Tailoring X-ray Beam Energy Spectrum to Enhance Image Quality of New Radiography Contrast Agents Based on Gd or Other Lanthanides

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ABSTRACT

Gadovist, a 1.0-molar Gd contrast agent from Schering AG, Berlin, Germany, in use in clinical MRI in Europe, was evaluated as a radiography contrast agent. In a collaboration with Brookhaven National Laboratory (BNL), Schering AG is developing several such lanthanide-based contrast agents, while BNL evaluates them using different x-ray beam energy spectra. These energy spectra include a "truly" monochromatic beam (0.2 keV energy bandwidth) from the National Synchrotron Light Source (NSLS), BNL, tuned above the Gd K-edge, and x-ray-tube beams from different kVp settings and beam filtrations. Radiographs of rabbits' kidneys were obtained with Gadovist at the NSLS. Furthermore, a clinical radiography system was used for imaging rabbits' kidneys comparing Gadovist and Conray, an iodinated contrast agent. The study, using 74 kVp and standard Al beam filter for Conray and 66 kVp and an additional 1.5 mm Cu beam filter for Gadovist, produced comparable images for Gadovist and Conray; the injection volumes were the same, while the radiation absorbed dose for Gadovist was slightly smaller. A bent-crystal silicon monochromator operating in the Laue diffraction mode was developed and tested with a conventional x-ray tube beam; it narrows the energy spectrum to about 4 keV around the anode tungsten's $K\alpha$ line. Preliminary beam-flux results indicate that the method could be implemented in clinical CT if x-ray tubes with ~ twice higher output become available.

Keywords: Radiography with contrast agent, CT with contrast agent, iodine contrast agent, gadolinium contrast agent, monochromatic x ray, x-ray monochromator, x-ray beam filtration, x-ray K-edge beam filtration, image contrast-to-noise ratio

1. INTRODUCTION AND RATIONALE

The current state of x-ray radiography with iodine-based contrast agents suffers from three inadequacies. First, such contrast agents cause adverse reactions in many patients, including those with allergies, asthma, kidney diseases, and diabetes [1-9]. These reactions can be severe or fatal. Second, iodine (Z=53) is not heavy enough to efficiently attenuate x rays at energies above ≈ 50 keV; gadolinium (Gd, Z=64), for example, is much better. Third, the filtered bremsstrahlung x-ray beams used are not ideal for contrast imaging because they are very broad and have little intensity just above iodine's (or gadolinium's) K-edge. A lanthanide-based agent may solve all these problems. The main reasons, in physical terms, for suitability of lanthanides for x-ray radiography, are that the energy of their K-edge is larger, and their attenuation coefficient for x rays > 50 keV is greater. Their larger K-edge (50.23 for Gd vs. 33.17 for I) allows the use of nearly monochromatic x-ray beam

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energies just above the K-edge of the contrast element for general radiography with adequate transmission through the human body. Iodine cannot be used for similar purpose except for imaging thin body sections. Fig. 1 shows a superposition of a 100 kVp x-ray spectrum and the attenuation coefficient curves of iodine and gadolinium. The spectrum was simulated using the Monte Carlo code EGS4[10]. The figure vividly demonstrates that a) the low K-edge of iodine makes its usage sub-optimal with the 100 kVp spectrum (and essentially with any other spectrum that is suitable for general radiography), and b) the 100 kVp spectrum is too broad for Gd imaging (the ideal spectrum for Gd imaging is a monochromatic beam above Gd's K-edge).

