THE YEAR BOOK *of*
CARDIOVASCULAR MEDICINE *and* SURGERY
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The material covered in this volume represents literature reviewed up to January, 1973.

NORMAL AND ALTERED CARDIOVASCULAR FUNCTION

HYPERTROPHY

Protein Synthesis and Amino Acid Transport in Isolated Rabbit Right Ventricular Papillary Muscle: Effect of Isometric Tension Development. Enhancement of protein and nucleic acid synthesis has been regularly found in myocardial tissue undergoing active hypertrophy, but study of the hypertrophic process has been hindered by the lack of a naturally occurring experimental model. Myron B. Peterson and Michael Lesch[1] (Harvard Med. School), with the technical assistance of Alan G. Ferguson, used the isolated rabbit right ventricular papillary muscle preparation to examine the relation of mechanical stress to myocardial protein metabolism. Muscles from rabbits were mounted and stimulated electrically in Krebs bicarbonate buffer with hexose-free inulin. Amino acids labeled with ^{14}C were introduced. Both *l*-phenylalanine and *l*-leucine were used in the studies.

Amino acid incorporation was linear for 6 hours in resting muscles and was totally inhibited by 10^{-3}M cycloheximide and 10^{-3}M puromycin. Phenylalanine incorporation into total protein was unaltered by 90 minutes of isometric tension development at peak tension at stimulation rates of 30, 50 or 100 per minute. Significant increases were noted in muscles stimulated at 50 and 100 per minute for 3 hours. Electric stimulation without isometric tension development was not responsible for the effect. Passive stretch also appeared to stimulate incorporation, though to a lesser degree than active tension development. Specific activities of the intracellular phenylalanine pools were identical in control and stimulated muscles. Using α-aminoisobutyric acid, enhanced transport was noted in muscles stimulated isometrically at 30, 50 or 100 per minute at peak tension. The increased transport ratios could not be attributed solely to active tension development, since passive stretch resulted in comparable changes.

Mechanical factors appear capable of altering the transport

(1) Circulation Res. 31:317-327, September, 1972.

of certain amino acids, but it is not clear if these factors function as specific mediators of protein synthesis. Both passive stretch and tension development appear to be important in regulating myocardial protein synthesis.

► [It is clear that the heart hypertrophies when exposed to a sustained increase in mechanical activity. This adaptation allows cardiac muscle to meet the increased work demands placed upon it. The advantage of the technic described in this article is that the nature of the load on the cardiac tissue can be clearly defined. Supravalvular aortic or pulmonic constriction in vivo, the usual model for producing cardiac hypertrophy, imposes an undefined mechanical stress on the heart and precise mechanical loads cannot be imposed in vivo or in a perfused heart in vitro. The results indicate that both stretch and active tension development are operative in the stimulation of amino acid incorporation into myocardial protein and are consistent with evidence from other laboratories indicating that intracellular free amino acids play a role in the regulation of the rate of protein synthesis in cardiac cells. The results are also consistent with the postulation that the rate of myocardial protein synthesis is closely related to the intracellular free amino acid concentration.

The precise mechanism that stimulates the development of hypertrophy is not clear; however, an increase in the synthetic capacity of nuclei of messenger RNA has been reported as early as 1 hour after outflow tract obstruction. This is followed by the synthesis of ribosomal RNA. An increase in cardiac load produced by left ventricular outflow tract obstruction has increased ribosomal RNA and myosin synthesis within 4 hours. Polyamine (putrescine, spermidine and spermine) synthesis substantially increased several hours after the imposition of a cardiac load and the ratio of spermidine to spermine is decreased in rapidly growing cardiac tissue as opposed to other rapidly growing tissues. The specific role of the polyamines has not yet been clarified (Russell *et al.*: Am. J. Physiol. 221:1287, 1971).—E.B.]

