

EVALUATION OF THE CARDIOVASCULAR SYSTEM
DURING VARIOUS CIRCULATORY STRESSES

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PROGRESS REPORT

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INTRODUCTION:

This is a progress report for the work carried out during the first 20 months of support by NASA Grant NGR 05-020-305, "Evaluation of the Cardiovascular System During Various Circulatory Stresses". The present report summarizes the work carried out from June 1, 1969 to May 30, 1970. During this period of time, many of the projects which were begun during the first 8 months of grant support were completed. Although these were first described in the initial progress report of June 1, 1969, the details of the completed reports and the published papers from these activities will be listed in the present progress report.

Studies utilizing animals were carried out both at Stanford and at the AMES Research Center installation at Moffett Field. All human studies performed with the support of this grant were carried out at Stanford University School of Medicine. The specific purpose of this report is to describe animal studies and human studies which have been initiated during the past year. A complete bibliography listing the abstracts, full length manuscripts, and presentations at national or international Meetings of the research supported by this grant are outlined in the final section of this report.

A. Progress with Studies in Experimental Animals

Several groups of animal studies were performed during the past year. In addition, a number of new studies were recently initiated and although not completed at the present time, significant progress has been made and will be reported.

I. Studies in Progress in 1969 and Completed During the Present Grant Period.

(1) Studies with a myocardial infarction model. An acute myocardial infarction experimental model has been developed. The use of high fidelity pressure transducers and electromagnetic flow transducers allows the recording of pressures and flows and the calculation of a number of circulatory variables such as peripheral resistance, pulmonary resistance and the mechanism by which ventricles develop pressure in animals subjected to coronary ligation following acute myocardial infarction. The degree of infarction can be established by both the hemodynamic changes noted and by injecting the coronary arteries of the hearts after they are fixed in a postmortem condition to determine the parts not receiving perfusion from the coronary arteries. After much initial investigation, a stable model has been perfected. The circumflex coronary artery is ligated and several large branches of the anterior descending coronary artery lateral to the septum are ligated. In this model, there is a reduction of cardiac output, a decrease in the rate at which ventricular pressure develops and increase in heart rate and an elevation of left atrial and left ventricular end-diastolic pressure. After approximately one hour, these animal preparations develop a stable hemodynamic pattern which does not change over a period of several hours, as long as the arterial P_h , PO_2 , and PCO_2 are regulated within normal limits.

In animal models of this type, several studies have been carried out to investigate the effects of drugs on the

depressed circulation produced by acute myocardial infarction. These studies are of important clinical relevance since the circulatory failure occurring in acute myocardial infarction is one of the most common problems facing cardiologists today. An understanding of the circulatory effects of these important drugs in a preparation where the degree of myocardial infarction can be quantitated, is not possible in patients at the present time. Thus, an experimental model of this type provides important insight into the circulatory effects of these drugs.

During the past year, three types of studies were completed.

A. Dopamine Studies - Dopamine is a naturally occurring catecholamine which is a precursor in the synthesis of the normal neurotransmitter substance, norepinephrine. It has been shown to have important circulatory effects in normal animals in that it increases cardiac output, increases the rate at which the left ventricle develops pressure, decreases the left atrial pressure and decreases systemic vascular resistance when given in small amounts. It has little effect on arterial pressure and heart rate when given in small doses. The circulatory effects of this drug were studied in normal animals before the production of acute myocardial infarction and its circulatory effects quantitated. Infarction of 37% of the left ventricle was produced by ligation of the circumflex and anterior descending coronary arteries. One hour after ligation there were significant increases in left ventricular and diastolic pressure, left atrial pressure and heart rate. The cardiac output was reduced to one-half of control (pre-infarction) and the left

ventricular dp/dt was markedly depressed. Following challenges with volume infusion to determine the quantitative reduction in the response of the circulation, the hemodynamic response to Dopamine given in the same dose as that prior to acute myocardial infarction was compared with its effects in the same animal. Dopamine infusion returned the cardiac output to near normal levels. Left ventricular end-diastolic pressure and left atrial pressure all decreased. The left ventricular dp/dt was markedly elevated to levels approaching those observed in control studies. Systemic vascular resistance was decreased, while arterial pressure did not change significantly. These studies suggested that dopamine is an excellent agent for the treatment of severely depressed cardiac function following acute myocardial infarction. Its circulatory actions represent improvements over the action of other catecholamines for the treatment of this condition. For these reasons dopamine has now been introduced for use in the treatment of patients in the Coronary Care Unit at Stanford University School of Medicine following acute myocardial infarction.