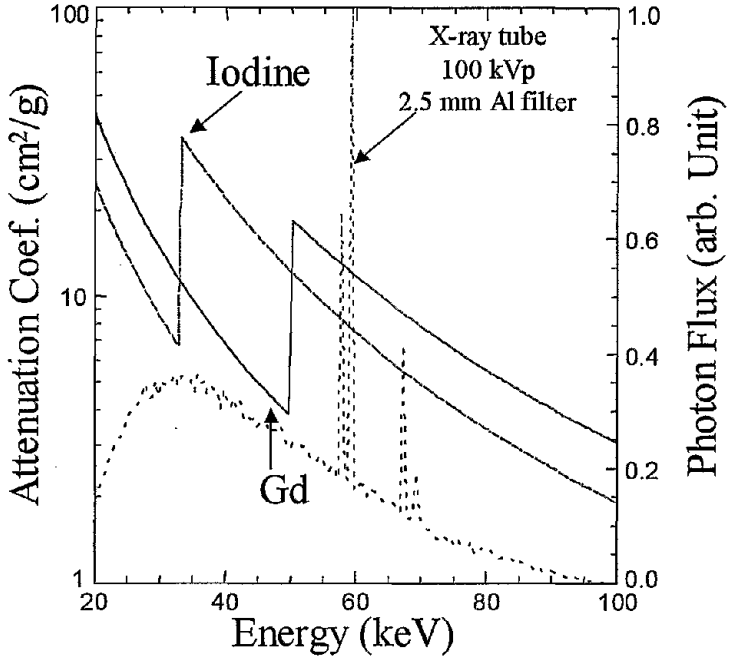


Fig. 1. Superposition of a 100 kVp x-ray energy spectrum with the attenuation coefficient curves of iodine and gadolinium.

In a collaboration between BNL and Schering AG, Berlin, Germany, Schering AG will develop safe contrast agents for radiography based on a lanthanide[11] (Gd, Dy, Er, or Yb) or Bi. The BNL group will evaluate the agents with a variety of spectral shapes of x-ray beams, including a) a "truly" monochromatic, synchrotron-generated x-ray beam from the National Synchrotron Light Source (NSLS), BNL, b) a beam from an x-ray tube with an energy spectrum narrowed to 3-8 keV around the K_α characteristic anode line, using a bent-crystal Si monochromator operating in the Laue diffraction mode[12-17], and c) a beam from an x-ray tube whose energy spectrum is narrowed around the anode K_α line using different combinations of kVp setting and beam filtration, including Cu beam filtration and K-edge beam filtration. The new agents will be evaluated with conventional planar radiography systems at BNL and at the Health Sciences Center, State University of New York at Stony Brook (SB), and with SB's computed tomography (CT) system.

A major objective of our present work is to construct a bent-crystal Laue monochromator to use with conventional x-ray tubes for planar radiography and CT, with an energy bandwidth of ~3-8 keV, compared to 25-50 keV in conventional sources. The bent crystal monochromator was chosen over the flat crystal device because of its larger yield resulting from its larger energy bandwidth, and larger angular acceptance angle (which makes the device more forgiving to misalignments and vibrations). The monochromator will be tuned to tungsten's characteristic line $K\alpha$ (58.9 keV) for a higher yield. This energy, which is only 8.2 keV above Gd's K-edge, will be remarkably suitable for use with Gd and Dy. Earlier, the basic design was tested successfully at BNL for a slightly different optical arrangement (i.e., parallel exit beam focusing configuration)[17], while the normally diverging geometry of the exit beam, which is the goal of this project, was evaluated recently. One feature of both these designs involves stacking thin (0.7-mm thick) Si crystals to enhance the monochromator's yield. The monochromator will be evaluated at both BNL and SB, using clinical radiography machines. The resulting x-ray-tube based monochromatic-beam systems then will be used to evaluate the new compounds. The factors

affecting the intensity of the beam reaching the patient are the integrated reflecting power of the bent crystal's diffraction, and geometry of separating the diffracted and the incident beams which puts a lower limit on the distance between the patient and the monochromator. Fig. 2 is a schematic view of a radiography system employing a bent Laue monochromator.

