Intravenous coronary angiography

W.-R. Dix for the NIKOS collaboration

HASYLAB at DESY, Notkestr. 85, 22607 Hamburg, Germany

Since 1981 the NIKOS-system for intravenous coronary angiography was developed at HASYLAB. Over the years 14 physicians from the University Hospital Hamburg-Eppendorf and the Heart Center Bevensen as well as 35 physicists, computer scientists and engineers from HASYLAB, the Physics Department of the University of Siegen, and the Physics Department of the University of Hamburg were involved. The work was strongly supported by the HASYLAB- and DESY-workshops and -services, by the machine group as well as by the directors of DESY and HASYLAB. In 2000 the project was successfully completed at DESY after investigation of a total of 379 patients.

The system

The development of the NIKOS-system was a continuous process. Several versions of the system were tested and applied for the human studies. Most of the patients, namely 303, were investigated with version IV of the system (Fig.1), which was installed end of 1996. Compared to systems for the same purpose installed at other institutions like NSLS, ESRF or KEK the version IV of the NIKOS-system is the most advanced, it is the world’s leading system for intravenous coronary angiography [1, 2].

![Figure 1: Schematic view of the NIKOS-system (version IV)](image)

For image formation the method of dichromography was selected [3]. Two images are produced simultaneously with monochromatic x-rays at energies bracketing the absorption K-edge of the contrast material, normally iodine with the K-edge at 33.17keV. After logarithmic subtraction of the images the contrast of the agent is increased remarkably while the contrast of soft tissue and bone tissue is suppressed. This allows the visualization of very low contrasts and thus of the very diluted contrast medium after intravenous injection.

In order to get subtraction images of good quality the energy of the two monochromatic beams must differ slightly only, maximal 300eV. Therefore, a maximal bandwidth of the beams of 250eV must be met.

The NIKOS-system was designed as a line scan system to reduce the background scattering in the images and to optimally match the conditions of a beamline at a storage ring. On the other hand the physicians demand to complete an image within a quarter of a heart cycle to enable
them to select by ECG-triggering a certain phase of the heart cycle for the scan. Therefore, about $3 \times 10^{11}$ photons/(mm$^2$·s) must be available in the monochromatic beams. The NIKOS(IV)-system is the only one which fulfills these conditions.

The system is installed in the DORIS storage ring (4.5GeV) at the wiggler beamline W2. The HARWI wiggler [4] has a field of 1.26T and the corresponding critical energy of 17keV is in the optimal range for this application. The total power is 6 kW at a machine current of 150 mA. Already at 54mA monochromatic beams with $3 \times 10^{11}$ photons/(mm$^2$·s) are available. Because the storage ring normally runs at 80mA to 150mA the available flux is reduced by a slit system in order not to exceed the maximal skin entry dose to the patient of 220mGy. That compares favourable with the mean of the skin entry dose of 410mGy for the conventional selective coronary angiography.

For the NIKOS-system the calculation of the maximal effective dose for the complete investigation results in 2.2mGy for males and 4.4mGy for females, respectively.

The monochromator [5] accepts the heat load due to the high power of the incident beam without problems. In a He-filled tube two bent Si(111)-crystals in Laue geometry are installed for the two monochromatic beams. These beams cross just in front of the patient at the focus of the beams with 0.5mm vertical. The sophisticated design of the mechanics and the water cooled crystals inside the monochromator results in two very stable, 13cm wide straight beams in front of the detector, 5.8 m behind the monochromator.

The safety system includes 3 independent very fast beam shutters [6], two of them are controlled by the patients chair and independent from computers. They close within less than 10 ms at any event which could increase the dose to the patient or the physician. The safety system guarantees that the dose to the patient will never be higher than the upper limit of 300mGy skin entry dose.

The scanning device with the seat for the patient distinguishes itself by compactness. For the ECG-triggered vertical scan the hydraulic system below the seat allows a stable speed of 50 cm/s over a distance of 20 cm. For the adjustment of the patient relative to the monochromatic beams as well as the projection angles a mechanical system is installed additionally.

The two-line detector is a 13 cm wide ionization chamber [7, 8] filled with 90% Kr and 10% CO$_2$ at 13.5 bar. It has very high dynamic range which additionally can be adjusted in four levels to the absorption of the individual patient. Depending on the level the measured dynamic range reaches from 191,000:1 to 328,000:1 and the photon equivalent noise from 3.1 to 14.8 photons.

The detector not only shows this high sensitivity but is very fast, too. The readout of the two lines with 336 pixels of 0.4 mm each can be completed within 0.17 ms to 0.23 ms. These outstanding parameters of the detector are essential for the completion of a scan within a quarter of a heart cycle and at the same time identification of very low contrast of 1 mm structures with a iodine mass density of 1.5 to 3.0 mg/cm$^2$ in front of lung tissue as well as bones.

