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CATECHOLAMINES AND ADRENERGIC MECHANISMS. DO THEY MEDIATE CERTAIN CONSEQUENCES OF ISCHEMIC HEART DISEASE?

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This review will evaluate a potential role for catecholamines and adrenergic mechanisms in mediating certain consequences of ischemic heart disease. In particular, it will assess whether alterations in catecholamines may contribute to cellular damage, alter metabolic responses, and/or contribute to the development of arrhythmias with acute and chronic ischemic heart disease.

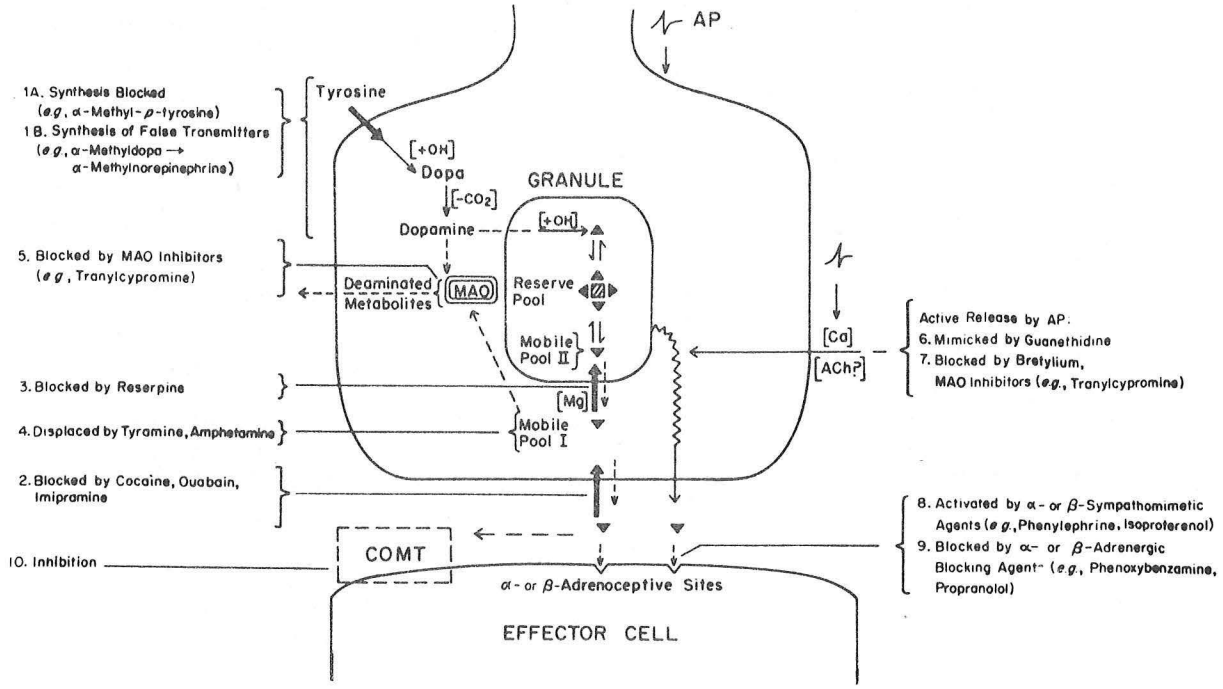
PHYSIOLOGICAL EFFECTS OF CATECHOLAMINES

Physiological effects produced by sympathetic amines resemble the responses produced by stimulation of adrenergic nerves. In general, the action of sympathomimetic agents may be classified into five broad types: (1) a peripheral excitatory action on certain types of smooth muscle, including blood vessels supplying the skin and mucous membranes as well as on salivary and certain sweat glands; (2) a peripheral inhibitory action on certain other types of smooth muscle including those in the wall of the gut, in the bronchial tree and in blood vessels supplying the skeletal muscle; (3) a cardiac excitatory action responsible for an increase in heart rate and force of contraction in cardiac muscle; (4) metabolic actions such as an increase in the rate of glycogenolysis in liver and muscle and the release of free fatty acids from adipose tissue; and (5) central nervous system excitatory actions including respiratory stimulation (1).

A. Alpha and Beta Adrenergic Receptors

Alpha and beta adrenergic agonists exert their physiologic effects after binding to specific receptors located in the cell membrane or sarcolemma (Fig. 1).

FIGURE 1



Proposed sites of action of drugs that modify synthesis, uptake, release and actions of norepinephrine at nerve terminals. Taken from Reference 1, page 425.

Ahlquist classified adrenergic receptors as alpha and beta on the basis of their responses to a series of sympathomimetic amines (2). Lefkowitz, Williams and others have elucidated factors that regulate adrenergic receptor density and binding in cardiac membranes (3-6). The concept of alpha and beta adrenergic agonists and receptors has simplified the classification of both stimulating and blocking agents.

In general, the effect of stimulating alpha receptors in smooth muscle is excitatory and that of stimulating beta receptors is inhibitory, that is, stimulation of alpha receptors causes constriction, whereas stimulation of beta receptors causes relaxation or dilatation of arterial smooth muscle. Stimulation of beta adrenergic receptors results in stimulation of various secretions including the release of insulin. Stimulation of beta adrenergic receptors causes increases in heart rate and myocardial contractility, whereas stimulation of alpha receptors causes an increase in coronary vascular resistance and a decrease in coronary blood flow with smaller (or no) increases in myocardial contractility.

Sympathetic effector cells may have alpha or beta receptors or both. The smooth muscle of blood vessels supplying skeletal muscle has both beta and alpha receptors. The activation of beta receptors by low concentrations of epinephrine causes vasodilatation, whereas stimulation of alpha receptors causes constriction of these vessels. When both receptors are stimulated, the response to alpha receptors predominates (1).

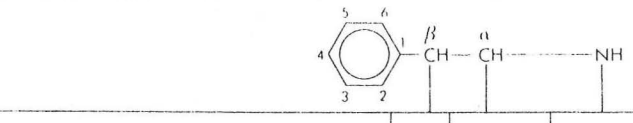
The response to sympathomimetic agents may be predicted on the basis of a knowledge of their selectivity in reacting with alpha or beta receptors. Isoproterenol, which acts on beta receptors and has little or no action on alpha receptors increases heart rate and the strength and rate of myocardial contraction, dilates vascular beds in skeletal muscle, and relaxes bronchial muscle. Phenylephrine, which acts on alpha receptors, but has little effect on beta receptors has little direct cardiac effect or may slightly increase myocardial contractility, increases coronary vascular resistance, decreases coronary blood flow, increase systemic arterial pressure by contracting peripheral vascular beds, and does not relax bronchial muscle.

Beta receptors in different organs have been classified as being of two subtypes: (1) β_1 in heart and small intestine, and β_2 in bronchi, vascular beds and uterus (7). There are non-selective beta adrenergic blocking agents (propranolol) and specific blocking agents for β_1 receptors, such as the β_1 antagonist, metoprolol.

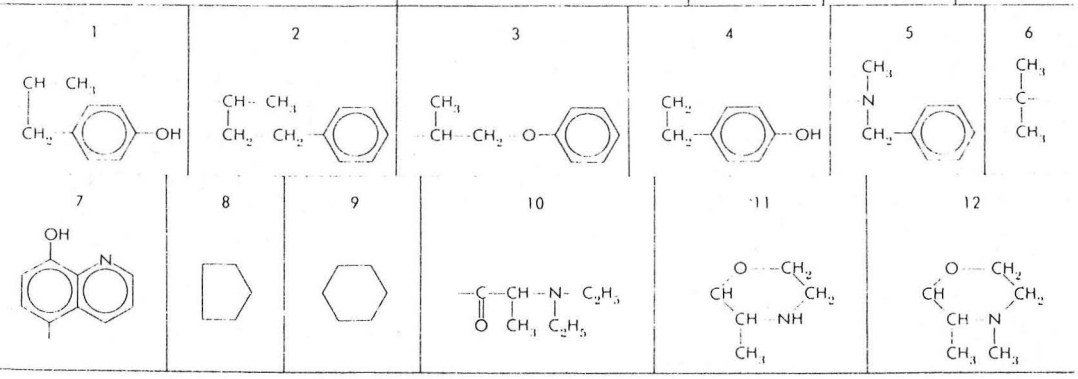
The above description of adrenergic receptors and the physiological effects of stimulation and antagonism of these receptors presents the simplest case for clarity. However, it should be recognized that all responses to adrenergic agents are not classified simply. In particular, the relative potencies of norepinephrine, epinephrine, and isoproterenol in causing hyperglycemia in man follow the alpha receptor pattern. In addition, the effects of alpha and beta adrenergic antagonists are complex. A summary of the structure, receptors utilized, and physiological effect of various alpha and beta adrenergic agonists in shown in Table 1.

TABLE 1

CHEMICAL STRUCTURES AND MAIN CLINICAL USES OF IMPORTANT SYMPATHOMIMETIC DRUGS †



					MAIN CLINICAL USES		
					α *Receptor* A N P V	β *Receptor* B C M	*CNS,0*
Phenylethylamine		H	H	H			
Epinephrine	3-OH,4-OH	OH	H	CH_3	A, P,V	B,C	
Norepinephrine	3-OH,4-OH	OH	H	H	P		
Dopamine	3-OH,4-OH	H	H	H	P		
Nordefrin	3-OH,4-OH	OH	CH_3	H	V		
Isoproterenol	3-OH,4-OH	OH	H	$CH(CH_3)_2$		B,C	
Isoetharine	3-OH,4-OH	OH	CH_2CH_3	$CH(CH_3)_2$		B	
Metaproterenol	3-OH,5-OH	OH	H	$CH(CH_3)_2$		B	
Terbutaline	3-OH,5-OH	OH	H	$C(CH_3)_3$		B	
Fenoterol	3-OH,5-OH	OH	H	1 *		B	
Metaraminol	3-OH	OH	CH_3	H	P		
Phenylephrine	3-OH	OH	H	CH_3	N,P		
Tyramine	4-OH	H	H	H			
Hydroxyamphetamine	4-OH	H	CH_3	H	N,P	C	
Nylidrin	4-OH	OH	CH_3	2 *		M	
Isoxsuprine	4-OH	OH	CH_3	3 *		M	
Ritodrine	4-OH	OH	CH_3	4 *		B	
Methoxyphenamine	$2\text{-}OCH_3$	H	CH_3	CH_3		B	
Methoxamine	$2\text{-}OCH_3,5\text{-}OCH_3$	OH	CH_3	H	P		
Salbutamol	$3\text{-}CH_2OH,4\text{-}OH$	OH	H	$C(CH_3)_3$		B	
Soterenol	$3\text{-}NHSO_2CH_3,4\text{-}OH$	OH	H	$CH(CH_3)_2$		B	
Amphetamine		H	CH_3	H			CNS,0
Methamphetamine		H	CH_3	CH_3	P		CNS,0
Benzphetamine		H	CH_3	5 *			0
Ephedrine		OH	CH_3	CH_3	N,P	B,C	
Phenylpropanolamine		OH	CH_3	H	N		
Mephentermine		H	6 *	CH_3	N,P		
Phentermine		H	6 *	H			0
Chlorphentermine	4-Cl	H	6 *	H			0
Fenfluramine	$3\text{-}CF_3$	H	CH_3	C_2H_5			0
Quinterenol	7 *	OH	H	$CH(CH_3)_2$		B	
Tuaminoheptane	$CH_3(CH_2)_3$	H	CH_3	H	N		
Cyclopentamine	8 *	H	CH_3	CH_3	N		
Propylhexedrine	9 *	H	CH_3	CH_3	N		
Diethylpropion		10 *					0
Phenmetrazine		11 *					0
Phendimetrazine		12 *					0



α Activity
A = Allergic reactions
N = Nasal decongestion
P = Pressor (may include β action)
V = Other local vasoconstriction (*e.g.*, in local anesthesia)

β Activity
B = Bronchodilator
C = Cardiac
M = Muscle vessel dilatation

CNS = Central nervous system
0 = Anorectic

* Numbers bearing an asterisk refer to the substituents numbered in the bottom rows of the table; substituents 7, 8, and 9 replace the phenyl ring, and 10, 11, and 12 are attached directly to the phenyl ring, replacing the ethylamine side chain.

† The α and β in the prototype formula refer to positions of the C atoms in the ethylamine side chain.

Taken from Reference 1.

B. Reflex Effects

Compensatory reflexes may play a significant role in determining cardiovascular responses to sympathetic amines. Several sympathetic amines cause a rise in arterial blood pressure due to stimulation of alpha receptors in vascular beds. This action elicits compensatory reflexes through the aortic carotid-aortic baroreceptor system resulting in a diminution of overall sympathetic tone that lessens the effect of the sympathetic amines and is accompanied by an increase in vagal tone thus slowing the heart rate (1). This type of compensatory mechanism is of importance for sympathetic amines having relatively small beta adrenergic stimulatory capability and therefore little direct effect to increase cardiac contractility. A relevant clinical example is the use of an alpha adrenergic agonist to raise blood pressure to treat supraventricular tachycardia, since increases in blood pressure reflexly reduce sympathetic cardioaccelerator tone and increase parasympathetic cardiodecelerator tone which may terminate tachycardia. Reflexes also influence the cardiac responses to norepinephrine. Norepinephrine raises the blood pressure, but causes concomitant increases in vagal activity, the net effect of which is to maintain heart rate at the same level or actually slow it. In contrast, epinephrine administration dilates blood vessels maintaining a lower diastolic blood pressure and thus is associated with less vagal tone. Consequently, epinephrine causes a tachycardia. Drugs that stimulate beta adrenergic receptors dilate blood vessels supplying skeletal muscle and lower mean arterial pressure; the compensatory reflex increase in sympathetic tone constricts other vascular beds and along with reduced vagal tone, augments the rate and force of cardiac contraction (1). This effect returns blood pressure toward its original level.

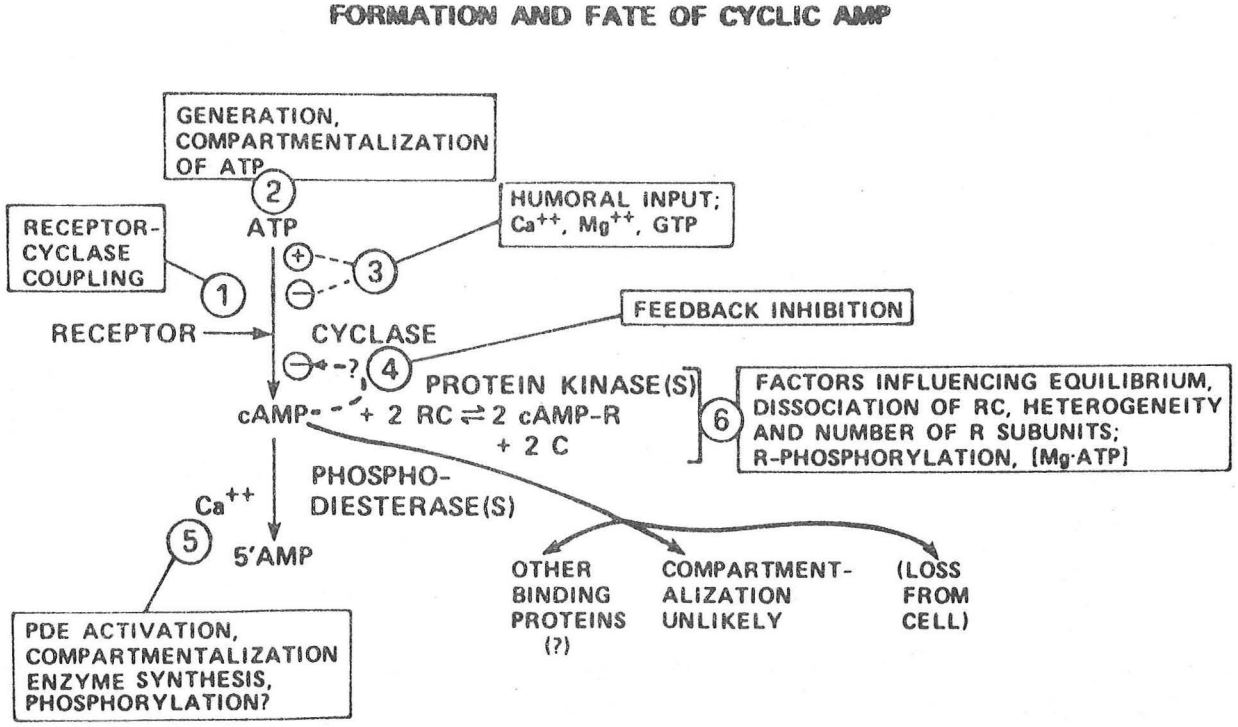
C. Cellular Biochemical Events

The specific effects of catecholamines on myocardial contractile state are complex and involve simultaneous changes in a number of parameters. In isolated cardiac muscle contracting isometrically, catecholamines increase the rate of development of both tension and relaxation; they also increase maximal contractile tension while decreasing time to peak tension and duration of contraction (8). Under conditions of isotonic contractions, there is an increase in both the magnitude and rate of shortening, while the duration of contraction is decreased (8). These effects of catecholamines are related to stimulation of beta adrenergic receptors and they may be blocked by beta adrenergic antagonists including propranolol. It has been suggested that the cyclic AMP is the primary second messenger for mediating the inotropic effects of beta adrenergic stimulation (9) (Fig. 2).