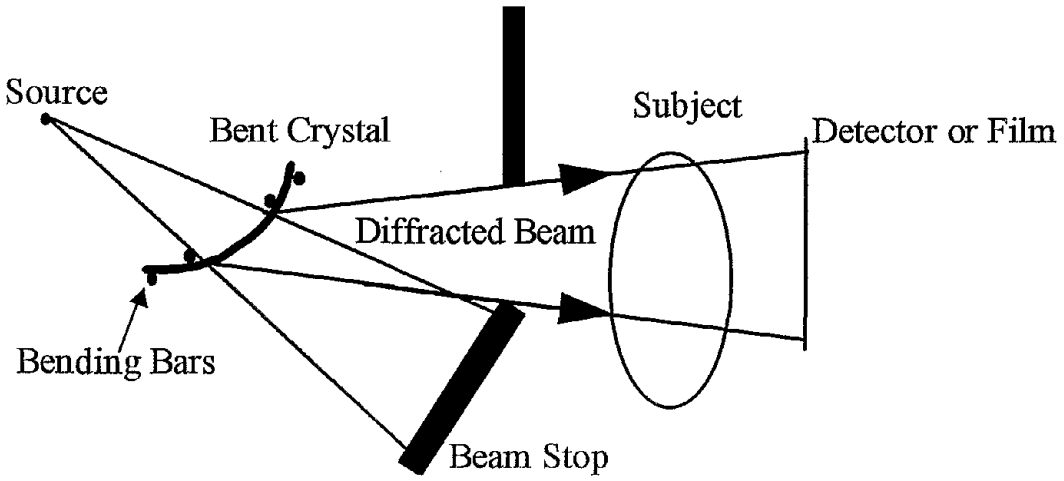


Fig. 2. Schematic view of a bent crystal monochromator incorporated in a radiography system.

All beam tailoring methods indicated above involve multi-fold loss of x-ray beam intensity. The enhanced transmission through the subject of x rays in the new spectra (filtered of obtained with the bent crystal monochromator) makes up for partial loss of x-ray flux. However, if the method is successful, its implementation in clinical radiography will require the development of special x-ray tubes with enhanced x-ray output.

The narrow energy bandwidth obtained with all the beam-tailoring methods discussed in this report are essential for radiography with lanthanide-based contrast agents because of the resulting large gain in image contrast and the lowering of image noise. However, narrow energy bandwidths are meritorious also in general radiography where no contrast agent is used because they allow the beam's energy to be reduced (which increases soft tissue image contrast) without increasing the patient's dose of absorbed radiation[18]. The beams are particularly beneficial to CT imaging[19-28], where, in addition, they reduce beam-hardening artifacts[29] and may allow (depending on the beam-tailoring method used) an optimal beam energy to be used for a given subject-size category.

2. EXPERIMENTAL METHODS

The experiments used Gadovist, a contrast agent developed by Schering for MRI with 1.0 molar Gd concentration[30] (compared to 0.5 in Magnevist), currently used in Europe for magnetic resonance imaging (MRI). All images were obtained in the planar mode. The rabbits imaged were of Giant Flemish strain and weighed about 7 kg each.

2a. Imaging rabbits' kidneys with Gadovist using monochromatic x-ray beams at the NSLS

The "white", fan-shaped, x-ray beam from the X17B1 superconducting wiggler of the NSLS was monochromatized using a two-crystal Bragg monochromator from the Diffraction Enhanced Imaging (DEI) program[31]. The horizontal fan-shaped beam was narrowed to 1mm height and 120 mm width. The anesthetized rabbit was laid in an almost vertical configuration on a stage positioned 1.5 m downstream of the monochromator. The source spot, 0.9 mm horizontal and 0.05 mm vertical, was 29 m from the rabbit. The detector, an imaging plate (IP), was sited 1.3 m downstream of the animal (to reduce scattering) on a second vertical stage. The imaging method included simultaneously scanning the animal and the IP vertically through the fan beam at the same speed. One rabbit was imaged at a beam energy just above the 50.23-keV K-edge of Gd (50.44 keV), and a second rabbit at that energy and an energy just below it (50.04 keV); the energy bandwidth was about 0.2 keV. After the anesthetized rabbit was positioned on the stage, and was imaged once without the contrast agent, it was

injected intravenously with 20 ml of Gadovist at the rate of ~ 10 ml/minute. It was then imaged at 3 minutes and 7 minutes after the completion of the injection. To simulate the thickness of the human body, rectangular acrylic water containers of 12 cm combined thickness (water and acrylic) were placed in the beam upstream of the rabbit.