Although the patient studies are few at the present time, the drug has greatly benefited several of these patients and in three particular patients has allowed their survival until a donor heart could be obtained and cardiac transplantation carried out. During the next two years, the circulatory effects of dopamine in man will be determined utilizing the microtransducer systems developed by AMES Research Laboratory and tested in a program supported by this grant. These studies are presently being initiated and will be described in greater detail in next year's progress report.

B. Lidocaine Studies - Lidocaine is the most frequently used antiarrhythmic drug in patients with acute myocardial infarction. Although its circulatory effect has been studied in a large number of animal preparations and in man, few studies have attempted to quantitate its action on the heart and circulation following acute myocardial infarction. A series of studies was performed in 22 anesthetized dogs with acute myocardial infarction utilizing both a single injection of Lidocaine and at several levels of infusion of Lidocaine up to 200 μgm per Kg. per min. These doses are comparable to the largest doses used in the treatment of acute myocardial infarction in man. This study provided insight into the circulatory effects of this drug in the damaged circulation and although its results cannot be extrapolated directly to patient care, several of them seem applicable and suggest further studies in man.

Both prior to and after production of acute myocardial infarction by coronary artery ligation, Lidocaine given by infusion produced no statistical change in left ventricular end-diastolic pressure, cardiac output, left ventricular dp/dt , arterial pressure, or peripheral vascular resistance. However, a single bolus of Lidocaine, 5 mg/kg, given before myocardial infarction produced transient but significant decreases in arterial pressure, heart rate, left ventricular dp/dt , cardiac output and left atrial pressure. The duration of these changes was less than five minutes and during a one hour followup period, no further changes occurred. Following coronary artery ligation and acute myocardial infarction in dogs, the injection of Lidocaine in the same dose resulted in significantly greater depressions in arterial pressure, left ventricular dp/dt

and cardiac output. At this time, there were elevations of left atrial pressure and left ventricular end-diastolic pressure which were not observed in the animals given Lidocaine as a single injection prior to myocardial infarction. The duration of these depressions in the performance of the heart was also significantly longer than prior to myocardial infarction.

The results of these experiments suggested that infusions of Lidocaine in clinically applicable doses does not significantly alter cardiac performance either in the normal or severely compromised heart. However, large single injections may depress even the normal heart function and certainly produces profound and prolonged depressions and circulatory impairment, after acute myocardial infarction. For these reasons, it seems likely that Lidocaine should be used by infusion whenever possible and that if it is given as a single injection the dose level should be markedly reduced. We have recommended these changes in protocol for using Lidocaine in the Coronary Care Unit at Stanford and they are presently being implemented.

C. Morphine Studies - Morphine sulfate is the most commonly used analgesic agent for relieving the pain of acute myocardial infarction. The effect of this drug has been evaluated in animals and in man with normal hearts. Our studies attempted to evaluate the effects of morphine in acute myocardial infarction when the cardiovascular performance was severely impaired. Twenty-three animal studies were carried out using instrumentation as described above. Morphine was injected intravenously into a series

of normal dogs and in 12 dogs with 32% infarction of the left ventricle. In the control animals the injection of morphine produced a decrease in heart rate and early decrease in left ventricular dp/dt which was followed by an elevated left ventricular dp/dt at five minutes. There is an initial decrease in cardiac output followed by sustained increase. These changes were interpreted as showing an initial peripheral pooling of blood followed by activation of the sympathetic nervous system and restoration of cardiovascular performance to levels above control. In the animals studied following acute myocardial infarction the qualitative changes produced by morphine were similar. However, the initial circulatory depression and peripheral vasodilatation appeared more severe in the animals following acute myocardial infarction and sustained increases in cardiac output, left ventricular dp/dt did not occur in the damaged hearts.

These studies suggested that administration of morphine to patients with acute myocardial infarction could result in further circulatory depression when a severely damaged heart was present. For this reason, we have instituted the circulatory effects of other important analgesic drugs. At the present time, the use of analgesic drugs in patients following acute myocardial infarction is being studied in our Coronary Care Unit at Stanford University School of Medicine with an intent to document the findings noted in these animal studies. If, indeed, a more potent and less depressing analgesic drug can be found its use will be

instituted into the Coronary Care Unit.

