A. INTRODUCTION

1. Objectives

Imaging and image processing of data from the heart and cardiovascular system have become increasingly important for evaluating cardiovascular function in patients with heart disease. While in the past, angiographic image processing has been the most important technique for evaluating ventricular volume, valve function, the presence or absence of shunts, and wall motion abnormalities, other techniques requiring imaging and processing of new types of imaging are also becoming increasingly important. These new methods include isotope scanning techniques and ultrasonic imaging.

The ability to measure ventricular volumes and quantitate wall motion provides powerful tools for assessment of the effects of coronary artery disease upon cardiac function. Since cardiac bypass procedures and the effects of myocardial infarction are being assessed in patients with increasing frequency, the need for developing improved methods for image analysis for angiography is readily apparent. Coronary artery disease results in the death of more than 650,000 Americans each year, and more than 8,000,000 Americans now have symptomatic coronary artery disease. Many of these individuals will undergo studies of catheterization and angiography to determine the extent of their disease and to quantitate the severity of the abnormality in cardiac function which has been caused by the disease.

The overall objective of this proposal is to develop methods for automatically defining the ventricular margin on contrast angiocardiographic studies. Utilizing the information gained by automatically defining ventricular margins on a long sequence of angiographic frames, it will be possible to assess quantitatively hydraulic function and ejection characteristics of the heart and to define quantitatively wall motion abnormalities. Thus the major objectives of this proposal are to:

a. Develop an automated computer system for margin definition which is based on mini-computer technology and can be readily utilized in a clinical setting;

b. Utilize the much more detailed information which will be gained from a frame-by-frame analysis of the cardiac cycle for the quantitation of functional characteristics of the ventricle and segmental wall abnormalities. In this process a model for ventricular contraction will be developed.

At the present time our ability to analyze quantitatively the large amount of information contained in a left ventriculogram is limited by the fact that a time consuming and expensive process of manual margin definition must be performed frame-by-frame on a long sequence of frames. There have been substantial advances in the field of image processing, many of which lend themselves to application to the particular problem presented by cardiac angiography. Several such advances have been made for image processing outside the field of medicine, and we hope to utilize these effectively in our technique development.

2. Background

Introduction

During the past seven years the Stanford Cardiology Division has focused a major area of its activities on developing computer systems for clinical applications. A computer system for the analysis of cardiac catheterization data, which was developed at Stanford and has become available commercially, has to date been adopted by

approximately 45 other catheterization laboratories (1). A dedicated CCU monitoring system for continuous ECG observation has been developed and will be made available on a widespread basis during 1975 (2). In addition, a small computer system for processing ECGs recorded on magnetic tape in ambulatory patients has been developed to provide accurate analysis in clinically useful formats (3).

Moreover, during the past three years our efforts have been directed towards developing a system for computer processing of not only hemodynamic data, but also angiocardiographic data, utilizing a video disc light-pen computer system (4). This system still depends entirely upon manual definition of ventricular margins; however, the light-pen and computer processing substantially reduce the time required for quantitative analysis. This system is now used for routine clinical processing of all left ventriculograms in the Stanford Cardiac Catheterization Laboratories.

a. Description of Video Disc Light-Pen Computer System

This system utilizes an Ampex DR-10 video disc for recording the left ventriculogram at frame rates up to a maximum of 30 fps. The present storage capacity is 600 frames. A variable speed control for playback is provided. At the time the ventriculogram is recorded, both the electrocardiogram and the left ventricular pressure (if simultaneously available) are converted into horizontal histograms, which are recorded synchronously with the video frames. Thus, superimposed on each video frame in the upper portion of the screen are two "bars," the length of which is proportional to the analog ECG and/or pressure signals. Calibration capability has been provided for the two "histograms."

A Tektronix 4551 light-pen unit is used to manually trace the margins of the left ventricle as it appears on the video monitor. A pressure-sensitive switch on the light-pen allows the operator to instruct a laboratory mini-computer to sample the X-Y coordinates of the light-pen position. The light-pen is interfaced with a Tektronix 4501 scan converter unit which permits retention of the traced margin. A video mixer incorporated in the Ampex video disc merges the scan converter output with the recorded picture on the video disc. Similarly, the laboratory computer (Hewlett-Packard 2100) generates alpha numeric and graphic data on the scan converter, which in turn is displayed on the video screen, mixed with the angiographic picture. Synchronization of the scan converter, light-pen and video disc is performed by a Telemation model TSG-200 broadcast synchronizing generator. Results of computational analysis are printed out on a Versatec hard copy unit which provides 8-1/2 x 11 sheets suitable for medical record use.

b. Digitization of the Video Image

We have developed a video digitization system as a prerequisite step towards automatic margin definition. The recorded left ventriculogram is digitized in the following manner. A single cardiac cycle recorded prior to contrast injection is digitized field by field. The recorded ventriculogram is digitized over two or three cardiac cycles. Frame advance and identification of frame number on the video disc is under direct computer control. The purpose of digitizing a single cardiac cycle without contrast is to provide data for subtraction on a field by field basis, based on timing with the QRS. The QRS is recorded as a horizontal bar at the top of the video screen. The length of the horizontal bar corresponds to the amplitude of the ECG signal at the time the video image is recorded. This visual ECG signal is in a format such that it can be readily detected by the computer for use as synchronizing information for the computer subtraction of frames which occur at the same times of different cardiac cycles.

A Colorado Video 260 unit is used for digitizing the standard video image. The CV-260 generates a buffer of 256 six bit values which represent the intensity (brightness) of the image along a vertical line which is located at a position determined by an external computer imput. The system is designed to separately digitize the two fields within each frame such that temporal information at 60 times per second is obtained. The CV-260 is interfaced to a Hewlett-Packard 2100 computer which controls the field selection and horizontal location of the digitizer.

