The Stimulus to Hypertrophy of the Myocardium

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Although myocardial hypertrophy is one of the major pathologic changes in cardiovascular disease, much uncertainty still prevails with regard to its pathogenesis. The clinical and experimental causes of cardiac hypertrophy, numerous and varied as they are, probably operate by a common mechanism in inducing the myocardial change. This assumption may not be true, but there are distinct advantages in searching for a basic common process. A change in any parameter of cardiac function that leads to hypertrophy of the myocardium will be defined as the “stimulus.” The purpose of this paper is to discuss some of the views about the nature of the stimulus and emphasize the concept that appears most plausible. The diversity of opinion is evident in the discussions of Friedberg, Gregg, Wartman, and others. A good presentation of the subject is by Hull in Sodeman’s Pathologic Physiology.

Progress has been hampered by the inability to assess accurately myocardial hypertrophy in the intact animal or man. The inability to know the control weight of a given chamber of the heart in vivo, coupled with the difficulty of studying various parameters of cardiac function and metabolism during the period of hypertrophy, make it almost impossible to establish correlations. Often the heart is studied after the hypertrophy has been fully established and has reached a steady state. At this stage the stimulus may have ceased to exist. Microscopic criteria for hypertrophy are unreliable and may not detect mild degrees. The frequently used heart weight to body weight ratio has too many variables to be sufficiently reliable, particularly if the hypertrophy is of a mild degree. Edema of the myocardium (e.g., beriberi, myxedema), excess fat, glycogen, and fibrous tissue must be excluded in order to assess true hypertrophy of the muscle fibers. All these factors plus the fact that many clinical and experimental conditions lead to cardiac hypertrophy have hampered a true understanding of the fundamental nature of the stimulus to hypertrophy.

The enormous mass of clinical and experimental data on cardiac hypertrophy and the relatively meager basic physiologic studies have led to various hypotheses, some of which are outlined below.

Defective Nutrition of the Myocardium

Cardiac hypertrophy is known to occur in chronic severe anemia and in some patients with occlusive disease of the coronary arteries. Also, it occurs in large arteriovenous shunts and in aortic regurgitation, both of which are characterized by a low diastolic pressure with a possible deficiency of the coronary circulation. It has been suggested that in these conditions poor nutrition of the myocardium may constitute the stimulus to hypertrophy. However, in all these disturbances other parameters of cardiac function (e.g., end-diastolic volume, stroke volume, mean ejection pressure, myocardial tension during systole, etc.) change concurrently and one can explain hypertrophy more plausibly on the basis of changes other than defective myocardial nutrition. For instance, in chronic severe anemia the heart dilates,
the exact mechanism being uncertain. Dilatation of the heart would increase the contractile tension and the energy expenditure of the heart beat. According to Stewart and his associates,\textsuperscript{18} the stroke-work of the left ventricle is reduced in severe anemia. This is due to a fall of both systolic and diastolic arterial pressures, despite the frequent increase in stroke volume. Again, in acute coronary occlusion there is evidence that the infarcted muscle bulges during systole\textsuperscript{19} and that the unaffected myocardium undergoes more forceful contractions as a result of ventricular dilatation.\textsuperscript{20} The latter may account for the hypertrophy in some cases. Likewise, in arteriovenous shunts the hypertrophy may be explained on the basis of increased end-diastolic volume due to increased venous inflow and possibly increased stroke volume-work.\textsuperscript{21} Similarly, in aortic regurgitation there is an increase in end-diastolic volume (regurgitant flow) and increase in stroke-work, but these changes are more marked than in arteriovenous shunts. Hence, the hypertrophy is more striking.

**Excessive Hormonal Secretion**

The role of the anterior pituitary hormones in controlling the mass of heart tissue is complex and not well understood. Beznák\textsuperscript{22} has studied this most extensively and believes that the pituitary growth hormone is essential for hypertrophy of the heart. De Grandpré and Raab\textsuperscript{23} have demonstrated that, in hypophysectomized rats, repeated doses of growth hormone induce cardiac hypertrophy without increasing cardiac work. This observation can account for the myocardial hypertrophy that may be seen in cases of acromegaly without hypertension.\textsuperscript{24} The anterior pituitary can also influence heart size by way of the thyroid and the adrenal cortex.