II. Studies Begun In 1969-1970

In anesthetized animals several types of studies were carried out during this year. All of these studies have not been completed and this initial summary will provide only preliminary results of these studies.

(1) The effects of digitalis glycosides in experimental myocardial infarction. Digitalis glycosides are frequently administered to patients following acute myocardial infarction. Although much is known about the action of these drugs from animal and human studies with normal hearts and those damaged by chronic processes such as rheumatic heart disease and hypertension, little is known about the circulatory effects of digitalis in experimental myocardial infarction. For this reason, the myocardial infarction model described in previous studies was utilized for evaluating the circulatory effects of acute digitalization following myocardial infarction. In a series of animals, acute myocardial infarction was produced by coronary artery ligation to produce infarction of 28% of the left ventricular weight. These animals were instrumented for pressure and flow studies. Acetylstrophanthidin was then infused continuously while hemodynamic changes were recorded. In a similar group of animals without infarction, the circulatory effect of acetylstrophanthidin was also evaluated. The specific findings from 23 studies in dogs are as follows:

- a. Acetylstrophanthidin produced toxic cardiac arrhythmias more readily in the dogs with acute myocardial infarction even though the arterial

oxygen tension, pH, and PCO_2 were maintained within normal limits. Thirty percent less acetylstrophanthidin was required to produce ventricular tachycardia, a toxic digitalis-induced arrhythmia, in these animals.

- b. Acetylstrophanthidin produced increased peripheral vascular resistance with no increase in cardiac output or left ventricular dp/dt . Left atrial pressure was significantly elevated and cardiac performance curves were depressed.
- c. The circulatory effects of acetylstrophanthidin were present by the time a 50% toxic dose had been administered and this was not changed by the administration of 80% of the toxic dose or of a full toxic dose.

The interpretation of these studies is important for understanding the circulatory effects of digitalis glycosides in patients with acute myocardial infarction. Clearly the drug presents more toxic hazards in the damaged circulation. The cellular mechanisms for this increased toxicity are not understood at the present time, but other studies in our laboratory utilizing radioactive digitalis are in progress in an attempt to determine if there are alterations in the uptake and binding of the drug. The digitalis glycoside used in these studies caused peripheral vasoconstriction and increased the afterload or work required of an

already damaged heart. The heart was not able to respond to this by improving its performance and thus the left atrial and left ventricular end-diastolic pressures rose, the cardiac output was further depressed and there was an overall deterioration in cardiac function. Finally, it appears that the circulatory effects of digitalis can be observed after 50% of the toxic dose is administered. This is at variance with the commonly held belief that the administration of digitalis glycosides to levels near toxicity are required to produce circulatory effects.

On the basis of this study, we have recommended that digitalis glycosides not be used in the circulatory depression following acute myocardial infarction. Perhaps if the circulatory depression persists for several days and there is some recovery of cardiac function, the drug may then be used with beneficial effects. The toxic hazards of the drug and its failure to produce improvement in the circulation should preclude its use in the coronary care unit following acute myocardial infarction in our opinion. We have instituted this pattern of utilization in the Coronary Care Unit at Stanford.

(2) An Evaluation of Factors Which Relate to Measurement of the Left Ventricular dp/dt . Review of our utilization of the left ventricular dp/dt as a measure of cardiac contractility has demonstrated several important problems. The recording of a dp/dt of high frequency is important for reproducible results. In

addition, the filling pressure or volume of the left ventricle and the arterial pressure or afterload that the left ventricle is facing are important determinants of the absolute level of dp/dt recorded. It has also been suggested that heart rate changes may also alter the recording of dp/dt . However, it is well known that changes in heart rate do induce an inotropic effect and whether or not the dp/dt follows this inotropic effect accurately is open to question.

During the past year, we have evaluated the effects of changes in heart rate on recorded left ventricular dp/dt . It is our view that the increase in dp/dt recorded under certain circumstances with changes in heart rate really represents a change in contractility. Secondly, the frequency response at which left ventricular pressures and left ventricular dp/dt must be recorded in order to obtain quantitative results is critical. We have evaluated the frequency of these recordings from 10 cycles per second to 200 cycles per second. There are clear quantitative differences if recordings below a frequency of 50 per second are used. We are at present attempting to standardize our recording devices for measuring dp/dt in animals. We are also evaluating changes in arterial pressure or afterload as they relate to the recording of accurate dp/dt in our laboratory. These studies are all in a preliminary stage and will be completed during the following two years.