The system control is performed with different dedicated VME modules. An Alphastation 400 4/233 is used for data storage, image processing and presentation. A very comfortable and rapid software package [9] allows the physicians to present their final diagnoses within minutes after the investigation.

**The human study**

230 of the 379 patients were included in a study with a fixed protocol and without any change to the NIKOS-system during this phase. Goal of the study was the validation of the NIKOS method versus conventional selective coronary angiography with the hypothesis that satisfactory diagnostic quality for follow-up patients can be reached with the new intravenous method compared to the conventional selective one as a 'gold standard' [10].

88% of the patients were male and 12% females, the age ranged from 36 to 81 years (mean 61) and the weight from 50 to 120 kg (mean 81 kg). 53 patients were post ACVB (bypass) patients,
165 were post PTCA (balloon dilatation) with 72% of those with stents. In most of the cases two different projection angles for different target vessels were selected for each patient. The target vessels divided in 35% left anterior descending coronary arteries (LAD), 25% right coronary arteries (RCA), 22% circumflex coronary arteries (Cfx) and 18% ACVBs. In 94% of the cases 30 ml of contrast material were injected into the brachial veins and in 6% into the superior vena cava.

During the study up to 6 patients per day were investigated with the NIKOS-system. No complications occurred. Some examples of the resulting angiograms are presented in Fig.2. 60 of the 230 patients had a selective angiogram within a period of 2 months, too. The angiograms of these patients were compared intra-individually. Several independent cardiologists, who had no training on the NIKOS-system before, looked to the NIKOS-angiograms and gave their diagnoses. For that the arteries and bypasses were divided artificially into three segments each and the physicians had decide whether there is a stenosis of 70% and more or not. Two different cardiologist worked on the selective angiograms in the same way. Though the agreement of these two was only 63%, the selective angiograms must be taken as the ’gold standard’ for comparison with the new method. As a result the independent reviewers reached a positive predictive value of 83% over all target vessels (mean of all reviewers 64%) and a negative predictive value of 96% in the mean. This shows the trend that the degree of the stenoses often was underestimated. Nevertheless practically all stenoses were identified in the NIKOS-angiograms.

In 18% of the segments a diagnosis was not possible. A very careful evaluation of the data and the images of the study showed that the number of these non-assessable segments could be reduced remarkably to about 5%, mainly by changes in the procedure during the investigations and to a small part by changes to the system. This would increase the predictive values, the sensitivity and the specificity of the method.

Most problems arise from the Cfx and the main stem due to superposition on large iodinated structures like aorta and left chambers. Here image processing algorithms like unsharp masking etc. [9] can support the diagnosis (see Fig. 2f).

Comparison of NIKOS, MRI and EBCT

The NIKOS method must be compared not only to selective coronary angiography but also to competing non-invasive or minimal-invasive methods like Magnetic Resonance Imaging (MRI) or Electron Beam Computed Tomography (EBCT). Contrary to selective coronary angiography all three methods have no risk to the patients and the investigations are ambulatory. But they have the disadvantage that the image quality is worse, image sequences are not available and interventions are not possible in the same session.

In most studies with MRI and EBCT the predictive values are not calculated. Therefore, the sensitivity and specificity must be compared. All three methods give similar values if all vessels are included, also the non-assessable ones. The values for the sensitivity are: NIKOS 23% to 77%, EBCT 59% to 69%, MRI (non-assessable ones excluded, number not published) 38% to 90%, and for the specificity NIKOS 85% to 92%, EBCT 63% to 76%, MRI (non-assessable ones excluded, number not published) 82% to 97%. It must be stressed that the NIKOS numbers include all segments of the arteries (proximal, middle, distal), the side branches as well as bypasses while for MRI and EBCT only the proximal and middle segments of the main arteries are included. The reason is that NIKOS has a much better image quality compared to MRI and EBCT. NIKOS allows to image arteries with a diameter of 0.8 mm, MRI and EBCT only 2 to 3 mm.

Furthermore NIKOS shows very good results at stents and bypasses. MRI cannot image stents and bypasses because metal leads to cancellations in the images. EBCT only shows stents and bypasses in very rare and special cases. Therefore, NIKOS is the optimal method for control of stents and
bypasses. Compared to NIKOS and EBCT, MRI has the advantage of no radiation dose to the patient and the possibility to image not only morphology but also function (myocardial perfusion). Additionally EBCT has the disadvantage that stenoses are not visible if there is superposition on calcium. EBCT and MRI have the disadvantage that a strong cooperation of the patients is required and arrhythmia lead to blurring in the images what is not the case with NIKOS. Because of the simple procedure there is a very high acceptance for NIKOS by the patients.

During the investigation EBCT and MRI only present cuts of the 3D-images while NIKOS presents the final images. On the other hand after reconstruction of the 3D-images EBCT and MRI allows a high number of projections to be presented and NIKOS only two.

