased 10 000 fold compared to that of tissue. Thus, this special method of digital subtraction angiography, termed dichromography, allows the imaging of very low iodine contrasts.*

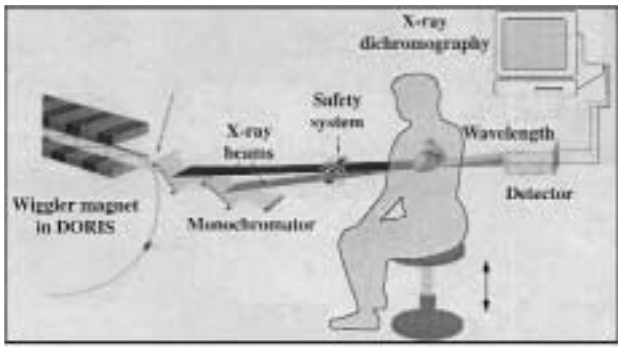
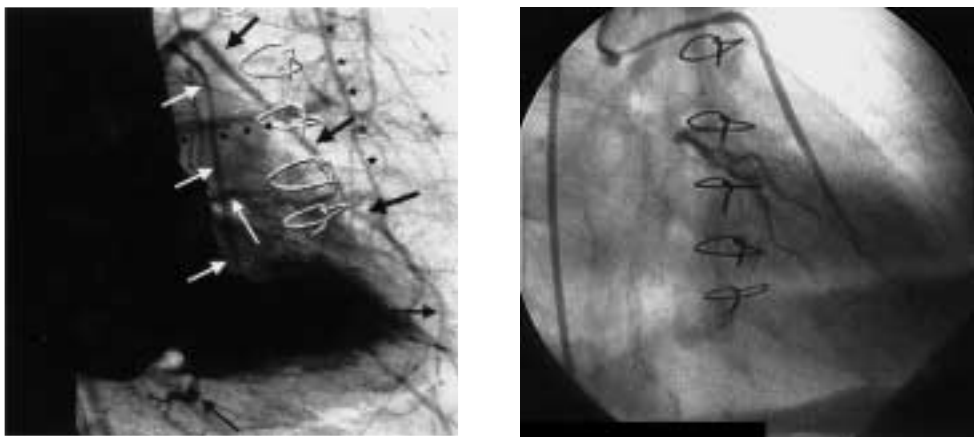


Figure 2. *Schematic view of the NIKOS system. During image acquisition the patient is sitting in an upright position in a specially designed scanning chair.*

Image acquisition. Under fluoroscopic control a 6F-introducer sheath was placed into the brachial vein for contrast injection (370 mg iodine/ml) with a commercially available injection pump. In patients with reduced left ventricular function, in whom a long transit time was expected, a 7F-pigtail catheter was advanced into the superior vena cava for injection of the contrast agent. Thus, excessive dilution of the contrast agent was avoided. Thereafter, the patient was placed on the scanning seat in an upright position and aligned to the beam by the physicians with the aid of a light frame. Each investigation was started with the determination of the individual transit time by injecting 5 ml of indocyanine green as an intravenous bolus. A sensor at the patient's ear and a visible light densitometer were used for determination of transit time between injection of the dye and its detection in the ear. Settings for the first diagnostic image were prepared according to the individual transit time. After injection of the contrast agent, the vertical scan was started with an ECG-triggered signal delayed by the measured transit time. The speed of the chair was 50 cm/s. The fast beam shutters were opened only as long as the

