EVALUATION OF THE CARDIOVASCULAR SYSTEM DURING VARIOUS CIRCULATORY STRESSES

A Progress Report for NASA Grant

- NGL 05-020-305 -

For the Period

June 1, 1970 - May 31, 1971

from

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Evaluation of the Cardiovascular System During Various Circulatory Stresses

A. Introduction:

For the past three years, the Cardiology Division at the Stanford University School of Medicine has worked in close cooperation with the Biotechnology Division of the NASA Ames Research Center in Mountain View, California. Support for the work at Stanford has been provided by the NASA Grant NGL 05-020-305 entitled The Evaluation of the Cardiovascular System During Various Circulatory Stresses. Much has been accomplished on this program, as has been documented in previous official reports to NASA and in various publications in national medical journals. The purpose of this present report is to update the continued progress which has been made on the project sponsored by this grant during the past year.

The initial purposes for initiating this grant were:

1. To develop, test, and validate equipment and techniques for measuring cardiovascular performance by non-invasive methods. These studies were designed to develop hardware and techniques which could be used to study man's circulatory performance in the space environment.

2. To develop and improve hardware for validating the non-invasive techniques for accuracy. This required the modification of invasive techniques and the development of new transducer systems. Specific work has been carried out to improve methods for volume angiography,

for testing new microtransducers and for developing new techniques for measuring cardiac output and peripheral blood flow.

3. To design studies which would provide a better understanding of cardiovascular control mechanisms when stress is placed upon the organism. These studies were designed primarily to determine the effect of weightlessness on man. Studies have been planned to use bed rest to simulate the space environment and use measurements of cardiovascular function to predict what may happen to the cardiovascular system when man is subjected to prolonged weightlessness.

Much of the progress which has occurred with these studies during the past twelve months is outlined in the request for new funds for the year beginning September 1, 1971, and in the summary progress report of February 1, 1971. Additional progress is presented in detail in the request for supplemental funds in June 1971. A copy of this report is attached. However, at this time reprints and a summary of the work performed under sponsorship of this grant will be provided.

B. Summary of Accomplishments During the Year June 1, 1970 through May 31, 1971:

The four specific areas of accomplishment during the past twelve months include:

1. Preliminary testing of a non-invasive method for measuring venous pressure. During the past year, working in association with the Ames Research Center engineering staff, a non-invasive method for estimating venous pressure has been developed. Preliminary studies with the method have demonstrated its feasibility and have provided us with

a list of limitations for the method. The principle for this technique is based on initial work done by the Air Force in the development of a "Flack tester." Utilizing a specially designed ultrasonic flow transducer which can be placed over a peripheral vein and sense phasic flow, coupled with a mouthpiece device which allows the accurate recording of the pressure within the major air ways of the chest during a forced expiration in which the epiglottis remains open, it is assumed that when intra-thoracic pressure exceeds peripheral venous pressure, flow will stop. Furthermore, it is assumed that the right atrium is a thin-wall structure and will transmit accurately the pressure within the thoracic cavity. The entire concept has been tested and flow does cease when intra-thoracic pressure exceeds peripheral venous pressure. Studies have been carried out in 30 individuals in whom an estimation of right atrial pressure by this technique could be compared with right atrial pressure measured directly during the course of cardiac catheterization. These preliminary studies have demonstrated that the technique is feasible but has a significant number of problems which must be overcome. These will be presented as a series of specific studies to be carried out in the coming year in the Proposed Research section of this progress report (See Abstract #4).

2. Association with Dr. Harold Sandler of the Biotechnology Division at Ames research field in development of computer graphic techniques for studying the function of the left ventricle, the main pumping chamber of the heart. Preliminary studies were performed, demonstrating that by utilizing data obtained from volume angiographies and analyzing it by the computer graphics method, small areas of malfunctioning ventricular muscle could be observed. These techniques

have been applied in several patients with ventricular aneurysm (small areas of dysfunction in the wall of the left ventricle) and it is planned to perform further studies utilizing these techniques during the coming year. This technique was the subject of a major press release by NASA which was circulated throughout the world as demonstrating NASA's activities in improving biomedical technology. Further studies utilizing this technique are outlined below.