2.b. Imaging rabbits' kidneys with Gadovist and an iodinated agent using a conventional x-ray radiography system

The following measurement compared Gadovist with an iodinated agent, Conray, at the same injection volume and nearly the same radiation dose, using a conventional radiography beam for Conray and a heavily filtered beam for Gadovist. Our first goal was to demonstrate Gadovist's applicability as a radiography contrast agent in existing clinical x-ray radiography systems. Our second goal was to demonstrate that virtually only the portion of the energy spectrum above the Gd K-edge contributes to the Gd image contrast, and, therefore, eliminating the spectral region below that energy lowers dose to the patient and improves the image contrast-to-noise ratio (image noise is reduced because the new beam has a better transmission through the body). Table 1, below, compares the parameters in these two measurements.

Table 1. Imaging parameters for the x-ray radiography of iodine vs. gadolinium

	Iodine-based compound	Gadolinium-based compound
Compound	Conray	Gadovist
Concentration	2.22 molar I (282 mg I/ml)	1 molar Gd (157 mg Gd/ml)
Manufacturer	Mallinckrodt Inc., St. Louis, MO, U.S.A.	Schering AG, Berlin, Germany
Volume administered intravenously into the ear vein	20 ml	20 ml
kVp setting of the x-ray system	74 kVp	66 kVp
Current x exposure time	15 mA· s	600 mA· s
Beam filter	3.2 mm Al	3.2 mm Al + 1.5 mm Cu
Skin dose to the rabbit	0.66 mGy	0.42 mGy

2c. Monte Carlo simulations of K-edge beam filtration of x-ray spectra from a conventional radiography system

The simulations were undertaken to estimate the applicability of K-edge filtration to produce narrow bandwidth spectra for Gd imaging . Because K-edge beam filtration allows larger high voltages to be used on the x ray tube compared to Cu beam filtration, it requires less mA·s compared to the Cu filtration option. Therefore, it may be suitable for machines with less mA·s capability. The EGS4 Monte Carlo code[10] was used for this simulation. Electron beam of 66, 74, and 100 keV energy was directed in a perpendicular direction to fall onto a thick tungsten plate. The energy spectrum of output photons, averaged over all emission angles, then was filtered with Al, Cu, or Yb filters.

2d. Testing the bent-crystal monochromator

In this preliminary study, we prepared a bent crystal monochromator and assessed its performance at the BNL's Medical Department using a tungsten-anode source operating at 100 kVp with an electron current of 8 mA. Because the machine, Philips RT-100, has been designed for use in experimental radiation therapy research and not in radiography, it has a large (about 6 mm) focal spot. Since the monochromator's performance is sensitive to the focal spot size in the diffraction plane (vertical), the output window of the tube was masked by a pinhole of 0.4 mm vertical x 4.0 mm horizontal to simulate an x-ray tube used for radiography. The detector, a Canberra germanium detector, was masked in front with a slit of variable vertical size. The detector and slit assembly could be scanned up and down to study the vertical profile of the diffracted beam. The detector was positioned 1.24 m from the source, which is a typical patient-to-source distance.

A "four-rod crystal bender"[15-17] was put on a stage which could adjust, under motor control, the crystal's Bragg angle, height, and the distance to the source. The crystal, a 0.7-mm thick Si wafer, was bent cylindrically, with the cylinder's axis being horizontal, using the crystal bender. It was positioned in front of the x-ray tube 78 cm from the source. The bending

radius was 90 cm, and concave side of the crystal faced the beam. To avoid variation of the beam energy with the vertical beam height, the bending radius and the source-to-crystal distance were chosen so that source spot was positioned at the crystal's "focusing point", i.e., the source spot was positioned on the Rowland circle (a circle with a diameter equal to the bending radius of the crystal, centered at the midpoint between the center of bending and the crystal[12]). In this geometry the divergence of the diffracted beam is the same as that of the incident beam, i.e., the monochromator does not introduce any beam focusing. The filter was 1.7 mm aluminum. The monochromator was tuned to about 58.9 keV, the average energy of the $K\alpha$ characteristic line of the tungsten anode. The germanium detector was used to measure the beam spectrum with and without the monochromator; the ratio of the diffracted spectrum to the incident spectrum then provided the absolute spectral yield of the monochromator.