During one field time (16.7 milliseconds) one point is converted from each of 256 horizontal raster lines in the selected fields. The vertical position is increased by the horizontal syne pulse. The horizontal location of the point on the line is determined by the voltage applied to the external horizontal scan input. The brightness of the point is converted to a six-bit number (64 Gray Scale Levels) and then inserted into a 256 word buffer. Under computer control, the buffer is transferred sample by sample to an array in computer memory. Four 256 sample vertical lines are buffered in computer memory and transferred as a single record to a Hewlett-Packard digital magnetic tape drive. Using a 2400 foot tape length, with an 800 bits per inch density and an interrecord gap of 0.6 inches, it is possible to store four seconds of real time video on a single reel of tape. The time presently required for digitization is 35 seconds per video field, or approximately two hours 15 minutes for a full four seconds of real time video. Clearly this digitization time is too long for clinical application. We specifically propose to implement in year 02 a higher speed digitizer which will require approximately two seconds per field (10 minutes for 150 frame study at 60 fields/second).

c. Collaboration with Stanford Artificial Intelligence Laboratory

Over the past two years the Stanford Cardiology Division has worked with the Artificial Intelligence Laboratory at Stanford in a collaborative effort to investigate the possibility of applying the state of the art image processing techniques to the problems of cardiac angiography. Vision research efforts at this laboratory date back to 1965 and were applied to projects such as the development of the robotics and automated assembly project (5-11). These efforts were directed towards developing the techniques for computer understanding of real scenes and resulted not only in a large collection of useful, debugged code, but perhaps more importantly, in a wealth of experience and insight into scene analysis technique. The fundamental design of this research effort has been strongly influenced by the problem solving philosophies which have been developed by this group. The following summarizes some of the relevant work of the Artificial Intelligence Laboratory:

Baumgart (12) developed a 3-D geometric modeling system for application to computer vision. In computer vision geometric models provide a goal for descriptive image analysis, an origin for verification image synthesis, and a context for spatial problem solving. Some of the design ideas presented have been implemented in two programs named GEOMED and CRE; the programs are demonstrated in situations involving camera motion relative to a static world. Baumgart's GEOMED system was developed for doing 3-D geometric modeling; used from a keyboard, it is an interactive drawing program; used as a package of SAIL or LISP accessible subroutines, it is a graphics language. With GEOMED, arbitrary polyhedra can be constructed, moved about and viewed in perspective with hidden lines eliminated. In addition to polyhedra, camera and image models are provided so that simulators relevant to computer vision, problem solving, and animation may be constructed. These techniques will be useful for building 3-dimensional models for the heart.

Nevatia (13) developed techniques for description and recognition of three-dimensional objects from range data obtained by a laser triangulation technique.

A complex object is described by decomposition into sub-parts and relations of these sub-parts. The individual parts are described by generalized cones, which are defined by a space curve known as the axis, and arbitrary shaped normal cross-sections along this axis. These techniques will be particularly useful for 3-dimensional analysis of bi-plane and multiplane ventriculograms.

Pingle (14) developed a fast, feature-driven program for extracting depth information from stereoscopic sets of digitized TV images. This is achieved by two means: in the simplest case, by statistically correlating variable-sized windows on the basis of visual texture, and in the more complex case by pre-processing the images to extract significant visual features such as corners, and then using these features to control the correlation process. The significance of this work is the feature-directed approach to information extraction from images, which will be useful to automatic margin detection.

Quam (15, 16) developed techniques for geometric registration and differencing of images to detect changes. Misregistration of the images was measured using a small area correlation technique. One of the images was then geometrically distorted to remove the misregistration. Finally, the images were point-by-point subtracted in such a manner that subtle differences between the images were made obvious. These techniques will be particularly important in the removal of background from ventriculograms.

d. Previous Work by Others

There are several prominent investigators who are actively working in the field of automated margin definition. At the present state of the art, it appears that no system has reached the point of routine utility in a clinical setting. Although somewhat different approaches are being taken by individual investigators, the general pattern is to process video images recorded on an analog video disc. Most present systems incorporate operator interactive pre-processing, either by masking areas around the ventricle, identifying areas for digitization, or manually selecting voltage levels to exclude background images. Most systems incorporate capability for operator input of manually defined margins, usually via a pen-tablet apparatus. A complex pre-processing system has been developed at the Mayo Clinic which incorporates many of the above features (17). The systems developed by Heintzen in Kiel, West Germany (18) and Reiber at NASA-Ames Research Center use pre-processing analog devices to identify the ventricular margin while scanning across the raster lines of the video image. Edge-finding computer algorithms, operating on digitized data alone, which avoid the limitation of horizontal raster lines, have been reported by Robb in Salt Lake City (19) and Kaneko in Yorktown Heights (20). Probably the most advanced margin detection system presently developed is that of Clayton et al. (21), which is the first system to constrain the edge detector using assumptions of smoothness and continuity of the margin in both space and time. Most systems described above utilize large-scale computer systems, with the exception of Stewart in Philadelphia (22).

The present trend in automated margin definition by most investigators is to utilize pre-processing hardware to perform the difficult task of eliminating extraneous densities which impinge upon the ventricular margin, relying heavily on operator interaction. Some systems are dependent upon the horizontal scanning lines of the video image, which causes considerable difficulty when approaching the inferior and apical portions of the ventricle, where the margin runs parallel to the video scanning lines. These systems impose severe limits on development of sophisticated techniques to handle low signal to noise ratio images with poor contrast. There has generally been limited use of computer software to solve the problems of automated margins

because of the complexities of programming such algorithms.

Because of the substantial expertise in vision research in the Computer Sciences Department, our approach will emphasize sophisticated computer handling of the angiographic images. We feel that our approach will differ from previous ones and be unique in the following major respects: 1) Provision for image subtraction capability; 2) Multidirectional capability of edge finding; 3) Detection not only of the position of the edge but also the direction in which the edge is traveling; 4) Use of modeling techniques to provide a set of expectations with capability to fill in "gaps" (static modeling); 5) Use of data from previous frames and models to provide increasing accuracy for later frames (dynamic modeling). It is anticipated that by application of the above sophisticated computer techniques and other differences in approach, preprocessing hardware can be minimized, as well as requirements for operator interaction.

3. Rationale

Introduction

At the present time ventricular volume and wall motion abnormalities due to disease of the heart are estimated by most sophisticated cardiovascular laboratories studying patients with coronary artery disease. High quality angiograms are recorded on film, the images projected upon a screen, and hand methods used to trace the outline of the ventricular chamber and cardiac wall with each cardiac cycle. These are frequently processed at 60 frames per second and require that a technician or physician manually draw each frame of the heart for up to five seconds. Thus, the result is the time necessary for tracing 100 to 200 images for each patient processed. Planimetric methods are used to determine the area and appropriate corrections made for magnification and distortion due to radiographic systems. Specific cords on the circumference of the wall of the ventricular chamber may be designated for study; this requires even more complex human interaction. Since such studies are carried out in more than 200,000 patients each year, the investment of time by the individual technicians and physicians is enormous. In addition, subjective criteria are used for defining the margins and for identifying individual segments of the wall on a frame-by-frame basis. The data are also obtained in a form difficult to manipulate by a computer.

