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Synchrotron Radiation Applications in Medical Research At Brookhaven National Laboratory

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I. INTRODUCTION

In the relatively short time that synchrotrons have been available to the scientific community, their characteristic beams of UV and X-ray radiation have been applied to virtually all areas of medical science which use ionizing radiation. The ability to tune intense monochromatic beams over wide energy ranges clearly differentiates these sources from standard clinical and research tools. The tunable spectrum, high intrinsic collimation of the beams, polarization and intensity of the beams make possible in-vitro and in-vivo research and therapeutic programs not otherwise possible. From the beginning of research operation at the National Synchrotron Light Source (NSLS), many programs have been carrying out basic biomedical research. At first, the research was limited to in-vitro programs such as the x-ray microscope, circular dichroism, XAFS, protein crystallography, micro-tomography and fluorescence analysis. Later, as the coronary angiography program made plans to move its experimental phase from SSRL to the NSLS, it became clear that other in-vivo projects could also be carried out at the synchrotron. The development of SMERF (Synchrotron Medical Research Facility) on beamline X17 became the home not only for angiography but also for the MECT (Multiple Energy Computed Tomography) project for cerebral and vascular imaging. The high energy spectrum on X17 is necessary for the MRT (Microplanar Radiation Therapy) experiments. Experience with these programs and the existence of the Medical Programs Group at the NSLS led to the development of a program in synchrotron based mammography. A recent adaptation of the angiography hardware has made it possible to image human lungs (bronchography). Fig. 1 schematically depicts the broad range of active programs at the NSLS.

The research covers a very wide range of physical dimensions: atoms and molecules (XAFS and protein crystallography), chromosomes and cells (X-ray microscopy), tissues and organs (angiography, computed tomography, bronchography and

mammography). Another way to differentiate the programs is between those which are in-vitro and those which are in-vivo. Of course the object of much of the in-vitro work is to impact the applications of medicine in the in-vivo health care world. This paper will not address any of the in-vitro research programs, but rather it will summarize the current in-vivo programs at the NSLS: MECT, mammography, coronary angiography and bronchography, MRT.

II. MULTIPLE ENERGY COMPUTED TOMOGRAPHY (MECT)

Monochromatic synchrotron x-ray beams have several advantages over the wide-energy band bremsstrahlung radiation obtained from x-ray tubes for computed tomography (CT). First, monochromatic x-rays do not undergo "beam hardening", an effect caused by high attenuation of the low energy end of the photon spectrum, resulting in an increase in the spectrum's mean energy as the beam penetrates the body, particularly the bone. The effect is particularly troublesome in slices with irregular bone shapes, such as the lower part of the skull. Second, for the same absorbed dose to the subject as conventional CT, monochromatic CT at the right beam energy for a given patient size has larger image photon count and, therefore, lower image noise because of the absence of the low energy tail of the spectrum. At the same time better image contrast resolution is obtained because the monochromatic beam lacks the high end of the polychromatic spectrum which is associated with low image contrast. Third, the 0.2-0.5 % energy bandwidth of the monochromatic beam, compared to about 50% for conventional CT, and the wide energy range of beam intensities allow efficient implementation of the energy-selective CT methods of dual-photon absorptiometry (DPA) and K-edge imaging of contrast elements. Dr. Avraham Dilmanian from the BNL Medical Department and his coworkers are developing such a CT system, called Multiple Energy Computed Tomography (MECT), at NSLS beamline X17B2 for imaging the human head and neck [1,2]. MECT has a fixed horizontal beam and a subject chair rotating about a vertical axis. It uses a fixed exit Laue-Laue monochromator employing flat Si<111> crystals, and a modular $CdWO_4$/PIN-diode linear array detector.

DPA will probably be MECT's main mode of research application in the study of carotid artery atherosclerotic plaque composition. DPA separates the tissue into two components of low-Z and intermediate-Z, which allows characterization of the plaque in terms of lipid/cholesterol, collagenous (fibrous), and calcified tissues. DPA involves acquiring two images at >40 keV and >100 keV, and analyzing them to produce the low-Z and the intermediate-Z images. It is currently used in clinical diagnostics and research, in both the planar and the CT mode, mostly for bone densitometry. DPA's current use in conjunction with conventional CT is called Dual-Energy Quantitative CT (DEQCT). MECT DPA should also allow soft tissue characterization, where DEQCT has a poor performance.

