EVALUATION OF THE CARDIOVASCULAR SYSTEM DURING VARIOUS CIRCULATORY STRESSES

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PROGRESS REPORT

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INTRODUCTION:

The work described in this progress report was carried out during the first eight months after activation of this NASA grant project (September 1, 1968). Although much of the initial four months was taken up by the purchase of equipment and the planning for the studies which were carried out, significant progress has been made during the past four months both in animal studies and in the initiation of studies in man. Animal studies were carried out at Stanford and at the Ames Research Center installation at Moffett Field, and human studies were carried out at Stanford University School of Medicine. It is the purpose of this progress report to present in summary form the initial studies which have been carried out and to discuss in detail some of the studies which will be carried out in the coming year. In addition, a list of publications, including papers in press and in preparation, will be presented.

A. Progress in Experimental Animal Studies.

Two groups of studies have been carried on in experimental animals during the past eight months. More than seventy animal studies of myocardial infarction have been carried out. The cardiac reserve before and after myocardial infarction was evaluated by studying the response to drugs which either elevated the arterial pressure or enhanced the performance of the heart. In addition, the compensatory mechanism used by the animal when subjected to the severe stress of myocardial damage produced by coronary artery ligation was evaluated. Anesthetized dogs were instrumented with a micro pressure transducer supplied by the Ames Research Laboratories, with standard catheters for pressure

measurements, and with flow transducers. Ventilation was maintained artificially with a Bennett Respirator. In one group of 20 animals the response to dopamine (a naturally occurring catecholamine) in a dose of 8 μg/Kg/min was evaluated. In another group of 27 animals the response to the antiarrhymic drug lidocaine, which itself depresses circulatory function, was evaluated prior to and after myocardial infarction. The effects of morphine were evaluated prior to and after myocardial infarction in a group of 23 animals. This drug has been shown both to be a circulatory depressant and stimulant. The details of each of these studies will be presented below.

Dopamine Studies:

The circulatory response to dopamine in the intact animal at rest prior to myocardial infarction includes an increase in cardiac output, an increase in the left ventricular dp/dt and decreases in left atrial pressure and systemic vascular resistance. No changes were noted in the response of arterial pressure and heart rate. Infarction of 37% of the left ventricle was produced by a two-stage ligation of the circumflex and anterior descending coronary arteries. This resulted in a significant increase in left ventricular end diastolic pressure and left atrial pressure. The cardiac output was reduced to one-half of control (pre-infarction) and the left ventricular dp/dt was markedly depressed. When challenged with a volume load averaging 20 ml/Kg of body weight an abnormal response was observed, the magnitude of which indicated severe deterioration of cardiovascular function. At this time an infusion of dopamine in the same doses as administered prior to myocardial infarction resulted in a marked and significant improvement in circulatory function. The

cardiac output returned to normal levels and the left ventricular dp/dt was markedly elevated. Left ventricular end diastolic pressure, left atrial pressure, and heart rate all decreased. Systemic vascular resistance was decreased while arterial pressure did not change significantly.

These studies suggest that dopamine is a preferable agent for the treatment of severely depressed cardiac function following acute myocardial infarction. Its action is an improvement over the actions of other catecholamines for the treatment of this condition. The fact that it does not increase heart rate nor arterial pressure but improves the inotropic state of the heart, as evidenced by an increase in cardiac output, a decrease in left ventricular end diastolic pressure, and an increase in left ventricular dp/dt, suggests that it has many advantages over isoproterenol (a selective beta-adrenergic stimulating drug) which has commonly been used to treat cardiogenic shock of this type. The results of this study were presented at the annual meeting of the American Physiological Society and was published in abstract form (A1) and has been submitted for publication in the American Journal of Physiology (A2).

Lidocaine Studies:

Lidocaine is a commonly used antiarrhythmic drug in patients with acute myocardial infarction. It has been shown to have depressant effects on circulatory function in normal hearts when given in large doses. The purpose of this series of studies was to evaluate alterations in cardiovascular function produced by lidocaine after the circulatory stress of acute myocardial infarction. Studies were performed on 27 anesthetized dogs with both single injections of lidocaine (5 mg/Kg) and infusions of lidocaine (200μg/Kg/min for 10 minutes) being carried out. These doses are comparable to those used in patients following acute myocardial infarction. An understanding

of the action of lidocaine and the compensatory mechanisms involved in the circulatory response of the patient to such stress may provide a more thorough understanding of the heart's response to other types of cardiac stress.