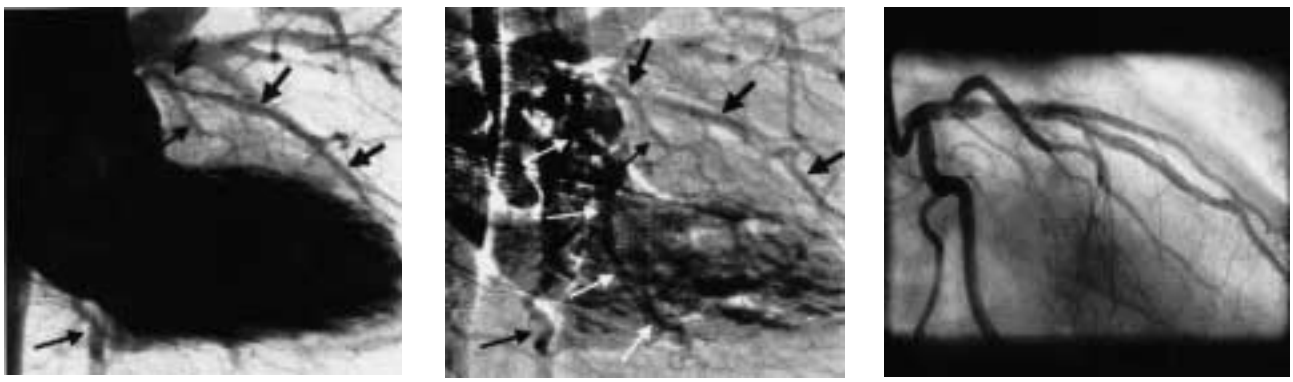
field of interest (12.5 × 12.5 cm^2) moved through the monochromatic beams. When the brachial vein was used, 30 ml of contrast agent were injected at a speed of 15-18 ml/s. If a pigtail catheter was employed, 30 ml of contrast agent were injected at a rate of 20-25 ml/s. ECG-triggering allowed imaging during systole. Thus, superimposition of the coronary arteries and ventricles was minimized. Because a high iodine background degrades the image quality, the second diagnostic image was taken after a delay of at least 30 min following the previous image. This break could be used for an image session with another patient. Routinely, two different projection angles were used obtaining 3 or 4 scans for each projection angle. The acquisition time per image was 250 ms.

Image evaluation. Acquired images were available on the computer screen for evaluation (Figs. 3-5). At the workstation the primary images could be remarkably improved by image post-processing. This included: 1) subtraction from the original image of all noniodinated structures; 2) employment of a special algorithm to reinforce small structures and filtering in order to level the contrast, and finally subtraction of the resulting image from the original one. This technique often allowed evaluation of the origin of the right coronary artery (RCA) in case of superimposition with the aorta. Images obtained at intravenous coronary angiography and at selective coronary angiography were evaluated by two different physicians. At the time of intravenous coronary angiography readers were blinded to the results of se-



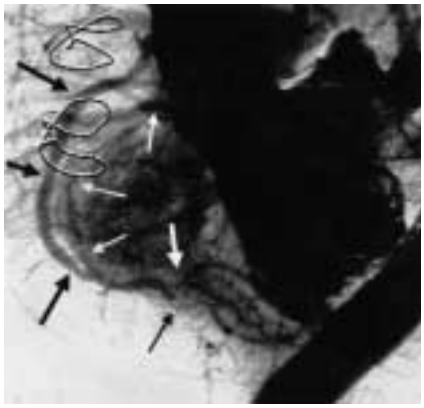
A **B**

Figure 3. A: *an intravenous angiogram in the right anterior oblique 45° projection shows a vein graft* (black arrows) *on the left anterior descending coronary artery (LAD) and a vein graft on the first marginal branch of the left circumflex coronary artery* (short, white arrows). *The proximal* (long, white arrow) *and distal* (long, black arrow) *segments of the native LAD are also visible. The right coronary artery is recognizable below in the picture* (long, black arrow). *The left interior mammary artery* (stars) *and the native LAD intersect near the periphery of the LAD. A pulmonary vessel* (points) *intersects with the vein grafts. No significant stenoses are recognizable.* B: *a selective angiogram in the right anterior oblique 25° projection of the vein graft on the LAD in the same patient.*



A **B** **C**

Figure 4. A: *an intravenous angiogram in the right anterior oblique 30° projection shows the left main stem, the entire LAD (*short, wide arrows*) and the ramus intermedius* (short, thin arrow). *In the proximal segment of the LAD a significant stenosis is recognizable. The right coronary artery is visible below in the picture* (long arrow). B: *all noniodinated structures are subtracted from* A *to better visualize the left circumflex coronary artery* (white arrows). *Contrast variations allow optimization of the image in the segment of interest.* C: *a selective angiogram of the left coronary arteries (right anterior oblique 13°) in the same patient 24 hours after intravenous coronary angiography. In the proximal segment of the LAD significant stenosis was detected. Thus, the intravenous coronary angiography result was confirmed. A percutaneous transluminal coronary angioplasty of the proximal LAD followed in the same procedure.*