3. Studies to demonstrate the validity of new intravascular pressure sensors. During the past year two types of intravascular pressure transducers were developed at the Ames Research Center. These two microtransducers were given preliminary evaluations in animals and in a series of selected patients. Several problems were encountered which has necessitated a change in design of the pressure transducers. These changes are now being made and during the next year, further validation studies utilizing these transducers are planned.

4. Ultrasound for determining ventricular volume and for estimating cardiac output. Since the initial demonstration by the cardiology group at Stanford University that ultrasound techniques could be used to record ventricular dimensions and thereby utilized for the calculation of ventricular volume, much work has been done to validate the techniques. In the past year, improved methods for obtaining ultrasonic measurements of the left ventricular size were developed, and a new type of transducer which allows the operator to focus on one segment of the heart, thereby permitting better recordings, was developed. In addition, a new graphic method for presenting data from ultrasonic studies was developed by the Electronics For Medicine

Corporation. This equipment will become available to the Cardiology Division at Stanford University School of Medicine during the coming six months and further studies to validate the measurement of stroke volume by ultrasonic techniques are planned, utilizing this type of equipment. Utilizing the new graphic method for presenting ultrasound data makes possible the recording of the stroke volume and cardiac output in a much higher percentage of patients than had been possible in the initial studies done by us.

During the past year, three other laboratories throughout the country were able to confirm the original observations of the cardiology group at Stanford. At the University of Indiana in Dr. Harvey Feingenbaum's laboratory, in the cardiology laboratories of the University of North Carolina School of Medicine, and in the cardiology laboratory at the University of Alabama School of Medicine in Birmingham, studies were performed to demonstrate the overall validity of recording and calculating stroke volumes from ultrasonically measured ventricular dimensions. The number of patients in whom these studies have been performed has been greatly expanded over the 51 original patients studied by Drs. Harrison and Popp at Stanford University School of Medicine. During the coming year extensive studies to validate further our initial observations and to expand the use of these techniques to a broader group of patients are planned. These studies will be outlined in the research proposals for the coming year.

C. Specific Research Proposals for the Year September 1, 1971 to August 31, 1972:

During the coming year, developing improvements in non-invasive techniques for measuring cardiovascular performance are planned. These changes in technique will require validation in a large number of patient studies. In addition, new studies to understand more precisely the way in which the circulatory system responds to stresses will be initiated. Specific studies will be performed in four areas:

1. Expanding and validating studies with ultrasound for determining ventricular dimensions. After a two-year assignment in the United States Army, Dr. Richard Popp will be rejoining the Cardiology Division at Stanford University School of Medicine and will be responsible for studies in this general area. Three specific types of studies are now in progress and will be expanded:

a. In order to improve our capabilities for recording ventricular dimensions by ultrasound and for increasing the number of patients in whom accurate measurement can be made, several steps are proposed. First, a new focusable transducer developed by the Smith Kline Instrument Company will be utilized for measuring ventricular dimensions in 50 patients in the cardiology service at Stanford University School of Medicine. Secondly, in each instance, the new Electronics For Medicine graphic methods for presenting the measurements will be utilized. Thirdly, a series of studies will be carried out in which ultrasonic measurement, determined in the manner outlined above, will be compared with those made in the course of volume angiography in 50 patients in whom volume angiography is performed as part of the routine

cardiac catheterization in the cardiology laboratories at Stanford. In these same patients, stroke volume will be determined by recording cardiac output either by dye-dilution techniques or the Fick method. These studies will allow a simultaneous comparison of cardiac output measured by ultrasound, volume angiography, and the standard Fick and dye methods. No doubt, there will be differences in the measurements recorded by these three techniques. The development of correction factors and specific regression equations for each patient category will be necessary. It is anticipated that such factors can be determined by studying a variety of patients with different cardiovascular diseases.

