Intravenous Coronary Angiography Utilizing K-Emission and Bremsstrahlung X-Rays Produced by Electron Bombardment

Summary

The screening of the general population for coronary artery disease would be practical if a method existed for visualizing the extent of occlusion after an intravenous injection of contrast agent. Measurements performed with synchrotron radiation at SSRL and NSLS have shown that such an intravenous angiography procedure would be possible with an intense source of monochromatic X-rays. Because of the high cost of an electron synchrotron, theoretical analysis and experiments using inanimate phantoms has been undertaken to demonstrate the feasibility of using the spectrum produced by two appropriately chosen anode materials when bombarded with electrons in the 100-500 keV energy range for angiography. By using the X-rays emitted at 120° to the incident electron direction, about 20-30% of the X-ray intensity would be due to K-emission lines. Calculations using the TIGERP Monte Carlo Code, have shown that high quality angiograms of human coronary arteries should be possible with a contrast agent containing ytterbium, if an electron beam pulses of 16 kJ were used for each anode target. The experimental program supported in part by the DOE has consisted of these theoretical calculations and experiments at the Dynamitron Electron Accelerator Facility at BNL.

Significance of the Research

Premature disease of the coronary arteries is the leading health-care problem today in industrialized countries. In the United States alone, there are approximately 3.5 million individuals with coronary disease; about 1.3 million new heart attacks occur each year.

Coronary disease manifests itself as a progressive occlusion of the coronary arteries, resulting eventually in their sudden blockage and irreversible injury or death to the associated heart muscle. Current methods of detecting these occlusions put the patient at high risk. The conventional method, the coronary arteriogram, requires that a catheter be inserted in the large femoral artery and into the aorta and the tip positioned, in turn, in the orifice of each of the two major coronary arteries. The cardiologist then injects a contrast agent through the catheter directly into the artery and takes X-ray radiographs of the heart, which enables him to visualize any blockages.

However, there are several risks associated with the arteriogram, including the precipitation of cardiac arrest or arrhythmias through mechanical irritation of the heart. Collectively, these risks are associated with 0.1 - 0.3% mortality and 1 - 4% morbidity rates, which are much too large to permit routine use of invasive coronary angiography as a screening test. Therefore, there is currently strong medical interest in developing a safe, non-invasive method of obtaining angiograms.

Non-invasive angiographic techniques involve the injection of a contrast agent into a vein instead of a coronary catheter. The contrast agent is substantially diluted before it enters the coronary arteries. To compensate for this dilution a more sensitive method of detection of the contrast agent is required. There are two approaches to the detection of a dilute solution of

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contrast agent in the coronary arteries. Both schemes are based upon the acquisition of two images: a first image of bone and soft tissue, and a second image of bone, soft tissue, and underlying coronary arteries which contain the contrast agent. The images are then subtracted logarithmically to enhance the artery contrast.

The first scheme, time subtraction DSA, involves the acquisition of the two images at two different times, one before the introduction of the contrast agent and the other after the introduction of the agent. The digital images are then subtracted, as described above. However, the cardiac position changes during the respiratory cycle, and the coronary arteries are in motion during the cardiac cycle. This movement occurs between component images and leads to significant artifacts in the resultant images.

The second scheme, dual-energy digital subtraction coronary angiography, or dichromography, overcomes this problem. This technique also requires two images, but it relies on the fact that the contrast agent is essentially invisible to X-rays at energies slightly below its K-edge. After injecting the contrast agent into the vein, the cardiologist takes two images, one below the K-edge and one above. The first image shows only tissue and bone because of the X-ray's low energy. The second, high-energy image shows tissue, bone, and the coronary arteries which contain contrast agent. The images are then subtracted logarithmically as before. There is no motion between the component images, which are acquired in quick succession; a typical time interval between images is less than 4 msec.

Dual-energy digital subtraction angiography requires an X-ray source capable of producing intense, monochromatic X-rays with an energy which can be quickly changed from a value below, to a value above, the K-edge of the contrast agent. One candidate source is synchrotron radiation.[Rubenstein 1986] The broad band, very intense synchrotron radiation is passed through a crystal X-ray monochromator to produce two very narrow bandwidth (.05%) X-ray beams, one with an energy just below the K-edge of the contrast agent and one with an energy just above (the typical energy separation is 300 eV). However, a synchrotron based imaging system is estimated to cost at least 30 million dollars. Our search for a lower cost system with similar imaging performance capability led us to consider a K-emission X-ray source.

A K-emission X-ray source is inherently monochromatic (narrow bandwidth). Our calculations based on the published data indicate that a K-emission X-ray source could be built that would have an X-ray flux comparable to that of a synchrotron radiation source. However, broad spectrum bremsstrahlung would also be present in an electron bombardment source in addition to the monochromatic K-emissions. Calculations made with the TIGERP[Halbleib 1988] Monte Carlo computer code developed at Sandia Laboratory have shown that high quality angiograms of human coronary arteries should be possible with an electron-bombardment K-emission X-ray source with suitable choices of electron energy, anode materials, filter materials, and contrast agent element. A new lower energy (100 - 300 keV) electron accelerator is being designed and built at the Dynamitron Accelerator Facility at Brookhaven National Laboratory (BNL) for performing X-ray experiments with an electron bombardment source. The high accuracy and low noise of the CCD TV camera system will allow this electron accelerator to be operated at relatively low current (10 mA) with a stationary anode and electron beam by using exposure times of as long as 20 minutes.
This research will lead eventually to the design of a high intensity, monochromatic, dual-energy X-ray source. This source will provide the basis for a commercially produced, moderate cost, dual-energy, DSA imaging system for hospital based, low risk screening for coronary artery disease.