Thus each of the three methods has advantages and disadvantages compared to the others and, therefore, each method has its niche for applications. The niche for NIKOS is obviously control of stents and bypasses.

**Outlook**

At DESY a very advanced system for intravenous coronary angiography was developed, tested and used for investigations of a large number of patients. Advantages and disadvantages of the method were determined as well as the limits. With some further changes to the procedure and the system it is expected to decrease the number of non-assessable segments by a factor more than 3. Overall the work shows that the method will not replace selective coronary angiography but it could be used for several applications without risk and with good results to the patients.

Now, in a next phase it must be decided whether the method can be installed in clinical routine. But in opposite to MRI and EBCT up to now there is no commercially available system for this method. Therefore, a feasibility study of a compact source on the base of a storage ring [11] for the method was prepared at DESY. The ring has a diameter of 21 m and two stations for investigations of patients. A very preliminary estimation of the costs gives 14.5 MDM per station plus 8 MDM for the buildings. This study could be the base for a final industrial study which should allow to reduce the costs.

The source could be installed in a large medical center. Assumed the costs given above and 7500 patients per year, the costs of one investigation are calculated to 870 DM. That is about half the costs of a selective coronary angiography (1300 DM and 2600 DM in hospitals). The number is in the range which was given by the reviewers (500 to 1000 DM for insurance patients and 500 to 1500 DM for private ones).

Whether 7500 patients per year are a realistic number for a center depends on the applications. One obvious application is the control of stents. In 1998 in Germany 528,000 selective coronary angiographies were performed, 30% of them were control investigations. Assumed 72% of those were patients with stents like in the NIKOS study, then 110,000 candidates were available for the center.

Another interesting application could be post operative control after bypass surgery. Nowadays this control usually is not performed. 6,000 to 12,000 candidates are expected.

Nevertheless the reviewers were not sure whether these two applications are sufficient to have 7500 patients per year for the center. Therefore, the future of the method depends, whether there will be a large medical community which has strong interest in the method, and if so, if there will be an investor who is prepared to install the source in a medical center.

**Acknowledgements**

The project was partly supported by the German Federal Minister for Education and Research (BMBF) under contract number 05350 GKA9, by the Werner-Otto-Stiftung, and by the Siemens AG.
The work on the NIKOS system has been conducted by a team of physicists, engineers and physicians, including: H.J. Besch (Dept. of Physics, University of Siegen - UniSI), W. Bleifeld (deceased) (Dept. of Cardiology, University Hospital Hamburg-Eppendorf - UKE), W.-R. Dix (HASYLAB), T. Dill (UKE), O. Dünger (HASYLAB), K. Engelke (Dept. of Physics, University of Hamburg - UniHH), C.-C. Glüer (UniHH), W. Graeff (HASYLAB), U. Großmann (UniSI), C.W. Hamm (UKE), G. Heintze (HASYLAB), J. Heuer (HASYLAB), K.H. Höhne (Dept. of Computer Science, University Hospital Hamburg-Eppendorf), C.P. Höppner (UniHH), H. Hultschig (HASYLAB), S. Iksal (UniSI), G. Illing (HASYLAB), H. Jabs (UniHH), D. Jowanowich (UniSI), H. Job (UKE), M. Jung (HASYLAB), B. Kaempf (UniHH), J. Knabe (HASYLAB), H. Krieger (UniSI), W. Kupper (Heart Center Bevensen), R. Langer (UniSI), M. Lohmann (UniSI), I. Makin (Fachhochschule Hamburg-Bergedorf), T. Meinertz (UKE), R.H. Menk (HASYLAB/UniSI), M. Mishima (UKE), T. Möchel (UniHH), W. Neef (UniSI), B. Reime (HASYLAB), R. Reumann (HASYLAB), C. Rust (UKE), H.W. Schenk (UniSI), L. Schildwächter (HASYLAB), L. Schlüter (UKE), S. Schröder (Dept. of Pathology, University Hospital Hamburg-Eppendorf), G. Seiffert (UKE), P. Steiner (UKE), K.-H. Stellmaschek (HASYLAB), U. Tafelmeier (HASYLAB/UniSI), R. Ventura (UKE), M. Wagener (UniSI), A.H. Walenta (UniSI), T. Wroblewski (HASYLAB), H.C. Xu (UniSI).

References


Figure 2: Angiograms after injection of 30ml of contrast agent into the brachial vein: (a) Schematic view of the coronary tree, (b) LAO60°-projection - RCA with in-stent restenosis (St1) and stenosis just behind the stents (St2), (c) RAO45°-projection - ACVBs to LAD (Ana = anastomose) and to a sidebranch of the Cfx (M1), (d) LAO30°-projection - ACVB to RCA, the RCA is filled retrograd (crux = crux cordis), (e) RAO30°-projection - LAD with two stenoses (St1 and St2), St2 at the site of the intervention, (f) RAO30°-projection - Cfx, LAD and main stem (HSt), image is processed with the unsharp masking method.