Report on Long Term project entitled "Human transvenous coronary angiography at the ESRF" (LS-2117)

The scientific case for the project was presented in the proposal submitted in March 2001. Very briefly, the goal of the angiography project is to develop a reduced risk imaging technique, which can be used to follow up patients after coronary intervention. After the intravenous injection of a contrast agent (iodine) two images are produced with monochromatic beams, bracketing the iodine K-edge. The logarithmic subtraction of the two measurements results in an iodine-enhanced image, which can be precisely quantified. The first human transvenous coronary angiography was carried out in early 2000 at the ESRF (Elleaume *et al.* 2000). A first research protocol was then completed within an 18 months period by recruitment of 30 patients. It was dedicated to the direct comparison between synchrotron coronary angiography and the conventional technique and was focused on the right coronary artery (Estève *et al.* 2001, Bertrand *et al.* 2002, Bertrand et al in preparation). This Long Term Proposal concerns the second research protocol including Human patients. The studies proposed were intended for the assessment of the synchrotron imaging method for left coronary artery stenosis. The research protocol is not completed, 26 patients have been enrolled up to now, and 6 patients are scheduled for April 2003 (last scheduled experiment for this Long Term Proposal). In the following, the medical protocol and principle of the method are briefly reiterated and the preliminary results obtained are presented.

1. Medical Protocols

Patients included in the protocol have previously undergone angioplasty. In 30% of the cases, re-stenosis occurs after angioplasty. If a re-stenosis is suspected, the patient is imaged at the ESRF, and within the next few days with the conventional technique at the hospital. The total radiation dose to a patient during the synchrotron imaging sequence is limited to 0.2 Gy by the medical protocol.

This second protocol was submitted to the Ethical committee of the CHU Grenoble and the "Comité Consultative de Protection des Personnes dans la Recherche Biomédicale Grenoble 2" (CCPPRB) approved it on July 2001.

2. Material and methods

The experiments were carried out at the medical beamline ID17, where a dedicated medical research facility has been commissioned (Elleaume *et al.* 1999). The x-ray energies and intensity are those required for the dual-energy digital subtraction technique to enhance the image contrast of the coronary arteries following venous injection of an iodinated contrast agent.

The dilution of the contrast agent prior to arrival in the coronary arteries, the background in the ventricles and the pulmonary veins, and the motion of the heart all present problems which are effectively solved by the K-edge subtraction technique. The monochromator is a single cylindrically bent silicon (111) crystal mounted in Laue geometry, which focuses the beam vertically. Two monochromatic beams are produced, one with an energy above and the other with an energy below the K-absorption edge of iodine at 33.17 KeV. The data acquisition system is

made of a high purity germanium detector associated with high dynamic range electronics (16 bits). The detector is electrically segmented into 864 strips distributed over two rows, resulting in a detection element pitch of 350 microns. Since the x-ray beam is fan-shaped (0.7 mm height and 150 mm width) it is necessary to move the patient through the beam in order to obtain two-dimensional angiograms. The positioning system, which allows both for positioning of the patient and the scan motions during the data acquisition, is a high precision stage with seven degrees of freedom. The speed is constant over a length of 200 mm, for a total displacement of 600 mm including the acceleration and deceleration phases. The vertical speed was set at 250 mm/s with an integration time of 1.4 ms corresponding to a vertical displacement of 350 microns per line. The image spatial resolution is therefore 350 μm x 350 μm and the temporal resolution is one image every 1.3 second. The x-ray dose received by the patient was monitored all along the experiment, it amounted 30 mGy/image on average.

3. Imaging parameters

Superposition of parts of the coronary arteries on larger structures filled with iodine is inherent to the intravenous injection of the contrast agent. To minimize this problem and obtain a clear presentation of all parts of the coronary artery, projection angles, and timing of the imaging relative to the bolus injection, must be optimized (Fiedler *et al.* manuscript in preparation).

- **Projection angles**

This is a crucial point after an intravenous injection of the contrast agent, due to the superposition of parts of the coronary arteries on larger structures like the ventricles or the pulmonary veins, which are still filled with contrast agent. The orientation of the patient is therefore a critical issue, especially for the left coronary artery visualization. The best orientation, to project the artery of interest into a clear field, was optimized during the first beam-times allocated.