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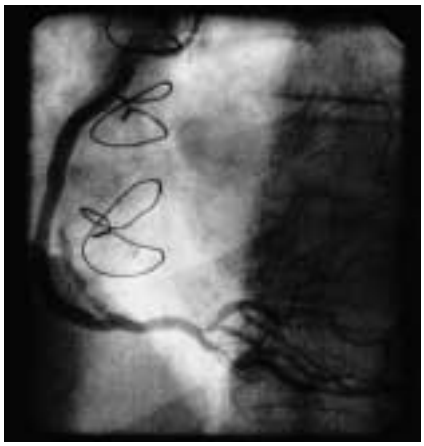

B

Figure 5. A: *an intravenous angiogram in the left anterior oblique 60° projection shows a vein graft on the right coronary artery* (black arrows). *The native right coronary artery is partially recognizable* (thin, white arrows). *A stent is visible in the posterolateral left ventricular branch* (wide, white arrow). *The low contrast in the stent indicates a significant in-stent restenosis. In the posterior descending branch an eccentric stenosis is recognizable* (thin, black arrow). B: *a selective angiogram of the right coronary artery (left anterior oblique 39°) in the same patient. Detection of a stenosis in the posterolateral left ventricular and posterior descending branch of the right coronary artery confirmed the intravenous coronary angiography results.*

lective coronary angiography, but they were informed on which vessels were treated by a percutaneous coronary intervention or by bypass surgery. Thus, in each patient one or more target vessels could be selected and the related projection angles for intravenous coronary angiography could be chosen. Criteria for coronary artery evaluation were: no stenosis, hemodynamically subsignificant stenosis (< 70%), hemodynamically significant stenosis (≥ 70%), or occlusion. Coronary lesions were classified as eccentric or concentric. In addition, stenoses were evaluated in order to assess their length as well as their location in the coronary vessel (proximal, middle and distal).

Results

Seventy (80% males, mean age 62 ± 8 years) patients underwent dual imaging by both intravenous and selective coronary angiography. All patients had coronary artery disease; 22 (31%) had single-vessel disease, 24 (34%) two-vessel disease and 24 (34%) patients had three-vessel coronary artery disease. Of the 70 patients, 27 (39%) had a previous myocardial infarction involving the anterior wall in 11 cases and the inferior wall in 16 cases. All patients had a coronary intervention; 61 (87%) patients underwent PTCA or rotational atherectomy, 40 (57%) had coronary stent implantation, and 20 (29%) patients had bypass cardiac surgery. Intravenous coronary angiography was performed without complications in all patients and none of them required hospitalization. The time interval between intravenous and selective coronary angiography was 4 ± 2 weeks. In the 70 patients, 187 target vessels were selected: left anterior descending coronary artery (LAD) 57, left circumflex coronary artery (LCX) 22, RCA 56, and bypass grafts 52. In 50 target vessels one or more stents were implanted. Among 187 target vessels 17 (9%) were not evaluated because of poor image quality. In 5 patients a transit time of > 20 s caused excessive dilution of the contrast agent in the coronary arteries, resulting in nondiagnostic image quality. Due to obesity a very high X-ray absorption was observed in 3 patients, resulting in a too low a signal and insufficient image quality. Intravenous compared with selective coronary angiography showed a sensitivity of 84% for detection of LAD lesions (specificity 93%), 85% for detection of RCA lesions (specificity 97%), 85% for lesions of bypass grafts (specificity 97%) and of 67% for detection of LCX lesions (specificity 90%). Vessels up to a diameter of 1 mm could be easily evaluated. Optimal imaging of the LCX was infrequently achieved due to superimposition of the left ventricle. The overall sensitivity of intravenous coronary angiography was 80% and the specificity 95%. The positive and negative predictive values were both 90%.