Studies done previously have demonstrated that stimulation of myocardial beta adrenergic receptors stimulates adenylate cyclase; in some circumstances, maximal stimulation of adenylate cyclase by catecholamines is increased by the presence of cyclic GTP (9). Adenylate cyclase and beta adrenergic receptors in the heart are localized in the cell membrane or sarcolemma (3-6,9).

The stimulation of myocardial cells by catecholamines following binding to specific adrenergic receptors results in increased cyclic AMP (9). This effect precedes or is coincident with the positive inotropic response to beta adrenergic receptors (9). The change in mechanical performance also is associated with a change in the action potential, including an elevation of the plateau phase indicating an augmentation of the slow inward current carried mainly by

FIGURE 2



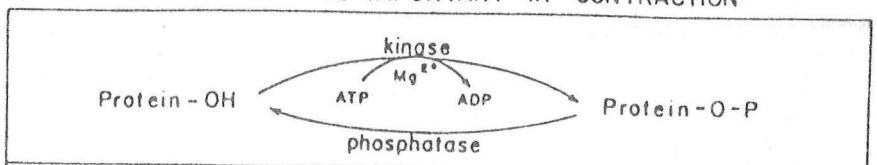
Taken from Reference 9.

calcium (9). This calcium current appears to be closely related to an increase in contractile state and may represent an action of cyclic AMP (9). Intracellular iontophoretic application of cyclic AMP mimicks the extracellular application of epinephrine (11). The effects of catecholamines on pacemaker potentials and their conduction in Purkinje fibers has been reproduced by intracellular administration of cyclic AMP (11,12). These data provide some of the more convincing evidence that cyclic AMP may be the mediator of the effect of adrenergic stimulation on myocardial contraction and responsible for the initiation and conduction of the slow channel activated portions of the action potential.

It also is apparent that certain cellular processes may be regulated by the phosphorylation of specific regulatory proteins (9). These phosphorylation reactions are catalyzed by a group of enzymes referred to as protein kinases. Cyclic AMP dependent protein kinase has been found in essentially every animal tissue examined thus far (9). The specific role for phosphorylation of cardiac muscle components in altering contractile responses is under study presently, but some of the possible cellular effects are shown in Fig. 3.

FIGURE 3

PHOSPHORYLATION OF CARDIAC MUSCLE COMPONENTS THAT MAY BE IMPORTANT IN CONTRACTION



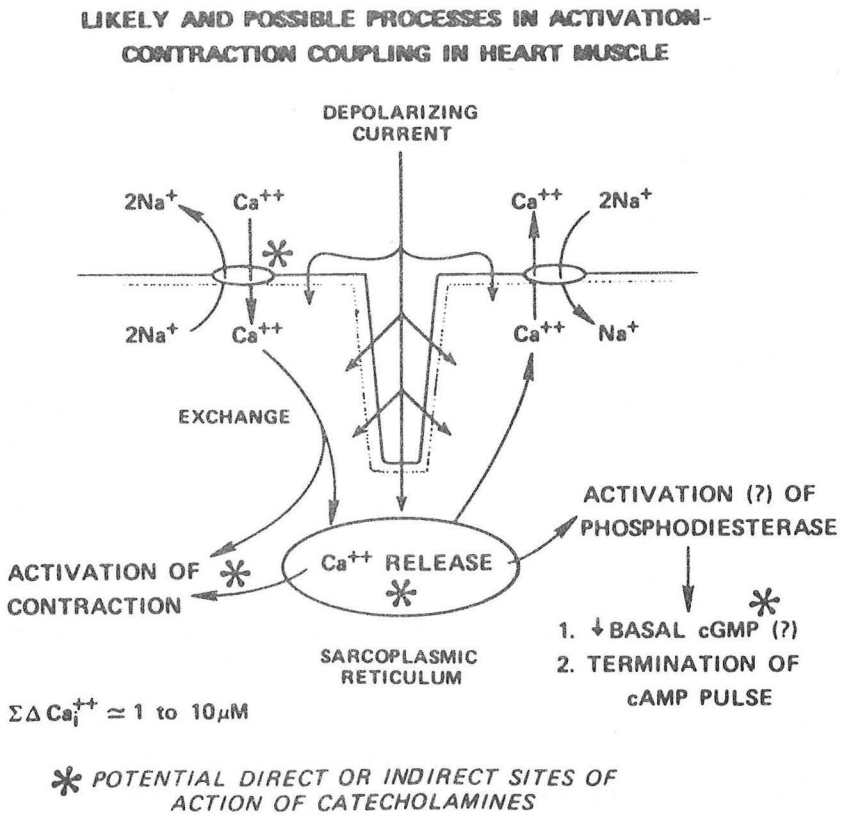
SARCOLEMMA	cAMP-Dependent Protein Kinase	↑Ca^{2+} Flux ?
SARCOPLASMIC RETICULUM	cAMP-Dependent Protein Kinase	↑Ca^{2+} Uptake
MYOSIN	Myosin Light Chain Kinase	↑ Myosin ATPase Activity ?
TROPONIN	cAMP-Dependent Protein Kinase	Ca^{2+} Sensitivity of Actomyosin ATPase?

Components of cardiac muscle that may be phosphorylated and thereby alter the inotropic state. Note that not all of these phosphorylations are cyclic AMP dependent, i.e., the myosin light-chain kinase.

Taken from Reference 9.

Calcium itself plays a central role in regulating the contractile activity of cardiac muscle (Fig. 4). As the action potential develops across the cell membrane, calcium enters from the outside and may be released from the terminal cisternae of the sarcoplasmic reticulum. Calcium then diffuses through the sarcoplasm and binds to troponin on the thin filaments of the contractile protein **(8,9)**. The consequence is augmentation of the interaction between the contractile proteins actin and myosin. Calcium is removed from the myofibrils and accumulates in the sarcoplasmic reticulum. Thus, an increase in the intracellular concentration of calcium stimulates contraction; removal of calcium from the myofilaments by uptake processes in specific membranes leads to relaxation. Both the sarcolemma and the sarcoplasmic reticulum of the cardiac cell appear to play an important role in regulating calcium availability to myofilaments. As reviewed previously, one effect of catecholamine stimulation is to alter the transmembrane calcium flux **(9)**. Catecholamines may influence calcium uptake and release in the sarcoplasmic reticulum as well.

FIGURE 4



Taken from Reference 9, page 755.

D. Cellular Electrophysiologic Responses

In general, catecholamines with beta adrenergic stimulating properties increase heart rate and some (in particular, isoproterenol) increase ventricular ectopic activity. A summary of the cellular electrophysiologic effects of catecholamines as suggested by Noble include the following (12):

1. The inward cellular calcium current is increased substantially . This effect is responsible for producing the increased height of the action potential, probably for the positive inotropic action, and for the increased pacemaker rate in sino-atrial and atrial tissue.

2. The activation curve in Purkinje fibers is shifted in a depolarizing direction. This effect is responsible for the acceleration of pacemaker activity in Purkinje fibers.

3. The potassium current is increased in amplitude and in some cases, its activation threshold is reduced. This effect is responsible for shortening the action potential and in sino-atrial and atrial tissue, for increasing the maximum negative potential in diastole.

4. The activity of the sodium, potassium exchange pump is increased. This effect may be responsible for the increased maximum negative potential in diastole in Purkinje fibers.

Maling and Moran have demonstrated that epinephrine and norepinephrine, in doses which cause little ectopic activity in unanesthetized, normal dogs, produces exaggerated ectopic responses about the fourth day after coronary ligation, when the arrhythmias caused by coronary ligation may have subsided (13). Further, observations with methoxamine, isoproterenol, and atropine indicate that ventricular tachycardia is induced easily after coronary artery occlusion in dogs by drugs which simultaneously increase the contractile state of the myocardium and slow the sinus node rate (9).

E. Cellular Toxicity from Catecholamines

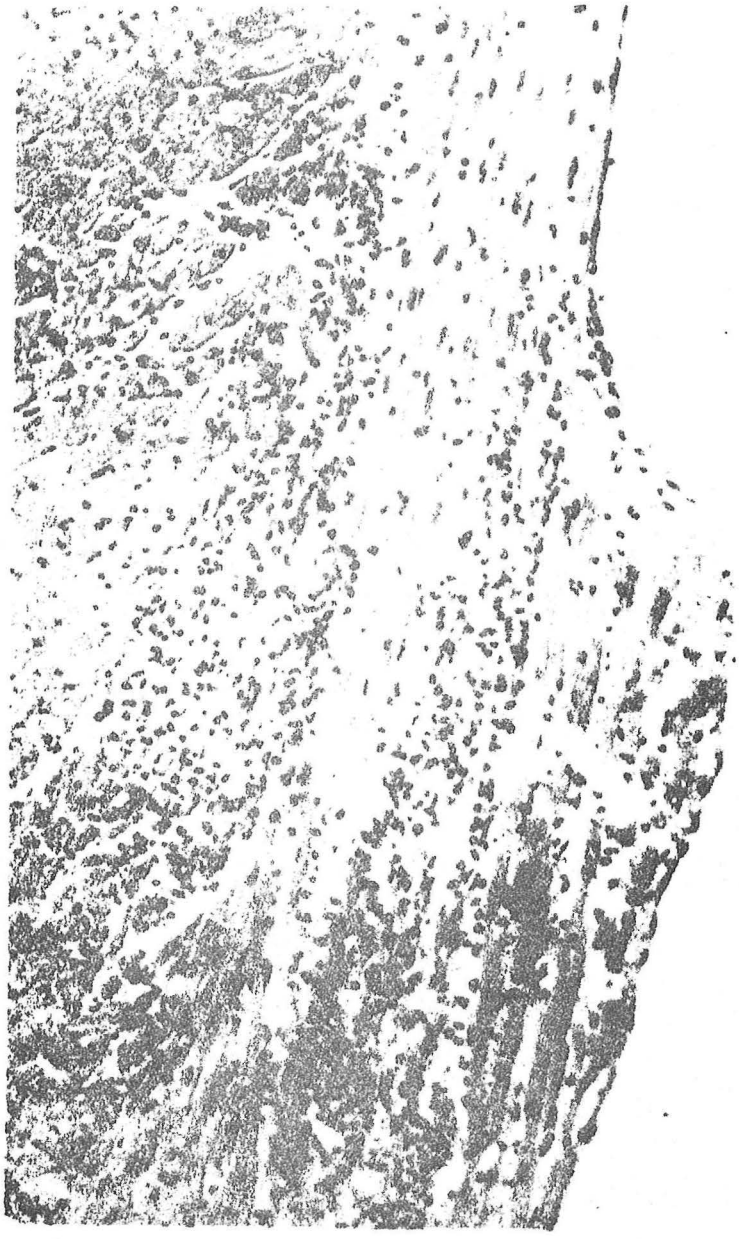
Excess catecholamines may result in an influx of calcium, the depletion of high energy phosphates, and the development of important pathological necrosis (Fig. 5). Rats given large doses of sympathetic amines systemically, particularly isoproterenol, develop myocardial necrosis (14-18). Slow-channel calcium antagonists including verapamil, D600, and prenylamine are capable of protecting the rat heart against structural damage if given in appropriate dosage at the same time as excess isoproterenol is administered (19,20). Thus, it appears that a crucial factor in the development of myocardial lesions is the development of an intracellular calcium overload induced by isoproterenol; perhaps, the calcium overload is related in part to high energy phosphate depletion (ATP and CP depletion) and consequent alterations in sarcolemmal membrane permeability allowing increased Ca^{++} influx. The high energy phosphate depletion associated with the administration of excess catecholamines and consequent myocardial necrosis is similar to the high energy phosphate depletion, altered sarcolemmal permeability to calcium, and intracellular calcium overload that occurs with ischemia or severe hypoxia (21,22). Calcium antagonists prevent the reduction in intracellular high energy phosphate concentration and cellular necrosis associated with the administration of excess isoproterenol (Fig. 5).

It also has been suggested that catecholamines may be oxidized to form "free radicals" and that the free radicals may cause some of the direct cellular toxicity and necrosis previously attributed to catecholamines.

ANATOMY OF THE ADRENERGIC NEURONAL SYSTEM AND STORAGE MECHANISMS

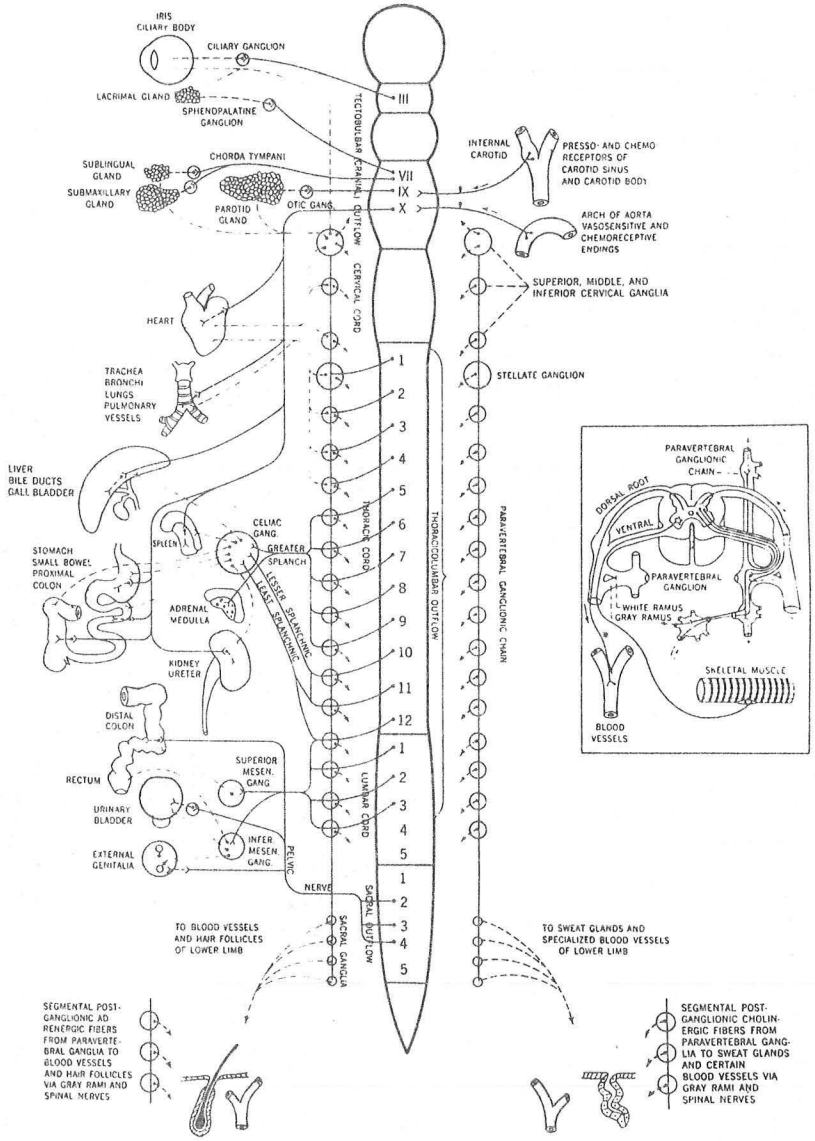
The anatomical aspects of the peripheral autonomic nervous system are presented schematically in Fig. 6. The neurohumoral transmitter for all preganglionic autonomic fibers, all postganglionic parasympathetic fibers, and a few postganglionic sympathetic fibers is acetylcholine. Adrenergic fibers, comprise the majority of the postganglionic sympathetic fibers; the transmitter for these fibers is norepinephrine. The neurotransmitter for primary afferent fibers has not been identified conclusively (23). The terms cholinergic and adrenergic are used to describe neurons that liberate acetylcholine and norepinephrine, respectively. The terms cholinoceptive and adrenoceptive describe postjunctional sites that are acted upon by the respective transmitters (23).

FIGURE 5



Myocardial necrosis in the left ventricular wall of a rat 24 hours after subcutaneous administration of isoproterenol (30 mg/kg). Taken from Harris P, and Opie LH: Calcium and the Heart, Academic Press, London, 1971, p. 162.

FIGURE 6



A schematic representation of the anatomy of the autonomic nervous system. Taken from Reference 1, page 406.

The cells that give rise to preganglionic fibers within the sympathetic nervous system lie mainly in the intermediolateral columns of the spinal cord and extend from the eighth cervical to the second or third lumbar segment. The axons from these cells are carried in the anterior nerve roots and synapse with neurons lying in sympathetic ganglia outside the cerebrospinal axis. The sympathetic ganglia comprise three group -- vertebral, prevertebral, and terminal.

The vertebral sympathetic ganglia consist of 22 pairs that lie on either side of the vertebral column to form the lateral chains. The ganglia are connected to each other by nerve trunks and to the spinal nerve by rami communicantes (23). The white rami are restricted to the segments of the thoracolumbar outflow; they carry the preganglionic myelinated fibers that issue from the spinal cord by way of the anterior spinal roots (23). The gray rami arise from the ganglia and carry postganglionic fibers back to the spinal nerves for distribution to various glands and blood vessels. The prevertebral ganglia lie in the abdomen and the pelvis near the ventral surface of the bony vertebral column and consist mainly of the celiac, superior mesenteric, aorticorenal, and inferior mesenteric ganglia. The terminal ganglia lie near the organs that they innervate and consist especially of those connected with the urinary bladder and rectum. In addition to the above described ganglionic system, there are small intermediate ganglia, especially in the thoracolumbar region, that lie outside the conventional vertebral chain. They vary in number and location, but are usually in close proximity to communicating rami and the anterior spinal nerve roots.