Myosin Synthesis and Degradation during Development of Cardiac Hypertrophy in the Rabbit. Amino acid incorporation into myocardial proteins appears to be increased when the heart responds to an increase in work load by increasing its weight, but the effects on protein degradation are unclear. E. Morkin, S. Kimata and J. J. Skillman[2] (Boston) measured the synthesis and degradation of a single cardiac muscle protein, myosin, during the initial phase of the metabolic response to an increased work load. The incorporation of amino acid into myosin and total left ventricular proteins was measured by injecting lysine-^{3}H into 26 rabbits 2, 3, 4, 9 and 15 days after sham operation or banding of the ascending aorta to produce 65% occlusion. The rabbits were killed 4 hours later. In 32 rabbits, lysine was injected 24 hours preoperatively, and the animals were killed at 3, 5, 7, 10 and 16 days.

Left ventricular peak systolic pressure increased from 97 to

(2) Circulation Res. 30:690-702, June, 1972.

163 mm. Hg. The ratio of left ventricular weight to body weight increased about 16% after coarctation. The disappearance of free lysine-^{3}H was similar in rabbits with aortic stenosis and those having sham operations. After the 2d day, myosin synthesis was greater in rabbits with aortic coarctation than in normal rabbits, reaching a maximum increase of 117% on day 7. The synthesis of left ventricular total proteins reached a maximum of about 56% on day 10. The decrease in specific radioactivity of myosin was slower in rabbits with coarctation than in those with sham operations.

When the results were analyzed by a computerized simulation of myosin metabolism that allowed the rate constant for myosin degradation to be calculated on successive days after coarctation, the best fit to the observed changes in myosin content was obtained when degradation was increased with the increase in synthesis. When degradation was assumed to be unchanged from sham-operated animals or was decreased, myosin content was overestimated. Decay in the specific radioactivity of labeled myosin was affected extremely little even by a 100-fold decrease in degradation.

Myosin synthesis is increased after aortic coarctation. It is concluded that the increased myosin content found during the development of cardiac hypertrophy is primarily a consequence of increased synthesis.

► [An important related article is that of E. Page (Circulation Res. 30: 430, 1972). After producing ventricular hypertrophy by means of coarctation of the aorta, these workers observed that the myofibrillar fraction of cell volume increased, an increase that exceeded the corresponding decrease in mitochondrial volume; therefore, a part of the expansion of the myofibrillar fraction must take place at the expense of cell volume made up of sarcoplasm.—E.B.]

Ornithine Decarboxylase in Cardiac Hypertrophy in the Rat. The specific biochemical mechanism initiating cardiac hypertrophy remains unclear. Ornithine decarboxylase, which catalyzes the formation of putrescine, is a possible rate-limiting enzyme in the synthesis of polyamines, and its activity is increased markedly in several rapidly growing tissues. S. Matsushita, R. K. Sogani and M. S. Raben[3] (Tufts Univ.) determined ornithine decarboxylase activity in the hearts of male albino rats with constricted aortas and in those of sham-operated rats. The aorta was constricted just beyond the innominate artery. The rats were killed after 2-18 hours or 2-21 days.

(3) Circulation Res. 31:699-709, November, 1972.

EFFECT OF ACTINOMYCIN D ON CARDIAC ORNITHINE DECARBOXYLASE ACTIVITY (NM. CO_2/ML. 30 MINUTES^{-1})*

	Saline control	Actinomycin D (160 μg, −40 min)	(400 μg, −40 min)	(160 μg, −1.5 min)	(400 μg, −1.5 min)	(160 μg, +30 min)
Sham operation	1.16 ± 0.23 (4)	1.26 ± 0.04 (2)	1.64 ± 0.29 (8)	0.98 ± 0.12 (4)		
Aortic constriction	2.71 ± 0.56 (9)	0.88 ± 0.19 (9)†	0.88 ± 0.19 (5)†	1.70 ± 0.66 (4)	1.89 ± 0.21 (5)	2.60 ± 0.76 (5)
P	<0.05	NS	NS	NS		

* Actinomycin D, 160 or 400 μg., dissolved in saline was given intravenously 40 minutes before the operation (−40 min), 1.5 minutes before the end of the operation (−1.5 min) or 30 minutes after the operation (+30 min). All rats were killed 4 hours after operation. Number of rats tested is shown in parentheses. P values indicate significance of difference between hearts of rats with sham operations and those with aortic constriction. NS, not significant.