3. RESULTS

3a. Imaging rabbit kidneys with Gadovist using monochromatic x-ray beams at the NSLS

Fig. 3 shows the rabbit imaged at 50.44 keV, i.e., above the Gd K-edge, before the injection of Gadovist, and 3 and 7 minutes after the injection. The rabbit kidney is well visible in the Gd images. The profiles depicted in the lower right quarter show the image contrast through vertical line profiles drawn on the side of the kidney in these three images. These profiles show that the image detection signal inside the kidney is about 60% larger after the injection of Gadovist, demonstrating the radiographic potential of Gadovist with an ideal beam energy. The profiles for the two time points of 3 and 7 minutes are very close to each other. The skin dose to the rabbit was 0.32 mGy.

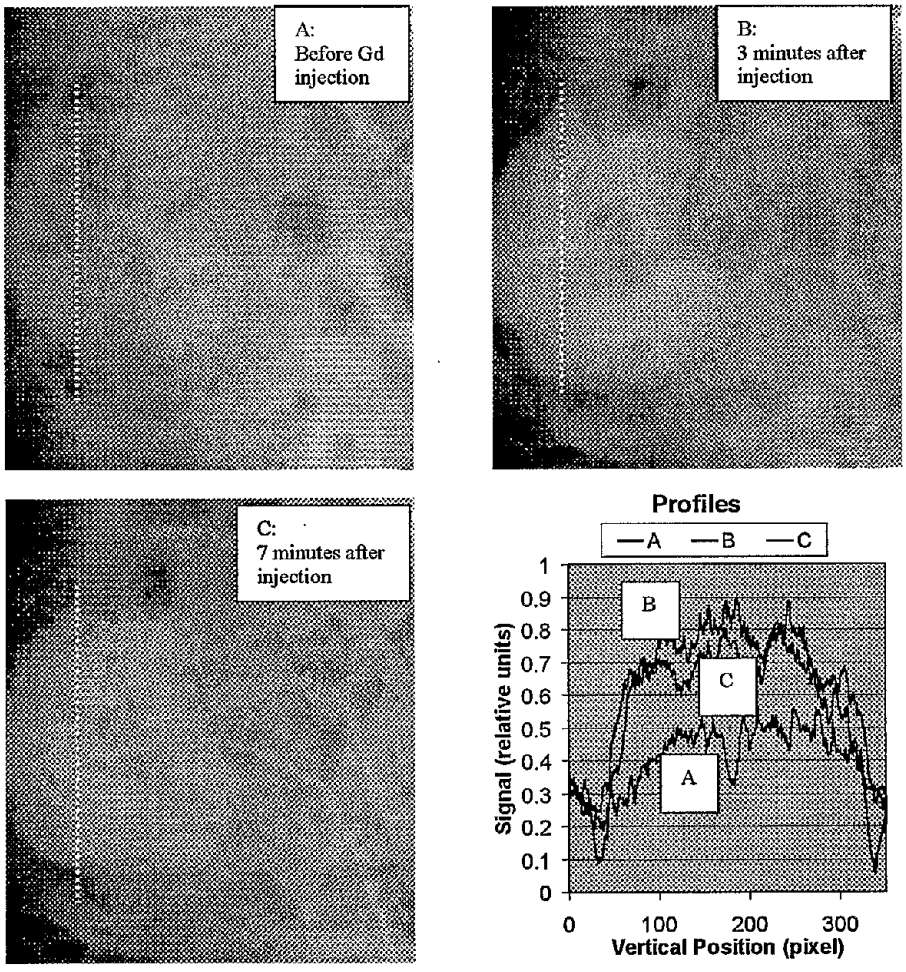


Fig. 3. Rabbit's kidney imaged with monochromatic x rays from the NSLS at an energy just above Gd's K-edge.

3b. Imaging rabbit's kidneys with Gadovist and an iodinated agent using a conventional x-ray radiography system

Fig. 4. shows the 66 kVp spectrum before and after filtration with 1.5 mm Cu. The spectrum with 1.5 mm Cu was enlarged 10-fold so that it is visible on a linear-scale plot. The energy bandwidth of the incident spectrum, full width-at-half-maximum (FWHM), is 26 keV (70% of the median energy) before Cu filtration, and 10 keV (18% of the new median energy) afterwards.