(3) Utilization of Multiple Flow Transducers for Recording the Distribution of Cardiac Output. During the past year a number of animals have been equipped with up to six flow transducers on large blood vessels. In animals so instrumented, it is particularly important to record the total cardiac output and the distribution of flow to the head, the abdominal viscera, the kidneys, the skeletal muscle in the extremities and to the coronary arteries. Utilizing these preparations, it has been possible to quantitate the level of flow to all of these areas in normal animals. These values agree in general with the values obtained by the injection of radioactively labeled microspheres. One of the projects planned for this type of preparation is to evaluate the effects of a host of pharmacologic agents on the distribution of cardiac output. The effects of adrenergic blockage and adrenergic stimulation are two of the first projects planned. These have been initiated in a limited manner during the past three months.

(4) The Circulatory Effects of Myocardial Infarction in Unanesthetized Dogs. An attempt to utilize unanesthetized dogs to determine the effects of anesthesia on the circulatory response to stress is now in progress in our laboratory. During the past three months, 16 animals have been equipped with ameroids around their coronary arteries so that gradual occlusion of the coronary artery will occur over a period of six weeks. These animals are in the process of developing acute myocardial infarction and four animals have thus far developed documented acute myocardial

infarction as demonstrated by changes in serum enzymes and changes in their electrocardiograms. Once myocardial infarction has been produced, these animals will be instrumented for the study of drugs in an unanesthetized state. This study is in an early formative period and awaits the development of acute myocardial infarction by most of the animals prepared.

During the coming year, many of the studies to be carried out in this laboratory will be carried out in unanesthetized animals. Studies by Dr. Sandler and his colleagues have demonstrated that the contraction pattern of the heart during anesthesia and during open chest studies is quantitatively and qualitatively different from the contraction pattern of the heart in the anesthetized state. For this reason, most of the drug studies relating to acute myocardial infarction and most of the studies which have been done to understand the circulatory dynamics in the intact animal in our laboratories will now be carried out in animals instrumented for study in an unanesthetized state. This has required the development of a number of microtransducers which can be permanently implanted in animals. In association with the electronics groups at Ames Research Center and with Dr. Sandler, a number of such transducers have been developed for measuring wall dimensions and ventricular volumes in animals. Transducers for pressure recording and flow recording have also been developed and are presently being tested. The testing of these transducers in animal models is an important part of this project and will be continued during the coming year. It is anticipated that the

cooperative efforts of the group in the Biotechnology Division at Ames and the Cardiology Division at Stanford will lead to important advances in instrumentation for studying cardiovascular stresses on a chronic basis.

B. Progress in Human Studies

In the initial grant period 1968-1969, very few studies were performed in human subjects. In the past year, 1969-1970, four specific types of human studies were performed. In some instances, studies were initiated and will continue for several more years in order to obtain the specific data needed to answer the problem. These studies will be described in detail below.

I. Ultrasound Studies

In view of the need to develop atraumatic techniques for studying cardiovascular function in man both in space and in the situation where chronic monitoring is important, we have concentrated our efforts on the evaluation of ultrasound for these purposes. Although there are a number of excellent instruments for clinical use, modifications of the transmitting and receiving crystal, the ability to manipulate the angle of the sound beam and be able to determine this in three dimensions precisely, an improvement in the methods for displaying the data continuously from ultrasound transducers, and the correlation of ultrasound measurements with other physiological parameters require many new innovations and techniques before the full value of applying ultrasonic methods to man can be realized. Much progress has been made as illustrated by the publications listed in Section III of the bibliography. Two studies have been completed and one other initiated which is

ongoing.

Ultrasound was used to determine ventricular dimensions along the short axis of the left ventricle in 52 patients. By appropriately directing the sound beam, it was possible to determine the short diameter of the left ventricle at end-diastole and end-systole. Using these diameters and assuming a prolate ellipse as the geometric structure of the left ventricle at end-systole and end-diastole, it was possible to calculate end-systolic and end-diastolic volume. Thus, the stroke volume could be determined and multiplied by the heart rate to provide the cardiac output. These techniques were performed in a series of patients without valvular regurgitation and compared to the cardiac output determined by the standard Fick method. The correlation between these methods allowed the calculation of a regression line and the application of this regression line for determining true stroke volume. There was a high degree of correlation between the two methods and the stroke volumes determined in this manner. In a series of patients with valvular regurgitation, the Fick cardiac output and stroke volumes were smaller than those determined by ultrasound. Thus the ultrasound can be used to determine regurgitant volume since this is not measured by the Fick cardiac output. Thus the ultrasound stroke volume minus the Fick stroke volume would give a true representation of regurgitant volume. This was checked in a qualitative manner by comparing the findings at angiography and roughly classifying the degree of regurgitation observed and comparing it to that calculated from ultrasound. The general agreement between these two methods was surprisingly good.