† $P < 0.05$ compared with saline controls having aortic constriction; no other values were significantly different from the appropriate control.

In the hearts of rats with constricted aortas, significantly increased ornithine decarboxylase activity was observed 2, 4, 6 and 8 hours and 3, 5 and 10 days after operation; except during the fall in enzyme activity at 18 hours, ornithine decarboxylase activity was elevated above the level in the sham-operated rats. Peaks of activity occurred at 4 hours and at 5-10 days. The increase was one of the earliest changes associated with cardiac hypertrophy. Changes in enzyme activity correlated well with the subsequent hypertrophy in the heart of rats with constricted aortas and with the regression in the hearts of sham-operated rats. The early rise in enzyme activity was inhibited by actinomycin D or 8-azaguanine given before operation. Actinomycin D given 30 minutes after operation or even at the time of aortic constriction failed to inhibit the rise in enzyme activity (table). Cycloheximide given an hour before death markedly decreased enzyme activity, and the estimated half-life of cardiac ornithine decarboxylase was comparable to that of the reported short-lived liver ornithine decarboxylase.

A quick, sensitive response of ornithine decarboxylase preceded cardiac hypertrophy or regression observed days later. The early changes in polyamine synthesis suggest an important role for these substances in the growing heart. If the polyamines are important in cardiac hypertrophy, the regulation of ornithine decarboxylase activity is of great interest. The findings indicate that RNA and protein synthesis are involved in the response to aortic constriction that results in a rapid, though modest, rise in the activity of ornithine decarboxylase in the rat.

► [One of the earliest events detectable in tissues that are preparing to grow is a marked elevation of polyamines. These are associated with elevation of ornithine decarboxylase activity. This enzyme catalyzes the decarboxylation of ornithine to form putrescine. Polyamines apparently can enhance RNA polymerase activity. Feldman and Russell (Am. J. Physiol. 222:1199, 1972) found that the activities of this enzyme and of S-adenosyl l-methionine decarboxylase increase in the left ventricle of the rat early after aortic constriction. Perhaps the increase in activity of these enzymes is one of the early key biochemical steps in the development of cardiac hypertrophy.—E.B.]

Biochemical Correlates of Cardiac Hypertrophy: V. Labeling of Collagen, Myosin and Nuclear DNA during Experimental Myocardial Hypertrophy in the Rat. John L. Skosey, Radovan Zak, Anne F. Martin, Vaclav Aschenbrenner and Murray Rabinowitz[4] (Univ. of Chicago) examined the significance of con-

(4) Circulation Res. 31:145-157, August, 1972.

nective tissue hyperplasia and increased collagen synthesis in development of cardiac hypertrophy.

METHOD.—In female Sprague-Dawley rats, the time course of enhancement of the synthetic activities of connective tissue and muscle cells of the heart was studied after constriction of the ascending aortas with silver bands. Connective tissue hyperplasia was measured by incorporating tritiated thymidine into purified nuclear DNA. Collagen biosynthesis was estimated by the incorporation of radioactive proline. The radioisotopes were given intraperitoneally at varying times after aortic constriction. The rats were killed at varying intervals after operation.

Heart weight increased sharply in the first 4 days after aortic banding and then rose slowly to a plateau. Free intracellular proline concentration was unchanged at 2 days but rose by 38% on the 5th postoperative day (table). Specific activity of free proline 3 hours after injection of proline-^{3}H was elevated by 40% on day 2 but was unchanged on day 5. Incorporation of labeled proline into collagen hydroxyproline rose to a sharp peak on day 2 in one study and on day 4 in another. The peak labeling of noncollagenous protein by proline-^{3}H was less than that of collagen.