The specific rationale for developing an automated method for evaluating angiographic images is to obviate the need for human interaction with the image analysis. Computer software to do better definition, to follow the borders through the various frames of the contraction cycle, and to specifically analyze the hydraulic function of the wall will be possible. Data recorded on a video disc, digitized, and placed into a computer in which advance technologic methodology for border definition can be incorporated will permit this automatic analysis. A number of graphic methods for presenting the data, for interacting with it mathematically, and for comparing it to models which have been developed of the normal contracting process will permit quantitative assessment of changes in wall motion and ejection characteristics.

The overall rationale will be to develop such a system utilizing technology developed in other basic disciplines of imaging and image processing, to test it in a non-clinical situation using models of the ventricle for validating many of the assumptions now inherent in angiographic volume measurement and ejection characteristic determination, to validate it in a clinical laboratory where it can be compared to presently available methods and techniques, to utilize it in clinical research to demonstrate its applicability for studying patients, to develop the computer imaging

system in a small computer so that it will be exportable to a number of laboratories throughout the country, and to utilize the technology developed for angiographic image processing for processing other types of images from ultrasounds and isotopes.

There are several important considerations which lead us to believe that this project can be successfully pursued at Stanford with the likelihood for achieving a clinically effective system.

a. The Cardiology Division has had substantial experience in developing computer systems with direct clinical application to problems in cardiology. These include the Cardiac Catheterization Laboratory system, the Coronary Care Unit monitoring system, a computer system for processing ambulatory ECG tape recordings, and a light-pen computer system for manual margin definition. Previous activities of the Cardiology Division in these areas have led to a close collaboration between computer scientists and cardiologists, with a mutual understanding that clinical utility and enhancement of medical knowledge are primary goals.

b. The presence of the Artificial Intelligence Laboratory at Stanford, with its high degree of expertise in image processing, provides significant ongoing system support for the code which has been produced, keeping it both continually up-to-date and improved. Moreover, Dr. Quam represents a large resource of expertise and experience in the field of computer image analysis.

c. Modelling techniques are an important prerequisite for defining both the normal and abnormal range for cardiac wall motion and ventricular geometry. Stanford is unique in having available wall motion data derived from postoperative patients who have implanted radio-opaque intramyocardial markers.

d. The availability of a large computer facility (SUMEX) which can be utilized for developing software and for processing data initially will aid this project.

e. The computer approaches we propose are relatively unique in the field of processing cardiac angiography. The use of both static and dynamic modelling of the ventricular margin to provide a set of expectations within which the contour is to be searched offers significant advantages. There is sufficient overlap of radiographically dense structures, such as ribs and aorta, and difficulty in discerning the systolic margin to necessitate a model-directed approach and image subtraction. Although these techniques will require computer extrapolation to complete missing perimeter segments, this approach closely resembles the approach normally used by experienced angiographic technicians.

B. SPECIFIC AIMS

The specific aim of the proposed program is to apply advanced image processing technology developed by other scientific disciplines to angiographic image processing. The ultimate goal is a reliable, validated system for automatic left ventricular margin definition which can be utilized for clinical application. In order to meet these objectives, a number of subsidiary goals must be accomplished.

1. Subsidiary Goals

a. Reliable Margin Detection

First, reliable techniques must be developed to locate the margin in the low signal to noise ratio video images that are typical in angiography. (Cine film based

digitization is rejected for actual clinical use because of the additional processing steps, and the problems in exposure control.) In typical angiogram sequences, portions of the margin are not visually apparent when looking at individual frames, but must be inferred from surrounding frames in the sequence, and from familiarity of the normal shape and dynamic motion of the margin.

The best available techniques for detecting weak, noisy edges are based on appropriate statistical averages of the data and least squares minimization. These techniques can be made more reliable and more efficient if there is a computer model to predict the approximate location and orientation of the margin. This necessitates a knowledge of dynamic ventricular wall motion, which is an additional goal of this proposal.

b. Two-Dimensional Dynamic Modelling

A two-dimensional dynamic model for wall motion will predict the normal outline of the ventricular margin in the right anterior oblique projection as a function of time in the cardiac cycle. We propose to develop this model using the above-mentioned margin detection techniques and using models of cardiac motion developed both from manually defined margins and from the motions of intramyocardial markers.

c. Quantitative Measurements of Left Ventricular Function

Having an accurate and reliable technique for locating the margin in a sequence of angiograms gives us the ability to evaluate the performance of the heart as a pump. Standard measures of end diastolic, end systolic, and stroke volumes can be calculated for each of the frames in the sequence. We can also calculate segmental shortening and wall motion to determine the contribution of each segment of the wall to the overall performance of the heart. Abnormal behavior can be detected by comparing these measurements with ones for a normal heart.

d. Biplane Angiographic Analysis

It is a goal of this project to adopt the single plane techniques, specifically reliable margin definition, modelling and ventricular performance evaluation, for biplane angiography. In order to do this, it will be necessary to develop reliable margin definition, not only for the right anterior oblique projections, but also for other projections such as biplane antero-posterior and lateral projections, or biplane RAO and LAO views. Dynamic modelling in the multiplane dimension will be needed, and for this purpose the intramyocardial markers will provide substantial assistance, since in the future these markers will be positioned in multiple dimensions. Similarly, techniques to evaluate ventricular performance and deviations from normal will be developed using biplane data.

e. Dedicated Computer Application

A critically important goal in this project is to implement the above single plane and biplane techniques on a small dedicated computer system, which in both software and hardware design automatically processes the ventriculographic images. The goal is to develop an automated system sufficiently compact and efficient in design that it might be readily exportable for general clinical application.

f. Routine Clinical Use

We propose to develop validation techniques for this automatic image processing

system which can be compared to the standard methods for determining ventricular volume and wall motion abnormalities now used in cardiovascular laboratories throughout the United States. We specifically plan to objectively evaluate the effectiveness of this system in processing routine clinical angiographic studies.

g. Research on Ventricular Performance

The development of a reliable system for automated margin definition, once completed, will become a valuable tool for further research studies in ventricular performance. Specific areas for proposed research applicability are an analysis of segmental wall motion abnormalities and analysis of cardiac motion during systole and diastole.

h. Application to Ultrasound and Isotope Image Analysis

Finally, our aims and objectives are to apply the techniques developed for angiography to processing of images obtained from ultrasound and isotope scanning techniques. Clearly this is a long range objective and will require from three to five years before it can be incorporated into any clinical studies. However, the techniques developed for processing of angiographic images should be applicable to processing of these more complex images when advances in hardware and transducer units have occurred.