Discussion

In the last decade numerous efforts have been made to image coronary arteries noninvasively. The driving force behind noninvasive coronary angiography is the need to reduce hospitalization, costs and avoid complications. Therefore, noninvasive techniques are to be safe, easy to perform, fast, cost-effective, and have to offer a sufficient image quality. Intravenous coronary angiography using synchrotron radiation is the most promising of these noninvasive techniques. However, intravenous coronary angiography has not yet been compared to conventional coronary angiography. The present study demonstrated that intravenous coronary angiography allows imaging of native coronary arteries, bypass grafts and stents with reasonable image quality. With intravenous coronary angiography, the image quality depends on the projection angle, because in the images superimposition of contrast-filled structures, such as the left ventricle, may occur. Therefore, the choice of an ap-

propriate projection angle allows one to avoid superimposition of iodinated structures in the region of interest. To limit the radiation dose to the patient, intravenous coronary angiography should be restricted to two projections. Thus, each projection should be adjusted to image one target vessel optimally. Therefore, the choice of projection angles adjusted for a target vessel allows an improvement in intravenous coronary angiography visualization. For this reason ideal candidates for intravenous coronary angiography are patients who have been submitted to percutaneous transluminal coronary artery interventions and bypass surgery, in whom target vessels can rather be selected. However, intravenous coronary angiography may also be performed as the primary diagnostic angiographic procedure in patients in whom conventional coronary angiography would be too risky. In our patients, optimal imaging was achieved for the LAD, RCA and bypass grafts, whereas, owing to superimposition of the left ventricle, a good quality image was more difficult to obtain for LCX lesions. In some cases no segment of the LCX was analyzable, explaining the relatively low sensitivity (67%). However, a left anterior oblique projection angle of 60-90° and image acquisition during late systole with only a little contrast agent remaining in the left ventricle may lead to improved assessment of the LCX. Further advances in image processing may facilitate evaluation in the regions of interest. In addition, technical progress may allow three projections during intravenous coronary angiography without increasing the radiation dose. In contrast to imaging techniques such as electron beam computed tomography and magnetic resonance imaging, intravenous coronary angiography also allows assessment of the distal segments of the coronary tree[2-8]. In the present study we could easily evaluate vessels with a diameter of 1 mm. A subanalysis conducted in our patient group revealed that the diagnostic sensitivity of intravenous coronary angiography was independent of whether the distal vessel segments were included in the evaluation or not. Since metals have not been observed to cause artifacts in intravenous coronary angiography, we also could evaluate coronary stents and bypass grafts (particularly the left and right internal mammary arteries). In these patients we found a sensitivity comparable to that of native coronaries. Moreover, coronary artery calcification, known to alter images obtained at electron beam computed tomography and magnetic resonance imaging by a local signal deletion, fails to compromise image quality at intravenous coronary angiography. Electron beam computed tomography has proved to be useful for the detection of arterial calcifications. However, coronary artery imaging as well as detection and evaluation of stenoses are still below the requirements necessary for routine application of this technique[2-4]. Some preliminary results for the new multislice computed tomography that have been presented seem promising. So far, no data about the detection and evaluation of coronary lesions are available[9,10]. The patient exposition to synchrotron radiation with a maximal skin entry radiation dose comparable to approximately half of the mean of the skin entry dose for selective coronary angiography, represents a disadvantage in comparison to magnetic resonance imaging. Magnetic resonance imaging also allows functional analyses, such as flow and perfusion measurements, which are not yet standardized for intravenous coronary angiography. However, at present some dynamic parameters could be individually evaluated. For each projection of intravenous coronary angiography a set of 3-4 ECG-triggered images is acquired. This technique allows estimation of the coronary flow. In addition, the iodine concentration at a chosen time and at any point in the vessel can be measured allowing a direct correlation between time and concentration. This correlation can be translated into a flow profile. Magnetic resonance imaging is a promising technique for imaging of the coronary arteries. But so far a sufficient image quality was achieved in only a few patients and the sensitivity and specificity were below those of intravenous coronary angiography. The combination of three-dimensional dataset acquisition, special contrast media and the new generation of cardiac dedicated scanner systems may improve the signal to noise ratio as well as the spatial solution[6-8]. However, patient studies comparing this technique to conventional angiography are limited[6-8]. Currently, intravenous coronary angiography requires bulky mechanical and electronic equipment to generate synchrotron radiation. However, more compact technical equipment is feasible. Although no exact estimation of its price is possible at present, speculative data suggest that it may vary from 1.5 to 3 million US dollars. Thus, the costs of intravenous coronary angiography may be 300 US dollars. These data refer to a prototype able to perform two intravenous coronary angiographies simultaneously. With industrial production, costs may be reduced notably. For further determination of the clinical value of this technique, larger scale comparative studies including cost-benefit analyses are encouraged.