MECT will be used in contrast imaging with I or Gd in a method called K-edge imaging, which involves tuning the beam energy immediately above the contrast element's K-edge. The method provides a 2-fold or more advantage in image contrast, depending on the contrast element and the polychromatic spectrum with which the comparison is

made. MECT will be used for CT Angiography, combining K-edge imaging and the "Helical" CT mode.

MECT is at its preclinical stage, carrying out the imaging experiments in SMERF where it is possible to achieve the final field-of-view of 19.5 cm. Its recent images of phantoms and a live rabbit show a 2-fold smaller image noise than conventional CT for the same spatial resolution and dose. They also show a 2-fold larger image contrast in I K-edge imaging. A new bent Laue-Laue monochromator is under construction. MECT's clinical system will allow DPA at 40 and 100 keV, and K-edge Angiography with I and Gd. It will be used in the Helical CT mode with a 5 s/revolution chair speed, and 1 - 5 mm slice height. Figs. 2a and 2b show a rabbit lower head imaged by MECT and by conventional CT, respectively. The MECT image was obtained in X17B1 at 43 keV, 2 mm slice height, and 6 cGy skin dose, while the conventional CT image was taken at 80 kVp and 800 mA (4 cGy), and 3 mm slice height. The two images have the same dose times slice height, which is an index for comparing image photon counts. The MECT image shows a better contrast resolution, apparent from its separation of muscle and subcutaneous fat. The dark bands in the conventional CT image along the continuation of the rabbit's jaws are most likely beam hardening artifacts.

III. MAMMOGRAPHY

Screening mammography has proven to be an effective procedure in identifying early breast cancer. The cancers found by mammography tend to be smaller and less advanced than those found by physical examination, resulting in better survival rates. Mammographic technology has dramatically improved in the last two decades, but approximately 10% of clinically obvious breast cancers are not visible with mammography. Further improvement in detection is expected with the advent of digital mammography which utilizes better source geometry and improved detector systems. It has been suggested very frequently that perhaps the use of the synchrotron source with its inherently highly collimated, tunable radiation could increase the signal to noise and increase the contrast resolution in the images, possibly at lower dose to the patient.

Experiments have been done by Dr. R. Eugene Johnston from the University of North Carolina and his collaborators using monoenergetic x-rays to explore the potential of monoenergetic photons for mammographic imaging [3]. The experiments done on the X27 beamline have shown that superior image contrast can be obtained relative to the conventional film-screen techniques. As an example of the results, Fig. 3 shows a comparison between contrast measured in a contrast detail phantom at 18 keV and the same data obtained on a conventional system. Images of various mammographic phantoms and real tissue have been carried out in the energy range 16 to 24 keV.

In these early experiments, it was clear that improved contrast at equivalent or less dose is obtained. Scoring of the phantom images according to American College of Radiology criteria shows improvement over the conventional systems, with similar or less mean glandular dose. The early work at the NSLS has utilized available image plate and conventional mammographic film detectors. It is planned to study digital detectors and new imaging optical configurations. The elimination of scatter is expected to produce images with higher contrast than conventional imaging systems.

Recently, a new radiographic imaging modality called Diffraction Enhanced Imaging (DEI) has been developed by D. Chapman and co-workers at the NSLS [4,5]. This new modality uses an x-ray analyzer crystal (Bragg or Laue geometry) as a scatter rejection optic that diffracts the beam which is transmitted through the object being imaged. Experiments performed with this scatter rejection optic revealed tah the system is sensitive to refractive ndex effects within the object in addition to the x-ray absorption and small angle scattering by the object. A simple algorithm has been developed to separate refractive index effects from absorption effects. The measured quantity is really an apparent absorption since it the combination of absorption and extinction processes. Extinction is the loss of intensity due to diffraction occurring as the beam traveses the object. In some phantom details, enhancement in the apparent absorption of an object has been as much as a factor of 17 when compared with a conventional synchrotron radiograph. Direct comparisons between the synchrotron DEI system and conventional systems being made using mammography phantoms and tissue samples obtained from patient specimens containing different types of cancers (masses, calcifications, and architectural distortions). In the long term, it may be possible to advance the program to human studies in the medical research facility at the NSLS.