b. During the coming year a series of bed rest simulation experiments for space flight will be carried out at the Ames Research Center in their new clinical facility. Recording of ventricular dimensions by ultrasonic techniques in these patients during the course of their bed rest will be performed. It is anticipated that these studies will provide a basis on which to expand our studies relating to the alterations in the cardiovascular system during prolonged weightlessness. Recordings will be made at 48-hour intervals on these patients undergoing the bed rest simulation experiments. These studies will be performed at Ames Research Center.

c. Since the rate at which the wall of the left ventricle contracts is an important measure of its performance, ultrasound will be used to record the rate at which the left ventricular wall moves. This value will be corrected for heart rate and

intervascular pressure and its validity as a measure of ventricular performance will be assessed against standard recordings of left ventricular pressure and volume measurements in patients with cardiovascular disease. In addition, since the compliance of the ventricular wall during relaxation is becoming increasingly important as a measure of performance characteristics of the heart as a hydraulic pump, ultrasound should provide some measure of this rate of relaxation, specific studies relating to a better understanding of the compliance characteristics of the ventricular wall are thus planned, utilizing ultrasound.

2. Continuing studies on the non-invasive methods for measuring central venous pressure. During the coming year, Dr. John S. Schroeder will continue his work in association with the engineering staff of the Ames Research Center in modifying and improving the "Flack tester" for estimating central venous pressure. A series of specific studies are planned utilizing the instruments now available in the cardiology laboratory at Stanford.

a. Utilizing the ultrasonic flow transducer placed on a peripheral vein and the mouthpiece device for estimating air-way pressure and thus intrathoracic pressure, venous pressure measurements will be estimated on 100 patients undergoing cardiac catheterization and the measurements made by this technique compared to those obtained from a catheter placed in the right atrium during the course of cardiac catheterization. Since the relationship between these two pressures will not be one to one, regression lines will be constructed so that cor-

rections of the estimated pressure by the non-invasive method can be made. It is hoped that this technique will provide methods for determining central venous pressure.

b. Since one of the major problems with this technique is that during forced expiration, the right atrial pressure rises and does not give a clear reflection of the resting right atrial pressure, an improved method for presenting the thoracic pressure changes occurring during the test to the patients and to the physician will be developed. This will allow the patient who is cooperative to develop an expiration pressure only a few millimeters above that necessary to stop venous flow in a peripheral vein. This should improve the correlation between the true right atrial pressure at rest and the right atrial pressure determined by the Flack test.

c. The gradients which exist in the great veins from a peripheral vein in the arm to the right atrium have not been determined accurately with advanced technology which has become available during the past ten years. In a series of patients undergoing cardiac catheterization, such determinations will be made using an intravascular pressure transducer so that a better understanding of the pressure-flow characteristics of the venous system can be made. This will allow an improvement in the conceptual design of equipment for estimating venous pressure and will be essential for determining the validity of the Flack test as a method for measuring central venous pressure by non-invasive techniques. These studies will be carried out in twenty patients

during the next six months.

It is anticipated that a full clinical evaluation of the "Flack tester" will be made during the next twelve months and that a final report summarizing its validity and limitations can then be made.

3. Improvement in techniques for volume angiography. During the past decade, it has been apparent that improvement in the techniques for determining ventricular volume by angiographic techniques was essential if the methods were to be adopted for widespread use throughout the world. Several promising techniques have been developed. These include: videodensitometry, in which a large computer is used to scan the projected image of the heart once it is made opaque by the injection of a radio-contrast medium. This work has been pioneered by Dr. Earl Wood at the Mayo Clinic. A second improvement has been the development of computer programs for recording the coordinates of the ventricular chamber when it is traced with a planimeter. These computer techniques have been developed by Dr. Harold Sandler and are being used in a number of laboratories, including our own. In spite of both of these developments, the method remains time-consuming, and for the videodensitometry method, extremely expensive, since a large computer is required. In view of these difficulties, we have developed a new concept which will be tested during the coming year which may make the technique of volume angiography much easier. The improvement in volume angiographic techniques is important so that the non-invasive methods for recording ventricular performance can be validated more fully. The development of this method is essential to the ongoing NASA activities at Stanford.