Prior to using these techniques in man with disease states, it seems essential to learn more about the geometry of the contracting ventricle in specific diseases and whether or not a prolate ellipse is a true representation of its shape. Studies of this type are now in progress in our laboratory utilizing angiographic techniques for determining end-systolic and end-diastolic volumes. This represents a continuation of some of the work begun by Dr. Harold Sandler several years ago, to determine the dynamic geometry of the human left ventricle in health and in disease. At the present time, these techniques are well enough developed to know that in normal man or in the nearly normal man, a reasonable approximation of the stroke volume can be given by ultrasonic techniques.

A common disease in which there is obstruction to the outflow tract of the left ventricle is known as muscular subaortic stenosis. The diagnosis of this condition in asymptomatic patients who present with a cardiac murmur, may be difficult. Since the disease in its earliest form is a variable one, i.e., an obstruction present at one time and absent at another time, it is necessary to develop techniques for studying this disease which are atraumatic. In addition, once therapy is begun, left heart catheterization cannot be done at very frequent intervals to determine the effects of therapy. Ultrasonic techniques have been applied to follow these patients and their degree of left ventricular outflow obstruction. Several specific signs of outflow obstruction are observed utilizing ultrasonic techniques. An abnormal anterior displacement of the mitral annulus during systole occurs and in some cases actual contact between this structure and the

interventricular septum occurs. For this reason, these abnormalities indicate obstructive outflow tract disease of the left ventricle. A series of 25 patients have been studied and correlation between obstruction and the changes on ultrasound have been excellent. Outflow tract obstruction was determined during the course of cardiac catheterization during which time ultrasonic measurements were also being made simultaneously. This technique is being widely adapted for use in clinical diagnosis throughout the country.

In order to estimate the degree of mitral regurgitation or aortic regurgitation utilizing ultrasonic techniques, it is essential that there be a comparison between the volume of regurgitation determined by angiography and the ultrasonic techniques. During the past four months such a study has been initiated for study of ventricular volume by angiography and a comparison of this ventricular volume at end-systole and end-diastole with that determined by ultrasound. Fourteen such patients have been studied. Preliminary indications suggest that there will be a general approximation between the degree of regurgitation determined by these two methods and that the atraumatic ultrasonic method may have wide application for patient study. These studies have just been initiated and their continuation during the next two years should answer these questions. It is our purpose to provide a more meaningful interpretation of the ultrasonic tracings obtained in all types of patients. It is with these various kinds of comparisons in mind, that angiographic studies were initiated.

II. Pressure Transducer Testing

During the initial year of the present grant, a small micropressure transducer developed at the Ames Research Laboratory became available for study in man. This model transducer has been extensively studied in animals and found to be extremely sensitive and to give reliable pressures. During the past year, human studies have been carried out utilizing this transducer. It has been compared with standard transducer techniques for recording pressure in all chambers of the heart and in the aorta, and pulmonary artery. High frequency components are recorded without difficulty. For the purpose of determining the rate of pressure rise in a chamber, the micro transducer system placed at the end of a catheter is essential. The AMES Research center transducer has proved to be reliable in every way. Its catheter mounting has presented several problems and during the past six months modifications have been made which allow the use of this catheter for repeated pressure measurements in man. This represents a major advance for pressure measurement and should prove useful for doing studies on dynamic geometry of ventricular contraction in patients undergoing cardiac catheterization. Testing of this transducer system will be carried out in the Coronary Care Unit on a long term basis during the coming year.