Both prior to and after the production of acute myocardial infarction by coronary artery ligation, infusions of lidocaine produced no statistical change in left ventricular end diastolic pressure, cardiac output, left ventricular dp/dt, arterial pressure or peripheral vascular resistance. A single injection of lidocaine given prior to myocardial infarction resulted in a significant decrease in aortic pressure, heart rate, left ventricular dp/dt, cardiac output and a slight elevation in peripheral vascular resistance. The duration of these changes was less than five minutes and during a one-hour follow-up period no other changes were apparent. Following myocardial infarction the injection of the same dose of lidocaine resulted in significantly greater depressions in arterial pressure, left ventricular dp/dt and cardiac output. At this time there were also elevations of left atrial pressure and left ventricular end diastolic pressure as well as increases in systemic vascular resistance. The duration of these depressions in the performance of the heart was also significantly longer than prior to myocardial infarction. The conclusions from these experiments are:

1. Infusion of lidocaine in clinically applicable doses does not result in significant alterations in cardiac performance in the normal state or in severely compromised hearts following myocardial infarction.
2. Large single injections of lidocaine result in decreased performance of the left ventricle in normal hearts and in markedly decreased performance in hearts following the stress of acute myocardial infarction.
3. The duration of alteration of performance of the heart produced by lidocaine is greater in the abnormally stressed heart following myocardial infarction than in the normal heart.

Although it is difficult to extrapolate from animal studies to patients, it seems likely that infusions of lidocaine should be the preferable method of therapy in patients with compromised circulatory function following myocardial infarction. If single injections are to be used, smaller doses will result in less circulatory depression. However, decreased performance of the left ventricle will still be encountered in many of these patients (B1).

Morphine Studies:

Morphine sulphate is a commonly used analgesic agent for the relief of pain of many etiologies. The experiments carried out in this protocol were designed to study the circulatory alterations produced by morphine in normal and abnormal hearts. The abnormal hearts were those produced by coronary artery ligation and resemble the clinical state of myocardial infarction where morphine is frequently used. The design of these studies is different from those used to study dopamine and lidocaine since morphine is a long-acting drug and can only be administered once in a period of study. Twenty-three anesthetized dogs instrumented as described above were used. Morphine, 100 μg/Kg was given intravenously to 11 dogs with normal hearts and in 12 dogs following the production of acute myocardial infarction (32% of the left ventricle infarcted). In the control normal heart, the injection of morphine produced a decrease in heart rate, an early decrease in left ventricular dp/dt which was followed by an elevated value after five minutes, and an initial decrease in cardiac output followed by a sustained increase. These changes show a decrease in cardiac performance following the administration of morphine to which the animals respond by activating the sympathetic nervous system. In other words, the carotid baro-receptors detect the fall in arterial pressure and increase the sympathetic nervous output to the

blood vessels and heart, resulting in a sustained increase in cardiac output and cardiac performance. In the animals studied after myocardial infarction, the early qualitative changes produced by morphine were similar, although the sustained increase in cardiac output and left ventricular dp/dt did not occur in the damaged hearts. The altered performance of the damaged heart to the depression produced by morphine injection was statistically more than that observed in the normal heart. Since this drug is frequently used in clinical situations in which cardiac damage is present, these studies suggest that care should be taken when morphine is given intravenously. An abstract of this paper has been submitted and a final manuscript is now in preparation (C1).

Preliminary studies in unanesthetized dogs.

During this eight-month period of time attempts have been made to instrument dogs for chronic study of the circulatory responses to drugs and changes in physical environment. New ultrasonic flow transducers have been placed around pulmonary arteries and aortas in these dogs and micropressure transducers have been placed in various chambers of their hearts and blood vessels. Adequate monitoring signals have been obtained in a series of six such dogs after complete recovery from surgery. These studies have been carried out in association with Dr. Harold Sandler at the Ames Research Laboratory. During the coming year it is anticipated that animals instrumented in this manner will be used to evaluate the effects of anesthesia on the compensatory mechanisms for increasing ventricular performance in normal and abnormal states. Studies such as those described for dopamine, lidocaine and morphine will be carried out in awake, unanesthetized dogs and compared with the data obtained in the dogs who were anesthetized. Although not

completely obliterated by anesthesia, the circulatory adjustments provided by the nervous system are either delayed or decreased in magnitude by anesthesia. The exact mechanisms by which this occurs will be investigated utilizing intact, awake preparations.

During the coming year it is also planned that the centrifuge at the Ames Research Center will be used to study the effects of circulation in instrumented animals. It is the purpose of such studies to determine the distribution of flow during circulation and the adaptive mechanisms used by the circulation during such stress. During the coming year this program will be closely integrated between the Cardiology Division at Stanford University School of Medicine and the cardiovascular research laboratory at Ames.