2. Scenario for Clinical Use

The following is a description of how the automated model-directed system for processing cardiac angiography will look to the user. Specifically, this scenario outlines our goals with respect to user (physician or technician) interaction with the computer system.

a. Left ventriculograms are recorded on a video disc during contrast injection. Immediately prior to contrast injection, a brief recording is made in order to provide pictures of the cardiac silhouette for subsequent subtraction.

b. The operator specifies (using a terminal) the beginning and end frame numbers for the sequence, as well as the frame number of dye injection.

c. The program automatically scans the sequence for ECG and left ventricular pressure. The electrocardiogram and left ventricular pressure are coded near the top of the video picture as a bright horizontal bar, allowing the computer to automatically identify end diastolic frames.

d. The ECG data and the operator specified reference points of the aortic valve and ventricular apex are used to predict a "normal" left ventricular margin shape to guide the margin detection in the first "good" frame. Once there is satisfactory margin definition on the initial "good" frame, the automatic margin tracking program, using appropriate static and dynamic models of ventricular motion, will proceed through the remainder of the frame.

e. Automatic digitizing and margin tracking programs do the rest.

f. The final outputs are (1) standard quantitative measures of ventricular performance; (2) graphic overlays on top of the replayed video disc images of the automatically detected margins for validation of the automatic system. Thus, the operator can either single-step through the sequence or randomly sample frames in the sequence

to view the computer generated margins and verify their accuracy; (3) graphic display of volume, pressure, wall motion and other measures as a function of time; (4) hard-copy graphic output of any of the traced margins or graphs on standard 8-1/2" x 11" paper for inclusion in the medical record; (5) permanent magnetic tape record of all digitized and reduced data which will expedite comparisons of system performance and individual patient performance over long periods of time.

C. METHODS OF PROCEDURE

Introduction

The primary components in developing an automated system for processing left ventriculography are illustrated in Figure 1. Specifically, they are: 1) technique research and development on the SUMEX PDP-10 machine; 2) implementation of margin detection system on a mini-computer system (PDP-11); and 3) clinical validation and applications. The proposed time scale for development over a three-year period is shown in Figure 1.

1. SUMEX PDP-10 Based Technique Development

We propose to start research in cardiac dynamic modelling and model guided margin detection using the SUMEX PDP-10 system and much of the image processing software which has been developed on the PDP-10 system at the Stanford Artificial Intelligence Laboratory. In particular, we will use the image enhancement, noise removal, image registration, image differencing, edge detection, and edge verification algorithms which are already developed for the PDP-10.

The use of the SUMEX facility will concentrate on experiments with techniques in wall motion modelling and model guided margin detection which do not require extensive interactive facilities. Line drawing graphics and grey level display facilities, which are essential for image processing research and the development of an interactive clinical system, are presently missing from the SUMEX system. We will assemble an interim display facility on SUMEX, using a slow scan scope and Polaroid camera. For a more complete automatic margin detection and dynamic modelling system, we will need the display facilities and dedicated computer system for which funds are requested in this proposal.

The specific techniques for automated margin detection, the processing steps to be followed, and the theory employed are outlined below. Shown in Figure 2 is an illustration of currently existing hardware which will be utilized at this initial phase of development.

The HP-2100 Cathlab system will be used to digitize sequences of angiograms stored on the video disc onto 9-track magnetic tape which is compatible with that used by the PDP-10 system, as shown in Figure 2.

Initial processing will transfer the image data from magnetic tape to the disc file system. The initial PDP-11 system will receive image data communicated over a 9600 baud line between the PDP-11 and the HP-2100, as shown in Figure 3. The image data will be separated from the ECG and LV pressure data, which will be stored in two separate arrays. The ECG signal will then be processed to accurately locate the R wave peaks and determine the length of the cardiac cycle.

The operator specifies the frame number of contrast injection. Using the previously determined length of the cardiac cycle, frames from corresponding times in the cardiac cycle, both before and after contrast injection, are differenced to remove background due to the diaphragm, ribs, and other parts of the anatomy which are not of interest. It is believed that automatic margin detection will be much easier and more reliable using these difference images.

Our approach to margin detection is the use of dynamic models of wall motion to predict the approximate location and shape of the margin as a function of time in the cardiac cycle and the location of the margin in preceding frames. Knowing the approximate location and orientation of the edge allows one to design edge detection algorithms which compare the brightness statistics on each side of the hypothesized edge. This technique gives an improvement in contrast to noise ratio roughly proportional to the square root of the number of image points used in the statistics. In order for other edge detection methods to find subtle, low contrast edges, they must use very low thresholds on the differences in brightness between adjacent points, making them much more susceptible to noise in the images. These individual processing steps used for margin detection are outlined in Figure 4.

Our initial dynamic model for wall motion will be derived both from manually defined ventricular margins and data derived from motion of intramyocardial markers. The intramyocardial markers are small tantalum coils (0.5 mm in diameter and length), which at the time of surgery are positioned within the myocardial wall and on the aorta near the level of the aortic valve such as to outline the ventricle as seen in the right anterior oblique projection. This project is funded by a separate National Institutes of Health grant and provides in postoperative patients highly reproducible and precise measurements of dynamic wall motion. Many patients having coronary bypass graft surgery have these markers placed, and in the absence of any evidence for preoperative or intraoperative myocardial damage, represent models of normal ventricular motion. The myocardial marker data derived from ventricles of patients with both normal and abnormal myocardial motion will be used to generate a dynamic model of wall motion, which provides predictions for computer detection of the contrast boundary. These projects do not in any way overlap with our proposals for an imaging and image processing system outlined herein. They complement them and permit the use of data from marker patients for modelling the ventricular contraction process.

Initially, we will require a human operator to specify two points in the first frame: the aortic valve and the apex. These points will be used to position and scale a simple model for the shape of the left ventricle at this particular time in the cardiac cycle. The model will approximate the margin by a collection of linear segments. The precise location of each segment will be determined by computing means and variances of intensities along lines parallel to and adjacent to the predicted segment. The location of the segment is then based on finding the edge in this one-dimensional array of means. The variances are used to measure the uniformity of the intensities on either side of the resulting edge as a measure of signal to noise ratio and likelihood that we have chosen the proper orientation for edge. Figure 5 illustrates the technique.