Postganglionic fibers issuing from the sympathetic ganglia reach visceral structures of the thorax, abdomen, head, and neck. Many of the upper thoracic sympathetic fibers from the vertebral ganglia form terminal plexuses, such as the cardiac, esophageal, and pulmonary. Preganglionic fibers emanating from the spinal cord may synapse with the neurons of more than one sympathetic ganglia (23).

The sympathetic system is distributed to effectors throughout the body and sympathetic fibers ramify to a great extent. A preganglionic sympathetic fiber may traverse a considerable distance of the sympathetic chain and pass through several ganglia before it finally synapses with the postganglionic neurons; also its terminals make contact with a large number of postganglionic neurons (23). In some ganglia, the ratio of preganglionic axons to ganglion cells may be 1:20 or more allowing a diffuse discharge of the sympathetic system (23).

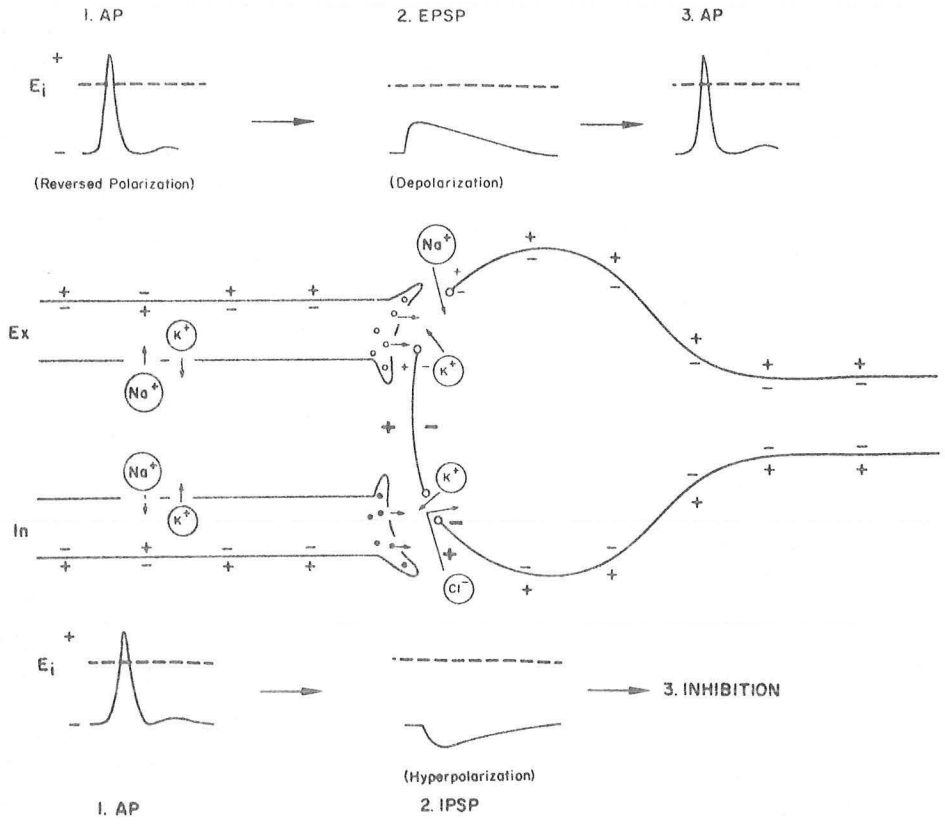
The neurohumoral transmitters are probably synthesized in the region of the axonal terminals and stored there within the synaptic vesicles, either in highly concentrated ionic form (as for acetylcholine) or as a readily dissociable complex or salt, as in the case of norepinephrine with adenosine triphosphate (ATP) and a specific protein (23). During the resting state, there is a continual slow release of isolated quanta of the transmitter ordinarily insufficient to cause initiation of a propagated impulse at the postjunctional site. The action potential causes the synchronous release of several hundred quanta. Depolarization of the axonal terminal triggers this process. One step in the process is the mobilization of calcium ion, which enters the intra-axonal medium and is believed to promote fusion of the vesicular and axoplasmic membranes (23). The contents of the vesicles are then discharged to the exterior by exocytosis (23). The transmitter diffuses across the synaptic or junctional cleft, a distance of 100 to 500 A, and combines with specialized molecular receptors on the postjunctional membrane;

this results in a localized, nonpropagated increase in the ionic permeability, or conductance, of the membrane. With certain exceptions, either of two types of permeability change can occur: (1) a generalized increase in permeability to all types of ions resulting in a localized depolarization of the membrane, i.e., an excitatory postsynaptic potential; or (2) a selective increase in permeability to only the smaller ions, i.e., potassium chloride, resulting in stabilization or actual hyperpolarization of the membrane, which constitutes an inhibitory postsynaptic potential (23). The neuronal alterations resulting in neurohumoral transmission are shown in Fig. 7.

SYNTHESIS, STORAGE AND RELEASE OF CATECHOLAMINES

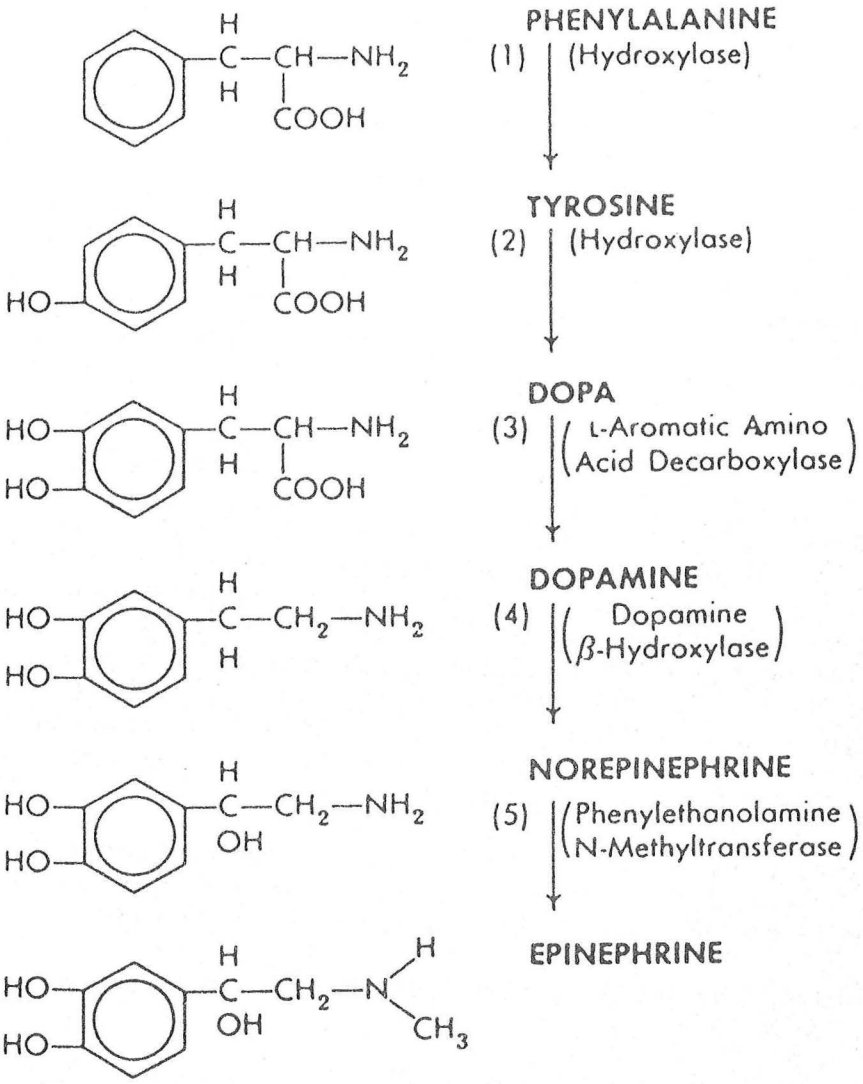
Epinephrine and norepinephrine are synthesized from phenylalanine Fig. 8.

FIGURE 7



Taken from Reference 1, page 414.

FIGURE 8



Taken from Reference 1, page 423.

Nearly all the norepinephrine content is confined to postganglionic sympathetic fibers. Epinephrine is localized in chromaffin cells. The main features of the mechanisms of synthesis, storage, and release of catecholamines and their modification by drugs are summarized in Fig. 1. Osmophilic granules have been isolated from the adrenal medulla, splenic nerves, and various regions of the CNS. Granules contain extremely high concentrations of catecholamines and ATP. The intragranular catecholamine-nucleotide complex constitutes a reserve pool which is the major storage depot of epinephrine in the adrenal medulla. Some reserve pool undoubtedly exists in active equilibrium with considerably smaller mobile pools within the granules and cytoplasm. In the course of synthesis of catecholamines, the hydroxylation of tyrosine to dopa and the decarboxylation of dopa to dopamine take place in the cytoplasm of cells within adrenergic nerve terminals (23). Dopamine then enters the granules where it is converted to norepinephrine. In the adrenal medulla, most of the norepinephrine leaves the granules, is methylated in the cytoplasm to epinephrine and then reenters a different group of intracellular granules, where it is stored until released. In the human adult, epinephrine accounts for approximately 80% of the catecholamines of the adrenal medulla, with norepinephrine making up most of the remainder, but in the heart, norepinephrine is the major catecholamine present.

There is a second major source of norepinephrine in addition to the synthesis pathway described above, i.e., its recapture by active transport of norepinephrine into the terminal portion of the adrenergic fibers. This process is probably the major one responsible for the termination of the effects of adrenergic impulses in most organs; the blood vessels apparently constitute an exception, where the immediate disposition of released norepinephrine is accomplished largely by a combination of enzymatic breakdown and diffusion (23). In order to effect the re-uptake of norepinephrine and to maintain the concentration gradients of synthesized norepinephrine within the aforementioned pools, at least two active transport systems appear to be involved: one, across the axoplasmic membrane from the extracellular fluid to the cytoplasmic mobile pool; and the other, from this cytoplasmic mobile pool to the intragranular mobile pool.

Adrenergic fibers can sustain a major output of norepinephrine during prolonged periods of stimulation without exhausting their reserve supply provided the mechanisms of synthesis and uptake of the transmitter are unimpaired.

ALTERATIONS IN BETA ADRENERGIC RECEPTORS DURING EXPERIMENTAL MYOCARDIAL ISCHEMIA

Experimental myocardial ischemia produced in dogs by proximal left anterior descending coronary artery ligation is accompanied by relatively rapid (within 1 hour) increases in the number of (-) [^{3}H] dihydroalprenolol binding sites (beta adrenergic receptors) without a change in the dissociation constants in ischemic left ventricular tissue (24,25) (Table 2) (Fig. 9). The changes persist for at least 8 hours and are accompanied by marked decreases in myocardial tissue ischemic region norepinephrine content (Fig. 9). In contrast, in the same canine model 1 hour of proximal left anterior descending coronary artery ligation does not result in significant change in the number of [^{3}H] quinuclidynl benzilate binding sites or their dissociation constants (muscarinic cholinergic receptor density) (24). Thus, the data suggest that proximal left anterior descending coronary artery occlusion for 1 hour significantly increases the number of beta adrenergic receptors in ischemic left ventricular tissue without changing the number of muscarinic

cholinergic receptors. The increase in beta adrenergic receptors in left ventricular ischemic tissue is not prevented by pretreatment with reserpine and prior depletion of myocardial catecholamine content and thus does not appear to be a manifestation of "up regulation" in beta adrenergic receptor numbers.

TABLE 2

Specific Binding and Dissociation Constant of (−)-[^{3}H]-Dihydroalprenolol in Crude, Microsomal, and Sucrose Density Gradient-Enriched Sarcolemmal Fraction and 5′-Nucleotidase Activity from LV Ischemic and Nonischemic Tissues in Canine Myocardium with 1 Hour of Proximal LAD Ligation

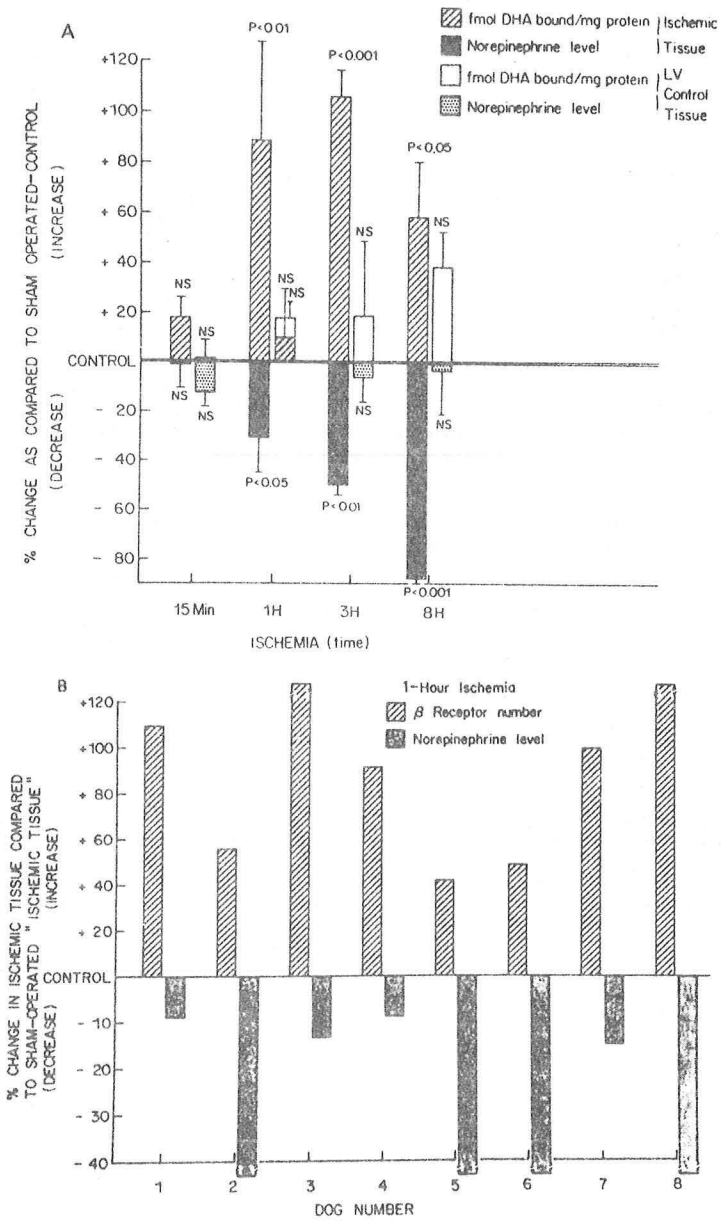
		β-Receptor numbers (fmol (−)-[^{3}H]-DHA bound per mg protein)			K_D (nM)			5′-Nucleotidase activity*
		1	2	3	1	2	3	
LV nonischemic tissue		101 ± 18	221 ± 27	667	9.86 ± 1.44	5.27 ± 0.76	6.21	421
	n	12	6	2	12	6	2	3
LV ischemic tissue		163 ± 18	369 ± 32	835	11.77 ± 1.06	5.75 ± 1.14	5.25	431
	n	12	6	2	12	6	2	3
		$P < 0.02$	$P < 0.001$		NS	NS		

Results are expressed as mean ± SEM; *n* = number of animals used.

* 5′-Nucleotidase activity is assayed in microsomal fraction and is expressed as nmol/mg protein per 10 min at 37°C. 1 = crude membrane preparation; 2 = microsomal fraction; 3 = 0.6 and 0.3 M sucrose density gradient interphase (enriched sarcolemmal fraction).

Taken from Reference 25.

FIGURE 9



The increases in beta adrenergic receptor density in the LV ischemic region after 1 hour of proximal left anterior descending coronary artery occlusion in canine models is shown in the top panel. Norepinephrine content decreases in the same region, but there is no correlation between the extent of norepinephrine depletion and the increase in beta adrenergic receptor density in the LV ischemic region (bottom panel). Taken from Reference 24.