B. Progress in Human Studies:

Although a great deal of progress was made in animal studies during the past eight months, only a few human studies have been carried out. Two types of studies have been most fruitful and are now being continued as part of a full-scale effort.

Ultrasound Studies

The development of indirect methods for studying the circulation and evaluating cardiac performance is essential for studies in man. During the past year considerable experience has been gained in collaboration with Dr. Richard Popp utilizing reflected ultrasound for evaluating cardiac performance. A method for the detection of stroke volume has been developed and has undergone preliminary tests in which it has been compared to standard laboratory methods for evaluating stroke volume (D1, D2). These studies were carried out in the cardiac

catheterization laboratory at Stanford andmust be confirmed on larger numbers of patients. The use of ultrasound for detecting changes in the performance of the transplanted human heart have been carried out in association with Dr. Norman Shumway and associates in the cardiac transplantation program at Stanford (D3, D4). It is possible to measure the thickness of the posterior wall of the left ventricle and the movement of this structure throughout the cardiac cycle using ultrasound. Once rejection of the transplanted heart commences, the left ventricular wall is thickened and becomes restricted in its motion. It has been possible to detect these changes quite early using ultrasound and to reverse them by treating the process of immunologic rejection. These studies were carried out in eleven patients undergoing cardiac transplantation and the results have been documented using other methods for evaluating rejection. This technique has proven to be both reliable and simple and its evaluation will be continued during the coming year. It seems possible that the use of these indirect methods will allow the study of cardiac performance in both normal and abnormal states under a variety of stresses. During the coming year we anticipate doing such studies in more than 40 patients since the techniques are atraumatic and do not require the introduction of catheters or other potentially harmful devices. It is proposed that such methods, once adequately calibrated, be used to monitor and determine cardiac performance during space flight. Abstracts describing the work for determining stroke volume and for detecting rejection have been published (D1, D2, D3).

Dynamic Geometry of the Human Left Ventricle

Dynamic geometry of the left ventricular chamber has been determined in 24 patients undergoing diagnostic cardiac catheterization for valvular or arteriosclerotic heart disease.

Chamber dimensions and change in dimensions were evaluated from left ventricular angiocardiograms in addition to standard measurements of cardiac output and ventricular pressures. Utilizing these studies it has been possible to evaluate the relationship between the ejection fraction and the performance of the human left ventricle. Since these ventricles are not functioning normally it has been possible to evaluate the mechanisms by which the abnormal ventricle compensates for its structural defects. The ejection fraction which represents the difference between end diastolic volume and the end systolic volume of the left ventricle has been demonstrated to be a reliable indicator of the abnormal performance. In addition, it appears that a different pattern of contraction has developed in some of these abnormal ventricles in order to compensate for an increase in the wall tension. The wall tension in these cases is abnormally high since in most of the diseased left ventricles the radius of the chamber is markedly increased and inorder to develop a given pressure within the ventricular chamber a higher degree of wall tension is necessary.

The essence of this study suggests that an evaluation of the ejection fraction gives an adequate representation of the decrease in ventricular performance. This, then, obviates the need for studying the dynamic geometry of ventricular contraction in order to more fully evaluate the performance of these diseased ventricles in usual clinical situations. These observations are preliminary, however, and in order to determine their precise role in evaluating ventricular performance additional studies comparing the more sophistocated angiographic measurements occurring throughout the cardiac cycle with those of the ejection fraction are needed. It is our purpose to study 12-15 such patients during the coming year in order to complete this project.

C. Projected Studies for 1969-70.

During this year three types of studies will be initiated as outlined in the original grant proposal. First, studies to monitor the cardiac performance of patients following myocardial infarction in order to evaluate transducers and techniques which have been developed during the past five years will be initiated. These patients will be in the coronary care unit at Stanford University Hospital and will undergo study during three or four days after the acute infarction. The studies will not only evaluate transducers but will allow better treatment of the patients under study. Secondly, the use of ultrasound for measuring changes in stroke volume and movements of left ventricular walls will be carried out in patients with ventricular abnormalities such as hypertrophic subaortic stenosis. Thirdly, the use of fiberoptic methods for determining ventricular volume at end diastole and end systole and thereby allowing calculation of ejection fractions will be investigated. It is intended to compare these methods with the angiographic methods. The initiation of these projects during the coming year and their continuation in subsequent years will lead to a better understanding of cardiac performance under a variety of stressful situations.

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