The method which we propose is as follows: First, that volume angiograms be performed during the course of cardiac catheterization in a method similar to that now being utilized. Secondly, that the ventricular images be recorded on a high-speed video disc which has been made available to us by the Data Memory Corporation. Once the video images have been recorded on the disc, a number of methods are available in our system for enhancing the video images. These include subtraction modes and adjustment of the contrasts of surrounding structures. On the same video discs, analog signals for pressure and electrical events occurring within the heart can also be projected. Thirdly, that specific video pictures for end-diastolic and end-systolic dimensions be chosen by the physician performing the study. Fourth, a light-pen which has been developed in preliminary form for us by the Tektronix Corporation will be used to trace the outline of the ventricle manually. We have demonstrated that this is feasible. Fifth, the coordinates traced by the light-pen will be transmitted to a computer in the cardiology laboratory at Stanford for analog to digital conversion. Sixth, the computer now contains programs for recording and calculating ventricular volumes, changes in ventricular volume, stroke volume, ejection fractions and movements of various segments of the ventricular wall from the coordinates of the light-pen tracing.

This technique has been tested in a preliminary manner and is feasible. During the next twelve months three specific studies are planned utilizing this new image processing method:

a. A series of radio-opaque casts of ventricular chambers have

been developed during the past two years. These will be photographed in a standard way utilizing the cine-recording equipment in the Cardiology Laboratory at Stanford. The same images will be recorded simultaneously on the video disc and on cine-film. The volumes will be determined for the standard models utilizing the conventional method for doing angiography and the new video disc light-pen method. This will allow a comparison of the two techniques and a way for determining the validity of the present method.

b. In specific, selected patients, simultaneous recordings of ventricular angiograms will be recorded on the video disc and on cine-film. Ventricular volumes and stroke volumes will be calculated independently by two groups of investigators so that these two methods may be compared.

c. Ventricular volumes determined by the video disc light-pen method will be compared with those determined by the ultrasound techniques described in Section 1 of our proposed research for the coming year.

If indeed this new video disc light-pen method is successful, it offers three specific advantages: First, it is simple, and utilizes the human eye to make decisions which are difficult for a computer to make. Secondly, it is inexpensive, since the entire system will cost no more than $25,000, if a small mini-computer with 8-K of memory is available. Third, it appears to us that the accuracy of using the light-pen may be much greater than using the planimeter scanning arm now

employed in conventional volume angiography. During the coming year, each of these specific points will be tested by experimental study.

4. Studies on cardiovascular control mechanisms. During the coming year, several types of studies on cardiovascular control mechanisms are planned. These include:

a. During the course of bed rest studies performed at Ames Research Center and on cardiac patients at Stanford University School of Medicine, ultrasound techniques will be used to determine the rate at which the left ventricular wall moves so that an estimation of the function of the heart can be made.

b. Studies relating to methods to determine peripheral blood flow will be carried out. The use of the Doppler ultrasonic flow measuring techniques developed by Dr. Francis McLeod of the Electrical Engineering Department at Stanford University will be utilized for these studies. Direct comparison between transcutaneous Doppler flow measurements and those made by electromagnetic flow meters will be made. These studies will be carried out in animals initially, and later during the second year in the operating room during the course of cardiovascular surgery.

c. Precise methods for estimating blood flow to a series of organs throughout the body are needed. In order to understand precisely the function of the cardiovascular system, the regulation of flow to specific vascular beds is essential. One such specific bed in which new and improved techniques are

needed at this time is the liver. The liver has a dual blood supply from the hepatic artery and the portal vein. In the past, substances which are removed by the liver from the blood have been used to estimate liver blood flow by determining clearance rates by the liver. During the coming year, such methodology will be studied using indocyanine green as the substance which the liver extracts. Arterial and hepatic venous concentrations will be determined in order to estimate the clearance of the substance from the liver. Other substances such as lidocaine will also be used as an indicator. Equations will be developed for determining the rate of clearance by the liver of the substances as they are removed from arterial blood. Perhaps it will be possible to develop a method for determining blood flow which does not require measuring the concentration in hepatic venous blood. The details of this study have not yet been developed, but will be planned for the coming year.