Some analysis of how the images are formed will allow us to predict the nature of the edge in this array of means. We assume that the only difference between the images before and after contrast injection is due to the contrast agent and Gaussian noise in the video signal. (The catheter will be dark in both images, resulting in zero in the difference images.) Although there may be other systematic differences due to frame to frame variations in the X-ray source, we can discover and correct them by comparing the background areas in the two images. Consequently, the difference image outside the heart should be constant (zero) in brightness plus noise.

Inside the heart wall the brightness will decrease according to the Lambert-Beer law.

$$I = I0 \cdot \exp(-k \cdot c \cdot d) \qquad \text{(eqn 1)}$$

where

I0 is intensity of the radiation source
I is the intensity of radiation after passing through contrast material
k is the absorption coefficient of the contrast material
d is the path length of the radiation through the contrast material
c is the concentration of the contrast material

$$\text{or} \quad \log I - \log I0 = - k \cdot c \cdot d \qquad \text{(eqn 2)}$$

In our previous discussion, we described the use of image differencing to remove the effects of background. The above equation suggests that we really want to subtract logarithms of the intensities, so that our difference data then corresponds to the left hand side of equation 2. If we assume that the heart has approximately a circular cross section, then we get the path length d as follows:

$$d^2(x) = 4 \cdot (r^2 - (x-xc)^2) \qquad \text{(eqn 3)}$$

where

r is the radius of the circle
x-xc is the distance of the radiation path from the center of the circle

$$\text{density}^2(x) = (\log I - \log(I0))^2 = (k \cdot c)^2 \cdot (r^2 - (x-xc)^2)$$

$$\text{or} \quad \text{density}^2(x) = p_1 \cdot x^2 + p_2 \cdot x + p_3 \qquad \text{(eqn 4)}$$

for parameters p_1, p_2, p_3. Figure 6 shows the expected shape of the edge due to the contrast agent.

Our method for accurately locating the wall will be based on finding the values of the background difference: p_0, edge location: x_{edge}, and the three parameters in equation 4 which best approximate the actual data by the method of least squares:

$$\sum_{x<x_{edge}} (\text{density}^2(x) - p_0)^2 + \sum_{x \geq x_{edge}} (\text{density}^2(x) - (p_1 \cdot x^2 + p_2 \cdot x + p_3))^2 = \min \qquad \text{(eqn 5)}$$

Segments for which the contrast is statistically too low will be marked as missing and filled in later using information from neighboring images in the sequence and using the wall motion models. It should be noted that we are using the Lambert-Beer equation only to approximate the density behavior of the edge so that it may be more accurately located, and not to quantitatively measure volumes or dilution rates.

2. Mini-computer Based Development

A PDP-11 mini-computer system is proposed for the development of the complete automated margin system for clinical application. A mini-computer system is chosen for several reasons. First, we believe that the techniques which we develop for the PDP-10

can be transferred to a PDP-11. Second, we believe that mini-computer systems are the most cost-effective for clinical use. The PDP-11 was selected because of its powerful instruction set, its ease of programming, the large range of software available from both DEC and its customers, the wide range of peripheral devices available, the ease of interfacing new devices, and the rapidly decreasing price to performance ratio (LSI-11). It is believed that within a few years, a PDP-11 compatible computer system capable of processing all of the data for clinical use will cost less than $30,000, including all of the necessary peripherals.

In general, it is not straightforward to transfer a given program from a large memory-space computer to a mini-computer with a significantly smaller address space. However, in the particular case of image processing (and other signal processing areas also), it is possible to process the data in relatively small pieces at any given time, rather than requiring that all of the data be resident simultaneously in the primary memory. It is also possible to segment the image processing and dynamic modelling algorithms into a number of independent modules which execute one at a time.

Figure 7 shows the configuration of the proposed mini-computer system for research and development of the automated margin detection system. Briefly, the computational portion of the system consists of a relatively fast PDP-11 processor connected to a medium capacity (28K words) primary memory and a pair of medium size and speed moving head discs. The user interactive facilities consist of a random access graphics display, a conventional hardcopy terminal, and a grey-level image display. The system also has a 9600 baud communication line connected to the SUMEX PDP-10 and the Cathlab HP-2100 system. Image data is transferred over this line from the HP-2100 system as shown in Figure 3. The line to the PDP-10 is used to access peripherals such as line printers, magnetic tape drives, and plotters which do not need to be duplicated on the PDP-11 system during this development phase. The individual components are explained in the budget justification. This mini-computer based system will be used to develop and test the techniques previously described. It is anticipated that most of the initial testing will be based on a relatively small number of sequences on images stored on removable RK05 disc cartridges.

As this phase of development is proceeding, the same methodology will be applied to other angiographic planes, particularly the left anterior oblique projection. The addition of this biplane will most likely improve the accuracy of the system. It is presently planned to use the split field technique for recording of biplane images.

3. Clinical Validation and Application

The final clinical system which evolves from the developmental stages is illustrated in Figure 8. It is this clinical system which will be utilized for making quantitative measurements of ventricular performance, analyzing ventricular wall motion abnormalities, and providing graphic overlays and plots of ventricular data as a function of time.

There are two stages in the clinical application of automatic computer processing of left ventriculography. The first is validation of the techniques developed, and the second is the development of quantitative analytic techniques for direct clinical application.

a. Validation of Methods

The clinical application of computer programs as complex as those required for automated margin definition requires careful validation. The validation testing must

check not only the reproducibility, precision, and accuracy of the margin definition programs themselves, but must also assess the ability of the system to process unselected and random ventriculograms and provide clinically useful information in formats which are readily usable by the physician. Thus, although the computer system from an engineering and technical point of view may successfully process selected high contrast ventriculograms, it is important to assess the percentage of patients to which the technique could be successfully applied. Moreover, the human engineering aspects of a completed image processing system are critical to its success, and therefore evaluation of these aspects of this system are important.

Clearly, both the radiographic equipment, technique, and the patient's physiognomy directly determine the final quality of the picture. Patients with large antero-postero chest diameters and those with heavy adipose or muscular tissue around the chest wall may require higher radiographic kilovoltage in order to adequately penetrate the patient. Radiographic contrast is critically important in determining the quality of the final image. Thin patients or those with emphysema or hyperaerated lungs may show "burn out" of the apical and lateral portions of the heart. The video recording system and the digitization hardware must provide for image recording and reproduction without degrading significantly the signal to noise ratio. All of these factors will ultimately determine the percentage of clinical left ventriculograms which can be satisfactorily processed by an automated margin definition system.