Hyperthyroidism in the experimental animal\textsuperscript{25} as well as in man\textsuperscript{26} may be accompanied by cardiac hypertrophy. Under these circumstances two types of influences act on the heart, (1) direct effect of thyroid hormone on the heart in the form of tachycardia and increased metabolic rate of muscle tissue due to excess hormone, and (2) increase in cardiac load secondary to circulatory changes such as increased minute output, stroke volume, and systolic pressure.\textsuperscript{27} Although these influences are believed to favor hypertrophy of the heart, yet clinically hyperthyroidism does not induce striking increases in the weight of the heart. Kepler and Barnes\textsuperscript{26} enumerate some of the factors that may be involved.

Another endocrine organ that can alter heart weight is the adrenal cortex. Chronic hypersecretion of the adrenal cortex (Cushing's syndrome, hyperaldosteronism) tends to cause cardiac hypertrophy and vice versa. The cardiac findings in these disturbances are believed to be secondary to alterations in the load of the heart rather than a direct effect of the corticoids on cardiac muscle mass. However, the latter possibility has not been adequately investigated and excluded.

In 1912, Stewart\textsuperscript{25} produced cardiac hypertrophy in rabbits by intravenous injections of epinephrine (100 to 200 µg. on alternate days). He attributed this to what was described as “myocarditis” which developed in these animals. It has been recognized that large unphysiologic doses of catecholamines will produce foci of severe anoxia and tissue damage in the heart, especially throughout the subendocardial layers of the left ventricle.\textsuperscript{29}

**Increased Mechanical Work of Myocardium**

For a given cardiac chamber, external work performed is roughly equal to the product of volume of blood ejected during systole and the mean pressure in the chamber during the same period (neglecting the kinetic energy imparted to the blood). This gives the approximate stroke-work for that chamber and applies to the atra as well as to the ventricles. Stroke-work times the heart rate per minute gives the minute-work. One of the most popular theories is that hypertrophy of a given chamber is due to an increase...
in its external mechanical work, but often it is not clearly stated whether the increased work is per stroke or per minute. The latter may occur simply as a result of increased heart rate (stroke-work being held constant). In support of the "work" hypothesis is the observation that hypertrophy is a common feature of conditions that increase either the pressure or outflow from one or more chambers of the heart. These include valvular lesions, such as stenosis or regurgitation, or cardiovascular defects such as shunts, or increased vascular resistance, or augmented cardiac output.

In healthy individuals or animals, repeated muscular activity increases the minute output of the right ventricle and the minute output and luminal pressure of the left ventricle for the duration of the exercise and for a variable period thereafter. These repeated bouts of increased work loads for both ventricles and atria are believed to constitute the stimuli for the so-called physiologic hypertrophy of the heart seen in athletes and in persons engaged in hard physical labor. According to Linzbach, such physiologic hypertrophy rarely exceeds a heart weight of 500 Gm., the fibers becoming thicker and longer with an increase in the number of sarcomeres. The hypertrophy is not excessive because the increased load is not continuous as in pathologic conditions. Also, it tends to regress if the exercise is discontinued.

One of the major difficulties of the "work" hypothesis is that often the degree of hypertrophy observed is not proportional to the calculated external mechanical work of the cardiac chamber. Indeed, there are some conditions that cause marked hypertrophy of the heart and yet external work is within normal limits. The explanation for this will be given in the next two sections. Another reason for the discrepancy between work and hypertrophy may be the fact that cardiac work is usually expressed per minute rather than per stroke. There are good reasons for believing that correlation would be better if stroke-work rather than minute-work was considered. We would like to emphasize this point in connection with the analysis of the data of earlier investigators.