Collagen labeling was maximum on either day 2 or day 4, depending on degree of hypertrophy. Labeling of myosin and noncollagenous protein reached a plateau on day 4. Incorporation of tritiated thymidine into nuclear DNA peaked on day 7.

Both muscle and connective tissue cells respond independently during cardiac hypertrophy with increased synthesis of specific proteins. Myocardial hypertrophy can be produced with or without increased collagen. Comparison of the mechanical

INTRACELLULAR FREE PROLINE CONCENTRATION AND SPECIFIC RADIOACTIVITY IN HYPERTROPHIED RAT MYOCARDIUM

	Extracellular space			Intracellular proline pool			
Operation	No. of rats	Hypertrophy (%)	^{35}S space (μliter/g w. wt.)	No. of rats	Hypertrophy (%)	Concentration (μmole/100 ml cell H_2O)	Specific radioactivity (dpm × 10^{-3}/μmole of proline
Sham, 2 days	8		247 ± 10	5		93.64 ± 4.05	258 ± 29
Banded, 2 days	8	29 ± 5	307 ± 19 ($P < 0.02$)	4	20 ± 4	95.93 ± 5.86 (NS)*	365 ± 19 ($P < 0.02$)
Sham, 5 days	10		270 ± 9	4		89.50 ± 5.49	395 ± 24
Banded, 5 days	8	41 ± 7	315 ± 13 ($P < 0.01$)	5	26 ± 8	124.14 ± 8.31 ($P < 0.02$)	327 ± 27 (NS)*

Intracellular proline was calculated on the basis of extracellular space values obtained in controls (sham operations). Per cent hypertrophy was calculated by comparison of ratios of heart weight to body weight of banded and control rats.
* $P > 0.05$.

properties of such preparations might help clarify the role of collagen in altering heart muscle function.

► [This article reminds us that in cardiac hypertrophy it is not only the myocardial cells but also the collagen and connective tissue that increase in mass.—E.B.]

Numerical Hyperplasia in Human Heart Hypertrophy. It is still not known whether the number of heart muscle cells is increased in hypertrophied human hearts or whether the enlargement is related only to that of single heart muscle fibers. The polyploidization that occurs in hypertrophic human hearts suggests that biochemical DNA determinations alone do not reflect cell numbers. W. Sandritter and C. P. Adler[5] (Freiburg, Germany) combined cytophotometric Feulgen DNA measurements with biochemical DNA determinations to calculate the number of heart muscle cells in human hearts obtained at autopsy within 24 hours after death. Heart muscle was sampled from 6 sites in both ventricles. The DNA determinations at 38 different sites of some hearts showed no significant differences in DNA amount or polyploidization pattern from those measured at the 6 chosen sites. Total DNA was determined by the diphenylamine reaction. The number of connective tissue cell nuclei was determined in slides from 38 areas of each heart. All these cells had a diploid DNA pattern.

Study of 6 hearts showed that, with increasing heart weight, the DNA content and amount of collagen increased. An increase of about 100% in the number of connective tissue cell nuclei was found in a 900-Gm. heart when compared with a 330-Gm. heart. Calculations were made of 2×10^9 heart muscle cell nuclei in normal hearts and an increase of up to 4×10^9 nuclei in maximally hypertrophied hearts. Only a few muscle fibers with double nuclei have been found in hypertrophied hearts. The authors therefore concluded that numerical hyperplasia of heart muscle cells occurs with hypertrophy and the weight increase in cardiac hypertrophy is a function of increase in volume, i.e., the dry mass, as well as a numerical increase in heart muscle cells.