- **Timing**

A second key-point is the synchronization between the iodine bolus arrival time in the coronary arteries and the imaging sequence. In order to minimize the superposition of the coronary arteries on ventricles or pulmonary veins, the bolus of iodine must be as short as possible. On the other hand a short bolus means that the imaging sequence must be very accurately synchronized with the bolus passage, since only a few images (3 to 5) will be recorded due to radiation dose limitation. The transit time (time between injection of the contrast material in a peripheral vein and its arrival in the coronary arteries) can vary greatly for different patients (about 10 to 20 sec). The values depend on the patient cardiac output and pulse rate. A reliable method was developed at the ESRF to measure the bolus transit time. A first imaging sequence called “Time to Peak” is performed at low x-ray dose and with a small amount of contrast agent injected. Five images are acquired at 3 sec interval time covering a time range from 9 to 21 sec. The time for the maximum opacification of the aorta is found in the “time to peak” sequence. From our experience, the maximum opacification of the coronary artery in the “imaging” sequence will be obtained, at the peak time plus a time delay of about 1 to 2 sec depending if the segment of interest is in the proximal part of the artery or distal part. The central image of the

"imaging sequence" is then set at "T peak + 1 or 2 sec" for obtaining the best coronary artery filling. This procedure has allowed the scan to be recorded at the optimal time in almost all cases.

The full procedure for patient imaging is the following:

1. Catheterization: The catheter is inserted into the brachial vein and advanced to the superior vena cava under fluoroscopy control, the patient is then installed in the scanning system, in the imaging room.

2. Positioning: The correct orientation of the patient is first checked by taking a single image at low x-ray dose (5 mGy) without injection of a contrast agent.

3. Transit time: The transit time between the injection of the contrast agent and the arrival of the bolus in the heart is measured using a series of five synchrotron images at low x-ray dose (5 mGy) with a small amount of contrast agent (10 ml).

4. Imaging: Few minutes later, once the contrast agent used for transit time estimation has disappeared from the venous circulation, the imaging sequence takes place. 30 to 45 ml of iodine (Iomeron® 350 mg/ml Bracco Italy) are injected into the superior vena cava using an auto-injector under remote control (18 ml/s). The image sequence is started a few seconds after the injection of the contrast agent depending on the transit time evaluation. Three to five images are then acquired to follow the iodine bolus through the patient circulation while the positioning system is moving up and down. The time delay between two images is 1.3 second.

4. Results

The left coronary artery has been investigated within the framework of the second medical protocol, which is still under progress. 26 patients have been imaged up to now. The number of patients imaged during the various allocated beam-times is listed Table 1.

Dates	Nb Patients included	
October 2001	6 (CHU 33-CHU 38)	
January 2002	6 (CHU 39- CHU 44)	Long Term Proposal
June 2002	8 (CHU 45- CHU 52)	Long Term Proposal
December 2002	6 (CHU 53 – CHU 59)	Long Term Proposal
April 2003	6 *To be performed*	Long Term Proposal

Table 1

- **Projection angles**

For the left anterior descending artery, the best projection angles were found to be small angulations in the Right Anterior Oblique (RAO) orientation (less than 50º). The last segments of the LAD are always completely imaged without superposition but it is difficult to obtain a good

projection angle for the main left stem visualization without having other iodine containing structures superposition.

- **Synchronization with the heart cycle:**

The synchronization of the imaging sequence with the patient heart cycle is difficult due to all the other time constraints (chair movements, bolus timing, variation of patient cardiac output etc…) After various trials, we decided to trigger only the first image of the sequence at a time equal to diastole + 20-30% of the cardiac cycle).

- **Stenosis measurement:**

A dedicated software tool for quantitative measurements of the stenosis was developed.
From the images, acquired above and below the iodine K-edge, one can calculate two images, one representing the iodine content and the second one a "tissue" image.

The images obtained by the K-Edge subtraction method are quantitative. One pixel contains the absolute value of the contrast agent concentration **ρ**, times the total thickness **t** integrated over the X-ray path. Therefore in order to evaluate the size of the arteries, one has to evaluate ρ first, and suppose it is constant along the artery path.

The arteries can be assumed of elliptical shape, where the small axis of the ellipse is the artery diameter d_1**,** parallel to the image plane, and the big axis is related to the orthogonal diameter d_2. The mass density ρ and the background signal level B are assumed to be uniform in the measurement vicinity.