Myocardial Dilatation (Increased Myocardial Tension during Systole)

In 1927 and 1928, Eyster and co-workers reported that, in dogs, aortic constriction that was released after 3 to 6 days led to cardiac hypertrophy comparable to that which followed sustained constriction. X-ray studies of the heart showed cardiac enlargement soon after the narrowing of the aorta. Eyster, therefore, postulated that cardiac dilatation that lasted 3 to 6 days was "injurious" to the myocardium and acted as a stimulus to hypertrophy even after the restoration of heart size. These experiments have been widely quoted but without attempts at confirmation until recently. In 1957, Kerr repeated these experiments using more critical methods of evaluating hypertrophy and found that if the aortic ligation was removed after 5 days, there was no evidence of cardiac hypertrophy after a sufficient period of time had elapsed. In contrast, if the aortic constriction was maintained for long periods (30 to 135 days), there was evidence of hypertrophy. Similar results have been reported by Beznák and Hajdu on white rats. In 1956, Stickney, Northup, and Van Liere reported that explosive decompression in white rats causes cardiac dilatation that may last 2 to 3 days, but none of the animals showed cardiac hypertrophy when sacrificed after 6 weeks. From these recent studies it may be concluded that the "acute dilatation-injury" hypothesis has little evidence in its support.

In contrast, chronic dilatation of any chamber of the heart leads to hypertrophy of that chamber. This observation has been well documented. Several authors have suggested that under these circumstances it is the increased tension in the wall of the cardiac chamber during systole that constitutes the effective stimulus. Tension in the wall of a distensible sphere or cylinder is given by the law of Laplace.

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For a sphere, \( T = \frac{Pr}{2} \); for a cylinder, \( T = Pr \). 

\( T \) is the force per unit length of the circumference and the entire thickness of the wall, \( P \) is the transmural pressure, and \( r \) is the radius of the sphere or cylinder. Accordingly, the larger the radius the greater must be the wall tension for a given transmural pressure. The importance of this relationship for the heart was pointed out by Woods, Bohnenkamp, Burch, Burton and others.

There exists a large group of myocardial diseases (some very poorly understood) that presumably change the "distensibility curve" or "diastolic tone" of the heart. These hearts are dilated in the absence of valvular lesions, or increased volume-pressure loads, or cardiovascular defects. For a given end-diastolic transmural pressure such hearts attain a volume greater than normal. In these cases the external work of the heart (or of a given chamber) is within normal limits. From the Laplace relationship it is obvious that dilated hearts must develop more than normal tension in their walls during contraction in order to maintain normal outflow and pressure. Diseases that seem to alter the distensibility curve of the myocardium include rheumatic myocarditis, diphtheria, cardiac beriberi, and degenerative diseases of the myocardium. However, a number of cases cannot be classified under any known etiologic factor and are classified as "idiopathic" dilatation, which is accompanied by marked hypertrophy of the heart. This has been described in children as familial cardiomegaly. It should not be confused with the cardiomegaly of glyco-gen-storage disease.

The contractile tension hypothesis also readily explains the hypertrophy that develops in a chamber when the resistance to the outflow of blood from that chamber is increased chronically. Increased resistance requires a greater pressure to maintain the flow. This necessitates a greater tension in the wall of the chamber during systole. Clinically, stenosis of cardiac valves, increased resistance of blood vessels due to narrowing or destruction of small vessels and chronic failure of the left ventricle with pulmonary hypertension are examples of such increased resistance. They constitute the most common causes of pathologic hypertrophy of the heart (concentric type).

Van Liere has produced myocardial hypertrophy in guinea pigs by exposing them to prolonged reduced barometric pressure (440 to 380 mm. Hg) which causes a low arterial \( pO_2 \). The hypertrophy may be explained on the basis of cardiac dilatation, which he has demonstrated and possibly an increase in volume-pressure load of the heart.

Finally, in some rare conditions that cause adhesions and anchorage of the epicardium to the adjacent structures (chronic mediastinopericarditis), the contractile tension of the myocardium might increase without invoking the law of Laplace. Here again, hypertrophy has been noted.