d. Studies of the response of animals to damage of the normal ventricle by myocarcial infarction. Myocardial infarction will be produced in acute and chronic animals by ligation of coronary arteries or by ameroid constrictors placed around coronary arteries. Serial measurements of changes in cardiovascular function as it relates to the size of the area damaged will be made. Specific drugs, such as lidocaine, isoproterenol and digitalis will be administered so that careful measurement of the effects of these drugs on cardiovascular mechanics can be recorded.

D. Bibliography:

The following papers and abstracts were published in national medical journals during the past twelve months and represent the accomplishments performed as part of the activities of this grant.

ABSTRACTS

1. Finegan, R.E., Popp, R.L., and Harrison, D.C.: Echography in the diagnosis of left atrial tumors in suspected mitral valvular disease. Clin. Res. 18:114, 1970.

> Although echocardiography (ECHO) has been widely used to diagnose the presence and severity of mitral stenosis, it has not been employed extensively to detect other lesions mimicking mitral disease. Recently we have detected two surgically proven atrial myxomas and studied their intracardiac motion with ECHO. In one patient with physical signs of mitral insufficiency, dyspnea of nine years duration and chronic atrial fibrillation, the diagnosis of an atrial tumor was suggested only by the ECHO and not confirmed by catheterization or angiography. In the second patient, exertional dyspnea, fever, varying signs of mitral stenosis and an elevated erythrocyte sedimentation rate suggested the correct diagnosis. In this patient ECHO demonstrated tumor echoes behind the mitral valve, and in addition, the anterior and posterior margins of the tumor moving within the heart. Angiography confirmed both the diagnosis and the pattern of tumor-motion suggested by ECHO.
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> ECHO is a useful, atraumatic method for detecting left atrial tumor and should be employed as a screening method in all patients with atypical presentations of mitral disease. This technique thus provides not only confirmation of suggested mitral stenosis but may identify the occasional patient with an atrial tumor leading to appropriate diagnostic procedures and avoidance of hazardous studies.

2. Kerber, R.E., Goldman, R.H., Alderman, E.L., and Harrison, D.C.: Hemodynamic effects of alprenolol in patients with heart disease. The Pharmacologist p. 233, 1970.

Alprenolol, a new beta-adrenergic blocking agent with some intrinsic beta-agonist properties, was administered intravenously, 0.2 mg/kg, to 14 patients with various types of acquired heart disease during cardiac catheterization. Hemodynamic measurements were made before and after the drug at rest, with isoproterenol challenge and, in 9 patients, with exercise. During exercise significant reductions were noted in heart rate response (an increase of 19% before the drug, 12% after), systolic pressure response (13% increase vs. 7% increase) and cardiac index response (43% increase vs. 37% increase). Right atrial mean and pulmonary artery mean pressures rose significantly at rest (43% and 10%), although left ventricular end-diastolic pressure was not significantly altered during either rest or exercise. Slight elevations in systemic and pulmonary vascular resistance occurred after alprenolol. It is concluded that in patients with heart disease, alprenolol has significant negative inotropic effects and a consequent deleterious effect on cardiac performance, probably secondary to its beta-blocking actions. (Supported in part by NIH Grant No. HE-09058, 5709, and 5866.)

3. Ridges, J.D., Sanders, W.J., and Harrison, D.C.: On-line computer analysis of cardiac catheterization data. Circulation 41, 42:370, (Suppl. III), 1970.

An automated real-time system using a small digital computer has been developed for the analysis of data during cardiac catheterization. Operator interaction with the computer is accomplished with a specially designed keyboard. Analog signals representing pressures, dye dilution curves, and QRS onsets are processed. The results are numerical values for atrial, ventricular and systemic pressures, cardiac output, heart rate and valve gradients and areas. The results are displayed immediately on a large-screen TV monitor in the laboratory. A complete report is printed at the end of the procedure. Following a trial period of operation, a "blind" comparison of computer and manual measurements was made. All of the pressure data comparisons showed an excellent agreement between computer and physician, with the largest standard error of the estimate being 6.5 mmHg and the smallest correlation coefficient being .90. This agreement is better than the variability in pressure measurements between physicians. It is concluded that automated hemodynamic data analysis is accurate and that rapid availability of results improves decision making during the procedure and aids in completeness of cardiovascular investigation.