Background, Technical Approach, and Potential Applications

The design of a non-invasive DSA imaging system based upon K-emission involves an overall system optimization while varying a number of different parameters. First it is necessary to choose a contrast agent element. Then anode elements can be chosen with emission lines just below and just above the K-edge of the contrast agent. Then the K X-ray yield and purity can be measured for prospective anode materials vs. electron energy, X-ray emission angle, and anode target thickness. Then an appropriate X-ray area detector system can be designed that has a high quantum efficiency for the K X-rays and is less sensitive to the high energy bremsstrahlung. In all of these choices it is desirable to maximize the signal to noise ratio, the spatial resolution, and the acquisition speed of the angiographic image, while minimizing the patient radiation dose and the overall cost of the system. In the following some of the necessary analysis that is involved in this optimization procedure will be briefly outlined.

In designing an electron bombardment X-ray source[Braun 1975] using K-emission lines, it would be necessary to look at what limits the X-ray intensity from conventional X-ray tubes used for medical diagnosis. Clearly the limitation doesn't come from electron gun technology. Electron guns have been designed for injection into high energy electron accelerators and for klystron tubes that emit much higher currents than those that are used in X-ray tubes. The limitation at present comes from the rotating anode target. The electron beam in an X-ray tube carries tens of kilowatts of power. The target will melt if a higher current is used in spite of the high speed rotation. To achieve a higher electron current a much faster motion of the anode past the X-ray beam is necessary. This can be achieved by deflecting the electron beam rapidly in one direction and rotating the anode so that its surface moves past the electron beam in the orthogonal direction. Alternately the electron beam can be swept in two dimensions in a raster pattern like in a television tube. To prevent a blurring of the resultant angiographic image, the image detection system must have the capability of moving the output image in a direction opposite to the electron beam motion, producing a tomographic slice. Actually, since the electron beam would need to be deflected by only a few cm, the tomographic effect would be very subtle, and the whole coronary artery structure would most likely remain in adequate focus. An X-ray image intensifier with a magnetic deflection yoke from a television tube has been demonstrated by Kruger to work well for producing tomographic images with a rapidly moving X-ray source.[Kruger 1985]

In order to produce a high purity of monochromatic X-rays from an electron bombardment K-emission source, it is necessary to use those K X-rays emitted between 120° and 180° with respect to the incident electron beam direction. This improvement of purity in the backward direction, demonstrated by measurements reported by the National Bureau of Standards in 1973,[Dick 1973] is a result of the fact that the monochromatic K-emission X-rays are emitted isotropically, while the broad spectrum bremsstrahlung is emitted preferentially in the forward
direction. The data on K X-ray yield, given in [Dick 1973] are quite complete, and allow an accurate determination of the intensity of K X-rays emitted from prospective anode materials. This yield data also agrees quite closely with the output of the TIGERP code for the energies and materials given in [Dick 1973]. The K X-ray yield data for copper, silver, and gold, given in [Dick 1973], are shown here in Figure 1.

Signal to Noise Ratio Calculations

One of the disadvantages of an intravenous injection of contrast agent for coronary angiography as compared with a selective arterial injection, is that the contrast agent will not be localized exclusively in the coronary arteries, but will also be present in the heart chambers and aorta. It is possible in some cases to orient the patient in such a way that the artery of interest is projected away from the ventricles and the aorta, but in the case of the left main coronary artery and the circumflex branch of the left coronary artery, it will be necessary to be able to image the artery through the left ventricle which will also contain contrast agent. Image processing techniques [Zeman 1991] have been developed that enable the broad-area contrast produced by the ventricle to be removed, making the fine detail of the arteries behind the ventricle easily visible. However, these techniques depend on there being adequate X-ray flux available through the filled left ventricle to yield accurate imaging data.

The signal to noise ratio (SNR) attainable for visualizing a coronary artery through the filled left ventricle can be calculated with the assumption that a detector can be built for which the noise is due entirely to the statistical noise on the transmitted X-ray beam. The SNR will depend on the contrast agent dose. If too little contrast agent is used then the contrast of the artery will be too small for accurate imaging. If too much contrast agent is used then too little flux of the above K-edge X-ray beam will be transmitted through the ventricle to allow for accurate imaging. For each contrast agent element there is an optimal contrast agent thickness in the ventricle that will give the highest possible SNR for viewing an artery through the ventricle. Figure 2 shows this optimal SNR calculated for monochromatic X-rays [Zeman 1990]. Figure 3 shows the variation of SNR with contrast agent dose for several representative contrast agent elements. For an iodine contrast agent, measurements on human patients made at SSRL with 33 keV synchrotron radiation X-rays have shown that a concentration greater than this optimal value can be obtained using an intravenous injection with a power injector into the superior vena cava. However for contrast agents with higher atomic number, the mass attenuation coefficient just above the K-edge will be smaller, and to achieve the optimal concentration such a contrast agent, a significantly higher mass of the agent would be needed. The mass attenuation coefficients [Hubbell 1969] of four representative contrast agent elements are plotted against X-ray energy in Figure 4. Eventually the effects of increased toxicity and reduced solubility will make such a high contrast agent concentration impossible. If toxicity and solubility are generally a function of mg/kg of body weight and mg/ml of water, respectively, then it is not unreasonable to consider the SNR achievable for a constant number of mg of contrast agent. The squares drawn on the four curves shown in Figure 3, represent the same number of mg of contrast agent element, where the square on the iodine curve is at its peak. A curve of SNR vs. the atomic number of the contrast agent is given in Figure 6 for monochromatic X-ray beams, where a constant mass of contrast agent and a constant photon count per pixel is assumed.
Anode Heating

For conventional X-ray tubes the heating of the anode is essentially surface heating. In this case the allowable electron current increases only with the square root of the speed of the anode because it depends on heat conduction in the anode material. However, as the speed increases greatly, the heat conduction becomes negligible compared with the effects of the heat capacity of the material. In this regime the range of the electrons in the material becomes crucial. The further the electrons travel into the anode, the greater volume of the anode is heated and the greater amount of heat can be stored. Hence, the use of higher electron energies greatly enhances the heat storage capability of the anode. The higher electron energy also increases the K X-ray yield and the K X-ray purity (see [Dick 1973]). The only requirement for making use of this regime of speed and electron energy is to have the electron beam travel over each spot that is used on the anode surface only once per electron current pulse. Hence, the anode needs to have a large enough surface area.