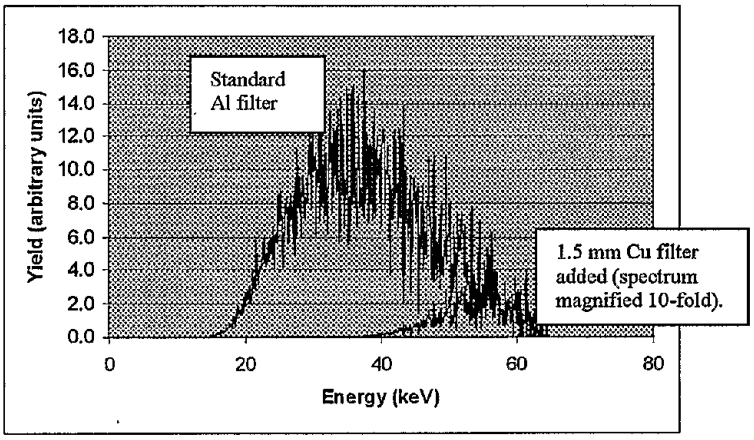


Fig. 4. A 66 kVp spectrum superimposed with the same spectrum after being filtered with and additional 1.5 mm Cu.

Fig. 5. shows the images of the two rabbits imaged with Gadovist and Conray taken 5 minutes after the injection of the contrast agents. The anesthetized rabbits were positioned flat on the imaging table. The source-to-film distance was 1 m. A conventional film-screen was used for image collection. The results indicate that Gadovist together with a nearly ideal beam energy spectrum produce a comparable image to that from Conray and a conventional beam at comparable doses.

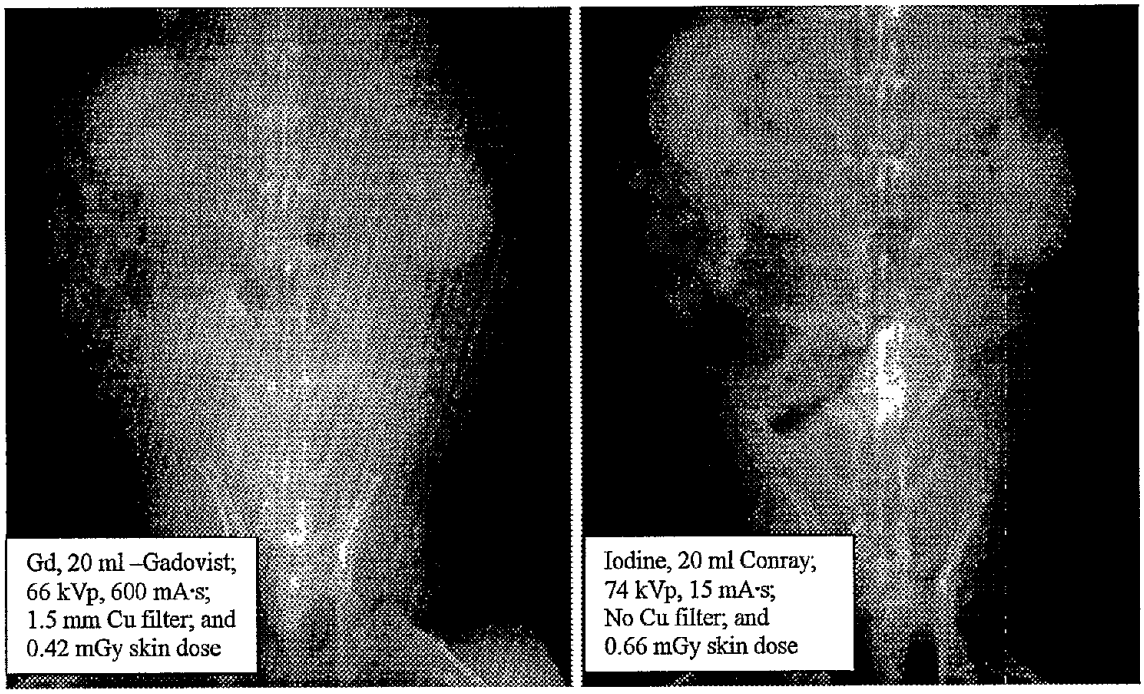


Fig. 5. Rabbits' kidneys imaged with iodine (Conray) (74 kVp, regular beam filtration) and Gd (Gadovist) (66 kVp, 1.5 mm Cu).