Relationship Between Beta Adrenergic Receptor Numbers and Physiological Responses During Experimental Canine Myocardial Ischemia

We have evaluated the physiologic responses of the increased numbers of beta adrenergic receptors in ischemic canine myocardium to in vivo stimulation by (-) isoproterenol and epinephrine (25). After 1 hour of temporary proximal left anterior descending coronary artery occlusion and during a 15-minute reflow period, dogs received (-) isoproterenol intravenously at a rate sufficient to increase their heart rates by 20 to 40 beats per minute (25). Following the infusion of isoproterenol, myocardial tissue was obtained from the left ventricular ischemic and nonischemic regions for measurement of beta adrenergic receptor numbers, cyclic AMP content, and phosphorylase b to a conversion. Beta adrenergic receptor numbers were significantly increased in the left ventricular ischemic tissue just as we had found previously (25) (Table 3 and 4). The administration of (-) isoproterenol was associated with significant increases in cyclic adenosine monophosphate content and phosphorylase b to a conversion in the left ventricular ischemic tissue (Table 3) (Fig. 10). However, 15 minutes of reflow after 1 hour of coronary artery occlusion in the absence of isoproterenol did not result in similar increases in cyclic AMP or increased conversion of phosphorylase b to a in the left ventricular ischemic region (Table 4) (25). Administration of (-) epinephrine significantly increased the phosporylase b to a conversion in left ventricular ischemic tissue over the nonischemic tissue and this conversion was blocked with

TABLE 3

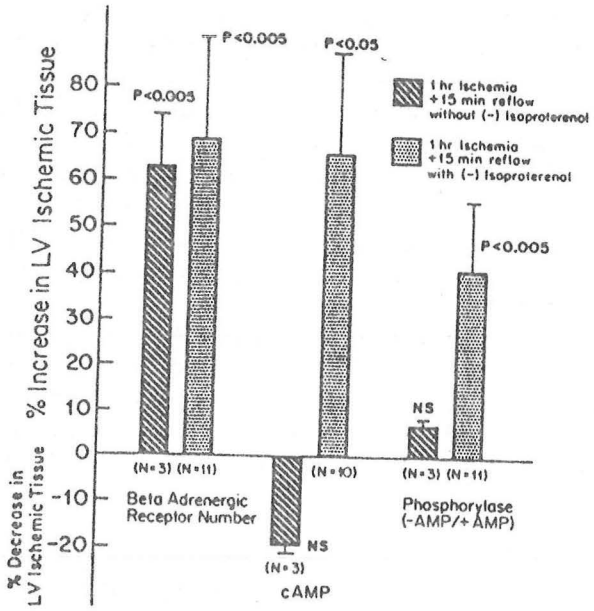
Membrane Protein, DNA Content, (−)-[^{3}H]-DHA Binding, Phosphorylase Activity (−AMP/+AMP), and Cyclic AMP Content of LV Ischemic and Nonischemic Tissue after 1 Hour of Proximal LAD Ligation and 15 Minutes of Reflow with (−)-Isoproterenol Infusion

	mg/g wet wt tissue		No. of (−)[^{3}H] DHA binding sites (fmol/mg DNA)	K_D of (−)-[^{3}H]-DHA (nM)	Cyclic AMP (pmol/mg wet wt tissue)	Phosphorylase (−AMP/+AMP)
	Membrane protein	DNA*				
Nonischemic LV tissue	2.41 ± 0.20	2.11 ± 0.29	114 ± 21	7.81 ± 0.86	0.54 ± 0.07	0.41 ± 0.04
Ischemic LV tissue	3.58 ± 0.37	2.02 ± 0.26	202 ± 37	8.23 ± 0.98	0.92 ± 0.20	0.58 ± 0.04
	(n =10)	(n =10)	(n =10)	(n =10)	(n =10)	(n =10)
	$P < 0.05$	NS	$P < 0.005$	NS	$P < 0.05$	$P < 0.005$

Results are expressed as mean ± SEM; n = number of animals used.
* DNA was measured in total homogenate.

Taken from Reference 25.

FIGURE 10



Taken from Reference 25.

TABLE 4

(−)-[^{3}H] DHA Binding, cyclic AMP Content, and Phosphorylase Activity (−AMP/+AMP) of LV Ischemic and Nonischemic Tissues after 1 Hour of Proximal LAD Ligation and 15 Minutes of Reflow without (−)-Isoproterenol Infusion

	No. of (−)-[^{3}H]-DHA binding sites (fmol/mg DNA)	K_D of (−)-[^{3}H]-DHA (nM)	CyclicAMP (nmol/mg wet wt tissue)	Phosphorylase (−AMP/+AMP)
Nonischemic LV tissue (n = 3)	106 ± 14	7.43 ± 1.21	0.44 ± 0.04	0.27 ± 0.02
Ischemic tissue (n = 3)	172 ± 21	8.20 ± 1.21	0.34 ± 0.01	0.29 ± 0.05

Results are expressed as mean ± SEM; n = number of animals used.

Taken from Reference 25.

pretreatment with (±) propranolol (Table 5). These data suggest that in open-ch anesthetized dogs with proximal left anterior descending coronary artery occlusion for 1 hour, there is an increased number of beta adrenergic receptors in canine left ventricular ischemic tissue and that these receptors are capable of translating physiological responses when they are activated with an appropriate agonist in vivo (25).

Autoradiographic Localization of Beta Adrenergic Receptors in the Canine Heart

Olson, Buja, et al. have utilized a light microscopic autoradiographic method to identify the topography of beta adrenergic receptors in the canine heart using (-) [^{3}H] dihydroalprenolol binding sites in frozen sections obtained from left ventricular ischemic and nonischemic tissue from open-chest anesthetized dogs with left anterior descending coronary artery occlusion for 1 hour (26). In control myocardium, specific binding (binding displaced by propranolol) was similar for cardiac myocytes and smooth muscle cells of medium-sized coronary arteries, whereas mean binding was over 5 to 8 times higher for smooth muscle cells of myocardial arterioles (26) (Fig. 11). Ischemic myocardium showed a significant increase in binding over cardiac myocytes but not over blood vessels (26). Thus, the increase in beta adrenergic receptor density appears to be over myocytes

TABLE 5

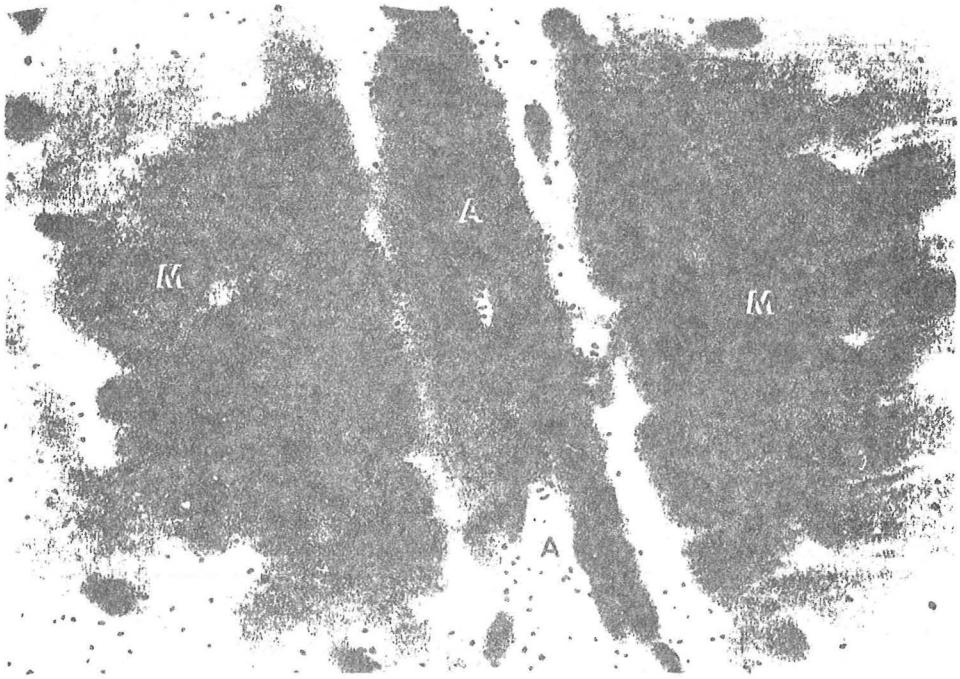
Effect of Propranolol on Phosphorylase Activity (−AMP/+AMP) of LV Ischemic and Nonischemic Tissues after 1 Hour of Proximal LAD Ligation and 7 Minutes of Reflow with (−)-Epinephrine Infusion

		Phosphorylase (−AMP/+AMP)	
		Nonischemic tissue	Ischemic tissue
(−)-Epinephrine		0.51 ± 0.04	0.61 ± 0.03
	n	7	7
			$P < 0.05$
(±)-Propranolol and epinephrine		0.30 ± 0.02	0.27 ± 0.02
	n	6	6
			NS

Results are expressed as mean ± SEM; *n* = number of animals used.

Taken from Reference 25.

FIGURE 11



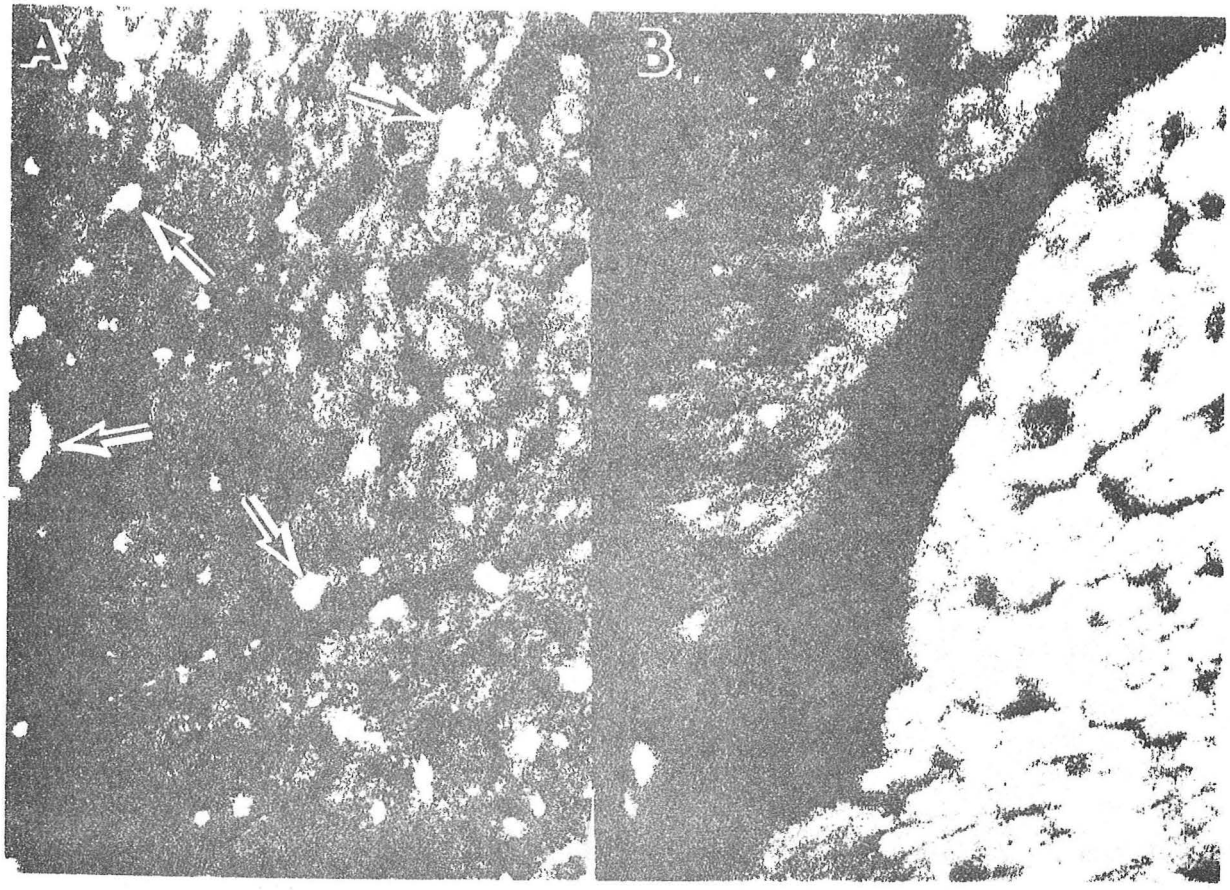
Autoradiograph of normal canine myocardium after incubation with 2 nM (-) [^{3}H] DHA (dihydroalprenolol). Silver grains mark beta adrenergic receptor binding sites. Note the moderate grain density over cardiac myocytes (M) and the more intense concentration of grains over the myocardial arteriole (A). X 940.

within the left ventricular ischemic region (24-26). Olson et al's study has demonstrated the topographical distribution of beta adrenergic receptors in the heart for the first time and indicated that myocytes and small arterioles are the predominant sites for beta adrenergic receptors in canine left ventricular myocardium.

Redistribution of Catecholamines in the Ischemic Zone of the Canine Heart

Muntz, Hagler, Buja, et al. have recently evaluated the relationship between alterations in catecholamines and indices of tissue damage during early myocardial ischemia in the dog. Eight animals were subjected to ligation of the left anterior descending coronary artery for 1 hour, and 10 animals for 3 hours, and the severity of ischemia determined using radioactive microspheres to estimate alterations in myocardial blood flow (27). Myocardial catecholamines were measured radioenzymatically and catecholamine-containing nerve terminals were visualized histochemically and quantitated using a point counting method. In dogs with 1 hour occlusions, ischemic tissue catecholamine levels were only slightly reduced and semiquantitative evaluation indicated that there were a reduced number of catecholamine-containing nerve terminals (Fig. 12). In dogs with 3 hours of left anterior descending coronary artery occlusion, catecholamine levels were not reduced significantly in the ischemic subepicardium although the percent volume of

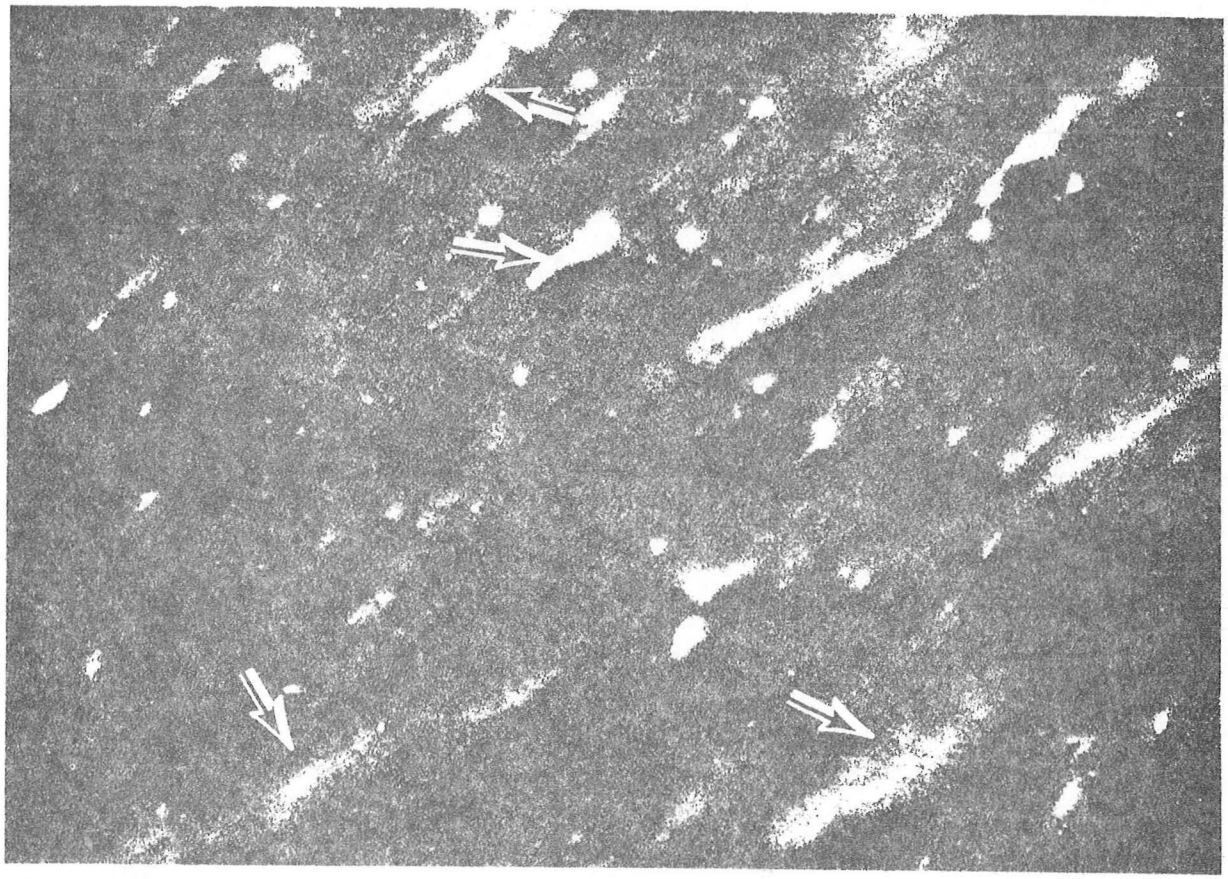
FIGURE 12



Canine heart after 3 hours of LAD occlusion. Tissue treated to demonstrate catecholamine-containing nerve terminals according to the method of Falck et al. (J Histochem Cytochem 10:348, 1961). The fluorescence micrograph on the left (A) (nonischemic myocardium) shows intact nerve terminals (several marked with arrows) while the micrograph on the right (B) shows marked reduction in number of fluorescing (catecholamine-containing) nerve terminals. X 700.

catecholamine-containing nerve terminals was reduced significantly in the ischemic subepicardium (58% of nonischemic tissue value) (27). In the ischemic subendocardium, catecholamine levels were reduced to 76% of nonischemic tissue, while the percent volume of catecholamine-containing nerve terminals was reduced to 50% of the nonischemic tissue values. These findings were confirmed in dogs in which the fluorescent dye thioflavin S was used to localize the ischemic areas both microscopically and macroscopically, after both 1 and 3 hours of ischemia. Diffusion of catecholamines from the nerve terminals was noted in the ischemic areas (Fig. 13). Degenerative changes in nerve terminals were demonstrated by electron microscopy (27). These data indicate that catecholamines are released from nerve terminals and accumulate in another tissue compartment in the ischemic myocardium during evolving myocardial infarction in this model (27). Quantitative light microscopic evaluations showed significant myocyte damage after 1 hour of ischemia in the endocardium although not in the

FIGURE 13



This micrograph demonstrates diffusion of catecholamines from nerve terminals (representative areas marked by arrows) in another region of the ischemic zone. This tissue is from the same animal shown in Figure 12.

epicardium. There was significant damage in the epicardium and in the endocardium after 3 hours of ischemia. Tissue calcium levels were increased significantly in the ischemic region after 3 hours, but not after 1 hour of left anterior descending coronary artery occlusion. Thus, ischemic injury is associated with a redistribution and abnormal localization of catecholamines in ischemic myocardium and this phenomenon precedes morphological and biochemical evidence of irreversible cellular damage (27).