► [The question whether in hypertrophy of muscle there is an increase in the number of cardiac cells, i.e., whether there is hyperplasia, or merely an enlargement of individual heart muscle fibers (hypertrophy) is an old chestnut. This interesting article presents strong evidence for an important role for hyperplasia. Interestingly, it would appear that hyperplasia occurs even with moderate increases in heart weight and does not

(5) Experientia 27:1435-1437, 1971.

require a doubling of heart weight as had previously been suspected.—E.B.]

Biochemical and Pharmacologic Studies

Activation of Phosphorylase by Cyclic AMP without Augmentation of Contractility in Perfused Guinea Pig Heart. Cyclic adenosine monophosphate (AMP) is a second messenger mediating several metabolic actions of catecholamines on heart muscle, but its role in mediating their positive inotropic effect has not been entirely clarified. It is believed that the failure of exogenous cyclic AMP to produce a positive inotropic effect is due to poor penetration or hydrolysis or both, in which case increased intracellular levels should augment myocardial contractility. John K. Kjekshus, Philip D. Henry and Burton E. Sobel[6] (Univ. of California, La Jolla) studied whether increased intracellular cyclic AMP, sufficient to activate phosphorylase but achieved without exogenous catecholamines, produces a positive inotropic effect. Guinea pig and rat hearts were perfused with cyclic AMP in solutions containing dimethylsulfoxide (DMSO) to facilitate transport into the cell. Myocardial phosphorylase *b* to *a* transformation was used as an index of increased intracellular cyclic AMP. Studies were done on guinea pig and rat hearts perfused with Krebs-Henseleit solution containing 10^{-5}–10^{-3}M cyclic AMP and related compounds. The isovolumic beating heart was assessed and myocardial phosphorylases, glucose-6-phosphate and glycogen were determined in perfused, empty, beating hearts. Hearts were perfused with or without 3% DMSO in the medium.

The DMSO did not significantly affect myocardial performance or mask increased contractility produced by epinephrine. Cyclic AMP, 10^{-4}M, with or without DMSO, depressed left ventricular pressure and dp/dt slightly, even when the heart rate was kept constant by pacing. Phosphorylase activation increased from 16.5 to 40% after perfusion with 10^{-4}M cyclic AMP with 3% DMSO. The DMSO alone increased phosphorylase much less. Phosphorylase was not activated by 5′-AMP with DMSO, compared with DMSO alone.

Increased intracellular cyclic AMP, achieved in the absence of adrenergic stimulation, does not increase myocardial contractility. The positive inotropic effect produced by catechol-

(6) Circulation Res. 29:468-478, November, 1971.

amines is not mediated by a direct action of cyclic AMP on the contractile apparatus. The findings do not exclude the possibility that the positive inotropic effect of catecholamines may depend on augmentation of a localized, partitioned intracellular pool of cyclic AMP unaffected in this investigation.

► [According to prevailing views, the positive inotropic effect of catecholamines is mediated by cyclic AMP acting through an as yet undefined pathway; the failure of exogenous cyclic AMP to produce a positive inotropic effect has been taken to be due to poor penetration or hydrolysis or both. The extent of phosphorylase transformation during cyclic AMP infusion in the presence of DMSO suggests that augmented intracellular cyclic AMP does not exert a positive inotropic effect. The findings of this study are consistent with the hypothesis that catecholamine activation of adenyl cyclase results in conversion of membrane-bound ATP to cyclic AMP, that calcium is released from the Ca^{++} membrane ATP complex and that catecholamine effects on contractility may depend on increased calcium released by this mechanism rather than on the direct effect of cyclic AMP itself. However, the extremely interesting study of D. H. Mann *et al.* (Circulation Res. 31:308, 1972) must also be considered in this regard. These investigators observed that cyclic AMP does not influence the rate or extent of the phosphorylation of the sarcoplasmic reticulum, suggesting that the cardiac sarcoplasmic reticulum is not the site of action of cyclic AMP in its role as a mediator of cardiac inotropic effects. B. G. Benfey (Brit. J. Pharmacol. 43:757, 1971) found that two sympathomimetic amines, dopamine and phenylephrine, that increase the contractility of the isolated heart do not increase cyclic AMP concentrations in rabbit heart slices, findings that also suggest that cyclic AMP does not play an essential role in the inotropic effect of sympathomimetic amines.—E.B.]