In order for such a system to achieve widespread application in cardiology and to set the stage for development of other types of automated margin definition systems, there must be evidence that a very large fraction of all clinical studies at a given center can be adequately processed. In order to provide a fair test of the system, randomly selected, routine, clinical ventriculograms will be used to assess the overall utility of such a system. An additional aspect of this evaluation includes testing of the capability of the system to process ventriculograms obtained in patients with both normal hearts and pathology of the heart. Distortions of ventricular geometry, i.e., static deformities, will impose one type of difficulty for automated margin definition. Dynamic abnormalities, such as the asyneresis commonly seen in patients with coronary disease, necessitate accuracy in both the dimensional and temporal aspects of analysis.

1) Internal Consistency and Accuracy (Program Testing)

This is the first phase of testing and will occur concomitantly with the development of margin definition programs, both on SUMEX hardware and on a mini-computer. In order to provide a means to test the success of specific developmental programs to define ventricular margins, a method for correlating manually defined margins and computer defined margins will be developed. Our present and proposed hardware configurations are designed to permit digitization of either the video image alone, the track of the light-pen (or electro-static pen) alone, or digitization of both mixed together. The ability to digitize the manually defined margin provides a means for mathematically comparing computer generated margins against those generated manually. For individual frames the differences could be displayed and the discrepant areas quantitated. In a sequence of frames exhibiting dynamic wall motion, differences in dynamic motion as measured from computer generated margins versus manually defined margins can be readily quantitated. This kind of information will be very important during the various developmental phases of the system since it will provide a basis for program modifications and enhancements.

The reproducibility and consistency of computer programs for margin definition are critically important. When computer algorithms are finely tuned to subtle nuances of the image, the possibilities for lack of reproducibility will tend to increase. It is anticipated that the use of model directed margin definition will reduce the variability

of margin detection when defined purely on the basis of small differences in grey levels.

2) Clinical Testing

The process of automated margin definition is dependent not only upon computer programs but also upon the quality of the images generated by the entire radiographic chain, including radiographic equipment, ventriculography technique itself, and video digitization. The degree of sharpness of the edge between contrast in the ventricular cavity and the myocardial wall is a critical determinant of the ability of the computer system to process video images. We propose to assess the degree to which improvements in the entire radiographic chain influence the quality of automated margin detection.

3) Physician-Technician Interface with Computer System

As previously defined under the specific aims of this project, a set of specifications have been developed which to a large extent govern system development. The specifications are oriented towards optimizing the human engineering aspects of the system. The system will place a premium on minimizing operator interaction at all levels of analysis. With respect to data input into the computer, the system will incorporate hardware which will provide for automatic digitizing of video pictures without operator interaction other than initiation. Functions such as video frame advance, initiation digitization of each frame, identification of the specific frame number, and digitization of associated physiologic parameters such as ECG and left ventricular pressure will be automatic. Computer processing of the digitized data will be automatic, other than initial program call-up and attachment of appropriate tape storage. Computer processing will proceed frame-to-frame, generating both geometric and time-oriented information.

Development of a method for computer generated margins to be displayed superimposed on the ventricular image is important to provide feedback for the physician in the catheterization laboratory. Our experience in developing both the cardiac catheterization laboratory system and the coronary care monitoring system indicates a strong and urgent need for the computer to echo back to the physician the results of its analysis. This feature has been very important in building confidence among physicians and paramedical personnel in a given computer system. It gives the physician an idea of the strength and limitations of the computer programs for margin definition and provides a framework upon which to judge and evaluate quantitative and graphic hardcopy outputs.

b. Clinical Application and Quantitative Analysis of Ventricular Performance

1) Standard Quantitative Performance Measures

It is anticipated that two types of data will be generated by the computer system. One type is a simple quantitative report of numeric data in tabular format. This type of report is presently generated on an electrostatic printer which provides paper on a standard 8-1/2 x 11 size suitable for standard medical record use. The hardcopy graphic copy output will be generated according to a preprogrammed format, which operates without requiring operator control. An example of such a report form currently generated by our computer system is shown in Figure 9.

2) Graphic Overlays of Ventricular Contours

Graphic output is particularly important to the physician for the identification of contraction abnormalities, overall wall motion, ventricular size, and detection

of significant shape abnormalities. The most clinically useful type of graphic output which we have employed is based on superimposition of contourograms generated from either end diastolic and end systolic frames or superimposition of multiple sequential frames. An example of the type of hardcopy output generated on a Versatec printer which we presently employ is shown in Figure 10.

3) Graphic Displays of Ventricular Data as a Function of Time

Other important types of graphic output include plots of volume, pressure, wall motion, and other data as a function of time. This type of information provides dynamic data concerning ventricular performance and can be used to compute the rates of ventricular filling or emptying.

4) Analysis of Segmental Wall Motion Abnormalities

Abnormalities of segmental wall motion are generally the consequence of coronary artery disease. Their severity and extent, to a large degree, determine an individual patient's clinical condition, prognosis, and potential operability. There are several methods which have been utilized for quantitation of segmental wall abnormalities, the quadrasection method being most widely employed. The quadrasection method divides the long axis of the ventricle into four equal segments, constructing perpendicular lines to the long axis which intersect the myocardial margin. The lengths of the lines connecting the long axis to the ventricular margin, when plotted against time, provide a measure of segmental contractility (23).

This method is, however, limited by the fact that the percentage shortening of a segment chord may be significantly affected by ventricular size and changes in stroke volume. In order to normalize wall motion for changes in cardiac size and stroke volume, we are in the process of assessing a measurement referred to as the "area displacement index." Basically, this method uses the quadrasection technique to subdivide the perimeter of the ventricle as seen in the RAO projection into eight segments. The area displaced from diastole to systole for each segment of perimeter can then be calculated. Since the total area displaced from end diastole to end systole reflects the entire stroke volume, it is possible to calculate the percentage contribution of each perimeter segment to the overall stroke volume. Thus, by calculating the percentage contribution of each perimeter segment during systole, changes in ventricular size and stroke volume are normalized.