MECHANISMS OF INCREASE IN PERIPHERAL LEVELS OF CATECHOLAMINES FOLLOWING ACUTE MYOCARDIAL INFARCTION IN EXPERIMENTAL ANIMALS

Staszewska-Barczak has demonstrated that within minutes of producing an experimental infarction by acute coronary artery ligation in the dog, the adrenal medulla begins to secrete catecholamines, predominantly adrenaline. The increase in catecholamines may occur without change in mean arterial blood pressure (28,29). Staszewska-Barczak et al. have found that the increased release of norepinephrine during the first hour after acute coronary artery occlusion in the dog may be largely prevented by the topical application of xylocaine to the infarcted area of the heart, spinal blockade at the C_1 level, bilateral section of thoracic splanchnic nerves, or ganglionic blockade (28). Norepinephrine secretion

following coronary artery occlusion may be abolished by bilateral vagotomy in 50% of dogs, decreased in 28%, but remains unchanged in approximately 22%. Bretylium or guanethidine have no effect on norepinephrine secretion in the early stages of myocardial infarction. Seventeen of 19 reserpinized dogs failed to secrete catecholamines during the first hour of coronary artery occlusion even though the adrenal medulla responded to bradykinin, acetylcholine or nicotine in Staszewska's study. The most effective means of preventing norepinephrine release after coronary ligation was by the topical application of xylocaine in the ischemic area of the heart or by ganglionic blockade (28). Staszewska and his associates have concluded that the adrenal medullary secretion of norepinephrine which occurs in the early stages of myocardial infarction is a major factor in the increases in peripheral catecholamine concentration and that it is induced reflexly following stimulation of cardiac receptors at the site and the boundaries of the myocardial infarction (28). The reflex involves vagal as well as extra-vagal pathways and supraspinal structures. Norepinephrine in the early stages of infarction also may be released from postganglionic sympathetic nerve endings in the heart (28).

CHANGES IN NOREPINEPHRINE STORES IN THE CANINE HEART FOLLOWING EXPERIMENTAL MYOCARDIAL INFARCTION

In experiments performed in anesthetized mongrel dogs from 1 to 42 days following myocardial infarction, Mathes and Gudbjarnason found that normal left ventricular muscle in the dog contained 0.98 µg norepinephrine per gram of tissue, but following coronary artery occlusion, the infarcted tissue loses its norepinephrine content completely by the fourth day and noninfarcted tissue shows a marked decline during the first 10 days reaching a level as low as 0.34 µg at the base and 0.14 µg per gram at the apical portion of the left ventricle (30). The decrease in myocardial norepinephrine content extended to the right ventricle and both atria as well. Norepinephrine levels rose again 2 weeks after infarction and reached normal values 6 weeks after the event. Mathes and Gudbjarnason found no correlation between norepinephrine content and tissue levels of lactate or high energy phosphate in the noninfarcted myocardium (30). They also concluded that the decline in recovery of left ventricular function after infarction was followed rather than preceded or accompanied by similar alterations in the norepinephrine content (30).

POTENTIAL CONSEQUENCES OF ALTERATIONS IN CATECHOLAMINES AND ADRENERGIC RECEPTORS DURING ACUTE MYOCARDIAL ISCHEMIA AND INFARCTION

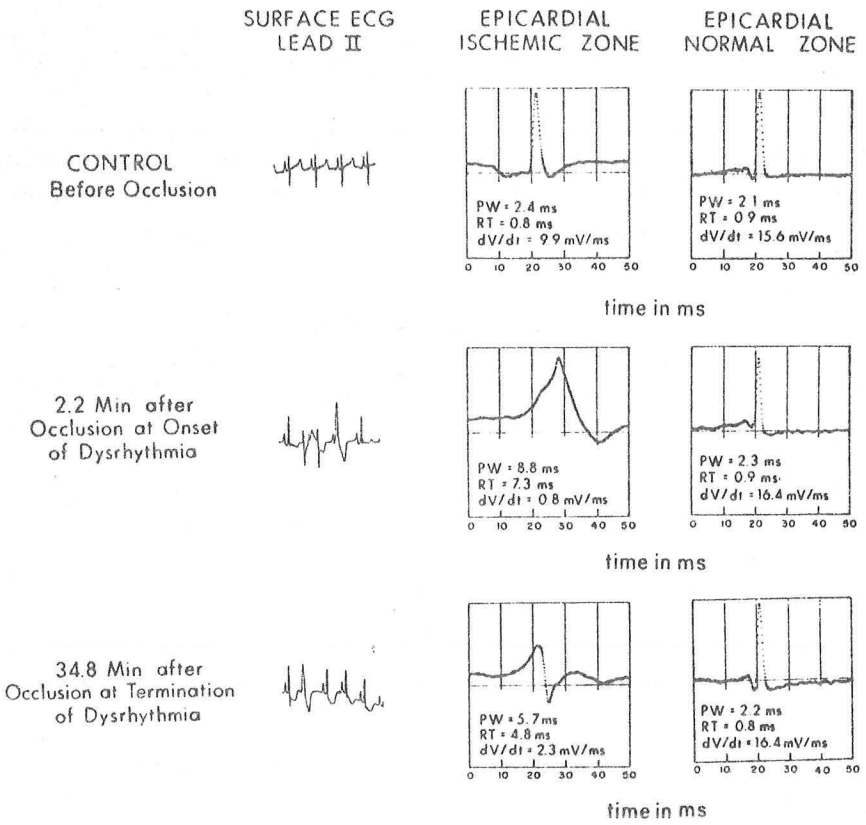
A. Direct Influence on Myocardial Arrhythmias

1. Beta Adrenergic Mechanisms

It has been suggested by others that increases in tissue cyclic AMP levels in ischemic tissue occur in association with the development of ventricular fibrillation (31,32). However, in dogs with distal coronary artery occlusions that do not develop ventricular fibrillation, cyclic AMP levels in ischemic tissue are reported not to rise (31). This suggests that stimulation of beta adrenergic receptors by catecholamines may play some role in arrhythmogensis during experimental myocardial ischemia.

Corr et al. (32) have used continuously recorded bipolar electrograms from epicardium, endocardium and midmyocardial regions of the ischemic and normal zones of the cat left ventricle after coronary artery occlusion and have compared alterations in electrophysiologic parameters with changes in regional cyclic AMP levels. Regional cyclic AMP content was used as an index of the combined local effects of: (a) efferent sympathetic nerve discharge; (b) release of myocardial catecholamines due to ischemia; and (c) circulating catecholamines. Ischemia resulted in a progressive increase in pulse width and rise time and a decrease in the rate of rise of voltage (dV/dt) of the local electrograms from ischemic zones reaching a maximum within 2.4 $\pm$ 0.3 minutes at the time of onset of severe ventricular dysrhythmias, all of which returned toward control before the cessation of the dysrhythmia (33.5 $\pm$ 1.5 minutes after coronary occlusion) (Fig. 14).

FIGURE 14



Computer-generated digital reconstruction of typical epicardial wave forms obtained from the ischemic (center panels) and normal zones (right panels) of the left ventricle both before and 2.2 minutes after occlusion and immmediately before the termination of the dysrhythmia (34.8 minutes after occlusion). The surface ECG shown depicts the rhythm at the moment when the wave forms were obtained. PW = pulse width, RT = rise time, and dV/dt = rate of change of voltage with time. The wave forms shown are digital reproductions obtained with a high-speed plotter with each pulse shown as 500 data points (50 ms at 10 KHz sampling rate).

Increases in cyclic AMP in ischemic zones preceded corresponding increases in the frequency of premature ventricular complexes. Propranolol inhibited the increases in cyclic AMP and reduced the frequency of premature ventricular complexes in animals without ventricular fibrillation. In animals with ventricular fibrillation, cyclic AMP was significantly elevated in normal and ischemic zones compared to animals with only premature ventricular contractions (32). Electrical induction of premature ventricular complexes or ventricular fibrillation in ischemic and nonischemic hearts failed to increase cyclic AMP. The results suggest that changes in regional adrenergic stimulation of the heart may contribute to perpetuation of ventricular dysrhythmia and the genesis of ventricular fibrillation early after the onset of myocardial ischemia (32).

In patients, the relation between sympathetic activity and ventricular arrhythmias after myocardial infarction has been controversial. At least 9 studies have dealt with this issue (33-42). Five have indicated a positive relation between plasma norepinephrine and arrhythmias, three did not, and one showed equivocal findings. The studies appear to have differed in the timing of blood sampling, with positive studies assessing arrhythmia frequency and plasma norepinephrine performed soon after admission (33,36-38) and negative studies assessing these factors later in the hospitalization (34,39,40,42). McDonald et al. (37) reported that high norepinephrine levels were associated with early but not late ventricular arrhythmias; and Videbaek et al. (42) found that patients treated with antiarrhythmic agents on admission had higher serum catecholamine levels than patients not requiring antiarrhythmic therapy, but that there was no obvious relation between the level of catecholamines and the frequency of ectopic beats when serial blood samples were drawn during the hospitalization. It therefore appears that increased sympathetic activity may be associated with ventricular arrhythmias soon after the onset of myocardial infarction, but not later during hospitalization.

Because norepinephrine concentrations associated with myocardial infarction have been lower than those sometimes demonstrated to produce ventricular arrhythmias during experimental infarction (42), it has been argued that sympathetic activity could not produce infarct-related ventricular arrhythmias. However, this argument ignores the fact that norepinephrine is a neurotransmitter, not a hormone. Only a small proportion of norepinephrine released into the synaptic clefts spills over into the general circulation, and so concentrations of norepinephrine in blood may be considerably less than at its site of action at the adrenergic synapse (43). Further, it is possible that ischemic areas surrounding the infarct may be unusually susceptible to the arrhythmogenic influence of sympathetic activity.

2. Alpha Adrenergic Mechanisms in the Genesis of Dysrhythmias with Coronary Occlusion and Coronary Occlusion Followed by Reperfusion

Corr et al. (44) and Mukherjee et al. (45) have demonstrated in cats and dogs that coronary artery occlusion for as short as 30 minutes will result in a significant increase in alpha adrenergic receptor density within the ischemic region. This alteration is not corrected by 10 minutes of reperfusion after coronary artery occlusions lasting 30 minutes to 1 hour (44,45). Thus, increases in alpha adrenergic receptor density occur earlier than beta adrenergic receptor density during experimental myocardial ischemia.

Sheridan et al. have demonstrated that reperfusion arrhythmias, i.e., arrhythmias occurring after temporary coronary artery occlusion followed by reperfusion may be blocked and prevented by alpha adrenergic receptor antagonists (46). Beta adrenergic receptor antagonists do not exert a protective effect against reperfusion arrhythmias. Williams et al. in studies in patients undergoing thrombolytic therapy have shown that reperfusion arrhythmias also may be prevented by alpha adrenergic receptor blockers (47). However, others have suggested that lidocaine and selected slow channel calcium antagonists also may prevent reperfusion arrhythmias so that the effect of alpha receptor blockers may not be specific in this setting (48).

EFFECT OF SELECTED CALCIUM ANTAGONISTS ON ALTERING ALPHA ADRENERGIC RECEPTOR STIMULATION

Karliner et al. have demonstrated in rat myocardium that verapamil competes with alpha adrenergic receptor agonists for binding to alpha adrenergic receptors (49). Mukherjee et al. have demonstrated in canine, rat, and rabbit myocardium that verapamil, D600, and diltiazem (all "slow-channel" calcium antagonists) partially antagonize the binding of alpha adrenergic agonists to alpha adrenergic receptors, whereas they exert minimal or no effect to alter beta adrenergic agonists binding to beta adrenergic receptors at similar concentrations (50).

3. Influence of Catecholamines on Free Fatty Acid Concentration: Relationship to Arrhythmias

Elevated plasma free fatty acids can cause arrhythmias during myocardial ischemia. Plasma free fatty acids increase to values of approximately 1500 μeq/L between 1 and 2 hours after the onset of symptoms and are asociated with an increased incidence of serious ventricular arrhythmias during myocardial infarction (51,52). In experimental myocardial infarction in dogs, elevation of plasma free fatty acids may cause ventricular arrhythmias (53). Norepinephrine-stimulated elevation of plasma free fatty acids may increase ischemic injury during experimental myocardial infarction in dogs and free fatty acids may cause a depression of myocardial contractility during myocardial hypoxia (51). Inhibition of catecholamine-induced elevation of plasma free fatty acids in dogs may lead to some reduction in the intensity of myocardial ischemia (51).

Plasma free fatty acids are increased principally by catecholamine stimulation of adipose tissue lipolysis. Appropriately controlled studies are needed to determine whether suppression of increases in plasma free fatty acids may be protective against life-threatening ventricular arrhythmias in animal models and patients with acute myocardial ischemia and infarction.

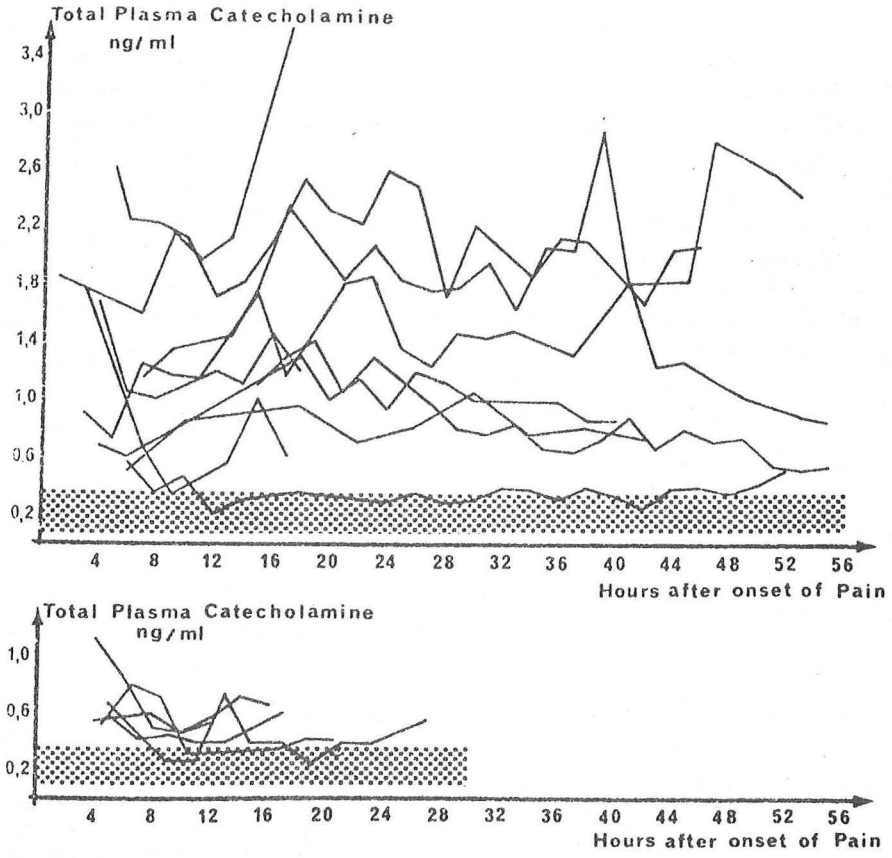
ALTERATIONS IN PERIPHERAL CATECHOLAMINE CONTENT IN PATIENTS AFTER ACUTE MYOCARDIAL INFARCTION

Serial Determination of Plasma Catecholamines in Patients After Myocardial Infarction

Using a precise and sensitive double-isotope derivative technique, plasma catecholamine concentration was measured at 4-hour intervals in 10 patients

during the first 48 hours after myocardial infarction (42). Plasma catecholamine concentration was elevated in most patients, but to an extremely variable degree (Fig. 15). In individual patients, the values were stable during the 48 hour evaluation period. High levels of plasma catecholamines (norepinephrine and epinephrine) were correlated with the clinical state of the patients. Patients receiving antiarrhythmic therapy on admission to the hospital had higher serum catecholamine values than untreated patients. There was no temporal correlation between plasma catecholamine concentration and ventricular arrhythmias. In contrast to the plasma catecholamine level, the heterotopic ventricular activity declined spontaneously in the untreated patients within the study period.

FIGURE 15



Dr. John Lovejoy (Cardiology Fellow at this institution) has evaluated the serial changes in norepinephrine content in peripheral blood samples in patients with acute myocardial infarction on admission to the coronary care unit at Parkland Hospital, 3 to 4 days later, and at hospital discharge (**54**). He has found mean serum norepinephrine concentrations of 934 pg/ml on admission, a mean value of 809 pg/ml on day 4, and a mean value of 611 pg/ml on day 14 in 26 patients with acute myocardial infarction. He also has evaluated patients with crescendo angina pectoris (unstable angina) and found values of 1318 pg/ml on admission, 861 pg/ml on day 4, and 717 pg/ml on day 14 in 16 such individuals. Normal control values for peripheral blood norepinephrine concentration at our institution are between 200 and 300 pg/ml.