The heating of a thick rotating anode by a pulsed electron beam can be calculated without including the heat conductivity by taking into account the heat capacity only, making use of the assumption that the electron energy is deposited uniformly throughout its range. To prevent the anode material from melting, the disk or drum shaped anode is rotated past the electron beam. At the same time the electron beam is deflected rapidly back and forth perpendicular to the anode motion. Hence, the electron beam illuminates a roughly square area on the anode during the pulse. The electron heating is assumed to be distributed over the volume given by the illuminated area and the electron range. To prevent blurring in the image, the electron image in the X-ray image intensifier tube needs to be magnetically deflected in a direction opposite to the motion of the electron beam, as described in [Kruger 1985], producing a linear tomographic image. The required area of anode illumination is given by

$$A = \frac{w \cdot t}{C \cdot r \cdot \delta T} \tag{1}$$

where $w$ is the electron heating rate in cal sec$^{-1}$, $t$ is the electron pulse length in sec, $C$ is the heat capacity in cal gm$^{-1}$ °C$^{-1}$, $r$ is the electron range in gm cm$^{-2}$, and $\delta T$ is the desired anode temperature change in °C. If a conventional CsI image intensifier is used, then the anode area is limited by the response time of the CsI scintillator, which is about 1 μsec.

Ytterbium Contrast Agent

From Figure 5 it can be seen that the elements between samarium (Z=62) and hafnium (Z=72) seem most likely to yield high quality angiograms when K X-ray sources are used with constant electron beam power, ignoring the effects of the broad spectrum bremsstrahlung or the effects of any variation in K X-ray yield with atomic number. In order to achieve a high X-ray flux both below and above the K-edge of the contrast agent, anode materials will be considered for which both of the K$_{\alpha}$ lines can be used for both the above K-edge and below K-edge anode. A modest thickness filter containing the contrast agent can then be used to eliminate the K$_{\beta}$ lines for the below K-edge anode. In Table I, the contrast agents with Z between 62 and 72 are listed,
along with the below K-edge and above K-edge anode materials that would have K-emission lines as close to the K-edge of the contrast agent as possible. A very important change occurs in the chosen below K-edge anode material between contrast agents Er and Tm. Because of a slow change in the relative positions of the K-edges and the emission lines one of the anode elements could be skipped (Ta), and as a result the line pairs become much closer together. This fortuitous condition lasts for three elements, and then the jump from Ir to Au is required in the above K-edge anode element. Hence, for Tm, Yb, and Lu a particularly close set of $K_\alpha$ line pairs are available from the chosen anodes.

<table>
<thead>
<tr>
<th>Table I</th>
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<tbody>
<tr>
<td><strong>Contrast Agent and Anode Choices</strong></td>
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<tr>
<td><strong>Contrast Agent</strong></td>
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</tr>
<tr>
<td>Gadolinium</td>
</tr>
<tr>
<td>Eu</td>
</tr>
<tr>
<td>Cerium</td>
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<tr>
<td>Terbium</td>
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<td>Dysprosium</td>
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<tr>
<td>Holmium</td>
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<tr>
<td>Erbium</td>
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<tr>
<td>Terbium</td>
</tr>
<tr>
<td>Ytterbium</td>
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<tr>
<td>Lutetium</td>
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<td>Hafnium</td>
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</table>

In Table II are listed the contrast agents between samarium and hafnium, along with the approximate costs per kg.[CRC 1988] From this list it is clear that thulium and lutetium would be far too expensive to use in a contrast agent for angiography. The price of ytterbium, on the other hand, is still reasonable. It is also interesting that the cost of the elements seems to vary such that elements with even Z are much less expensive than those with odd Z.

In Table III are listed the anode material from Table I along with their melting points and boiling points. If one requires that an anode material have a melting point above 1000°C, then it would be necessary to skip over erbium and ytterbium as anode materials. This would mean that for gadolinium contrast agent, it would be necessary to use holmium and lutetium as anode materials. Hence, gadolinium is especially unfavorable with regards to the available anode materials, while ytterbium seems to be especially favorable. However, osmium cannot be used as an anode material for ytterbium contrast agent because of safety considerations. Osmium oxidizes at a relatively low temperature to form Os$_2$O$_4$, which evaporates readily and is highly toxic. Because of this property, Os is never fabricated into foils or other shapes for industrial use. Hence, the next element, iridium, would have to be used along with rhenium as the two anode materials for use with a ytterbium contrast agent. It might also be possible to use an alloy of Os and Ir as the second anode material, because this alloy is less chemically reactive than pure Os metal. This means that because of cost and safety considerations, it is not possible to take advantage of the especially close emission lines available for Tm, Yb, or Lu contrast agents. However Yb
still appears to be a promising contrast agent candidate due to its relatively low toxicity and modest cost. In addition, the anode materials used with ytterbium, namely rhenium and iridium, have very high melting points, both over 2400°C, and low chemical reactivity.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Contrast Agents</th>
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<tbody>
<tr>
<td>Z</td>
<td>Element</td>
</tr>
<tr>
<td>62</td>
<td>Samarium</td>
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<tr>
<td>63</td>
<td>Europium</td>
</tr>
<tr>
<td>64</td>
<td>Gadolinium</td>
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<tr>
<td>65</td>
<td>Terbium</td>
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<tr>
<td>66</td>
<td>Dysprosium</td>
</tr>
<tr>
<td>67</td>
<td>Holmium</td>
</tr>
<tr>
<td>68</td>
<td>Erbium</td>
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<tr>
<td>69</td>
<td>Thulium</td>
</tr>
<tr>
<td>70</td>
<td>Ytterbium</td>
</tr>
<tr>
<td>71</td>
<td>Lutetium</td>
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<tr>
<td>72</td>
<td>Hafnium</td>
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Gadolinium-DTPA is already approved by the FDA as a contrast agent for MRI. Hence, it would be particularly desirable to be able to use gadolinium as a contrast agent for angiography as well. The choices of anode materials for gadolinium and ytterbium are shown graphically in Figure 6. Note that the anode materials available for ytterbium are more favorable than those for gadolinium.