The measurement of ρ is done by selecting an healthy segment of the artery and assuming it is circular with diameter d. Thus ρ and d are extracted by fitting a profile drawn across the image, y = P(x) :

$$P(x) = B + 2\rho\sqrt{d^2 - x^2}$$

Knowing ρ, it is then possible to measure the 2 diameters d_1 and d_2 in a segment where one suspects a stenosis by fitting again the profile:

$$P(x) = B + 2\rho d_2\sqrt{1-(x/d_1)^2}$$

A measurement tool following these specifications has been implemented in the software for the angiography images reconstruction. Figures 4 and 5 show examples of such measurements.

- **Images**

Figure 2 shows the angiography sequence of a 69 years old man patient with a body weight of 90 kg, together with his electrocardiogram, recorded during the imaging procedure. This image was taken in the RAO 50º projection. The images were recorded at 13, 14.3 and 15.6 sec

respectively, after the contrast agent injection. The bolus transit time to the aorta was measured to be 12 sec in the "Time to Peak sequence"(Figure 1).

Figure 3 is the angiogram of a 62 old man patient, weighing 80 kg in a RAO 50º projection view. Two stenoses were detected on the left coronary artery, one intra-stent stenosis estimated to be 30% and the second one 45%.

Figure 4 and Figure 5 illustrate the quantification tool capacity. Figure 4 refers to a patient 62 years old, weighing 72 kg. The artery transverse profile and its gaussian fit, are shown on the left side of the image. From this measurement, the artery diameter and the iodine concentration are estimated to be 3.57 mm and 19.7 mg/ml, respectively. This measurement can then be used to evaluate the diameter of the artery elsewhere and search for potential stenosis.

Figure 5 concerns a 43 years old man weighing 75 kg. The first concentration profiles (a.) is drawn in the artery where the first part comports a stenosis and the second part is normal. The second part (segment b.) is drawn in the background, assumed to be uniforme, next to the coronary artery.

5. Conclusions

To validate the diagnostic sensitivity and specificity of the method in comparison with the conventional coronary angiography, experienced physicians will evaluate the results obtained on the left coronary artery. Preliminary analysis shows that a good agreement in terms of stenoses diagnosis was obtained. The synchrotron method provides a good way to assess the status of known stenosis on the distal part of the left coronary artery, while being a less invasive method compared to conventional coronary angiography. The main stem and the very proximal part of the left coronary artery is however difficult to assess. A new protocol, with "direct benefit" for the patient, could be envisaged. The radiation dose delivered to the patient can then be increased, allowing more projection views to be performed (the actual x-ray dose limit is 20 cGy for the overall procedure).

Since the present method uses venous catheterization, the coronary arteries are not artificially pressurized. The resulting images are therefore in a true physiological state. The virtual absence of complications with this method allows it to by used for research protocols where conventional angiography may not be allowed. In patients with stents, the synchrotron method allows simultaneous visualization of the stent and the perfusion of the vessel. The disadvantages of the synchrotron method are mainly the possible superposition of the venous structures over the arterial tree, and the filling of the ventricles with the contrast agent. These inconveniences can be overcome by carefully selecting the projection views.

Figures

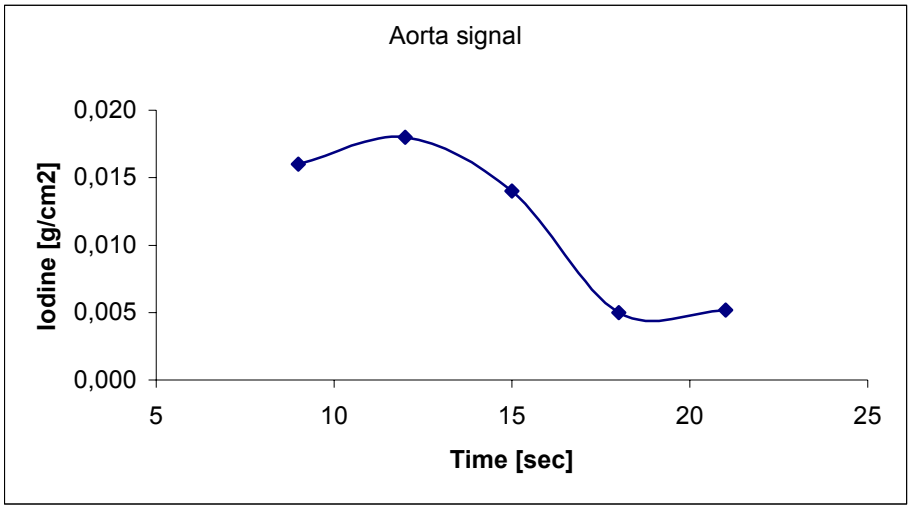

Figure 1: Patient CHU # 35 - Signal recorded in the aorta during the Time to Peak sequence