IV. CORONARY ANGIOGRAPHY

The most advanced of the applied medical research programs at synchrotron facilities are those doing human coronary angiography. The field traces its origins back to the proposal by Rubenstein, et al that the intensity of the synchrotron x-ray beams would be high enough to allow imaging of the coronary arteries following venous injection of an iodine containing contrast agent [6].

The reason such a procedure is desirable is that the standard arterial catheterization method (contrast agent injected directly into the coronary arteries) presents significant enough risks that it is not used for clinical screening or research even though the images obtained are excellent. For coronary artery disease research to use humans subjects for imaging, the venous technique is highly desirable. Using conventional sources, this method proved to be a failure due to motion artifacts in the images and not enough flux to allow sufficient contrast to image the small arteries containing highly diluted contrast agent overlying the large coronary structures. Even applying digital subtraction imaging at the iodine K-absorption edge proved a failure with conventional sources.

The concept of synchrotron based coronary angiography was first developed at Stanford University and the early human studies were done at the Stanford Synchrotron Radiation Laboratory [7,8]. In 1989 the project moved to the NSLS where the hardware was installed in the SMERF medical research facility [9-11]. The NSLS program has been a collaboration between Stanford University, North Shore University Hospital and SUNY Stony Brook. Thus far a total of 28 patients have been imaged, 7 at SSRL and 21 at the NSLS.

The technique takes advantage of the wide horizontal, narrow vertical beam profile from the superconducting wiggler on X17. The patient is aligned and then translated

vertically through the cross-over point of two fan beams, one above the iodine K-edge energy and the other below the edge. An iodinated contrast agent is injected into the Superior Vena Cava, the large vein near the entrance to the heart. After a delay time for the iodine to reach the coronary arteries, the image scan is started. As the patient moves through the beams, successive lines of data are taken, with each line of data taken in 4 milliseconds with a complete image built up from 256 lines. Spatial resolution is either 0.25 or 0.5 mm. Excellent images of the right coronary artery (RCA) and of the left anterior descending coronary artery have been obtained. The circumflex artery has been more difficult to image, but can be seen in particular patients with the proper angulation for the image. Fig. 4 is an example of an intravenous angiogram taken at the NSLS showing the full RCA.

In Germany, Dr. Rainer Dix and his co-workers at HASYLAB have made two major advances in this technology. They have developed a system by which the images are gated from the patient's ECG signal. In addition, they have shown that the contrast agent can be injected into a peripheral vein [12,13] and result in images comparable to those with injection near the heart.

The recent work at the NSLS has centered on determining the optimal projection angle for studying each artery. These studies, along with the demonstrated gating of the images from the ECG and peripheral injection in Germany, have advanced the technology to a point where definitive medical research can begin. HASYLAB is undertaking a major program to validate the synchrotron angiography against the standard arterial procedures. At Brookhaven National Laboratory the project is continuing to commission an advanced low noise image acquisition and display system which will lead to increased contrast in the images [14].

V. BRONCHOGRAPHY

Recently, Rubenstein et al have described a medical imaging procedure using xenon as a contrast agent for K-edge dichromography of the respiratory air passages [15]. The process could provide the opportunity to image anatomic structures and pathologic processes that cannot be visualized by conventional x-ray based imaging methods. For example, detection of lung cancer, the leading cause of cancer related deaths in the US, is an important application. At present, standard x-ray procedures cannot detect tumors less than 1 cm in diameter. It has been calculated that synchrotron imaging with xenon could detect significantly smaller, earlier tumors leading to enhanced five-year survival. For the synchrotron bronchography, the airway structures are imaged after inhalation of a gas mixture containing stable xenon. The amount of inhaled gas is limited to the anatomic dead space volume of the upper and lower air passages. The subjects hold their breath for several seconds while the images are recorded using the dual-energy imaging system developed for coronary angiography. Initial studies on human volunteers have been carried out at the NSLS [16]. For these studies, the X17 beamline was aligned to bracket the xenon K-edge at 34.56 keV. The procedure was identical to the angiography imaging except that the contrast agent was inhaled instead of being injected.