Hence, it is of great interest that experiments have already been performed with ytterbium-DTPA as a potential intravascular contrast agent. [Unger 1986] Ytterbium-DTPA is somewhat less toxic than gadolinium-DTPA according to [Unger 1986]. However, ytterbium-DTPA is about four times more toxic per gram of contrast agent element than iodine containing Renografin. If one assumes that these chelated heavy element compounds are somewhat toxic because the chelating agent is not stable enough to prevent the heavy element from being released into the body before the chelated compound is eliminated by the kidneys, then it would be reasonable to imagine that a more stable compound would be less toxic. Measurements of the stability of a new compound gadolinium-DOTA [Magerstaedt 1986] in saline solution show it to be 10⁶ times as stable as the gadolinium-DTPA presently approved for use in MRI. Recent measurements [Allard 1988] [Bousquet 1988] comparing Gd-DOTA with Gd-DTPA have shown that Gd-DOTA has only half the toxicity of the presently approved agent. The results in [Allard 1988] and [Bousquet 1988] suggest that Yb-DOTA might only be twice as toxic as Renografin per gram of contrast agent element. Squibb has a chelated Gd contrast agent under test which may have a lower toxicity than Gd-DOTA. This contrast agent, called ProHance, has an 0.5 mole/liter concentration. If the same 0.5 mole/liter concentration were available in a contrast agent containing Yb, this agent would have 84 mg of Yb per ml of agent. The standard diatrizoate meglumine contrast agents containing iodine have 370 mg of I per ml of agent. This higher concentration of iodine is due to the fact that diatrizoate meglumine has three atoms of iodine per molecule, while the presently available Yb or Gd contrast agents have only one atom.
per molecule. Clearly much work is left to be done to develop a high concentration contrast agent with a high Z element such as Gd or Yb.

<table>
<thead>
<tr>
<th>Z</th>
<th>Element</th>
<th>Melting Point (°C)</th>
<th>Boiling Point (°C)</th>
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<tr>
<td>66</td>
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<td>Erbium</td>
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<tr>
<td>69</td>
<td>Thulium</td>
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<td>1947</td>
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<tr>
<td>70</td>
<td>Ytterbium</td>
<td>819</td>
<td>1194</td>
</tr>
<tr>
<td>71</td>
<td>Lutetium</td>
<td>1663</td>
<td>3395</td>
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<tr>
<td>72</td>
<td>Hafnium</td>
<td>2227</td>
<td>4602</td>
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<tr>
<td>73</td>
<td>Tantalum</td>
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<td>74</td>
<td>Tungsten</td>
<td>3410</td>
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<tr>
<td>75</td>
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<td>76</td>
<td>Osmium</td>
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<tr>
<td>77</td>
<td>Iridium</td>
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<tr>
<td>79</td>
<td>Gold</td>
<td>1064</td>
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**Theoretical and Experimental Results of the DOE and NSF Funded Research Project**

**Calculations with the TIGERP Computer Codes**

The performance of electron bombardment X-ray sources for intravenous coronary angiography has been calculated using the TIGERP computer code developed at Sandia Laboratories. The geometry of the angiographic system assumed in these calculations is described as follows. An electron beam is incident at 30° to the surface of a water cooled rotating anode structure plated with Ir and Re. The K X-rays emitted close to normally to the anode surface are transmitted through the patient and detected with an X-ray image intensifier tube or with two other detector systems. The light from the intensifier tube is detected by a cooled CCD TV camera. The anode is made thick enough to absorb the entire incident electron beam, except for that part of the beam which is scattered backwards.

The calculated spectra for iridium and rhenium anodes are shown along with the mass attenuation coefficients from [Hubbell 1999] for ytterbium in Figure 7. About one third of the light output of the X-ray image intensifier tube detecting these spectra would be due to the monochromatic K-emission lines, which therefore can greatly enhance the efficiency of imaging at the K-edge of the contrast agent compared with using the bremsstrahlung spectra only.

However, the bremsstrahlung spectra can be used to good advantage, along with the K-emission lines by using appropriate filters. For the below K-edge anode spectrum, it is important to filter away as much of the X-ray intensity as possible that lies just above the K-edge of the contrast agent. Hence, a filter made from the contrast agent itself is ideal for the low energy
spectrum. For the above K-edge anode spectrum, it is actually desirable to make use of the bremsstrahlung spectrum which lies not too far above the K-edge energy. Hence a filter with a K-edge considerably higher than that of the contrast agent would be effective. For a ytterbium contrast agent, ytterbium would be chosen for the below K-edge filter, and as heavy an element as possible would work best for the above K-edge filter. Bismuth was chosen because Bi is the heaviest non-radioactive element available.

To calculate the signal produced by an X-ray image intensifier tube, or by the Kodak Lanex Regular intensifying screen used in our experiments, the TIGERP program was used to calculate the pulse height distribution of absorbed energy in the different screens for X-rays of different energies. One set of pulse height distributions for 60 keV monochromatic X-rays for both the X-ray image intensifier and the Lanex screen are shown in Figure 8. The spectral data shown in Figure 7, combined with the pulse height data shown in Figure 8, allowed calculations of the signal expected in angiographic examinations when the mass attenuation coefficients from [Hubbell 1969] were used.