From the above discussion it is noted that increased tension in the contracting myocardium can offer a satisfactory explanation for a large number of experimental and clinical hypertrophies of the heart. As will be indicated below, the contractile tension hypothesis is closely linked with the concept of augmented myocardial energy expenditure, which the writer favors most. Unfortunately, this concept has not received the attention it deserves from pathologists and cardiologists.

**Increased Myocardial Metabolic Rate per Beat**

If the foregoing hypotheses are carefully analyzed one can note a common denominator. In all of them there seems to be an increase in the metabolic rate (as measured by the \( O_2 \) uptake) of the myocardium. However, it appears that the effective stimulus is an increase in the metabolic rate per heart beat rather than per unit of time (e.g., minute). This is based on the observation that although tachycardia increases the oxygen consumption of the heart per minute, yet clinically myocardial hypertrophy is uncommon in cases of sinus tachycardia uncomplicated by cardiovascular pathology. Under steady-state conditions it is justifiable to use
the oxygen consumption of a tissue as an index of its metabolic rate or energy expenditure. In this paper these terms are used interchangeably.

The origin of the view that stroke energy expenditure might be the stimulus to hypertrophy can be traced back to Weizsäcker,49,50 who proposed it in 1921. Unfortunately, it has failed to gain a foothold in the Anglo-Saxon literature. Grosse-Brockhoff51 has clearly stated this concept in his textbook. Reference to the same hypothesis has also been made by Schumann.52 Obviously, the increased energy expenditure per beat must be maintained for a sufficiently long period of time in order to induce hypertrophy. The time required would be expected to vary with the intensity of the stimulus and probably also the animal species. In dogs, Kerr53 reported that aortic constriction lasting 5 days was inadequate to induce hypertrophy of the heart. At least several weeks were required. Gerbode and Selzer54 showed that pulmonic or aortic stenosis in dogs can cause definite hypertrophy of the right or left ventricle within 3 weeks. It is reasonable to expect that different animals and man would require different lengths of time even if the intensity of the stimulus were the same.

The following working hypothesis may be proposed. Any condition, in health or disease, that increases the metabolic rate of a chamber of the heart per beat and is maintained for a sufficiently long period of time may lead to hypertrophy of the wall of that chamber. Initially, one would expect to find an increase in the stroke oxygen uptake per unit mass of heart tissue. As hypertrophy develops and progresses slowly, the total mass of contractile tissue is increased in that chamber of the heart. During this process the oxygen consumption per beat per unit mass of tissue of the hypertrophied myocardium gradually returns to the control value. At this stage, the stimulus to hypertrophy ceases to exist and there is no further hypertrophy. Now, the oxygen consumption per beat of the hypertrophied chamber is greater than normal simply on account of the increased mass of muscle tissue in that chamber. This point of view is based on the observations of Bing and his associates.54 They reported that in hypertensive subjects the oxygen consumption per minute per unit mass of hypertrophied left ventricle was within the range of normal values. Similar results were noted by West and co-workers55 in renal hypertensive dogs. Unfortunately, the data of Bing do not permit the calculation of myocardial oxygen uptake per stroke in normal and hypertensive subjects because heart rates were not reported. However, in dogs, the data of West55 indicate no difference in stroke oxygen consumption per unit mass of tissue between normal and hypertensive animals. On the other hand, apparently contradictory data were obtained by West and associates56 in studies of left ventricular hypertrophy following aortic insufficiency in dogs. In these animals, cardiac oxygen consumption per unit mass per minute was distinctly greater than that of control animals. However, the animals with aortic insufficiency exhibited a tachycardia and if one were to express the oxygen uptake of the left ventricle per gram of tissue per heart beat in the two groups of animals, the difference would disappear to a large extent.