Griffiths and Leung also have evaluated the sequential alterations in plasma catecholamines occurring in patients after acute myocardial infarction (**36**). Twenty-five men aged 29 to 68 admitted to the cardiac intensive care units at the hospitals in the Vancouver, Canada area with recent myocardial infarction were evaluated. Blood samples were obtained from patients with confirmed myocardial infarction on admission to the intensive care unit and at approximately 6, 12, and 24 hours thereafter. Patients were divided according to complications of their acute myocardial infarction. Patients in Group A comprised 9 individuals in cardiogenic shock. Patients in Group B comprised 8 patients without cardiogenic shock, but with a reduced systemic arterial pressure. Patients in Group C comprised 8 patients with a normal admission systolic arterial blood pressure. The mean levels of plasma catecholamines established in 50 healthy subjects were as follows: norepinephrine, 0.24 ng/ml, with a range of 0.15 to 0.33 ng/ml; epinephrine, 0.04 ng/ml with a range of undetectable to 0.08 ng/ml (**36**). In patients in Group A with the highest mortality rate, there was a significant elevation of norepinephrine ($p < 0.001$) and also of epinephrine ($p < 0.001$) (Table 6). In patients

TABLE 6

Clinical group	*Mean initial amine levels**		
	Norepinephrine (ng./ml.)	*Epinephrine (ng./ml.)*	*Histamine (μg/ml.)*
A	4.1 ± 0.6	0.27 ± 0.10	0.064 ± 0.020
B	1.5 ± 0.42	0.12 ± 0.06	0.056 ± 0.030
C	0.61 ± 0.22	0.09 ± 0.04	0.045 ± 0.035
Patients without myocardial infarction	0.29 ± 0.06	0.08 ± 0.04	0.054 ± 0.030

in Group B with a lower mortality rate, the elevations of norepinephrine and epinephrine were less, but they were still significantly elevated ($p < 0.001$) when compared to normal resting values and to control patients in the intensive care unit without myocardial infarction. In patients in Group C, with the lowest mortality rate, there was a progressive reduction in the mean initial plasma levels of norepinephrine and epinephrine, but both were elevated significantly compared to normal resting values ($p < 0.001$).

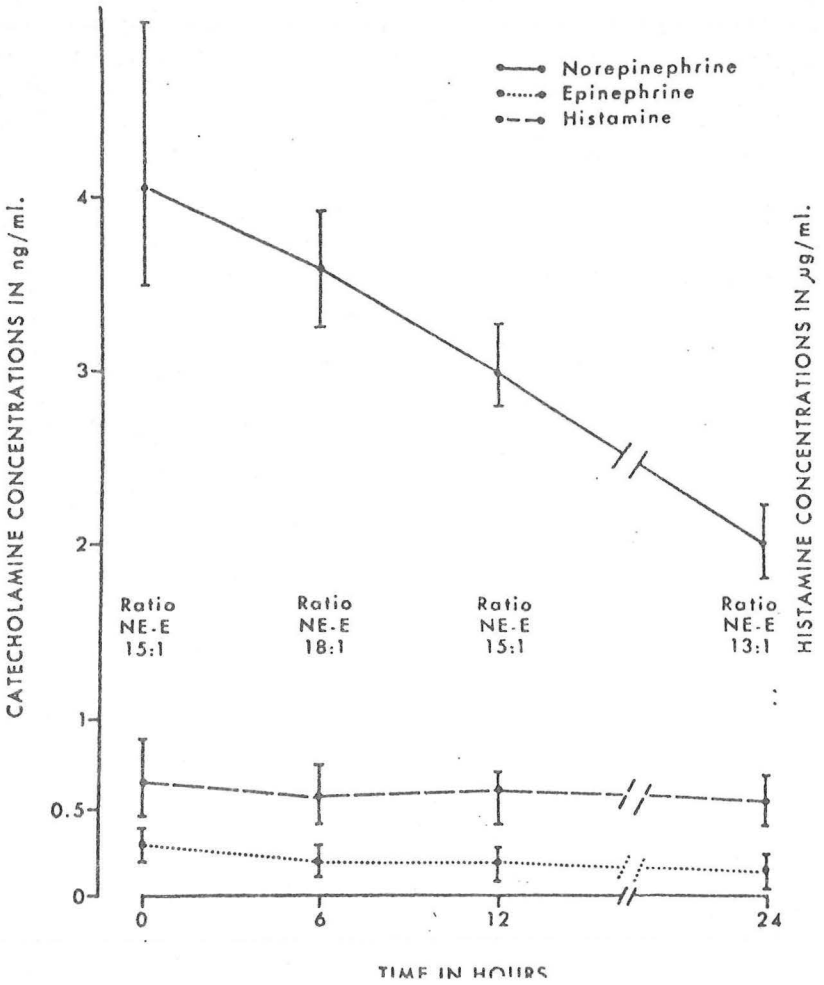
If norepinephrine levels were compared within the 3 clinical groups (Groups A-C), each group showed a significant elevation compared to one another and to the group of patients without infarction. For epinephrine levels, however, when the clinical groups were compared to one another, Group A showed a statistically significant elevation when compared to Groups B and C, but the values for patients in Groups B and C were comparable.

Table 7 relates the type of arrhythmias to initial mean plasma levels and indicates a striking relationship of cardiac arrhythmias to elevations predominantly in norepinephrine but to a lesser extent, epinephrine too (**36**). In 12 of the 25 patients, no significant dysrhythmias were found; atrial dysrhythmias occurred in 5 and ventricular dysrhythmias in 8. The 5 patients with atrial dysrhythmias showed a mean initial norepinephrine level of 3.74 ng/ml, with a range of 3.22 to 4.26 ng/ml. The 8 patients with ventricular dysrhythmias showed a mean norepinephrine level of 3.94 ng/ml with a range of 3.42 to 4.46 ng/ml. Alterations in catecholamines over the first 24 hours in patients in Group A, B, and C are shown in Figs. 16-18 (**36**). As mentioned earlier, several other investigators have indicated that there is a close association between the development of cardiac arrhythmias and high plasma catecholamine concentrations in patients with acute myocardial infarction (**37,39,55**).

TABLE 7

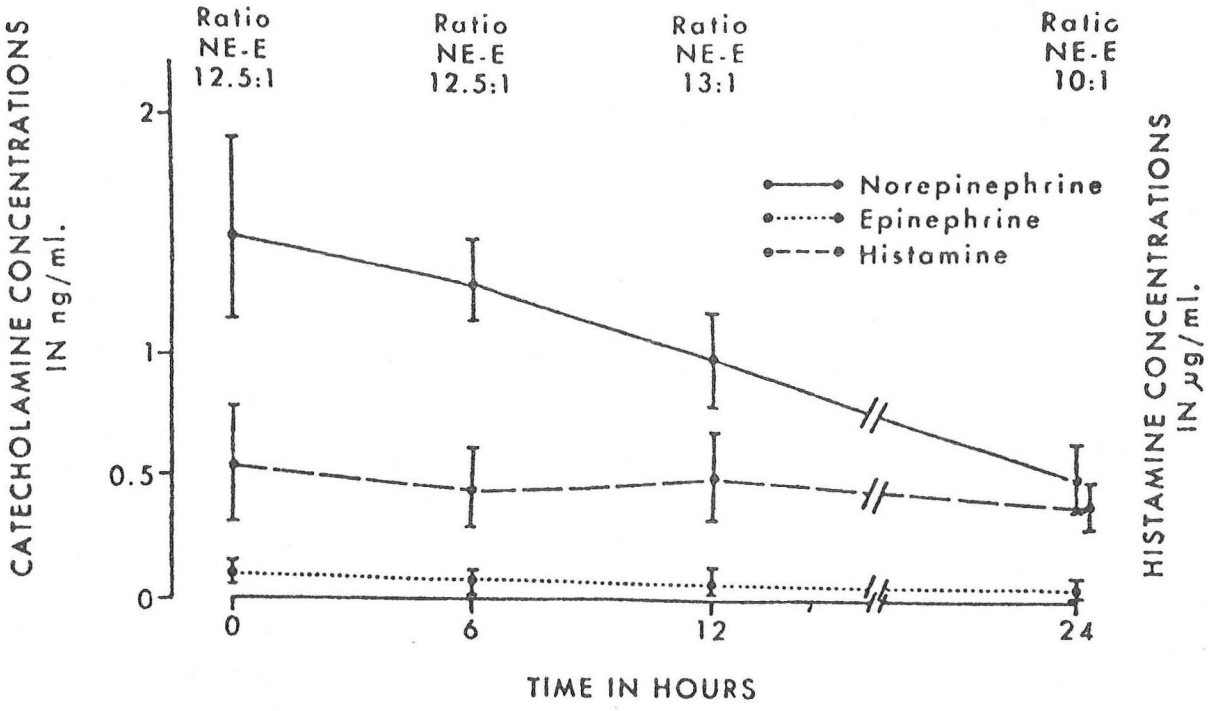
	No. of patients	*Mean initial amine levels**	
		Norepinephrine (ng./ml.)	*Epinephrine (ng./ml.)*
No significant dysrhythmias	12	0.96 ± 0.12	0.07 ± 0.05
Atrial dysrhythmias	5	3.74 ± 0.52	0.26 ± 0.11
Ventricular dysrhythmias	8	3.94 ± 0.52	0.27 ± 0.09

FIGURE 16



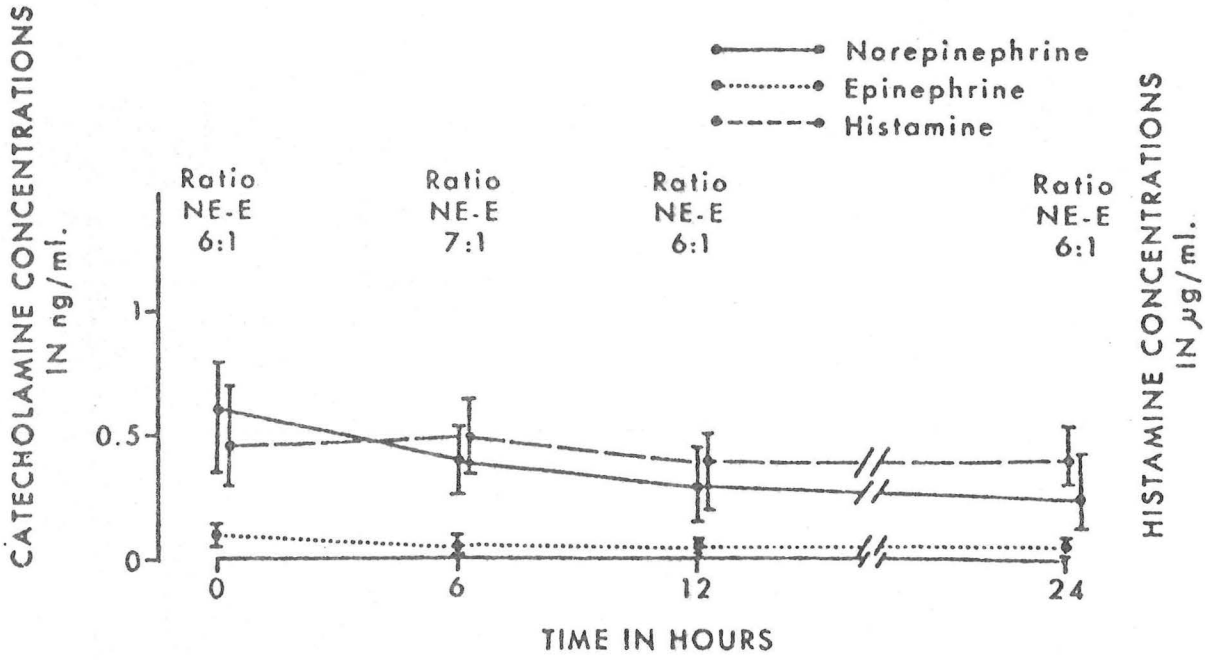
Plasma norepinephrine is markedly elevated in patient with cardiogenic shock and acute myocardial infarction. Taken from Reference 36.

FIGURE 17



Plasma norepinephrine is moderately elevated in patients with reduced systemic arterial blood pressure (but not cardiogenic shock) after acute myocardial infarction. Taken from Reference 36.

FIGURE 18



Plasma catecholamines and histamine are lowest in patients with relatively uncomplicated acute myocardial infarction.

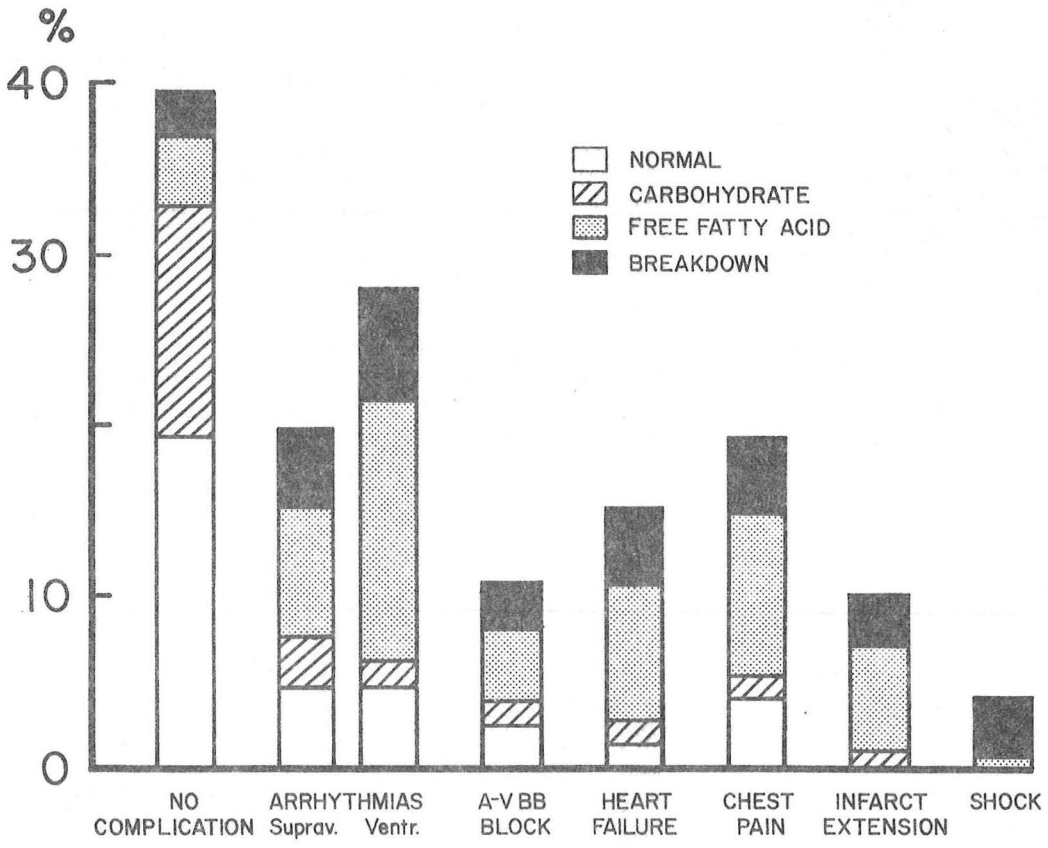
Benedict and Grahame-Smith also have demonstrated that in patients with myocardial infarction, plasma norepinephrine and epinephrine concentrations are increased (**56**). However, plasma norepinephrine concentrations were considerably higher in patients with cardiogenic shock when compared with those of uncomplicated myocardial infarction (**56**). Plasma norepinephrine and epinephrine concentrations demonstrated a sustained increase up to the time of death in patients with cardiogenic shock, whereas they returned toward normal by the end of the third day in patients with uncomplicated myocardial infarction.

Kondo et al. evaluated plasma concentration of norepinephrine, adenosine cyclic 3', 5'-monophosphate (cyclic AMP), and guanosine cyclic 3', 5'-monophosphate (cyclic GMP) serially for 2 weeks after myocardial infarction in 17 patients (57). The mean concentrations of norepinephrine in patients without complications were significantly higher during the first 2 days following the event. There was a significant correlation between the maximum concentration of plasma norepinephrine and of plasma creatine kinase. The mean concentrations of plasma cyclic AMP and GMP in patients without complications were significantly elevated on the first day and for 8 days after acute myocardial infarction. The concentration of plasma cyclic AMP on admission in patients with complications was significantly higher than in patients without complications. There were significant correlations between the maximum concentration of plasma cyclic AMP and those of plasma creatine kinase, SGOT, and LDH. Significant but weak correlations between the concentrations of plasma norepinephrine and those of cyclic AMP and cyclic GMP were found. These authors concluded that their data suggest an enhanced sympathetic nervous system activity during the early stages of acute myocardial infarction, a prolonged enhancement of parasympathetic nervous activity during acute myocardial infarction, and the potential value of plasma cyclic AMP concentrations as a useful index to estimate the seriousness and size of acute myocardial infarction.