These calculations of the signal from one of the intensifying screens were used to determine the best choices of electron energy and filter thickness for the Re and Ir anode sources. To visualize the contrast agent after an intravenous injection it is necessary to remove the contrast due to soft tissue and bone simultaneously. For any one choice of electron energies for the two anodes and any one choice of Bi filter thickness it was possible to calculate the required Yb filter thickness and the required coefficient for a weighted logarithmic subtraction so that there would be simultaneous removal of bone and soft tissue contrast to first order in the bone and soft tissue thicknesses. An example of this soft tissue and bone removal is shown in Figure 9. The removal of contrast due to bone and soft tissue is so complete that the range of thicknesses of bone and soft tissue had to be 100 times greater than that of the ytterbium contrast agent for the bone and soft tissue contrast even to be visible on the graph.

For each thickness of bismuth filter on the iridium anode spectrum there is a corresponding thickness of the ytterbium filter used with the rhenium anode for which this first order bone and soft tissue contrast removal obtains. The thicker the filters are made, the lower will be the radiation dose to the patient. Using thicker filters will not necessarily decrease the quality of the angiographic image, because the filters will improve the spectra produced by the two X-ray sources. However it is desirable not to have to use filters that are too thick, because such thick filters would waste a large amount of the available X-ray flux. Hence, the choice of electron energies was in part dictated by the need to have similar thicknesses of the filters for the two X-ray beams. Figure 10 shows a plot of the Yb filter thickness vs. the Bi filter thickness for three examples of electron energy for the two spectra. The screen used was the Lanex Regular intensifying screen. Note that by using a lower electron energy to produce the lines that are above the K-edge of the contrast agent it is possible to reduce the required thickness of the Yb filter substantially.

The signal to noise ratio was calculated for viewing a coronary artery through the left ventricle which is also filled with contrast agent.[2 eman 1990] The results of this signal to noise ratio calculation using the data from the TIGERF program for three different combinations of electron beam energy incident on the Ir and Re anodes filtered with Bi and Yb are plotted in
Figure 11 vs. the Bi filter thickness. For these calculations the X-ray tube power was 800 kW, the exposure time was 4 msec per energy, the distance between the anode and the detector was 1 meter, and the patient was assumed to be equivalent to 20 cm of water plus any contrast agent present.

It would be almost impossible to build a rotating anode structure that could withstand a stationary 800 kW electron beam, especially for the present case where the K-emission lines are to be utilized. The anode heating is more critical when K-emission is used, because the X-rays must be emitted normally to the anode surface in order to maximize the purity of the K-emissions. Normal emission prevents the use of an elongated electron beam focal spot which could spread out the heat load on the anode. In order to overcome this heating problem, it would be necessary to deflect the electron beam rapidly back and forth in one direction while the anode rotates in the orthogonal direction as described above.

In order to choose the ideal combination of electron energies and filter thicknesses it is necessary to calculate the radiation dose to the patient as well as the signal to noise ratio shown in Figure 11. The radiation dose was calculated by using the TIGERP program to calculate the energy deposited by the X-ray beam in the first 2 mm of the patient, which we called the skin layer. Figure 12 shows the result of these TIGERP calculations for X-ray energies between 10 and 2000 keV. The rapid rise in energy deposited per photon as the photon energy increases from the K X-ray energies around 60 keV to the peak at 1000 keV requires the use of relatively low electron energies in order to minimize the patient dose, in spite of the fact that the maximum K X-ray yield for 60 keV K-lines occurs for electron energies around 1100 keV (see Figure 1).

In order to display the results of the filter thickness, signal to noise ratio, and patient dose calculations in a readily intelligible form, plots were made of patient dose vs. electron beam pulse energy for a constant signal to noise ratio of 5 for viewing a coronary artery through a ventricle 10 times the artery thickness, for a patient equivalent to 20 cm of water. The range of different filter thicknesses for which simultaneous removal of contrast due to soft tissue and bone obtains are represented by a curve on this plot for each combination of electron energies for the two anode materials. The electron beam pulse energy and the exposure time (4 msec) for the two anodes are made equal. Figure 13 is an example of three of these plots for combinations of energies for the two anode materials which yield the best combination of low dose and low electron beam power when used with the X-ray image intensifier. Figure 14 is a similar set of plots for a solid CsI intensifying screen that is 3 mm thick. Note that by using a thicker CsI screen, lower electron energies are required, and that the patient dose and the electron beam pulse energy can both be reduced by about a factor of 2.

**Imaging System for Angiographic Phantom Imaging**

For the experiments carried out so far at BNL for the K-Emission Angiography Project, a Kodak Lanex Regular intensifying screen coupled to a liquid nitrogen cooled CCD TV camera system from Astromed, Inc. with a 42 mm f 1.0 macro lens optimized for 5:1 demagnification has been used as the X-ray detector.
In order to measure the small changes in X-ray transmission due to a dilute solution of contrast agent located in narrow vessels, the X-ray detector must have a high spatial resolution along with high quantum efficiency to reduce X-ray quantum noise and high precision in X-ray flux measurement. The CCD TV System purchased for these measurements from Astromed Ltd. has 384 x 578 pixels, each of which is 0.022 x 0.022 mm in size. The entire array is read out to 16-bits accuracy in about 6 seconds. In order to reduce the dark current of the CCD to an immeasurable 1 electron per pixel per hour, the CCD is cooled to -110°C with liquid nitrogen.