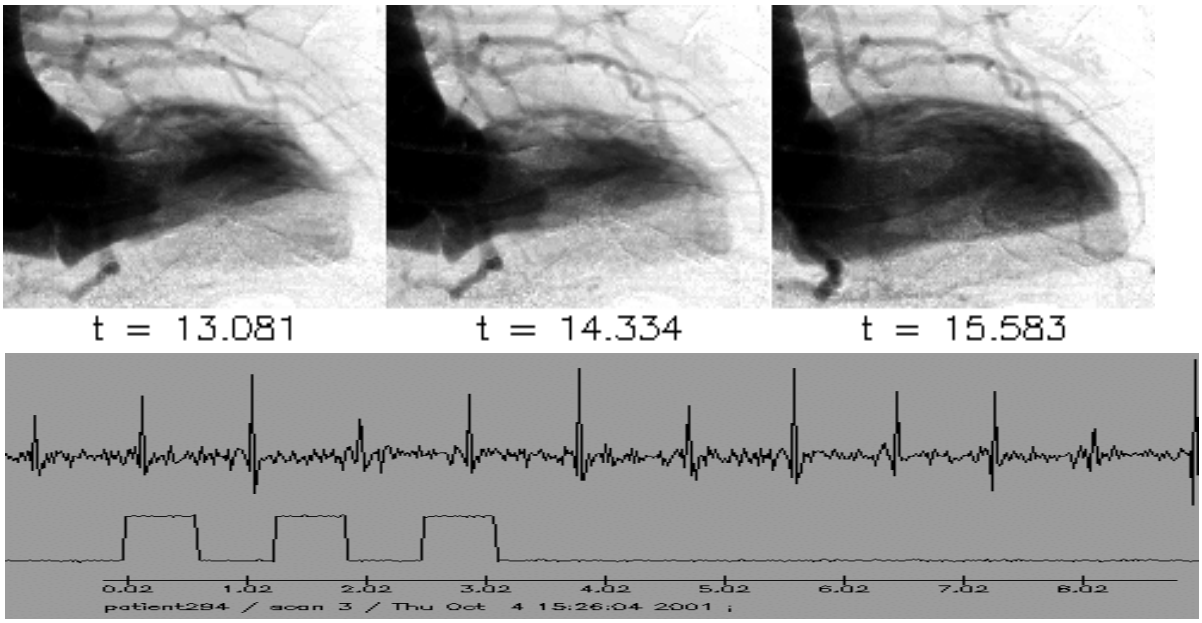

Figure 2: Patient CHU # 35 - Imaging sequence of the left anterior artery together with the electrocardiogram output.

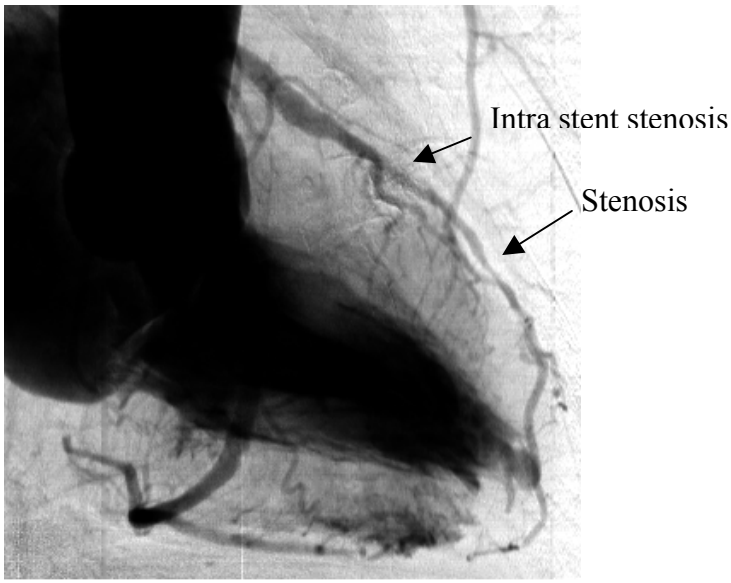

Figure 3: Patient CHU # 45 – Two stenosis are visible on the left coronary artery.