3c. Monte Carlo simulations of K-edge beam filtration of x-ray spectrum from a conventional radiography system

Fig. 6 shows a 100 kVp spectrum on the side of one filtered with 0.5 mm ytterbium and 0.5 mm copper. This combination of Cu filtration and K-edge filtration allows cutting the low and the high part of the spectrum, respectively, at the right proportions. The K-edge filtration allows the use of 100 kVp spectrum instead of 66 kVp that we used when only Cu filtration was intended; as a result, large beam outputs are reached. The price to pay for this large beam intensity is some beam contamination at the far low and far high end of the spectrum, which does not exist with Cu filtration of 66 kVp spectrum, neither with the spectrum from the bent crystal monochromator.

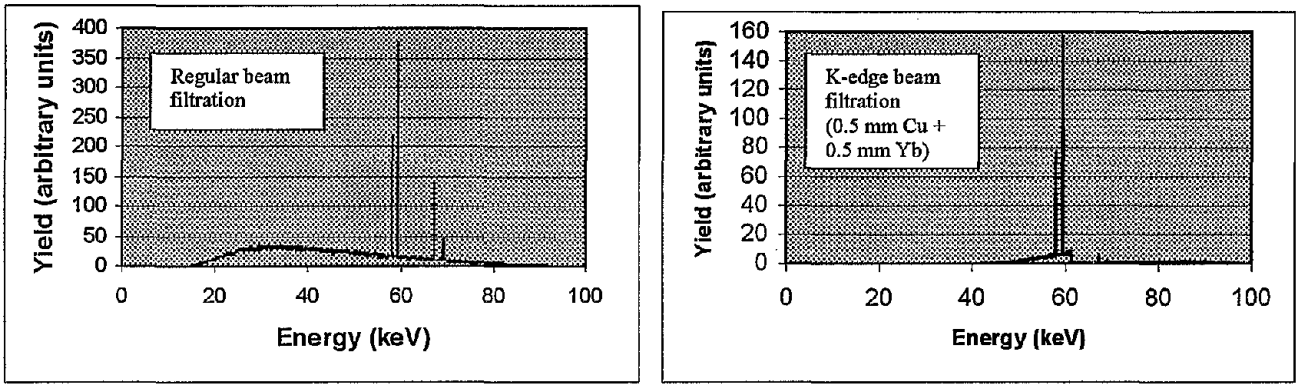


Fig. 6. A 100 kVp spectrum (on the left), and one filtered with 0.5 mm Cu filter and 0.5 mm Yb K-edge filter. The vertical scales in the two figures relate to each other in the proper ratio.

3d. Testing the bent-crystal monochromator with a conventional x-ray tube

Fig. 7 shows the spectrum of the diffracted beam from the bent crystal, superimposed with that of the incident beam. The following points summarize the results. First, The absolute reflectivity of the monochromator at the tungsten $K\alpha$ line was about 12%. Second, the total spectral count yield of the diffracted beam was 1.2% of that of the incident beam. This yield would essentially be about 1.7% if the beam filtration of the incident beam was about 3.2 mm (instead of 1.7 mm used), which is the standard in clinical radiography. Third, the background in the incident spectrum was not completely suppressed. The measured spectral count yield with three wafers stacked (not shown) was 3.2%, giving a total count yield of 4.5% with standard beam filtration. This number should be augmented by the advantage factor in the transmission of the spectrum through the patient's body because of the larger mean energy of the monochromatic beam, which may be several folds depending on the size of the subject. Furthermore, the x-ray tube can be operated at very high kVp setting when the monochromator is used, increasing further the yield of the anode $K\alpha$ line. The missing factor, therefore, to reach the yield necessary for human imaging with the new monochromator may be a four- to six-fold. Because most of the x ray machines can accommodate much of this additional intensity need, we expect the only about 2-fold additional maximum throughput of the machine will be necessary for the implementation of the monochromator in clinical radiography. Further development of the monochromator will include the following steps: a) better aligning the crystal on the bender, and the system, b) decreasing the crystal's bending radius to reduce distance between the source and subject, c) stacking 3 or 4 wafers for better yield, and d) reducing the background.