Inotropic Agents in Hypoxic Cat Myocardium: Depression and Potentiation. Kenneth M. Kent, Theodore L. Goodfriend, Zena T. McCallum, Peter J. Dempsey and Theodore Cooper[7] studied responses to inotropic agents in isolated cat papillary muscles to circumvent the profound reflex changes in ventricular performance induced by hypoxia. A level of hypoxia was used that produced reversible reductions in contractile force but not rapid deterioration of the preparations. Right ventricular papillary muscles from adult male cats were mounted in modified Krebs-Ringer's solution equilibrated at 25 C. with 95% oxygen and 5% carbon dioxide for control studies; hypoxia was induced with a mixture of 5% oxygen, 5% carbon dioxide and 90% nitrogen.

Hypoxia produced a 32% decrease in tension in normal papillary muscle and a 14% decrease in catecholamine-depleted papillary muscles. The maximum responses to ouabain (Fig. 1) and norepinephrine were depressed during hypoxia. Deteriora-

(7) Circulation Res. 30:196-204, February, 1972.

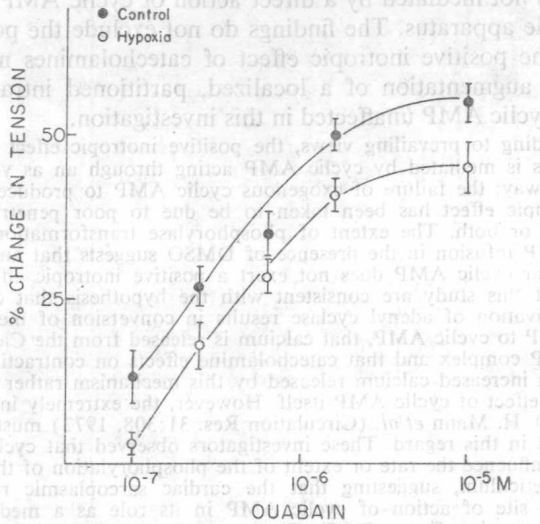

Fig. 1.—Dose-response curves for ouabain under control and hypoxic conditions. Responses to concentrations above 2×10^{-6}M are different ($P < 0.005$). Isometric force before drug addition: control 4.1 ± 0.9 Gm/sq. mm., hypoxia 2.7 ± 0.5 Gm/sq. mm. (Courtesy of Kent, K. M., *et al.*: Circulation Res. 30:196-204, February, 1972; by permission of The American Heart Association, Inc.)

tion of the developed tension of muscle preparations occurred at concentrations of norepinephrine 5×10^{-7}M and greater. The dose-response curve for angiotensin II was unchanged by hypoxia, but the curves for two heptapeptide analogues, 1-des-5-Val-angiotensin II and 1-des-5-Ile-angiotensin II, were higher during the hypoxia than under control conditions. The inotropic effects of the analogues under control and hypoxic conditions were the same in normal and catecholamine-depleted muscles.

The potentiation by hypoxia of the inotropic effects of angiotensin II analogues is unique among the agents studied. These analogues exert the greatest inotropic effect under hypoxic conditions. This peculiar inotropism may be related to the ability of these substances to stimulate mitochondrial-oxidative metabolism selectively under hypoxic conditions.

► [Inotropic agents are often required clinically for treating the hypoxic or ischemic heart, and for this reason the present study has considerable practical significance. The same group of investigators also studied this problem in intact hearts (J. Clin. Invest. 51:2459, 1972). Norepinephrine and isoproterenol dose response curves were shifted to the left. The mechanism responsible for this effect was not clear but perhaps