The CCD system is used to measure the light emitted from a Kodak Lanex Regular X-ray intensifying screen. This screen uses gadolinium oxysulphide phosphor, the peak light emission of which is centered at 550 nm.[Buchanan 1972] At this wavelength the CCD has an optical quantum efficiency of about 30%. For the K-emission lines used for the angiography measurements, the X-ray quantum efficiency of the Lanex screen is about 30%, from preliminary experiments comparing the light output of the Lanex screen with that of a 3 mm thick CsI(Tl) crystal.

In order to couple the Lanex screen to the Astromed CCD system, we have been using a combination of two camera lenses to achieve the 5:1 optical demagnification required. A Nikkor 50 mm f 1.2 lens designed for a 35 mm camera is mounted front to front with a Bausch and Lomb 250 mm f 4.5 lens designed for a 125 x 175 mm view camera. The combined lens is a 42 mm f 1.0 macro lens optimized for the 5:1 demagnification factor. The lens combination has very little fall off in speed towards the corners of the field of the CCD. Even for the full 35 mm camera field of view, the lens cuts off only the extreme corners of the frame. Measurements of image noise made with this lens and the Lanex screen with 90 keV monochromatic synchrotron radiation X-rays from beam line X-17B1 at NSLS, have demonstrated that the imaging system is not X-ray quantum limited, but is in fact light quantum limited.

Clearly, for studies with patients, a higher X-ray quantum efficiency and a higher light collection efficiency would be desirable. For future studies, the use of an X-ray imaging intensifier tube is planned. However, for the present phantom measurements, these inefficiencies could be made up with a longer exposure time, and hence a higher dose.

**Experimental Results at the BNL Dynamitron Accelerator**

Because the preliminary modeling calculations performed before DOE and NSF funding was available for this project indicated that electron energies in the 500 - 800 keV range would be optimum for angiography, a beam line at the Dynamitron Electron Accelerator[Cleland 1993] at BNL was constructed that could deliver 0 - 10 mA of electron current in the energy range of 500 - 3000 keV, which is the normal operating range of the Dynamitron. The far more accurate and complete calculations reported here and shown in Figures 7 - 14 now show that electron energies in the range of 100 - 300 keV would be superior for achieving both a low anode heat load and a low patient dose. Unfortunately, attempts to operate the Dynamitron Accelerator at 250 keV weren’t successful. Hence, the imaging measurements made so far at the Dynamitron have all been at 500 keV.
The beam line used for these experiments is an extension of the positron beam line used for many experiments at the Dynamitron at BNL. [Asoka-Kumar 1993] The Dynamitron beam travels downward from the accelerator, travels through two sets of steering coils and a focusing solenoid, and enters a 90 degree bending magnet. The bending magnet can be rotated around a vertical axis in order to direct the beam into the different target areas. The angiography target area (see Figure 15) was in a room shielded with 122 cm of concrete, which would be adequate shielding for electron beams of 10 mA at 3 MeV. The electron beam from the bending magnet passes through two solenoids and one set of steering coils before reaching the angiography target chamber. The target chamber contained pieces of Re and Ir foil, 1 mm thick, soldered to a water cooled copper block. Between the Re and Ir targets was a thin Ta foil that glowed red hot in the electron beam, allowing the position of the beam to be seen with a TV camera. The whole target chamber could be moved accurately up and down, so that the electron beam position could be adjusted using the Ta foil, and then either the Re or the Ir target could be moved into the beam.

Because the Dynamitron had been used only for positron beams for many years, the conversion to electron operation required various safety approvals to be obtained. For our first experimental tests, it wasn’t possible to obtain final safety approval. Hence, temporary approval was obtained for limited use of the electron beam. Our operations were limited to 500 keV and 0 - 100 μA. At these low currents, exposures as long as 20 minutes were required to image realistically thick phantoms. It should also be realized that the total length of the beam line from the accelerator to the target was about 6 meters, and that a very small change in electron energy would cause the electron beam to move around on the target. The computer control for the electron energy, which had been used with great success with the positron beam, broke down during the angiography experimental run. Hence, the drifting of the electron beam created for these experiments an effective focal spot size of as large as 10 mm, which was much larger than the 1 - 2 mm size of the focused electron beam itself. Hence, the spatial resolution for the system as tested was very poor, and was worse for the longer exposures required for thicker phantoms.

In spite of all these problems encountered during the first tests at the Dynamitron, it is gratifying to see that several of the predictions of the modeling calculations were in fact verified by these experiments. The first experiment performed was of a thin phantom consisting of two plastic test tubes and a Lucite wedge. The test tube on top was filled with a calcium solution representing bone, and the test tube on the bottom was filled with a dilute ytterbium solution similar to what would obtain in the left ventricle after an intravenous injection of a ytterbium containing contrast agent. The thickness of the Lucite wedge varied from left to right across the whole image. Figure 16 shows the results of this test. The field of view shown is 4.2 cm wide and 6.4 cm high. The logarithmically subtracted image on the bottom of Figure 15 demonstrates the ability to remove contrast due to bone and soft tissue simultaneously in an angiographic image with only two X-ray spectra. The thickness of the ytterbium and bismuth filters used in this image were calculated with the methods described above for the case of 500 keV electrons used for both spectra. Clearly, the calculated filter thicknesses were correct.

Figure 17 demonstrates the ability of the angiographic imaging system to see contrast agent through a phantom with a thickness comparable to a human chest, 20 cm of Lucite. Again, the contrast due to the calcium solution and the changes in Lucite thickness are removed.
and only the ytterbium contrast remains. Figure 18 demonstrates the ability of the system to visualize a model coronary artery filled with a diluted ytterbium contrast agent solution. The object imaged is a Lucite heart made to be part of an accurate human chest phantom to be used in these angiographic studies. The whole chest phantom couldn’t be imaged during this first experimental run because of the impossibility of achieving high spatial resolution for long exposures without computer control of the electron energy. However, the heart itself could be imaged, along with two pieces of aluminum to represent the ribs in a human patient. Note that both the aluminum ribs and the variations in Lucite thickness are successfully removed from the logarithmically subtracted image, and that the artery is clearly visible where it is projected away from the aorta and the left ventricle. On the TV monitor of the image display computer, one can also just see the artery behind the aorta and ventricle, but a clear visualization of the artery behind the ventricle will have to wait for an improved electron source at lower energies.