III. Fiberoptics Studies

During the past year, it has been possible to adapt the use of a fiberoptic catheter and ratio recorder as a densitometer for studies in man. Cardiac output can be determined without the

withdrawal of blood as the bolus of dye in the arterial blood stream passes the tip of the fiberoptics catheter, and standard densitometer type curve can be obtained. The area under this curve can be integrated and cardiac output determined in a reliable manner. This technique was used to record cardiac output in 15 patients in the Coronary Care Unit at Stanford during the past year. It is anticipated that these indwelling catheters will be used in the Coronary Care Unit for monitoring oxygen saturation in arterial blood and for determining cardiac output by the indocyanine green method. In the next two years, these techniques will be adapted to a computer for rapid printout of the cardiac output in patients in our Coronary Care Unit.

IV. Dynamic Geometry of the Human Left Ventricle

During the past year, volume angiography studies for measuring ventricular volume and for determining changes in the geometry of contraction of the left ventricle have been carried out in 25 patients. Much of the data from these studies has not been fully analyzed. The purpose of the studies was to determine whether or not myocardial infarction and coronary artery disease alter the patterns of ventricular contraction. It is well known that qualitative changes do occur but the techniques devised under this protocol are for determining whether or not they can give meaningful information regarding the function of the ventricle. If it is possible to quantitate the specific changes in ventricular function with the prognosis from the disease, it should be

possible to design surgical therapy for removal of segments which do not function properly. For this reason, it is essential that these studies continue in a large number of patients.

It should also be possible to determine the mechanisms by which the abnormal ventricle compensates for its structural defects. The ejection fraction which represents the difference between the end-diastolic volume and the end-systolic volume of the left ventricle has been demonstrated to be a reliable indicator of abnormal performance. Work of this type has been carried out during the past year and it appears that a different pattern of contraction has developed in some abnormal ventricles in order to compensate for an increase in diameter of the chamber and for an overall increase in the wall tension necessary to develop a given pressure. This becomes particularly important in studying patients with coronary artery disease since their major limitation is in the delivery of myocardial oxygen needed to meet certain stresses. During the next year, it is our hope to study 40 or 50 patients with abnormal dynamic geometry of the left ventricle and to relate the changes in left ventricular contraction to the patients' ultimate prognosis and to search for therapy for their coronary artery disease. In addition, numbers of these patients will be treated with specific drugs and subjected to specific stresses. It is anticipated that an evaluation of the

dynamic geometry of left ventricular contraction will be of some benefit in determining the ultimate response to drugs and to stresses.

C. Proposed Studies of 1970-1971

In each section presented above, proposed studies in specific areas which will be continued during the coming year were outlined. In many instances, more studies were required to answer the original questions asked and in others additional questions have been raised by the initial studies. These include:

1. A critical evaluation of the angle of the transducer for sound wave in the ultrasonic techniques for evaluating ventricular function. It is anticipated that a transducer holder which can be moved about the chest and which can be located by angles on a three-dimensional model will be developed. This should allow a more standardized placement of the ultrasound transducer and a more precise definition of ventricular dimension measurement in the future. Work in this area has been begun and will continue. Work will primarily be carried out at the AMES Research Center and in cooperation with Smith-Kline Instrument Company who makes the standard commercially adaptable ultrasound machine that we use.

2. The ultrasound Doppler technique for measuring peripheral blood flow will be instituted in the Coronary Care Unit. The evaluation of this instrument for the purpose of determining

peripheral blood flow to the skeletal muscles during various situations will be assessed. It is important to know whether this peripheral blood flow is altered by myocardial infarction which damages left ventricular performance. This will be the first problem which is assessed. The overall cardiac output will be determined by the fiberoptics densitometer method and the degree or change in peripheral flow will be determined by the ultrasound Doppler technique. This should provide interesting observations on the distribution of peripheral blood flow under a variety of stresses.

3. Volume Angiography - Experiments determine whether or not coronary artery disease without myocardial infarction alters the dynamic geometry of the left ventricle will be carried out. It is anticipated that 50 or so patients will be required for this study. (See Section B).

4. It is anticipated that a comparison between stroke volume determination and the movement of the posterior wall by ultrasound techniques will be made. Perhaps it will be easier to record posterior wall movement continuously on a strip chart recorder and to follow continuously this measurement as a reflection of ventricular performance. A comparison of both the stroke volume and movement of the posterior wall will be made with other indirect methods for assessing the circulation. In particular, the ejection time has been used as an indirect means for assessing ventricular performance. We will compare the ultrasonic techniques for assessing ventricular performance with this indirect method during the coming year.

Most of these studies will require more than one year for their completion. Their initiation will be made during mid 1970 and it is anticipated that they will be finished in 1972 and 73.