Mueller and Ayres evaluated the adrenergic responses of the heart in patients following acute myocardial infarction (58). They studied 50 patients with acute transmural myocardial infarction beginning on average 8 hours after the clinical onset of infarction and continuing up to 60 hours after the event. These patients were instrumented so as to have an indwelling catheter in their coronary sinus, in a systemic artery, and they had hemodynamic measurements including cardiac output and measurements of pulmonary arterial and capillary wedge pressures, systemic arterial pressure, coronary blood flow, heart rate and an analysis of substrates in the arterial and coronary sinus blood. Forty percent of patients demonstrated a pattern of predominant myocardial free fatty acid uptake (mean extraction ratio, 24%) in the presence of elevated plasma free fatty acids and glucose (respective means 1181 μmol/liter and 210 mg/100 ml). Myocardial extraction ratios for glucose, lactate and pyruvate were low (respective means 1.1, 4, and 11%). Twenty-one percent of the studies revealed normal myocardial metabolism and 18% showed enhanced carbohydrate uptake, as evidenced by increased myocardial extractions of lactate and pyruvate (respective means 42%) and of glucose (mean 5%). Plasma contents of glucose and free fatty acids were lower than in the predominant free fatty acid group (respective means 156 mg/100 ml and 743 μmol/liter). The remaining 20% of studies showed high plasma substrate contents and low myocardial substrate uptake suggesting metabolic breakdown. The free fatty acid metabolic pattern was observed in more than 50% of the studies performed at the time of or close to the occurrence of important clinical complications (Fig. 19), including ventricular arrhythmias, chest pain, extension of the infarction or heart failure (58). Propranolol, 0.1 mg/kg intravenously, shifted myocardial substrate utilization from free fatty acids toward carbohydrates.

Mueller and Ayres have concluded from these data that the metabolic patterns of the myocardium are influenced by catecholamine stimulation in the majority of patients with acute myocardial infarction. Beta adrenergic blockade changed substrate utilization of the myocardium further suggesting that adrenergic activation plays an important role in the metabolic responses elucidated in this evaluation (58).

FIGURE 19



Taken from Reference 58.

ALTERATIONS IN SERUM CATECHOLAMINES DURING ANGINA PECTORIS

Raab demonstrated that catecholamine concentration was increased in the sera of patients with angina pectoris during physical exertion (**59**). These findings were confirmed by Richardson (**60**). Plasma norepinephrine increased in 8 of 10 angina patients after exercise in Richardson's studies; epinephrine increased in 5 patients (**60**). Gazes et al. also have demonstrated that patients have elevated plasma catecholamines during angina produced by exercise as compared to normal subjects during exercise (**61**). Thus, hyperactivity of the sympathetic nervous system appears to occur during exercise in patients with angina pectoris. Stareich and Ambanelli reported an increase in circulating levels of catecholamines during angina pectoris (**62**).

BETA ADRENERGIC BLOCKERS IN THE TREATMENT OF PATIENTS AFTER MYOCARDIAL INFARCTION

Several large controlled, clinical studies have shown that beta adrenergic blocking agents reduce mortality in patients after myocardial infarction.

A. The Timolol Study

A multicenter double-blind randomized study in Norway was performed to test the hypothesis that timolol (10 mg twice daily) is capable of reducing mortality in patients surviving acute myocardial infarction (**63,64**). Timolol maleate is a noncardioselective beta adrenergic blocking agent without intrinsic sympathomimetic activity (**63**). Twenty clinical centers in Norway were involved in this evaluation and the minimum duration of follow-up was 12 months (**64**). Table 8 demonstrates the selection of patients in this study and Table 9 the clinical characteristics of 1884 randomized patients for treatment. Table 10 demonstrates the numbers of patients withdrawn for all reasons except death. Table 11 describes the distribution of death and reinfarction that occurred in this evaluation. Figure 20 demonstrates the results from this study and emphasizes the reduction in mortality that occurred in patients treated with timolol. Timolol treatment was started 7 to 28 days after infarction in 1884 patients (945 received timolol and 939 placebo) and this represented 52% of the patients evaluated for entry into the study. The patients were followed for 12 to 33 months, mean 17 months.

There were 152 deaths in the placebo group and 98 in the timolol group. When deaths that occurred during treatment or within 28 days of withdrawal were considered, the cumulated sudden-death rate over 33 months was 13.9% in the placebo group and 7.7% in the timolol group -- a reduction of 44.6% (p = 0.0001) (Fig. 20). The cumulated reinfarction rate was 20.1% in the placebo group and 14.4% in the timolol group (p = 0.0006) (Fig. 21).

TABLE 8

Category	Risk Group *						Risk Groups Combined	
	I		II		III			
	P	T	P	T	P	T	P	T
	no. of patients							
Number randomized	174	178	543	547	222	220	939	945
Withdrawal during follow-up month:								
1	11	20	28	43	3	13	42	76
2–12	37	35	70	100	30	22	137	157
13–24	12	12	18	22	4	5	34	39
25–33	1	1	4	2	1	0	6	3
Total	61	68	120	167 †	38	40	219	275 †
Length of treatment (months)								
>6	125	121	428	412	190	186	743	719
>12	109	109	398	380	180	176	687	665
>24	41	40	150	146	77	72	268	258
Average	15.4		17.7		19.4		17.3	
On treatment at end of study	88	94	362	351	172	170	622	615

*P denotes placebo, and T timolol.

†P<0.01. P values are given only for the total number of withdrawn patients.

Taken from Reference 64.

TABLE 9

CHARACTERISTIC	TREATMENT GROUP	
	PLACEBO (n = 939)	TIMOLOL (n = 945)
	per cent	
Sex		
Men	78	80
Women	22	20
Age *		
≤64 yr	59	63
65–75 yr	41	37
Clinical history		
Previous infarction	19	19
Angina	38	38
Treated hypertension	22	18
Smoking	53	54
Therapy before admission		
Digitalis	14	15
Diuretics	23	18
Beta blockers	10	10
Risk factors for this study		
Heart failure	34	32
Enlarged heart	23	21
Lowest systolic blood pressure <100 mm Hg	25	23
Atrial fibrillation or flutter	12	11
Maximum level of aspartate aminotransferase >4 times upper-normal level	53	52
Arrhythmias in acute stage		
Supraventricular tachyarrhythmias	29	26
Ventricular tachycardia or fibrillation	14	10
Site of qualifying infarct †		
Anterior	41	39
Inferior	38	38
Other or uncertain	21	23

*The mean age was 61.4 years in the placebo group and 60.3 years in the timolol group.

†The mean interval from onset of symptoms to randomization was 11.6 days in the placebo group and 11.4 days in the timolol group.

Taken from Reference 64.

TABLE 10

Adverse Reactions and Reasons for Withdrawal from Treatment among 1884 Patients.*

CATEGORY	ADVERSE REACTION †		WITHDRAWAL DUE TO REACTION ‡	
	PLACEBO	TIMOLOL	PLACEBO	TIMOLOL
	no. of patients			
Cardiac failure, nonfatal	63	73	20	27
Pulmonary edema, nonfatal	7	16	2	8
Heart rate <40 beats/min	3	47 §	2	37 §
Hypotension	15	29 ¶	11	26 ¶
Atrioventricular block, 2d or 3d degree	5	4	3	3
Sinoatrial block	7	8	7	6
Claudication	27	31	5	13
Cold hands and feet	6	73 §	0	4
Raynaud's phenomenon	1	6	0	0
Bronchial obstruction	7	18 ¶	4	10
Cerebrovascular disease	20	27	6	10
Thrombotic or embolic disease (excluding central nervous system)	9	16	3	2
Appearance of hyperglycemia	18	30	0	0
Hypoglycemia	2	0	1	0
Nausea or digestive disorders	57	71	5	11
Urogenital disorders	17	26	0	2
Nervous-system disorders	23	24	2	3
Psychiatric disorders	35	28	1	6
Asthenia or fatigue	11	45 §	1	4
Dizziness	34	53	0	11 ‖
Syncope	13	10	0	0
Skin disorders	25	25	4	2
Musculoskeletal disorders	38	35	1	1
Pneumonia or bronchitis	27	45 ¶	0	0
Other infections	34	41	0	1
Trauma	12	11	0	2
Malignant processes	11	8	3	2
Miscellaneous	59	73	1	5
Arrhythmia requiring treatment >21 days	38	13 §	38	13 §
Condition requiring beta-adrenergic blockade	68	32 §	68	32 §
Unconsciousness after heart arrest	—	—	6	4
Nonmedical withdrawal reasons	—	—	25	30

*Transient occurrences complicating recurrent infarctions are included only if they caused withdrawal.

†When an adverse reaction recurred in a patient, it is listed only once.

‡Only principal reason for withdrawal in each patient is listed.

§P<0.001. ¶P<0.05. ‖P<0.01.

Taken from Reference 64.

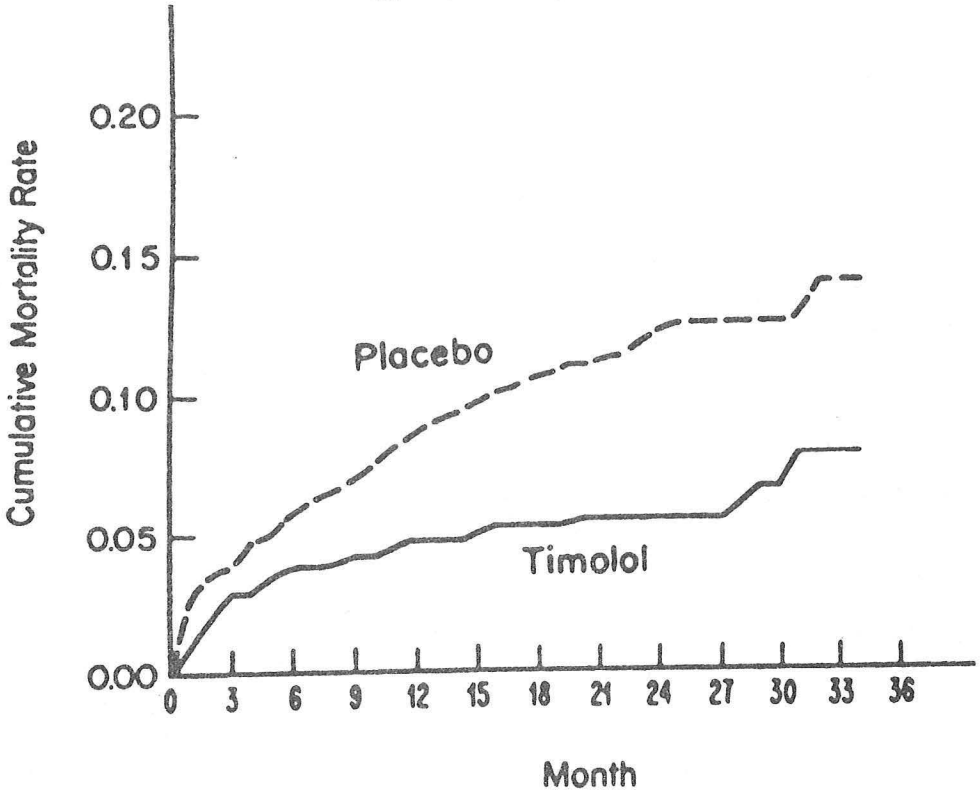
TABLE 11

Frequency Distribution of Deaths and Reinfarctions.*

CATEGORY	RISK GROUP						RISK GROUPS COMBINED	
	I		II		III			
	P	T	P	T	P	T	P	T
	no. of patients							
Deaths during treatment or within 28 days of withdrawal								
Sudden cardiac death	23	13	62	28 †	10	6	95	47 †
Other cardiac death	7	3	9	5	2	3	18	11
All cardiac death	30	16 ‡	71	33 †	12	9	113	58 †
Noncardiac death	1	3	3	6	0	0	4	9
All deaths	31	19	74	39 §	12	9	117	67 †
During treatment	25	16	61	30 †	12	9	98	55 †
Within 28 days of end of treatment	6	3	13	9	0	0	19	12
Deaths after more than 28 days of withdrawal								
All cardiac death	9	10	13	14	7	1	29	25
Noncardiac death	2	5	2	1	2	0	6	6
Total deaths ¶	42	34	89	54 §	21	10 ‡	152	98 †
Initial reinfarction on treatment or within 28 days of withdrawal ‖	37	23	67	41 ‡	37	24	141	88 †

Taken from Reference 64.

FIGURE 20



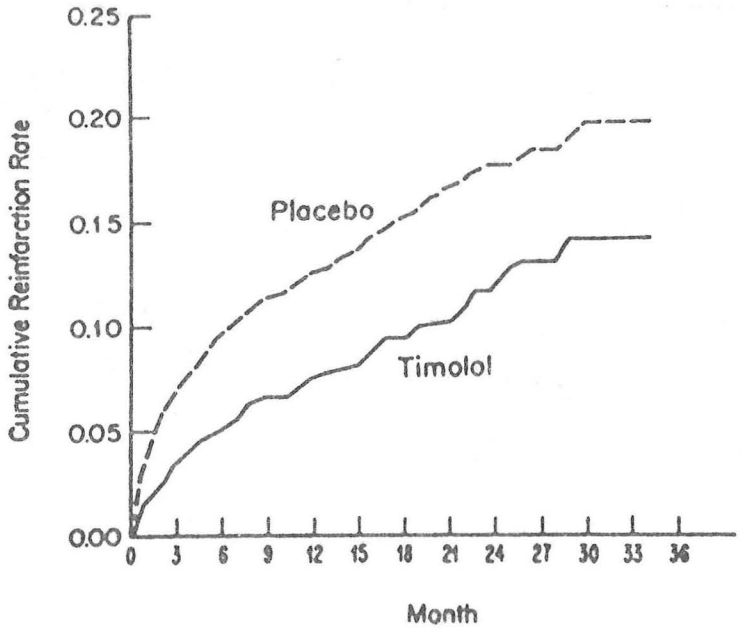
Taken from Reference 64.

Adverse reactions in the timolol treated patients were due mainly to known side effects of beta adrenergic blockade.

The number of cardiac deaths was 113 in the placebo and 58 in the timolol group (< 0.001). The number of sudden deaths was 95 in the placebo and 47 in the timolol group ($p < 0.001$); the number of instant deaths (within a few seconds) was 38 and 11, respectively ($p < 0.001$). Treatment with timolol was superior to treatment with placebo in the analysis of overall mortality; the difference was significant statistically in all groups combined ($p < 0.001$).

A total of 250 deaths occurred in the entire series (Table 12) and these deaths were analyzed according to the patients' original randomizations. There were 152 deaths in those initially randomized to placebo and 98 in those randomized to timolol (Fig. 20). When the placebo and timolol groups were compared for total mortality, the differences were significant in all risk groups combined ($p < 0.001$). The cumulative probability of death at 33 months for all patients combined was 21.9% in the placebo group and 13.3% in the timolol group, representing an observed reduction of 39.3% by timolol ($p = 0.0003$). The differences in mortality were significant when patients were evaluated according to age and infarct site (Table 12).

FIGURE 21



Taken from Reference 64.

Table 12

Cardiac Deaths and Reinfarctions during Treatment or within 28 Days of Withdrawal, According to Age and Site of Infarction before Study Entry.

CATEGORY	CARDIAC DEATH		INITIAL REINFARCTION	
	PLACEBO	TIMOLOL	PLACEBO	TIMOLOL
	no. of patients			
Age				
≤64 yr	54	30 *	72	55 †
65–75 yr	59	28 *	69	33 ‡
Infarction location				
Anterior	44	29	61	38 †
Inferior	36	16 *	52	24 ‡
Other or uncertain	33	13 ‡	28	26

*P<0.01. †P<0.05. ‡P<0.001.

Taken from Reference 64.

The number of initial reinfarctions (during treatment or within 28 days of withdrawal) was lower in the timolol-treated than in the placebo-treated patients (Table 12) (Fig. 21). The differences in the frequency of reinfarction reached statistical significance for all groups combined (Fig. 21). Five of the reinfarctions occurred within the first 28 days after withdrawal -- 3 in the placebo group and 2 in the timolol group. The cumulated reinfarction rate at 33 months of treatment was 20.1% in the placebo group and 14.4% in the timolol group -- a reduction of 28.4% ($p = 0.0006$). In the patients with a confirmed reinfarction in the study or within 28 days of timolol withdrawal, 42 in the placebo group and 26 in the timolol group died later. Thirty-one of these deaths in the placebo and 19 in the timolol groups occurred during treatment or within 28 days of withdrawal. More than one reinfarction occurred in 16 placebo-treated patients and in 6 timolol-treated patients. The difference in cumulated reinfarction rate between placebo and timolol patients was unchanged after 6 months of follow-up (Fig. 21).

This study demonstrated a substantial reduction in mortality and reinfarction in patients surviving an acute myocardial infarction when treatment with timolol was started 7 to 28 days after the event and continued for 33 months. The treatment effect could not be explained as a result of inhomogeneity of the groups at base line. Differences in mortality were highly significant when analyzed for deaths occurring within 28 days of withdrawal of timolol (when this was necessary) and when analyzed according to the intention-to-treat principle.

The reduction in mortality by timolol applied to all cardiac deaths and also to overall mortality. Thus, the demonstrated effects were not dependent on some bias of classification.

There was a widening gap in cumulated mortality between timolol and placebo-treated patients during the first 24 months (Fig. 20) indicating that the protective effect lasted at least throughout this period. Among patients treated for more than 24 months, the number of patients at risk was too small to permit definite conclusions.

The mechanism(s) responsible for the protective effect of timolol in this patient population have not been clarified. Since timolol has no intrinsic sympathomimetic activity, this property of beta adrenergic blocking agents seems to be without importance for the effect. Mean heart rates during rest were decreased from 73 to 55 beats per minute ($p < 0.001$), but the optimal dose of timolol producing a beneficial effect has not yet been determined.

Timolol treatment was terminated in 275 patients during the trial, but the withdrawal syndrome reported with beta adrenergic blockers by others was not a problem. No excess in mortality or reinfarction was observed during the first month after withdrawal of timolol. Only 18% of patients evaluated for entry were excluded from participation because of contraindications to long-term beta adrenergic blocking treatment.