If the foregoing hypothesis is accepted, it becomes important to know the factor or factors that determine the stroke oxygen consumption in a given chamber of the heart, both in health and in disease. Recent studies of Sarnoff and associates57 suggest that the tension in the myocardium during systole is of paramount importance. Sarnoff has expressed this in the form of tension-time index per beat. He noted, in the isolated supported heart, a very good correlation between stroke oxygen uptake and the tension-time index per beat. He also found that the latter is greater with rise of arterial pressure due to increase in peripheral resistance than with a proportional increase in stroke volume (pressure being held constant).

This index, for the first time, offered a clear explanation for the old observation
of Evans,58 later confirmed by Gollwitzer-Meier58 and others, that increase in cardiac output (heart rate and pressure constant) increased myocardial oxygen uptake only slightly (slope less than 45°), whereas increase of arterial resistance (rate and output constant) increased the oxygen uptake of the heart in proportion to the increase in mean arterial pressure (slope 45°). From these studies, it is clear that the stroke oxygen uptake of the heart does not necessarily vary with the stroke-work. Sarnoff57 demonstrated this in an experiment in which, with constant heart rate, the left ventricular minute work was progressively increased by augmenting cardiac output while the mean aortic pressure was reduced to a lesser extent by decreasing the arterial resistance. Whereas work increased by 128 per cent, myocardial oxygen uptake decreased by 20 per cent.

These physiologic studies may explain why hypertrophy would develop more readily in conditions that increase the pressure in a chamber of the heart during systole than in those that increase merely the volume of blood ejected. Examples of the former are stenosis of valves and increased resistance of peripheral vessels. When there is an increase in outflow from a cardiac chamber and the cavity pressure remains unchanged by a reduction in the resistance ahead, there is little hypertrophy. Examples of this are arteriovenous shunts and anemia. Furthermore, any increase in heart rate will have a significant effect in reducing the stroke volume (hence decrease the tension-time index per beat) and therefore tend to reduce the stroke energy expenditure and the severity of hypertrophy. This may partly explain why in anemias, hyperthyroidism, and arteriovenous shunts, where tachycardia is common, hypertrophy is not a very prominent finding.

The concept that increase in stroke metabolic rate of myocardium is the stimulus to hypertrophy receives additional support from observations on skeletal muscle. The well-known hypertrophy of somatic muscles in persons undergoing physical training and in athletes is best explained on the basis of increase in metabolic rate of active muscles. It has been pointed out60 that hypertrophy of skeletal muscles occurs when contractions are forceful with the development of great tension. This is best achieved by the so-called “resistive” exercises. According to Herxheimer,61 repeated exercises of speed or intense effort induce hypertrophy of skeletal muscles with little or no hypertrophy of the heart, whereas exercises of endurance cause hypertrophy of the heart but have little effect on the size of the skeletal muscles. Atrophy of muscles from disuse also fits in well with the concept of metabolic rate.

It should be pointed out that although hypertrophy is generally considered to be irreversible, this does not always hold, at least in the early stages. When the causative factor is removed, the weight of the heart may return to or toward normal62-65.

The important question as to how an increase in metabolic rate per stroke may bring about structural changes in heart muscle fibers remains unanswered. Conjectures to explain hypertrophy biochemically in terms of enzymatic processes and protein synthesis do not seem to be justified at the present state of our knowledge. Much work remains to be done at the cellular level before the metabolic processes involved will be understood.

**Summary**

Opinion is still divided concerning the fundamental nature of the stimulus to myocardial hypertrophy in various clinical and experimental conditions. Some of the current hypotheses, such as nutritional deficiency of the myocardium, excessive hormonal secretion, increased external work, myocardial dilatation, and increased myocardial energy expenditure were discussed, and an attempt was made to identify a unifying concept. The hypothesis that chronic increase in myocardial metabolic rate per beat per unit mass of tissue constitutes the stimulus was favored most on the grounds that it was more inclu-

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sive than any other in explaining hypertrophy. This view was far from proved, however, and deserves serious attention and experimental verification by future investigators in this field.

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Circulation. 1964;30:128-136
doi: 10.1161/01.CIR.30.1.128

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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