D. Bibliography

During the past 20 months, a number of significant observations have been made in the program supported by this grant. These have been published in abstract form and in full manuscript form. A list of the specific projects as they apply to specific parts of this grant proposal follows. The various sections will list the abstracts and papers which relate to each part of this progress report. Reprints are attached when available. Further documentation and reprints of abstracts may be obtained from the Cardiology Division, Stanford University School of Medicine, if so desired.

Bibliography

1. Section one - Animal Studies Completed

1. Schroeder, J.S., Schroll, M. Robison, M. Harrison, D.C.: Dopamine in experimental myocardial infarction (MI). Fed. Proc. 28:671, 1969.
2. Hamilton, J.R., Paaso, B.T., Corday, S.R. and Harrison, D.C.: The circulatory effects of morphine sulfate following myocardial infarction. The Physiologist 12:245, August 1969.
3. Wintroub, B.U., Schroeder, J.S., Schroll, M., Robison, S.L., Harrison, D.C.: The Hemodynamic response to dopamine in experimental myocardial infarction. Amer. J. Physiol. 2170: 1716-1720, 1969.
4. Wintroub, B.U., Robison, S.L., Pirages, S., and Harrison, D.C.: The pulmonary and systemic circulatory response to dopamine infusion. Brit. J. Pharmacol. 37: 618, 1969.
5. Robison, S.L., Schroll, M., and Harrison, D.C.: The circulatory response to lidocaine in experimental myocardial infarction. Am. J. Med. Sci. 258:260, 1969.

2. Section two - Animal Studies in Progress

1. Nola, G.T., Pope, S., Harrison, D.C.: Assessment of the synergistic relationship between serum calcium and digitalis. The Physiologist, 12:316, August 1969.
2. Ridges, J.D., Hunter, D.K., Clark, W.A. and Harrison, D.C.: The transplanted mouse heart: A model for studying cholinergic stimulation on ventricular myocardium. The Physiologist 12:341, August 1969.
3. Hamilton, J.R., Pope, S.E., and Harrison, D.C.: Comparison of the Cardiodepressant Effects of D-Propranolol and AY 21,011. Clin. Res. 18:162, 1970.
4. Nola, G., Pope, S. and Harrison, D.C.: Assessment of the synergistic relationship between serum calcium and digitalis Amer. Heart J. 79:499, 1970.
5. Goldman, R.H., and Harrison, D.C.: The effects of hypoxia and hypercarbia on myocardial catecholamines. J. Pharmacol and Exptl. Therap. (In press).

3. Section three - Human Studies

1. Popp, Richard, Harrison, Donald: New uses for ultrasound: Study of homograft valve motion and left ventricular stroke volume. Clin. Res. 17:103, 1969.
2. Flamm, Melvin D., Harrison, D.C., Hancock, E.W.: Prevention of latent and labile outflow obstruction in idiopathic hypertrophic subaortic stenosis (IHSS) with propranolol. Am. J. Card. 21:98, 1968.
3. Popp, R. L. and Harrison, D.C.: Ultrasound in the diagnosis and evaluation of treatment of idiopathic Hypertrophic Sabaortic Stenosis. Circulation (Supplement III, 1969) 40: III - 164, 1969.
4. Popp, R. L. and Harrison, D.C., Ultrasonic Cardiac Echography for determining stroke volume and valvular regurgitation in man. Am J. Card. 25: 121, 1970.
5. Popp, R.L. and Harrison, D.C.: Ultrasound for the diagnosis and evaluation of therapy in patients with idiopathic hypertrophic subaortic stenosis. Circulation 40: 905, 1969.
6. Schroeder, J.S., Popp, R.L., Stinson, E.D., Dong, E., Jr., Shumway, N.E., and Harrison, D.C.: Acute rejection following cardiac transplantation: Phonocardiographic and ultrasound observations. Circulation 40:155, 1969.
7. Popp, R.L. and Harrison, D.C.: Ultrasonic cardiac echography for determining stroke volume and valvular regurgitation. Circulation. 41: 493, 1970.
8. Popp, R.L., Schroeder, J.S., Stinson, E.B., Shumway, N.E., and Harrison, D.C.: Ultrasound in the early detection and study of post-transplantation cardiac rejection. Chapter in Book - Meeting of Amer. Inst. of Ultrasonics in Med.