Moreover, utilizing this method the time course of the area displaced by each perimeter segment can be plotted and compared against one another. In this manner asynergy of specific myocardial segments can be readily identified. At the present time manual margin definition of individual frames is necessitated in order to acquire this type of information. The use of automated margin definition will provide a rapid means to measure both the extent of wall motion abnormalities and the temporal sequence of these abnormalities.

5) Analysis of Cardiac Motion

The motion of the heart during the cardiac cycle is a complex function of rotational, lateral, cephalad, and anterior components. Various components of cardiac motion during systole and diastole are palpated and recorded from the anterior chest wall. Apex cardiograms record one vector of cardiac motion, which is a complex summation of motion in the horizontal sagittal and frontal planes along with rotational components. Using a combination of biplane radiographic imaging and intramyocardial markers, it may be possible to analyze the vectors of motion during the cardiac cycle. It is the particular goal of this project to assess the abnormalities of overall

cardiac motion which are produced as a result of localized myocardial damage. Specifically, segmental wall motion abnormalities would be anticipated to affect overall cardiac motion during systole and diastole. The extent to which these segmental wall abnormalities influence total cardiac motion is of particular interest in determining how one should best superimpose end systolic contours upon end diastolic contours.

c. Application of Automated Computer Processing of Left Ventricular Margins to Ultrasonic Imaging

A long-range goal of developing margin definition on the basis of ventriculographic studies is the application of similar models to ultrasonic and isotopic imaging. At the present time, echographic methods largely depend upon technician placement and aiming of a single transducer. Under development at the present time are transducers which oscillate rapidly in a single plane, providing imaging on a 60 degree arc at a frequency of 30 frames per second. This sector scanner technology is rapidly developing, and it is probable that the sector arc will increase such that a single scanner could encompass the entire dimensions of a single plane through the left ventricular chamber. With a modest engineering effort a sector scanner could be mounted on a pivoting arm such that its position could be computer monitored.

Specifically, sector scanners can be oriented so as to provide images in the horizontal plane. Using computer monitoring of the sector scanner transducer position, the transducer could be moved cephalad or caudad, thus permitting imaging of the entire left ventricle. Timing of the scanner images from the electrocardiogram would be required to provide appropriate sequencing of sector scanner images. The recording would need to be made during a brief period of suspended respiration. Although this application of angiographic image processing is not a direct part of this proposal, successful pursuit of our present goals will direct us towards this kind of future application.

D. SIGNIFICANCE

There are four aspects of automated margin definition which must be considered in assessing the significance of this project. These are: 1) clinical utility; 2) reasonable cost-effectiveness; 3) capability to provide new clinical and research information; and 4) application to future areas of ultrasonic and isotopic imaging.

1. Clinical Utility

At the present time contrast ventriculograms are either processed entirely by manual methods or by use of some type of sonic, electrostatic, or light-pen for margin definition, using either a large or small scale computer for computation of simple quantitative indices of overall pump performance. For the most part these systems involve logistic problems since they are largely dependent upon cine film handling. Moreover, the relatively limited amount of quantitative information which is derived requires substantial input of time and effort.

The importance of an automated system would be to 1) expedite the logistics between actual performance of the ventriculogram and final data output; 2) reduce the technician and/or physician time required for manual margin definition, particularly where frame-by-frame analyses are being undertaken; and 3) provide a system which can operate and function with minimal operator interaction.

It is likely that a model directed automated margin tracking system, such as we

propose, would provide more reliable and reproducible tracings than those presently generated by human observers. Although the sensitivity of the human eye to grey-scale changes is greater than that of the computer, and human image integration capabilities are greater, we feel that by utilizing a model directed approach it should be possible to process in a satisfactory manner essentially the same percentage of ventriculograms as human observers are able to.

2. Reasonable Cost Effectiveness

It is recognized that the equipment costs involved in an automated margin tracking system are quite high. However, a large component of the costs are related to the video recording and digitization of the recorded ventriculogram. The significance of using video as a recording medium is that it minimizes logistic delays between actual performance of the ventriculogram and computer processing. The video picture offers the advantages that contrast and brightness can be readily adjusted and that there is much greater latitude in brightness levels inherent in video recording techniques than in cine film. Although video disc recording techniques are quite expensive, more and more laboratories with large clinical volumes are utilizing video discs to provide instant replay capabilities.

The computer hardware costs are probably of equal magnitude to those of the video recording devices and digitization hardware. Many cardiac catheterization laboratories already have computer systems dedicated to either pressure measurements or processing of manually defined ventricular margins. We believe that the core requirements in program size necessary for the final mini-computer based automated margin tracking program will not be so great that the software could not potentially be adapted to other small scale computer systems. Moreover, the cost of mini-computer systems is rapidly declining with the development of semiconductor memory, microprocessors, and other technological advances.

3. Capability to Provide New Clinical and Research Information Concerning Ventricular Performance

A system which is capable of processing frame-by-frame information provides an analytic tool for dissecting out subtleties of ventricular dynamics which occur within a single cardiac cycle. Currently there is substantial interest in the detailed features of ventricular systole, relaxation, and filling, which necessitates accurate volume data measured at frequent time intervals during a single cardiac cycle. Present manual methods for margin definition are both time-consuming and tedious when applied to frame-by-frame analysis of a single cardiac cycle. Moreover, the consistency and reproducibility of tracings is of variable quality and likely to be enhanced by reliance upon specific computer based criteria.

This system will have the capability to generate quantitative data concerning not only the dynamics of ventricular systole, relaxation, and filling, but also a detailed analysis of abnormalities of segmental wall motion. This data can be used to quantitate wall motion abnormalities prior to and following coronary surgery.

4. Application to Future Areas of Ultrasonic and Isotopic Imaging

We believe that the techniques developed for automated computer processing of left ventricular margins can be successfully applied to ultrasonic and isotopic camera images. Although it is not a specific part of this proposal, it is planned that the design of automated margin defining techniques and modelling will take into consideration potential future applications to echocardiography and isotopic cardiography.

With respect to echocardiography, it is probable that sector scanner technology will develop over the next two to three years to such an extent that the entire left ventricle can be encompassed in a single video slice. By using the sector scanner in conjunction with a computer monitored mechanical arm, it would be possible to provide three-dimensional images of the entire left ventricle to the computer. Although the specific details of such a system cannot at the present be known, it appears likely that the techniques developed from conventional contrast angiography will have direct application to analysis of ultrasonic and isotopic imaging.