VI. RADIOTHERAPY

Radiotherapy is that process whereby ionizing radiation (gamma-rays, x-rays, or charged particles) are targeted to a tumor in order to kill or retard growth of cells. The dose can be delivered by external beams generated by machines or by the decay of radioactive sources such as Co-60. The dose can also be delivered by use of radioisotopes which are transported to the tumor site pharmacologically via antibodies or chelators. Some radioisotopes are encapsulated and inserted surgically or by stereotaxic injection into the region of the tumor. Radiotherapy is limited by the radiation dose tolerance of normal tissues in the region of the tumor or, in the case of external beam therapy, of normal tissues between the skin and the tumor and, often, beyond the tumor.

There are two ways synchrotron radiation may be advantageous in radiotherapy. The first is to increase the sensitivity of the target tumor cells to the radiation, leading to increased death of the cells while sparing normal cells. The tunability and monochromaticity of the synchrotron radiation makes this approach possible. An example of an application in the field of radiobiology is Photon Activation Therapy (PAT) [17]. The second approach [18], is to use the inherent collimation of the synchrotron beams to create a beam geometry that optimizes dose delivery to the tumor site and effectively avoids damaging the intervening normal tissue.

One of the most effective means of increasing the dose to the tumor and sparing intervening normal tissue is to use stereotactic radiosurgery. In that procedure one or more highly collimated radiation beams are directed at the tumor from varying directions. The crossing point of the beams is at the target tumor, thereby delivering a dose equal to the sum of all the beams to the target and delivering a fraction to all other tissue.

Synchrotron radiation beams can be very highly collimated in either planar or cylindrical beam geometry and can be either focusing or non-focusing. With the development of high energy sources it is now possible to have beams with energies in the range of 50 keV and above. Microbeam Radiation Therapy (MRT) is a concept developed at BNL by which a lesion is irradiated in a stereotactic fashion using bundles of multiple, parallel, microscopically narrow beams of x-rays [19-22]. The energy range required is 50-150 keV. The microbeams are planes several millimeters high and 25-75 μm wide. The beams in each bundle are separated by 75-200 μm on center. The detailed spacing and beam widths are determined by experimentation and by Monte Carlo photon- and electron-transport simulations. The central phenomenon is that endothelium and other kinds of vital self-renewing cell systems that are destroyed by high absorbed doses within the paths of microbeams regenerate from similar cells in the minimally irradiated contiguous segments between the microbeams. Tissue necrosis is thus avoided except in the crossfired zone (a superposition of parallelepipeds), where the tissue-sparing effects of the microbeams are eliminated.

Experiments have been carried out at the NSLS in which it has been shown that MRT is effective in increasing the survival of rats with imminently lethal brain tumors [21,22]. In these experiments, the beams were 4 mm high and 25 microns wide, filtered by Gd on the X17 beamline at the NSLS. The microplanar beams were separated by 100 micron intervals, center to center. The skin entrance dose rates were about 400 Gy/s. The present efforts at the NSLS and in Grenoble at the ESRF [23,24] are continuing both

experimentally and theoretically in order to understand optimal beam parameters for MRT and to study dose distributions theoretically.

VII. CONCLUSIONS

The projects discussed in this paper are, for the most part, still in their infancies and no one can predict the direction in which they will develop. Both the basic research and applied medical programs are sure to be advanced at the new facilities coming on line, especially the ESRF and Spring-8. However, success is not guaranteed. There is a lot of competition from advances in conventional imaging with the development of digital angiography, computed tomography and functional magnetic resonance. The synchrotron programs will have to provide significant advantages over these modalities in order to be accepted by physicians and their patients. Advances in image processing and the development of compact sources [14,25] will be required in order to move the synchrotron developed technologies into the clinical world. In any event, it can be expected that the images produced at synchrotrons will establish "gold standards" to be targeted by conventional modalities. More work needs to be done to bring synchrotron radiation therapy and surgery to the level of human studies and, subsequently, to clinical applications.

