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NEUROHUMORAL AND MECHANICAL FACTORS IN THE MODULATION OF LEFT VENTRICULAR MASS  
Final Report, Covering Period September 23, 1983-October 31, 1986

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# NEUROHUMORAL AND MECHANICAL FACTORS IN THE MODULATION OF LEFT VENTRICULAR MASS

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## Goals of the Research

The goals for the research were to define, describe, and study those neuro-endocrine and mechanical mechanisms that may play a role in the initiation and maintenance of an increase in, or cause regression of, the mass of the left ventricle. Dynamic changes in heart mass have been observed to occur in man and animals: (1) enlargement of the heart is frequently encountered in patients with hypertensive disease, and (2) decrease in heart mass has been reported for men exposed to prolonged space flight. The basic physiologic processes which may explain how these changes occur, and the effects of gain or loss of myocardial mass on cardiac performance were considered significant questions to be answered for the benefit of the National Aeronautics and Space Administration.

## Personnel and Organization for Performance of the Agreement

The team of 13 investigators formed for the performance of the research were organized as the "Committee for the Study of Cardiac Function", and represented expertise and experience in the following disciplines: cardiovascular physiology, pathology, clinical cardiovascular pharmacology, clinical cardiology, cardiovascular surgery, bioengineering, and surgical technical personnel. A total of four (4) graduate students and three (3) medical students were in training at some time during the project period, and their contributions to this final report are indicated in the next section.

## Studies Completed or Currently (\*) On-Going

1. Development of a Method for Chronic Monitoring of Changes in Left Ventricular Mass in Canine Models (Hawthorne, Franklin, Coleman and Cothran)

In order to follow changes in left ventricular mass over the time course of exposure to any given intervention or forcing function in the awake dog model, it was necessary to first develop a reliable means for direct measurements of selected dimensions of the ventricle, and using an appropriate geometric analog of the ventricle, arrive at reproducible estimates of actual mass. Furthermore, validation of appropriate experimental models which would allow for a variety of experimental protocols was necessary. Preliminary studies had shown that it was possible to produce an experimental animal which when instrumented for chronic study, would allow for this variety. The initial year of the project was largely devoted to accomplishing these methods and to validation of the techniques. We were able to demonstrate that in the chronic dog, studied in the awake state, not only was it possible to follow changes in left ventricular mass over a period of 2 to 3 months, but also to make a variety of measurements of changes in flows, resistances, pressures, volumes, and myocardial contractile properties as indices of changes in cardiac function. Appropriate computer software was also developed to facilitate the handling of large volumes of data specifically suited for these types of studies.

The technique for monitoring changes in left ventricular mass was reported in the American Journal of Physiology and is listed in the bibliography section.

## 2. Neuroadrenergic Activity and Left Ventricular Mass (Franklin, Cothran, and Hawthorne)

Inferences from reports from other laboratories and from our own experiences suggest an important role of the sympathetic adrenergic nervous system in the development of left ventricular hypertrophy. Studies were therefore designed to observe the effects of carotid sinus denervation on cardiac performance and left ventricular hypertrophy in the two-kidney one-clip Goldblatt dog preparation. After three weeks of observation, it was determined that such dogs did develop a significant hypertrophy and characteristically had high cardiac outputs along with increased myocardial contractility. A mild hypertension usually develops in the two-kidney one-clip dog model but the hypertension is transient and disappears within 2 to 4 weeks. A significant hypertrophy in the absence of a significant hypertension but in the presence of increased neuroadrenergic activity lends support to the view that the hypertrophic process requires a neural component.

A more detailed report of this study was submitted as a technical report and appended to the interim report, October 1, 1984 to June 30, 1985.

## 3. Hypertrophy and Peak Diastolic Rapid Filling in Chronic Dogs (Lewis, Franklin, Curry and Hawthorne)

The effect of left ventricular hypertrophy on the peak diastolic filling rate of the left ventricle was tested in conscious, chronically instrumented, normotensive and hypertensive animals with left ventricular hypertrophy. The hypertensive dogs showed a significant decrease in the peak diastolic filling rate (normalized for end systolic volume) compared to the controls. These findings are similar to those reported for patients, and confirm the depression in this diastolic function in the presence of left ventricular hypertrophy.

Of special value to the series of studies planned in order to characterize the effects of mass changes on cardiac function is this finding of depressed diastolic function in hypertrophied hearts. The animal model is thus very useful in assessing and predicting the types of changes one could expect in humans.

A detailed draft of this study was appended to the interim report for October 1, 1984 to June 30, 1985.

## 4. Atrial Systole and Left Ventricular Myocardial Properties in Dogs with Renovascular Hypertension (Mouton\*\* and Franklin)

Very little attention has been given to the period of atrial systole and the associated ventricular dynamics in hypertension. This study was a preliminary examination of ventricular responses to atrial systole during the development of single-kidney and two-kidney hypertension as produced in series in the same animal. Changes in left ventricular pressure-volume relations and length-tension relations in association with the development of hypertension were compared to the normotensive behavior of the left ventricle during atrial systole, the terminal diastolic period of the left ventricle. Under conditions where one artery is constricted and the other kidney is normally perfused, the heart functions from a smaller size and appears to be more

compliant in diastole. Changes in mean arterial pressure following constriction of the one renal artery shows a transient, mild hypertension for a period of approximately two weeks. When the second renal artery is also constricted, a frank hypertension develops which persists and the heart functions from a larger size with some reduction in its diastolic compliance. During the early periods (first two weeks) of these hypertensive responses to renal artery constriction, there may be some material changes in the myocardium which affect the ability of the heart to receive the atrial contents. It is also apparent that differences in the ventricular size prior to atrial systole can affect the compliance of the ventricle.