Graduate Student Training Associated with this Project

Two graduate students were involved in the K-Emission Angiography Project and were supported by the NSF and DOE funding for this project. Both students have completed their work for the Masters of Science Degree at the University of Tennessee, and have written Masters Theses on their angiography research. One student, Gunnar Lovhoiden, wrote a thesis entitled “Phantom and Test System Design for Intravenous Coronary Angiography Using K-Emission X-Rays.” Gunnar will remain at UT to continue his angiography research for the Ph.D. degree. Another student, DongZhou Liao, wrote a Masters Thesis entitled “Computer Modeling of Dual-Energy Coronary Angiography.” DongZhou has taken a job at the Mayo Clinic to do Monte Carlo modeling calculations for molecular biology.

300 kV Electron Accelerator

Figure 19 shows the design of the 300 kV electron accelerator presently under construction at BNL as an X-ray source for use with the angiography project. The accelerator column is manufactured by Radiation Dynamics on Long Island for the Dynamitron Accelerator. The accelerator column consists of a total of 48 dynodes. The high voltage (100 - 300 kV) is applied to the top plate on the high voltage terminal, and is resistively divided equally along the 48 dynodes. Twelve 1 MΩ resistors, each with a 750 V rating, are soldered together, placed inside a Tygon tube, and connected between each pair of dynodes.

Seven Helmholz coils are mounted on a support table. Each coil consists of a round aluminum frame with an inside diameter of 57 cm and a width of 13 cm. 350 turns of #10 gage square profile copper wire are wound around each frame. The magnets model Helmholz coils with a diameter of 61 cm and are designed to provide a magnetic field of 100 Gauss. The magnets provide a magnetic field that keeps the electron beam at a constant diameter from the cathode where it is emitted all the way to the anode target, without the need for any adjustable focusing lenses.

Two PVC pipes, one inside the other, are mounted inside the magnet frames with the center axis of the pipes coinciding with the center axis of the magnets. The larger PVC pipe has an O.D. of 51 cm, and a wall thickness of 2.2 cm, while the smaller pipe has an O.D. of 46 cm
and a wall thickness of 1.9 cm. The PVC pipes insulate electrically between the high voltage terminal and the grounded magnets. The thickness of the two pipes together is adequate to prevent high voltage breakdown at 300 kV even without any additional insulation due to the air gap. The PVC pipes are capped on both ends, with the cap on the high voltage end being as thick as the two pipes. The use of the PVC pipes allows the accelerator to be operated in dry air, without any SF₆ being required.

The magnet table provides support for the complete accelerator assembly. The magnets are bolted to the table. The PVC pipes are connected together and supported by the magnet table. The accelerator column is supported by the PVC pipe. The four way cross and the target chamber are clamped in place relative to the magnet table. This is to keep the two parts from being pulled together when the accelerator is brought under vacuum. The supports for the cross and the Cryo pump are not shown in Figure 19. The target chamber has to be shielded with 1 cm of lead in order to keep the radiation levels as low as reasonably achievable in all directions except through the lead collimator. The lead shielding is not shown in Figure 19. The complete assembly, including the high voltage power supply and the isolation transformer will be enclosed in an interlocked cage to protect personnel from radiation and high voltage hazards.

The 300 kV accelerator is being assembled at B. L with parts borrowed from a variety of sources. The accelerator column is being made from spare acceleration sections from the BNL Dynamitron accelerator. The high voltage power supply and isolation transformers are borrowed from the Department of Applied Science at BNL and are rated only for 0 - 100 kV.

**Figure Captions**

Figure 1: The K X-ray yield per unit solid angle and per unit incident electron beam energy for copper, silver, and gold, from [Dick 1973].

Figure 2: The optimal signal to noise ratio achievable with $10^6$ total X-ray photons per pixel and a patient thickness equivalent to 20 cm of water, when the artery being imaged lies behind the left ventricle which has 10 times the thickness of the artery.

Figure 3: The signal to noise ratio under the same conditions as in Figure 2 plotted against the dimensionless measure of contrast agent concentration. Results are given for contrast agents containing bismuth, hafnium, gadolinium, and iodine. The results are shown at the optimal relative intensity of the two beams. The squares indicate the points on the four curves where the total mass of contrast agent is the same as the optimal mass of iodine.

Figure 4: The mass attenuation coefficients of iodine, gadolinium, hafnium, bismuth, bone and water plotted against the X-ray energy.

Figure 5: The signal to noise ratio achievable through 20 cm of water, a ventricle 10 times the artery thickness, and a constant contrast agent mass equal to the optimal mass for iodine. $10^6$ photons per pixel are used for each case.
Figure 6: The mass attenuation coefficients of water, bone, gadolinium, and ytterbium vs. X-ray energy plus the K-emission X-ray lines that would be used for angiography. Note that Yb has high melting point anode materials with K-emission lines closer to its K-edge than does gadolinium.

Figure 7: The mass attenuation coefficient ytterbium plotted with the emission spectra from rhenium and iridium anodes filtered with ytterbium and bismuth all shown vs. X-ray energy.

Figure 8: The pulse height distribution of 60 keV X-ray photons in the input CsI intensifying screen of an X-ray image intensifier tube and in a Kodak Lanex Regular (Gd$_2$O$_2$S) intensifying screen.