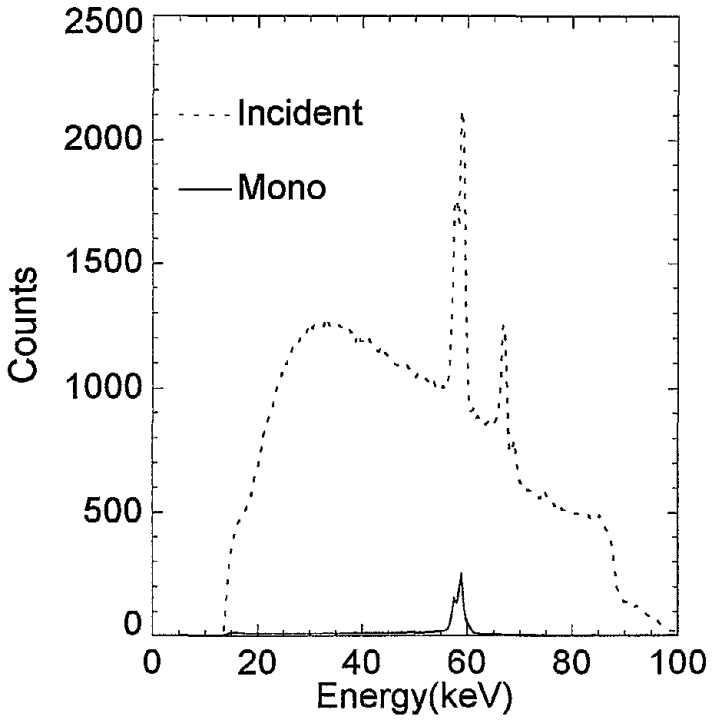


Fig. 7. Spectra of the diffracted beam when the monochromator is tuned to the Kα characteristic line of the tungsten anode and the spectrum of the incident beam (filtered only with 1.7 m Al).

4. CONCLUSIONS

The following conclusions can be drawn from our results:

a. Synchrotron-generated monochromatic x-ray beams tuned just above the K-edge of Gd produce the images with a higher contrast-to-noise ratio (conceptually the highest) than any other beam spectrum.

b. For the same volume in a rabbit and comparable radiation absorbed doses to the skin, Gadovist and the iodinated contrast agent Conray produce comparable image contrast-to-noise ratios when the Gd image is acquired at 66 kVp and with 1.5 mm Cu filter in the beam while Conray is imaged at 74 kVp and conventional beam filtration.

c. K-edge beam filtration of radiography systems allows the use of higher than 66 kVp high voltage on the x-ray tube. However, the spectrum commonly includes contamination components at the higher- and lower-energy ends.

d. Optimization of the bent Laue monochromators, stacking three together, provides ~4.5% spectral count yield. Increasing the high voltage on the x-ray tube will increase the yield of the anode Kα line further. Considering the better transmission of the resulting beam through the patient, the effective yield can be 15-25% or higher.

e. Although beam filtration methods can be implemented readily on a large number of clinical radiography systems with no additional modifications except for adding the filters, in general the beam tailoring methods all involve the loss of a substantial portion of the spectrum, and, therefore, require x-ray tubes with a higher output. Implementing the bent crystal monochromator in clinical systems requires, in addition to a higher beam flux, provisions to accommodate the new angle of the diffracted beam.

f. The advantage of Gd imaging with narrow energy bandwidth increases with increasing thickness of the subject's body. Therefore, we expect the advantage in patients to be larger than that presented here with rabbits.

g. Finally, Gd contrast agents together with tailored beams have a great prospect in coronary and carotid angiography, where attempts have been made to develop narrow-energy systems to be used with iodinated contrast agents[32].

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