\*\*This study was conducted along with a third-year medical student who presented these findings at a two-day research symposium in 1986 at the Howard University. Additional data are currently being analyzed for more dogs prepared in this manner in preparation for publication.

#### 5. Spatial Orientation and Myocardial Fiber Size in Left Ventricular Hypertrophy (Hunter\*\* and Franklin).

Left ventricular myocardial fibers oriented in the planes of the principal equatorial stresses (meridional and hoop stress) were examined for morphological differences. Specimens were obtained from normotensive canine hearts arrested in diastole, and rapidly fixed via coronary perfusion, *in situ*, while the operating end-diastolic pressure was maintained at or below 8 mm Hg. Fiber orientation was determined across the free wall with light microscopy in serial paraffin sections. Indices of fiber size (area, perimeter, Dmax) were measured in regional paraffin blocks of the epicardium, midwall, and endocardium. The meridional and hoop stresses were calculated based on the thick-walled model of Walker, Hawthorne and Sandler. Fiber orientation changes smoothly from about +80 degrees at the endocardium to about -75 degrees at the epicardium, with respect to the equator. The majority of fibers near the midwall were arranged circumferentially. Results indicate that the midwall fibers are significantly larger than the epi- and endocardial fibers. Further, the endocardial fibers are significantly larger than the epicardial fibers for all parameters. While these data indicate a significant difference in the size of fibers oriented in the plane of the larger hoop stress, it does not explain the observed differences between the endocardial and the epicardial fibers.

\*\*This study was carried out largely by Miss Hunter who will present all of her findings in her doctoral dissertation. The summary presented here represents an abstract of her paper presented at the Spring meetings of the American Physiological Society, 1985.

#### 6. Effects of Prazosin and Hydralazine in 2K2C Hypertension and Hypertrophy (Drummond\*\* and Franklin)

Studies were conducted to analyze the effects of two commonly used anti-hypertensive drugs on myocardial performance when infused for acute lowering of arterial blood pressure in normotensive and hypertensive dogs. The evaluation of the two agents, Prazosin and Hydralazine, revealed that both were effective in lowering blood pressure in both the normotensive and the hypertensive state. In addition, the parameters of heart rate, ejection fraction,

stroke work and cardiac output along with  $dP/dt$  were observed as indices of ventricular performance and contractile behavior. Observations were also made of changes in total peripheral resistance, end-diastolic pressure and end-diastolic volume during the acute response to the infusions and following 24-hours postinfusion. Prazosin produced negligible effects on cardiac performance in the normotensive as well as the hypertensive state. However, Hydralazine, in both conditions, significantly increased the contractile behavior of the heart as was shown by a marked increase in heart rate, cardiac output, ejection fraction and  $dP/dt$ . These observations suggest that great caution should be taken in the use of this drug in the treatment of certain hypertensive patients, particularly if there is a known compromise of myocardial tissues already existing.

\*\*This study was carried out during a summer by a third-year medical student (J. Drummond) who presented it at the 1986 Eastern Student Research Forum in Miami, Florida.

#### 7. Absence of Hypertrophy in 2K2C Goldblatt Hypertension (Franklin, Coleman, Cothran)

In chronically instrumented dogs, studies were carried out in two forms of Goldblatt experimental hypertension - 1K1C and 2K2C. Findings from the measurement of left ventricular mass, volumes, pressures, flows, wall tension, aortic pressure, total peripheral resistance and indices of myocardial contractility showed that after 3 weeks, mean arterial pressure and left ventricular end-systolic pressure were similar in the two forms, however a significant hypertrophy had occurred in the 1K1C preparation, and no evidence of hypertrophy had occurred in the 2K2C model. The 1K1C hypertensive was characterized by a high cardiac output, normal myocardial wall tension, and low total peripheral resistance. The 2K2C hypertensive was characterized by a normal cardiac output, slightly elevated wall tension, and very high total peripheral resistance. The data suggest that the mechanism of hypertension development in the 2K2C dog is different from that of the 1K1C dog, and that the increase in neuroadrenergic activity (viz., myocardial contractility) is necessary for the development of left ventricular hypertrophy. Further study of these models may provide insight into the relative roles of the neuroadrenergic and volume-vasoconstriction components in the pathogenesis of hypertension and cardiac hypertrophy.

The results of these studies will be presented at the meeting of the American Society of Hypertension in May, 1987, in New York City.

#### \*8. Current On-Going Studies

One of the features of the original proposal which has not been successfully carried out is the need for baseline and serialized measurements of plasma renin activity and catecholamine levels in the normal and hypertensive dogs. New personnel have been recruited to the investigative team who are presently performing these analyses. Such information is essential to the evaluation of these hormones in the hypertrophic process.

Another feature which the investigators regard as important, especially in the 2K2C hypertensive model where total peripheral resistance is high, is

a critical analysis of the components of total resistance, viz., total input impedance. With the availability of non-constricting flow probes and sonic flowmeters, such studies can be made in a chronically instrumented dog. Some preliminary studies have shown that this is feasible in our laboratory and it is expected that experimental work will be proceeding within the next three weeks.

Studies using selective blocking agents for angiotensin and for adrenergic receptors are currently under way, but data analysis of these is not yet ready for reporting. These studies are designed to interrupt suspected pathways by which development of hypertension and hypertrophy are initiated and maintained. Two students are involved in these studies which have been designed as dissertation projects, and when completed, will partially fulfill the requirements for the Ph.D. degree.

The proceedings of the Symposium on Myocardial Hypertrophy were initially planned to be edited by Dr. Hawthorne whose unfortunate death has delayed that process. It is the plan of the Co-Principal Investigator (Dr. Franklin) to complete that task by the end of this year.

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