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Appendix

The NIKOS system set-up consists of six main components.

The wiggler. The wiggler is a special magnetic structure installed in a straight segment of the storage ring. The wiggler forces the

positrons in the storage ring into a curved path and thereby enhances the intensity of the white synchrotron radiation. The magnitude of enhancement depends on the number of poles in the wiggler. The wiggler used (HARWI)[17] has 20 poles and a length of 2.4 m and 0.12 m for the endpoles. After installation of a variable vacuum chamber the minimal vertical magnetic gap amounts to 30 mm with a maximum field strength of 1.26 T. The resulting critical energy is 17.0 keV and the horizontal opening angle is 6.4 mrad. At 100 mA machine current, the power in the white synchrotron radiation beam is 4 kW. During patient studies the storage ring operates at energy levels of 4.5 GeV with a current of 56 to 126 mA.

The monochromator. The two monochromatic X-ray beams are diffracted out of the white synchrotron radiation beam by a two-crystal monochromator which is placed 31.6 m behind the wiggler[18]. A perfect Si (111) crystal is installed in Laue geometry for each monochromatic beam. Photons of 33.17 keV are diffracted with a Bragg angle of 3.42°. The crystals are bent in order to focus the beam on the patient; they are placed in a He-filled housing and cooled by water. The bandwidth of the monochromatic beams is $\delta E \leq 163$ eV. The flux in front of the patient is adjusted to be 2.7×10^{11} photons/mm^2/s. The intensity is not limited by the system output but by the upper limit of the skin entry radiation dose to the patient. This upper limit is set to 50 mGy per scan which corresponds to an effective dose of 0.5 mGy (male) to 1.0 mGy (female). The flux is adjusted to these numbers by reducing the height of the white synchrotron radiation beam at the entrance of the monochromator.

Safety system. The critical safety issue of the present system relates to the radiation dose to the patient. For a standard scan a skin entry radiation dose rate of 64 Gy/s is estimated. The NIKOS safety system consists of three independent shutters which can switch off the monochromatic beams within < 10 ms. The measurements of the ionization chambers in the safety system are routinely used for each scan to predict the expected dose. The system can only be activated after approval of the physician based on the predicted dose.

The scanning device. A line scan system has been developed to reduce radiation scatter and optimally match the X-ray source to the size of the patient's heart. The scanning device is equipped with a seat which allows vertical movements of the patient over a distance of 20 cm at a speed of 50 cm/s. Thus, a scan can be performed within 250 ms and 0.8 ms/line. The seat is driven by a hydraulic system. During the vertical movement of the chair the readout of the detector is controlled by an optical scale. In addition, the chair can be rotated in the horizontal and lateral axes to allow angular projections.

The detector. A fast low-noise, two-line ionization chamber[19] is installed as detector which simultaneously records the two lines with the energies above and below K-edge respectively. The detector has a common drift cathode and for each line, a Frisch grid and 336 Cu-strips as anodes. The center-to-center distance of the strips is 0.4 mm thus defining the horizontal pixel size in the images. The chamber is filled with 90% Krypton gas and 10% CO_2 at a pressure of approximately 13 bars. The ionization current of each strip is transferred into a sample-and-hold register and thereafter digitized with a 20-bit ADC. The dynamic range of the complete detector system was measured to be 328 000:1 (gain 4). Every 0.17 ms the two lines can be read in parallel. The data are transmitted to the computer via a glass fiber link.
The computer system. The computer system consists of an Alphastation 400 4/233 for coordination of the computer system, for data acquisition, for image processing and presentation, and a VEM-system for control. All three machines are linked.

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