4. Schroeder, J.S., Graham, A.F., Rositano, S.A., Sandler, H.L., and Harrison, D.C.: A non-invasive method for measuring right atrial pressure. Amer Heart Assoc 44th Scientific Sessions, 1971.

A method has been developed which can estimate right atrial pressure using Doppler monitoring of peripheral venous flow and measuring intrathoracic pressure during a modified Valsalva maneuver. Using a Doppler signal, the basilic vein yields a pulsatile venous flow when the vein is filled to the right atrium. The patient gradually blows into a mouthpiece with an open glottis while monitoring intra-oral pressure which represents developing intra-thoracic pressure. When intra-thoracic pressure exceeds peripheral venous pressure, venous flow stops. A comparison has been made of right atrial pressures estimated by this technique and those recorded directly through a catheter in the right atrium in 50 patients undergoing cardiac catheterization. The right atrial pressure correlations were excellent when the pressure developed during the Valsalva maneuver was used as the standard. However, the correlation with basal (non-Valsalva) right atrial pressures in some patients who developed sharp elevations of right atrial pressure during the Valsalva maneuver was variable. This technique appears to be a reliable and reproducible non-invasive method of assessing right atrial pressure in man under select and specific conditions.

5. Branzi, A., Alderman, E.L., Sanders, W.J., Brown, W., and Harrison, D.C.: Comparison of pulse-pressure methods for determining cardiac output. Amer Heart Assoc 44th Scientific Sessions, 1971.

Several mathematical analyses of the pulse pressure for determining stroke volume have been employed widely as a rapid method of monitoring critically ill patients. Forty-two patients with mitral or coronary disease undergoing diagnostic catheterization had simultaneous stroke volume determinations by the pulse pressure method and by the dye dilution method under a variety of hemodynamic conditions. All calculations were performed by a small on-line digital computer. Homer Warner, Kouchoukos, and Herd formulas were compared. Fifty-nine comparisons were made during exercise, fourteen comparisons during isoproterenol infusion, and seventeen comparisons following pentazocine or practolol administration. The correlation coefficients for the exercise comparison ranged from .75 to .85; for the isoproperenol comparison from .85 to .94; and for the drug comparison the range was .65 to .80. Although the stroke volume comparisons were statistically significant between patients, absolute changes in stroke volume from the resting condition were not as reliably determined by the pulse pressure method as by dye dilution.

PAPERS

1. 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 Meeting of Amer. Inst. of Ultrason. in Med. (In press).

2. Sanders, W.J., Ridges, J.D., and Harrison, D.C.: An automated system for the collection and analysis of cardiac catheterization data. Proc. 23rd Ann. Conf. on Eng. in Med. and Biol. 312, 1970.

3. Finegan, R.E., Schroll, M., Robison, S., and Harrison, D.C.: Action of pharmacologic agents in experimental cardiac tamponade. Amer. Heart J. (In press).

4. Sinclair, A.J., Miller, H.A., and Harrison, D.C.: An electro-optical monitoring technique for heart cells in tissue culture. J. Appl. Physiol. 29:747, 1970.

5. Schroll, M., Robison, S.C., and Harrison, D.C.: Circulatory responses to hypoxia in experimental myocardial infarction. Cardiovasc. Res. (In press).

6. Finegan, R.E., Marlon, A.M., and Harrison, D.C.: Circulatory effects of practolol. Amer. J. Cardiol. (In press).

7. Ridges, J.D., Sanders, W.J., and Harrison, D.C.: The on-line analysis of atrial pressures using a digital computer. Proc. 23rd Ann. Conf. on Eng. in Med. and Biol., p. 11, 1970.