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FIGURE CAPTIONS

Fig. 1 "Bioman" representing the many biomedical research areas at the NSLS.

Fig. 2 Theoretical monochromatic contrast (solid line) compared with the synchrotron measurements at 18 keV using the image plate detector. The phantom was 15 mm thick Lucite with additional thickness of Lucite (x axis). The diamond points represent data for the same phantom taken using a conventional clinical based mammography unit operated at 25 kVp.

Fig. 3 Intravenous angiogram taken at NSLS in the Left Anterior Oblique 30^0 projection following injection of the contrast agent into the Superior Vena Cava. The scan was performed 13.2 sec after injection and was not gated. This scan took 1.0 sec to complete. RCA is the right coronary artery, AO is the aorta and LV is the left ventricle.

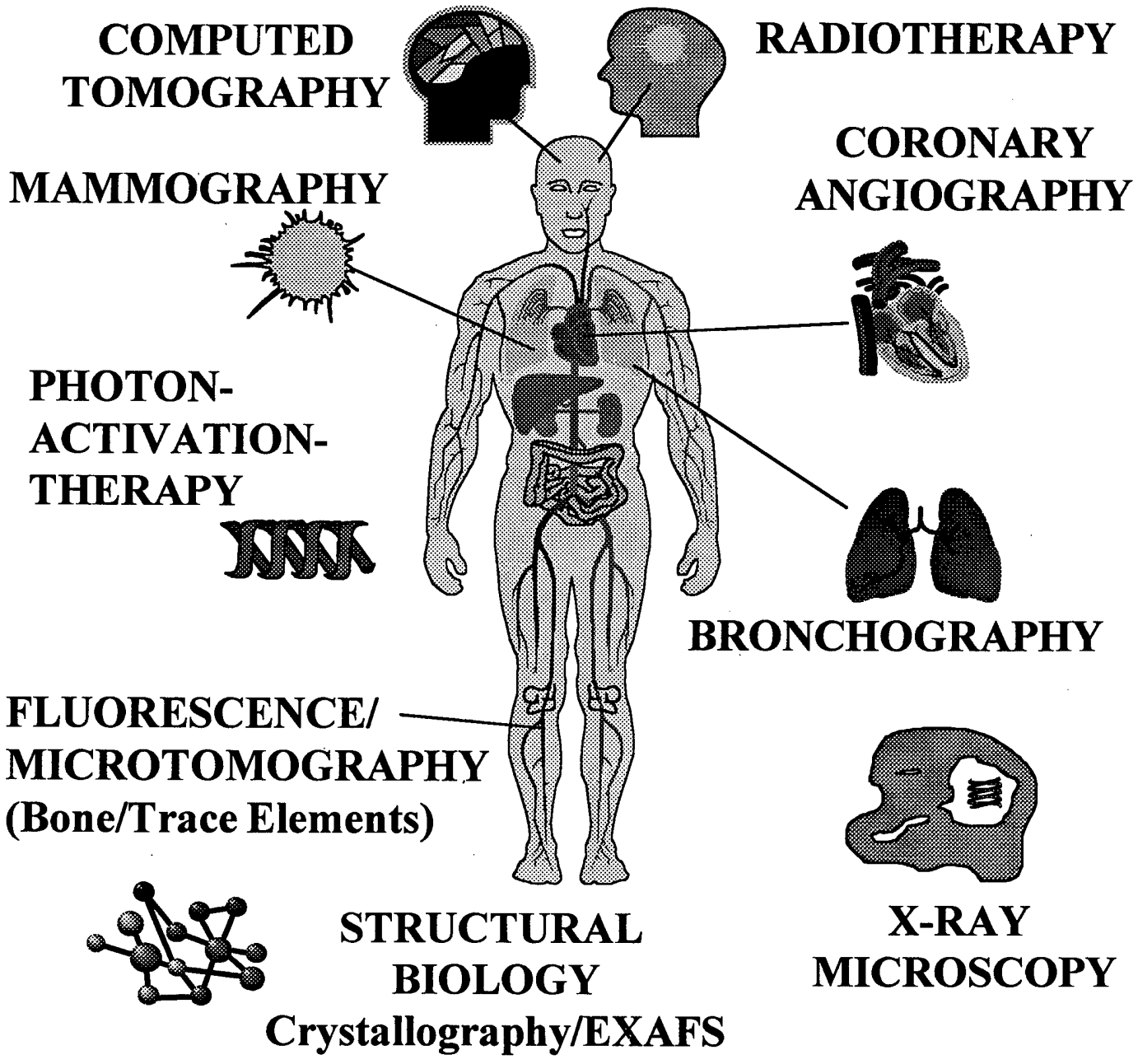
COMPUTED TOMOGRAPHY
RADIOTHERAPY
CORONARY ANGIOGRAPHY
MAMMOGRAPHY
PHOTON-ACTIVATION-THERAPY
BRONCHOGRAPHY
FLUORESCENCE/ MICROTOMOGRAPHY (Bone/Trace Elements)
STRUCTURAL BIOLOGY Crystallography/EXAFS
X-RAY MICROSCOPY