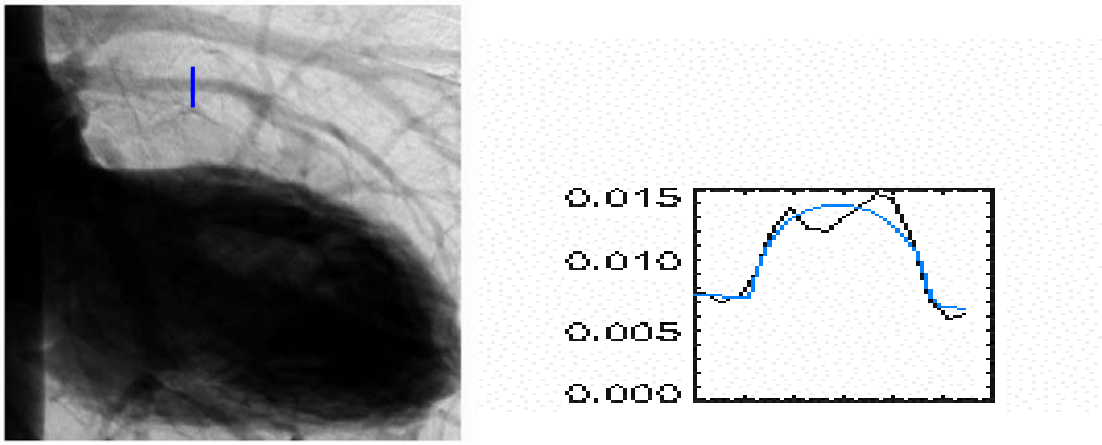

Figure 4: Patient CHU # 47 - Transverse profile and its gaussian fit, performed on a healthy part of the artery. Concentration ρ=19.7 mg/ml and diameter: d=3.57 mm

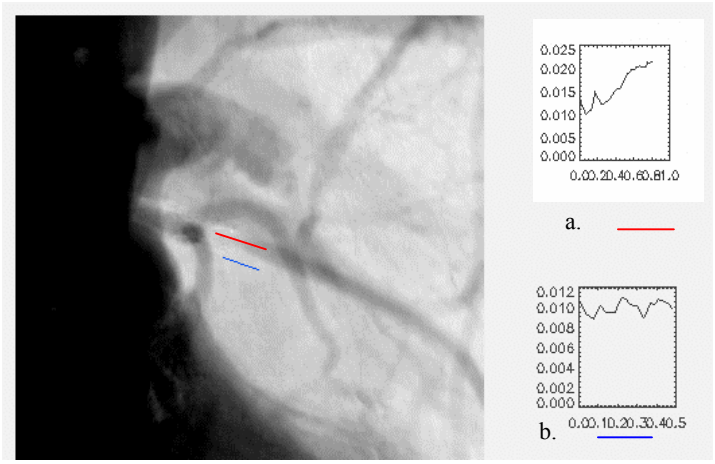

Figure 5: Patient CHU # 46 - Longitudinal profiles:
a. Profile in the artery.
b. Profile in the background.

References:

H. Elleaume, Charvet AM, Berkvens P, Berruyer G *et al.* 1999 Instrumentation of the ESRF medical imaging facility Nucl. Instr. Meth. A 248 513-527.

H Elleaume, S Fiedler, F Estève, B Bertrand, AM Charvet, P Berkvens, G Berruyer, T Brochard, G Le Duc, C Nemoz, M Renier, P Suortti, W Thomlinson, JF Le Bas 2000. First Human transvenous coronary angiography at the European Synchrotron Radiation Facility. Phys Med. Biol. 45 L39-43.

F. Estève, B. Bertrand, H. Elleaume, L. Hammer, C. Nemoz, M. Renier, S. Fiedler, G. Le Duc, A. Bravin, W. Thomlinson, J. Machecourt, J.F. Le Bas. Diagnostic de resténose après angioplastie coronaire avec l'angiographie intraveineuse par rayonnement synchrotron. Premiers résultats d'une étude comparative avec l'angiographie conventionnelle. Journées française de radiologie 2001, Marseille France.

B Bertrand, F Estève, H Elleaume, S Fiedler , L Hammer, J Machecourt, W Thomlinson , JF Le Bas. Diagnosis of restenosis after PTCA with intravenous coronary angiography using synchrotron radiation. Comparative study with conventional angiography. Poster XIV world congress of cardiology 5-9 May 2002 Sidney Australia.

B Bertrand *et al.* Diagnosis of restenosis after PTCA with intravenous coronary angiography using synchrotron radiation. Comparative study with conventional angiography (manuscript in preparation).

S Fiedler *et al.* Methods and developments for intravenous coronary angiography with synchrotron radiation at the ESRF (manuscript in preparation).