Figure 9: The thickness measurement signal for ytterbium K-edge imaging using 130 and 200 keV electrons incident on iridium and rhenium anodes filtered with bismuth and ytterbium respectively. The signal due to bone is shown for 0-20 gm cm$^{-2}$ of thickness, the signal due to water (representing soft tissue) is shown for 20 (the full thickness of the patient) to 0 (no patient at all) gm cm$^{-2}$ of thickness, while the signal for the ytterbium contrast agent is shown for 0-.2 gm cm$^{-2}$ of thickness.

Figure 10: The thickness of Yb filter required to ensure simultaneous removal of contrast due to soft tissue and bone plotted against the Bi filter thickness. The Kodak Lanex Regular X-ray intensifying screen is used. Three different combinations of electron energies for the Re and Ir anodes are shown.

Figure 11: The signal to noise ratio for three different combinations of electron energies on the Ir and Re anodes plotted against the Bi filter thickness. For each Bi filter thickness, the optimum Yb filter thickness (see Figure 10) is chosen to achieve the first order removal of soft tissue and bone shown in Figure 9.

Figure 12: The energy deposited in the first 2 mm thickness of a human patient per incident X-ray photon plotted vs. the energy of the incident monochromatic X-ray beam.

Figure 13: The skin dose and electron beam pulse energy for a constant signal to noise ratio of 5 for an artery viewed through a ventricle 10 times the artery thickness and through a 20 cm thick patient, an exposure time of 4 msec, and a detector using of an X-ray image intensifier.

Figure 14: The skin dose and electron beam pulse energy for a constant signal to noise ratio of 5 for an artery viewed through a ventricle 10 times the artery thickness and through a 20 cm thick patient, an exposure time of 4 msec, and a detector using of a CsI crystal 3 mm thick.

Figure 15: Target room at BNL used for angiography phantom measurements. The UNIX PC is used for the control of the Astromed CCD system, while the DOS PC is used for the remote control of the position of the CCD camera and the phantom, as well as for the control of the NaI(Tl) X-ray energy spectrometer. The lead shielding is needed to prevent the X-rays from reaching the CCD camera directly and producing extraneous noise on the image.
Figure 16: An image of two test tubes and a Lucite wedge. The top tube is filled with a calcium solution, the bottom tube is filled with a ytterbium solution of a concentration similar to that after an intravenous injection of a ytterbium contrast agent. The upper left image was taken with a rhenium anode and a ytterbium filter. The upper right image was taken with an iridium anode and a bismuth filter. The bottom image is the weighted logarithmic difference.

Figure 17: An image of a 20 cm thick Lucite phantom. At the top is a chamber filled with a dilute calcium solution. From the top to the middle of the image is a chamber filled with a ytterbium solution. At the bottom is an area of increased Lucite thickness. The upper left image was taken with a rhenium anode and a ytterbium filter. The upper right image was taken with an iridium anode and a bismuth filter. The bottom image is the weighted logarithmic difference.

Figure 18: An image of a Lucite heart phantom. The phantom has an aorta at the top left, a left ventricle below the aorta, and a circular coronary artery on the right, which overlays both the ventricle and the aorta. The upper left image was taken with a rhenium anode and a ytterbium filter. The upper right image was taken with an iridium anode and a bismuth filter. The bottom image is the weighted logarithmic difference.

Figure 19: The 300 kV, 10 mA electron accelerator under construction at BNL. The Helmholz coils provide a guiding magnetic field that ensures that the electron beam remains well focused and stationary on the anode target. The bellows allows the target chamber to be moved up and down allowing the two different K-emission targets and the Ta foil viewing screen to be placed in the stationary electron beam.
Figure 1: The K X-ray yield per unit electron energy for copper, silver, and gold.
Figure 2: The optimal signal to noise ratio looking through 20 cm of water and a filled ventricle 10 times the artery thickness for $10^6$ total photons/pixel.
Figure 3: The signal to noise ratio looking through 20 cm of water and a filled ventricle 10 times the artery thickness for $10^6$ total photons/pixel.
Figure 4: The mass attenuation coefficient of water, bone, iodine, gadolinium, hafnium, and bismuth vs. X-ray energy.
Figure 5: SNR with 20 cm of water, a ventricle 10 times the artery, $10^6$ photons/pixel, and constant contrast agent mg (optimal for i).
Figure 6: The mass attenuation coefficient of water, bone, gadolinium, and ytterbium vs. X-ray energy plus selected K emission lines.
Figure 7: Ir & Re X-ray spectra and Yb mass attenuation coefficient.
Figure 8: Pulse-height distribution of 60keV photons in two different screens.
Figure 9: Signal of different materials in the subtracted image.
200 kVp Re X-ray beam & 130 kVp Ir X-ray beam; 0.35 g/cm² Bi filter; Lanex Screen.

(1) thickness of soft tissue = [20 - (thickness index)] g/cm²;
(2) thickness of bone = (thickness index) g/cm²;
(3) thickness of Yb = [(thickness index) * 0.01] g/cm².
Figure 10: Filter thickness for the Gd₂O₂S screen with different electron energies to generate X-rays.
Figure 11: SNR vs. the Bi filter thickness at different electron energies.
Figure 12: Energy deposited in the skin layer vs. incident photon energy.
Figure 13: Dose and electron beam pulse energy at SNR=5 and 4 msec/pulse for an image intensifier with a CsI screen.
Figure 14: Dose and electron beam pulse energy at SNR=5 and 4 msec/pulse for a 3mm thick CsI crystal X-ray detector.
Figure 15: Target room at BNL used for angiography phantom measurements. The UNIX PC is used for the control of the Astromed CCD system, while the DOS PC is used for the remote control of the position of the CCD camera and the phantom, as well as for the control of the NaI(Tl) X-ray energy spectrometer. The lead shielding is needed to prevent the X-rays from reaching the CCD camera directly and producing extraneous noise on the image.
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