FIG. 1

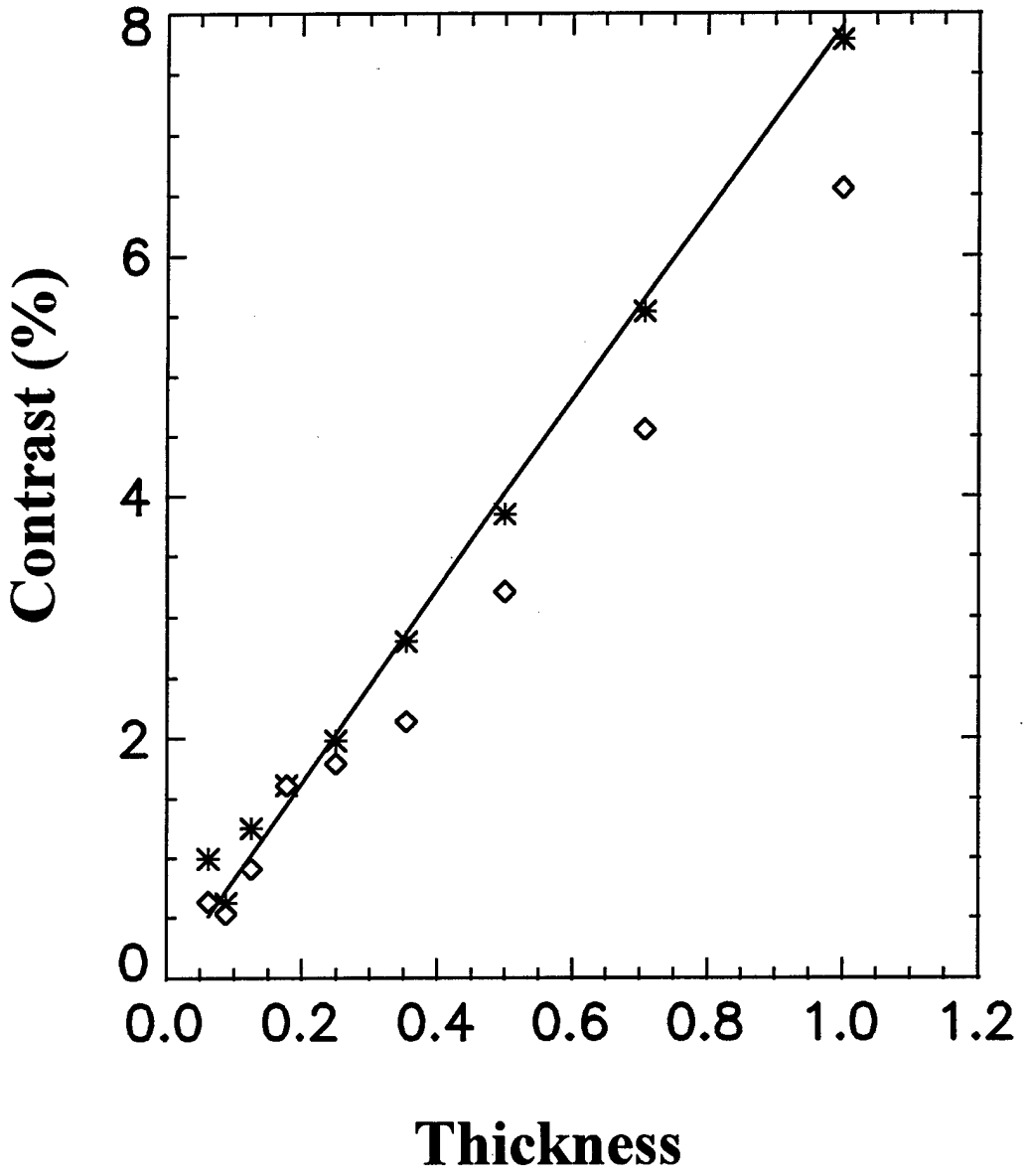

FIG. 2

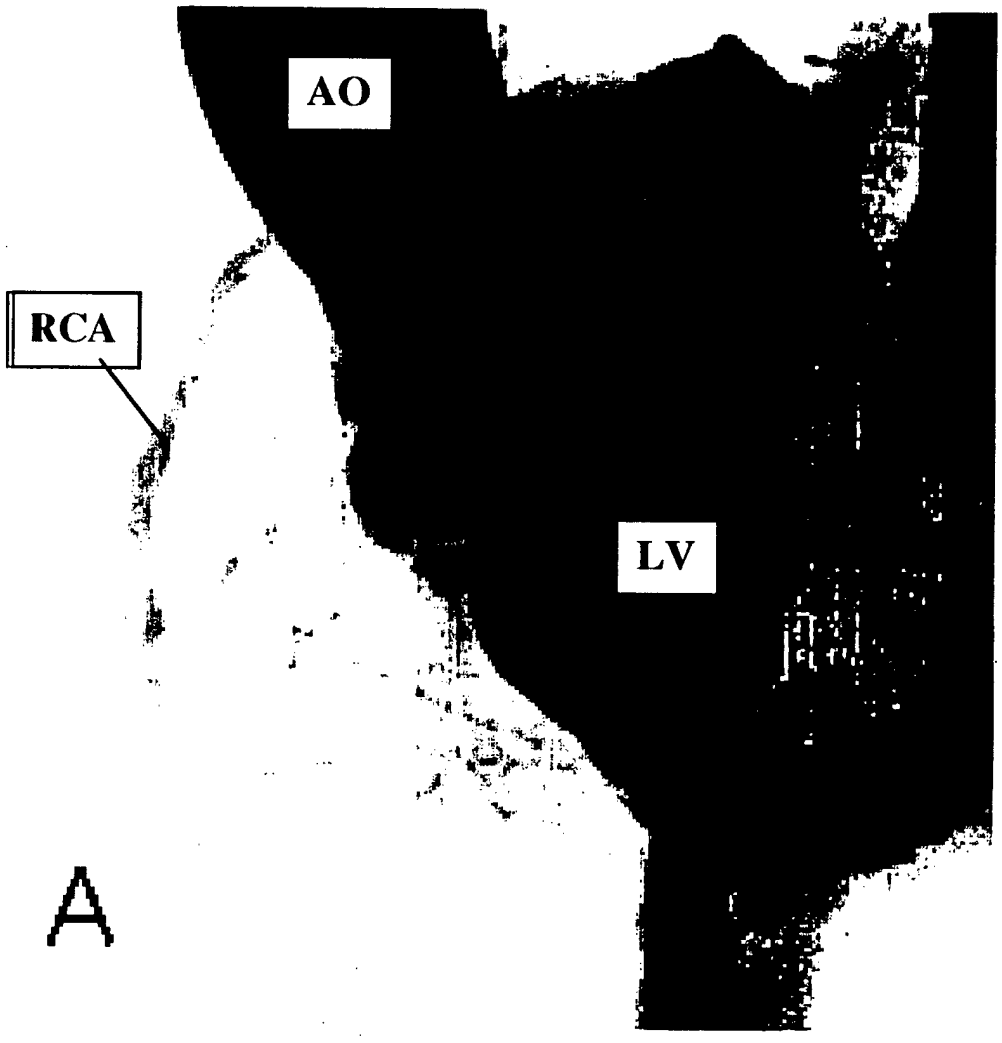

FIG. 3

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