E. FACILITIES AVAILABLE

The Stanford Cardiology Division:

1. SUMEX-AIM PDP-10 System

The SUMEX computer facilities have been made available for this project without charge for computer time. Dr. Joshua Lederberg, director of this facility, has 40% of the time on the PDP-10 computer system available for sharing with other medical investigators. The SUMEX machine is a PDP-10 system which provides the advantages of direct linkage via the ARPA net to the PDP-10 located in the Artificial Intelligence Laboratory, on which much of the image processing development at Stanford has taken place to date. Moreover, this system has the capacity for handling large developmental programs.

The SUMEX-AIM facility contains a PDP-10 TENEX timesharing system based on a Digital Equipment Corporation KI-10 processor. Numerous high-level programming systems such as LISP, SAIL, and FORTRAN, as well as assembly language systems, text editing, and program debugging facilities, exist and are well documented.

It will be possible to import much of the image processing software which has been developed on the PDP-10 system at the Stanford Artificial Intelligence Laboratory. In particular, we will use the image enhancement, noise removal, image registration, image differencing, edge detection, and edge verification algorithms which are already developed for the PDP-10 at the Artificial Intelligence Laboratory in our initial research and development of techniques for automatic margin detection.

2. Cardiac Catheterization Laboratory Computer System

A Hewlett-Packard 2100 system is directly linked to the Cardiac Catheterization Laboratory for pressure measurement and for digitization of images recorded on our video disc recorder. This computer is not available for development because of its commitment to support four separate catheterization laboratories. It presently contains all the programs and linkages to the catheterization laboratory video system which are necessary for digitization. A digital tape unit is attached.

3. Complete video recording capability is provided by an Ampex DR-10A video disc. Together with the video disc, the specific hardware for video mixing, video synchronization, and video distribution is installed. This hardware is presently in clinical use in the catheterization laboratory and is available to this project. It is anticipated that over the next year a high-quality video tape recorder will be acquired to provide large scale storage capability. Using a time base corrector, segments of the video taped information can be transferred onto the video disc for subsequent digitization and analysis.

4. Technical support services are located in the core area of the Cardiology Division which provide capability for hardware development and servicing. Computer programming support, bioengineering capabilities and high-level cardiac consultation are available to the investigators.

F. COLLABORATIVE ARRANGEMENTS

In order to accomplish the specific aims and objectives of this proposal, collaboration with a number of units in the Medical School and at the NASA-Ames Research Center, Moffett Field, California will be essential. The specific collaborative arrangements which have been made can be outlined as follows:

1. NASA-Ames, Moffett Field, California

Dr. Harold Sandler, Director of the Biotechnology Unit at the NASA-Ames Research Center, was one of the pioneers in the development of quantitative ventricular angiography. He is a Clinical Associate Professor in the Division of Cardiology at Stanford University School of Medicine and has worked closely with the Cardiology group in developing new angiographic techniques during the past eight years. He has been a close collaborator in the development of video disc technology in the cardiac catheterization laboratory and the present angiographic analysis system which we now have. In addition, he has pioneered the development of models of the ventricular chamber in normal hearts from both man and animals. It is the models he has developed which will be utilized in our validation studies before human comparisons. Dr. Sandler will be a full and collaborating partner in this program. Animal studies for ventricular image processing will be carried out in his animal laboratories at Ames Research Center, where biplane angiography for animal studies of the latest technological types is available.

2. SUMEX Computer Facility

Dr. Joshua Lederberg is the director of a large computer facility within the Stanford Medical School for the application of artificial intelligence techniques as they apply to medicine. Forty percent of the time on the PDP-10 computer system is available for sharing with other medical investigators. The angiographic image processing proposal now incorporated into this grant was initially part of the SUMEX proposal when an application for an overall computer facility for the Medical School was planned. Initial funding of SUMEX was for Dr. Lederberg's programs only. However, SUMEX is now available to be shared, and it is the intention of the investigators working with this image processing grant to utilize SUMEX for software development, for image processing, and for the initial stages of development. Attached is a letter from Doctors Lederberg and Levinthal specifying the interrelationships of this image processing grant with SUMEX.

3. Myocardial Markers

Dr. Edwin Alderman is a co-principal investigator with Dr. Neil Ingels, Jr. and George Daughters of the Palo Alto Medical Research Foundation on an NIH grant for studying myocardial markers. In collaboration with the Cardiovascular Surgery Department at Stanford, myocardial markers are placed in the endocardial area of the hearts of patients undergoing cardiac surgery. These markers are placed in a manner so that they outline the chamber of the left ventricle. The markers can then be studied on a day-to-day basis in patients undergoing cardiac transplantation or coronary bypass

surgery by using fluoroscopic techniques without the necessity for injecting angiographic contrast media. A number of such studies are now in progress to demonstrate the effects of drugs and other treatment methods upon wall motion in these groups of patients. It is from these markers that modeling of the ventricular contraction process in the abnormal heart for this grant will be determined. Close collaboration with the Palo Alto Medical Research Foundation and the investigators in this present image processing proposal will be available. As can be readily appreciated, the myocardial markers can only be placed in abnormal hearts of patients who have undergone surgery. Therefore, the image processing techniques to be developed under this grant proposal are not competitive with the marker studies now being carried out. The myocardial marker studies are largely for the purpose of determining the clinical effects of treatment upon heart disease. Our present proposal is for the quantitative determination of ventricular volume, ventricular ejection characteristics and wall motion abnormalities in patients who have not yet undergone surgery. Such patients may well be followed up by marker techniques once the surgery has been accomplished in both groups of patients.

4. Cardiovascular Surgery

A close collaborative working arrangement with the cardiovascular surgical group has been assured for the purpose of studying patients postoperatively and evaluating whether or not ventricular function and wall motion abnormalities have been changed by surgical techniques. Dr. Edward Stinson is one of the co-principal investigators on the myocardial markers grant mentioned in item #3 above. He will also be a consultant and close collaborator with this group of investigators.

5. Cardiovascular Radiology

Dr. Lewis Wexler and Dr. James Silverman work closely with the Cardiology group and the members of this investigative staff in carrying out angiographic techniques. Close collaboration with this group will be necessary for maintaining radiographic equipment of the most advanced technological type for obtaining cardiovascular images. These individuals are consultants and collaborators with the Cardiology group in day-to-day clinical patient care and will be collaborators on the various research projects planned with the techniques developed.

The undersigned agrees to accept responsibility for the scientific and technical conduct of the project and for provision of required progress reports if a grant is awarded as the result of this application.

Date

Principal Investigator or Program Director