B. The Metoprolol Study

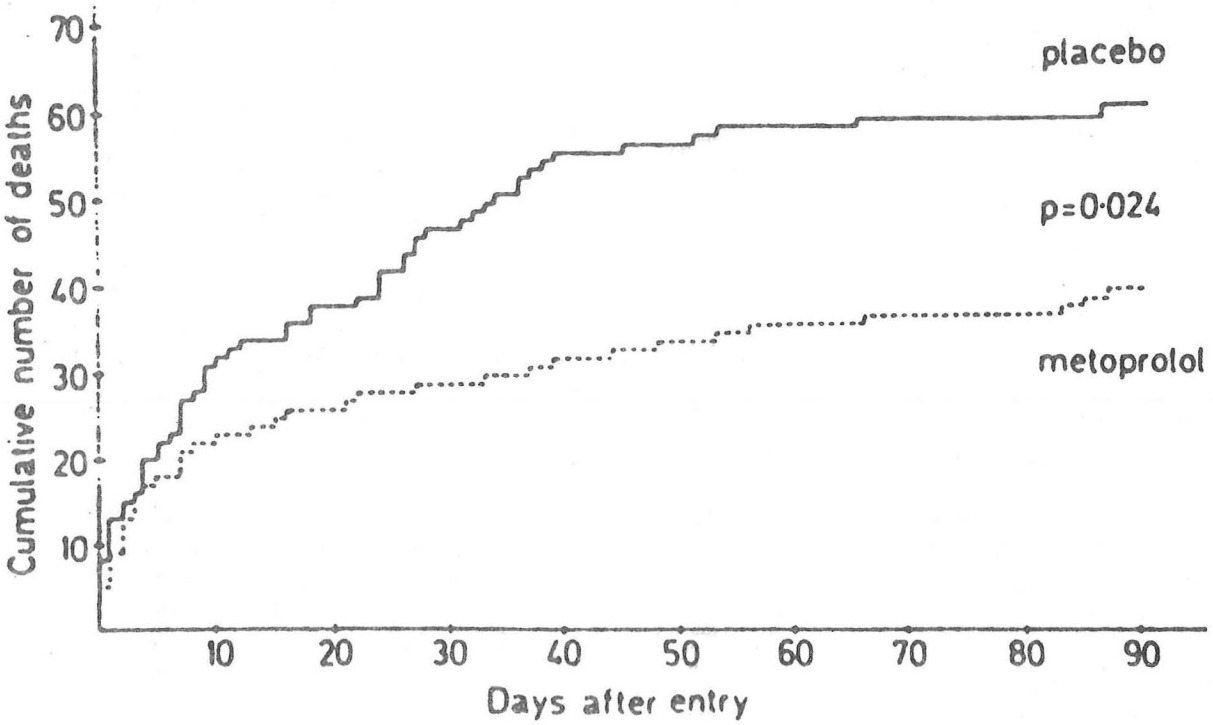
The effect of metoprolol on mortality was compared with that of placebo in a double-blind, randomized trial in patients with definite or suspected myocardial infarction (65). Treatment with metoprolol or placebo began as soon as possible after the patients' arrival in the hospital and was continued for 90 days.

Metoprolol was given in an intravenous dose of 15 mg followed by the oral administration of 100 mg twice daily. 1395 patients (697 on placebo and 698 on metoprolol) were included in the trial. Definite acute myocardial infarction developed in 809 and probable infarction in 172. Patients were allocated to various risk groups and within each group, patients were assigned randomly to treatment with metoprolol or placebo. There were 62 deaths in the placebo (8.9%) and 40 deaths in the metoprolol group (5.7%), a reduction of 36% ($p < 0.03$) (Fig. 22).

Metoprolol reduced total mortality by 36% (Fig. 22). Total mortality in each patient group is shown in Table 13. Metoprolol significantly reduced 3 month mortality as a whole by 36%, in those aged 40 to 69 years by 37%, in those aged 65 to 74 years by 45%, and by 34% in patients in whom definite myocardial infarction developed.

Figure 22 demonstrates mortality for patients in the placebo and metoprolol treated groups who continued for 3 months on the treatment to which they had been allocated, those who stopped their allocated treatment during this period, and in patients with missing data. For patients who continued treatment for the whole 3 month period, metoprolol reduced mortality by 47%. There was no difference in mortality between the placebo and metoprolol groups in patients who withdrew prematurely from the allocated treatment. There were no deaths in the patients in whom tablet intake was uncertain.

FIGURE 22



Taken from Reference 65.

TABLE 13

TOTAL NUMBER OF DEATHS IN ALL PATIENTS IN VARIOUS SUBGROUPS RANDOMLY ALLOCATED TO PLACEBO OR METOPROLOL

Group	No. of deaths/patients (%) in groups: Placebo	Metoprolol	Significance (p)	Effect* (%)
All patients	62/697 (8·9)	40/698 (5·7)	0·030	36
No history of previous infarction	44/539 (8·2)	30/550 (5·5)	0·101	33
History of previous infarction	18/158 (11·4)	10/148 (6·8)	>0·20	41
Not on chronic β-blockade at entry	46/520 (8·8)	30/522 (5·7)	0·071	35
On chronic beta-blockade at entry	16/177 (9·0)	10/176 (5·7)	>0·20	37
Ages 40–69 years	51/627 (8·1)	32/629 (5·1)	0·039	37
Ages 70–74 years	11/70 (15·7)	8/69 (11·6)	>0·20	26
Ages 40–64 years†	26/453 (5·7)	21/464 (4·5)	>0·20	21
Ages 65–74 years†	36/244 (14·8)	19/234 (8·1)	0·032	45
Definite MI†	56/410 (13·7)	36/399 (9·0)	0·046	34
No definite MI†	6/287 (2·1)	4/299 (1·3)	>0·20	36

*Percentage reduction in mortality = $\frac{(\text{mortality rate placebo} - \text{mortality rate metoprolol}) \times 100}{\text{mortality rate placebo}}$

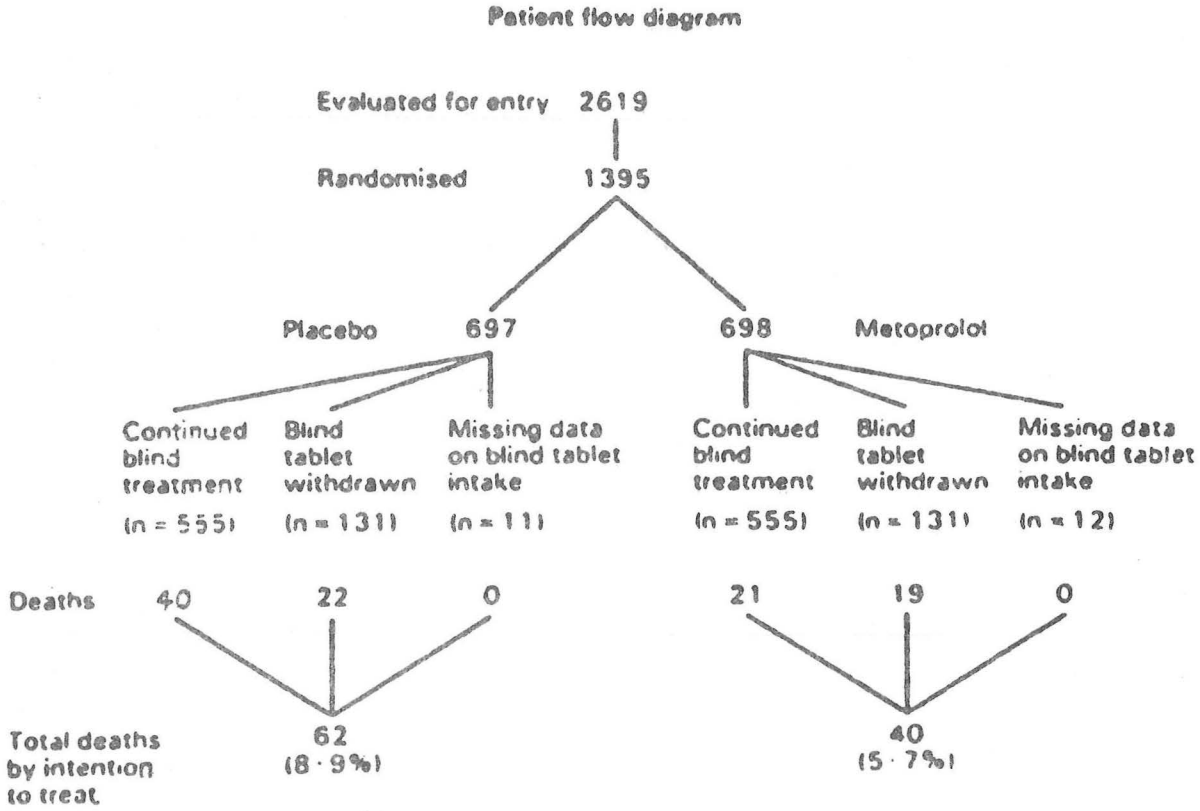
†Analysis of retrospectively formed subgroups.

Taken from Reference 65.

Tablet treatment was withdrawn in 19% of both groups during the total 90 day period of treatment (Table 14). Clinical characteristics of patients treated with placebo or metoprolol are shown in Table 15. Most patients were withdrawn from treatment when this was necessary because of suspected adverse cardiovascular effects.

This study demonstrated a reduction in total mortality in patients with definite or suspected myocardial infarction when metoprolol treatment was started on admission to the hospital and continued for 3 months. This was the first study to demonstrate a beneficial effect of beta adrenergic blockers on survival during the early phase of myocardial infarction. This also is the first study to show a significant effect of a β_1 selective blocker on mortality. Therefore, it appears that neither intrinsic stimulating activity, β_2 receptor blockade, nor membrane-stabilizing properties are necessary for the protective effect.

TABLE 14



Taken from Reference 65.

TABLE 15

CHARACTERISTICS OF PATIENTS ON PLACEBO OR METOPROLOL

Characteristics	Treatment group	
	Placebo (n=697) %	Metoprolol (n=698) %
Sex:		
Men	76·2	75·5
Women	23·8	24·4
Age:		
<64 years	65·0	66·5
65–74 years	35·0	33·5
Clinical history:		
Previous infarction	22·7	21·2
Angina pectoris (5)*	34·7	35·7
Hypertension	29·7	29·1
Therapy before admission:		
Digitalis (6)	12·9	12·5
Diuretics (5)	18·7	18·7
β-blockers	25·4	25·2
Clinical status at entry:		
Pulmonary râles	9·0	11·6
ECG signs of infarction (1)	47·8	49·9
Heart-rate >100 beats/min (1)	6·2	4·7
Systolic blood-pressure <100 mm Hg (2)	4·4	3·3
Dyspnoea at onset of pain (29)	30·8	28·8
Treatment in hospital before blind injection:		
Morphine (3)	53·9	53·6
Atropine (3)	3·5	2·9
Isoprenaline or analogues (2)	0·0	0·0
Diuretics (3)	9·8	10·8
Digitalis (3)	1·9	2·3
Lignocaine (3)	2·7	2·3
β-blocker or verapamil (5)	1·6	2·2
Mean age±SEM	60·0±0·3	60·0±0·3
Mean time from onset of symptoms to blind injection±SEM (16)	11·4±0·4	11·1±0·4

*Numbers in parentheses are numbers of patients for whom data were missing.

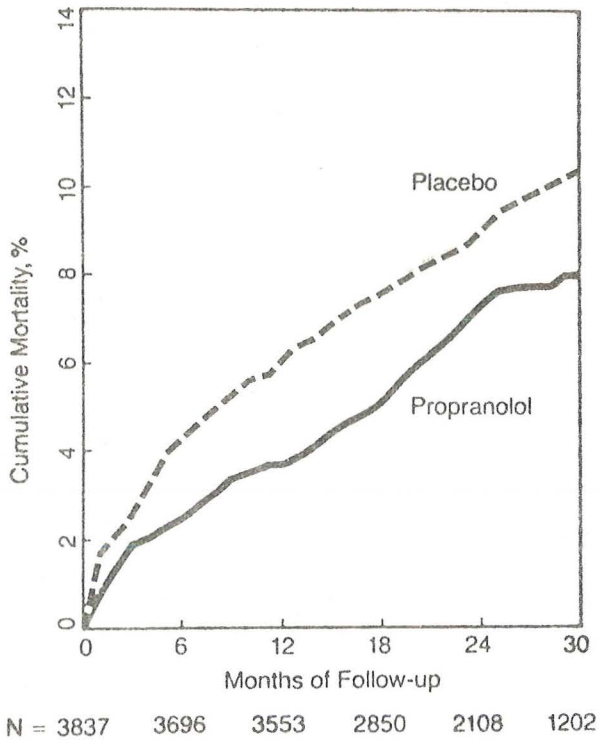
Taken from Reference 65.

The reasons for the reduction in mortality with metoprolol are not certain, but it appears that metoprolol was protective during the early phases of myocardial infarction, perhaps because of its ability to reduce infarct size, as well as during the later chronic stages, perhaps because of its influence on protecting against ventricular arrhythmias.

C. Influence of Propranolol

A preliminary report from the National Heart, Lung, and Blood Institute has demonstrated that propranolol administration resulted in a 26% lower mortality from all causes than did placebo therapy in 3837 patients after acute myocardial infarction (Fig. 23). This study was a randomized, double-blind, multicenter clinical trial of propranolol vs placebo in patients enrolled 5 to 21 days after the onset of acute myocardial infarction (**66**). From June 1978 to October 1980, 3837 men and women, ages 30 to 69 years, with documented myocardial infarctions were enrolled and randomized to one of two study groups (1916 to propranolol and 1921 to placebo). Baseline comparability between the two groups was excellent. Average time from the infarction to randomization was 13.8 days. All patients were

FIGURE 23



Taken from Reference 66.

assigned initially to receive 40 mg of propranolol hydrochloride or placebo 3 times a day before hospital discharge. Depending on serum propranolol levels as measured several days after enrollment, a maintenance dose of 60 mg 3 times a day or 80 mg 3 times a day was prescribed at the one-month follow-up visit. To maintain the blind control, patients were assigned matching placebo tablets. Patients were seen in 31 Clinical Centers every 3 months for evaluation and distribution of additional study medication. The study was scheduled originally to end in June 1982, but it was discontinued early based on a significant reduction in mortality of 26% in favor of the propranolol-treated patients.

Patients in the propranolol group did not have an increased frequency of congestive heart failure. Hypotension, tiredness, faintness, depression, and gastrointestinal problems were more common in the propranolol-treated group. Mean heart rates at the one-year visit were 65 beats per minute in the propranolol group and 73 beats per minute in the placebo group. Approximately two-thirds of the patients in each group complied with the treatment regimen. Another 15% were receiving less than protocol dose, and the remainder took no study medication. The site of infarction did not appear important in the beneficial effect from propranolol. A more extensive report from this Study Group is anticipated in the near future.

REBOUND PHENOMENON AFTER WITHDRAWAL OF BETA ADRENERGIC ANTAGONISTS

It has been noted that following the abrupt discontinuation of a beta adrenergic antagonist such as propranolol, a few patients develop ventricular arrhythmias, severe angina, myocardial infarction and even death **(67-71)**. The incidence of this phenomenon is debated, but in my opinion, it is relatively uncommon. The mechanism appears to be as follows. During the administration of high dose beta adrenergic antagonists (such as propranolol), there is an "up-regulation" of beta adrenergic receptors, i.e., an important increase in beta adrenergic receptor density. Following withdrawal of the beta adrenergic antagonists, the increase in receptor number persists, but there is no antagonism of catecholamine effects. This may allow an 8 to 18 hour period during which catecholamines may cause excessive adrenergic responses in patients with important coronary artery disease resulting in important complications from ischemic heart disease. For this reason, many cardiologists have advocated a gradual tapering of propranolol dosage when one plans to discontinue the agent rather than its sudden discontinuation. I believe that the propranolol withdrawal syndrome is real but rare.

SUMMARY

The data available indicate that serum catecholamines increase following acute myocardial infarction, during unstable angina pectoris, and with exercise-induced angina pectoris. In experimental animal models, there is an increase in beta adrenergic and alpha adrenergic receptors in the ischemic region with coronary artery occlusion periods of 30 minutes to 1 hour. The increase in beta adrenergic receptors is located over myocytes within the ischemic region and the beta adrenergic receptors are connected functionally to intracellular biochemical events. Furthermore, during experimental coronary artery occlusion, there is a leaking out of catecholamines from nerve terminal storage sites so that injured myocardial cells are exposed to higher catecholamine concentrations during the period of evolving cellular injury. Excess catecholamines can cause cellular

necrosis, arrhythmias, and alter heart rate and contractile responses so as to increase myocardial oxygen demand, thus potentially extending myocardial injury.

At least three carefully controlled and randomized clinical studies have demonstrated that beta adrenergic blockers reduce mortality in patients after acute myocardial infarction. The relationship between the fundamental alterations that occur in myocardial catecholamine concentration, adrenergic receptors, and biochemical and contractile responses and the protection afforded by beta adrenergic blocking agents remains to be elucidated, but it is attractive to postulate that beta adrenergic blocking agents are protective because of their ability to prevent access of catecholamines to adrenergic receptors during myocardial ischemia, thus altering the severity of subsequent cell damage and the frequency and severity of life threatening arrhythmias.

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