THE EFFECTS OF ISOPROTERENOL AND PROPRANOLOL ON MYOCARDIAL INFARCT SIZE

by

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ABSTACT

Isoproterenol and propranolol are two drugs that are often given to patients for the treatment of secondary effects of myocardial infarctions. The effects that these drugs have on the infarct are considered in this study. Dogs are used for the study, and electrocardiography is the mechanism by which the infarcts are evaluated.

ACKNOWLEDGEMENTS

Many thanks to Dr. Fife for the faith that he had in me, and for the time he somehow found to help me when I needed him. And many thanks for letting me find out so much on my own and for not laughing at my mistakes. Thanks also to Keller Mathews who assisted me in the surgery.

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INTRODUCTION

Cardiovascular disorders are the leading killers in America today. Myocardial infarctions (MIs) represent a significant part of these deaths, and indeed most people know of someone who has suffered from a "heart attack". An MI is the occlusion of an artery supplying blood to a portion of the heart muscle (myocardium). The extent of myocardial damage following an acute MI is a major factor in the prognosis. The specific area of damage, the amount of damage and, where circulation can be reestablished, the amount of time elapsed are of major importance. Two drugs often prescribed by doctors for treatment of cardiogenic shock and cardiac arrhythmias are isoproterenol and propranolol. The researcher artificially induced MIs in dogs and investigated the effects of these drugs on the extent of the myocardial damage. These effects were measured by electrocardiography.

BACKGROUND

The portion of the nervous system that controls the visceral function of the body is called the autonomic nervous system. There are two main subdivisions. The sympathetic nervous system originates in the sympathetic motoneurons of the intermediolateral horns of the spinal grey matter and extends to two long sympathetic chains. These chains run the length of the spinal cord and house the post ganglionic nerve bodies and they terminate in one of the organ systems. The parasympathetic nervous system leaves the CNS in the 3rd, 4th, 5th and 10th cranial nerves having the nerve body in the excited organ. The parasympathetic also has a lower

section from the sacrals. Seventy-five percent of the parasympathetic nerve fibers are located in the vagus nerve (10th cranial nerve) and since this is the bundle that affects the heart, it is of primary interest in this work. These autonomic nerves are further classified on the basis of their secretory substances. Those secreting acetylcholine (skeletal nerve endings, preganglionic neurons of both the sympathetic and parasympathetic systems, and the parasympathetic postganglionic neurons and a few sympathetic postganglionic neurons) are termed cholinergic. Those that secrete norepinephrine (the majority of the postganglionic endings of the sympathetic system) are termed adrenergic. The adrenergic fibers are further classified by the effects that certain drugs have on them. They are termed alpha and beta adrenergic neurons.[1] A beta receptor is one that can be blocked by dichloroisoproterenol (DCI) and propranolol and stimulated by isoproterenol and epinephrine. DCI, propranolol, and isoproterenol have little or no direct action on the alpha receptors. It has been recently shown that there are at least two types of beta receptors distinguished by reaction to two different drugs. The first, β_1 or excitatory beta receptor (β_e) is blocked by 4-(2-hydroxy-3-isopropyl aminopropoxy) acetanilide. And the second, β_2 or inhibitory beta receptor (β_i), is blocked by dimethyl isopropylmethoxamine. The β_e are found in the heart (SA node, AV node and associated conduction system, the atria, and the ventricles) while the β_i are found in the coronary arterys.[3]

Epinephrine can be formedfrom norepinephrine by N-methyl transferase. Large quantities of this enzyme are found in the adrenal medulla, so much more epinephrine is released from this organ than norepinephrine. Both

catecholamines do many of the same things, but norepineqhrine excites the alpha and beta receptors equally.[2] Both catecholamines stimulate adenyl cyclase at the receptor sites to make cATP from ATP. The resulting cAMP alters Ca^{++} levels causing the muscle to contract or relax.[4]

The heart cells have a semipermeable membrane that allows K^+ and Cl^- to enter the cell but excludes the Na^+ ions. Therefore, the concentration of Na^+ is greater outside the cell, so a relative positive charge is maintained on the outside of the membrane and a corresponding relative negative charge is maintained on the inside of the cell, establishing an electrochemical gradient across the membrane. This state is defined as the resting state. (Note that the resting cell is polarized). Since by convention the potential of the cell is determined relative to the inside of the cell, a resting cell has a negative potential (between -60 and -100 m.V.). When the cell membrane is excited by a flow of ionic current or other external energy, the membrane changes its characteristics somewhat allowing some Na^+ ions to pass. This movement causes an ionic current flow that further reduces the barrier to Na^+ ions causing a further influx of Na^+. In an attempt to counteract this positive influx, the K^+ ions try to diffuse out, but simply cannot keep up with the Na^+ influx. These activities cause the cell to have a slightly positive potential (+20 m.V.) and the cell is considered to be depolarized. The Na^+ in the cell is then pumped out by sodium pumps (ATPase transport enzymes) and the membrane is again made impermeable to Na^+. This action is called repolarization and the cell is again in the resting state - polarized. The action potential required to initiate depolarization is called the threshold and this threshold

must be reached to cause depolarization. After depolarization, the cells do not have the capability to respond to further stimuli.[5] The muscle cells of the heart are connected in series (a functional syncytium) with an intercalated disc between cells. The resistance through the intercalated disc is one four-hundredth that of the outside membrane of the fiber, so the action potential can travel from cell to cell through the intercalated discs without significant hinderance. This is the way the action potential travels from cell to cell in the heart, gradually reaching every part of the functional syncytium. The heart has two functional syncytiums: the atrial and the ventricular, separated by fibrous tissue and valvular rings.[1]

The action potential -- or impulse -- enters the interior of the muscle cell by way of the T tubules of the sarcoplasmic reticulum. This causes a release of the Ca^{++} from the cisternae of the sarcoplasmic reticulum. These Ca^{++} ions diffuse rapidly into the myofibrils and catalize a chemical reaction that promotes the sliding of actin and myosin (the substances responsible for muscle contraction) thus causing contraction. At the end of the action potential, Ca^{++} is transported to the longitudinal tube of the sarcoplasmic reticulum so that within a few milliseconds, the density of Ca^{++} around the myofibrils falls below that needed to maintain contraction, whereupon the cell relaxes.[1]

In the posterior wall of the right atrium, beneath and medial to the opening of the superior vena cava, there is a collection of specialized fibers called the sinoatrial (SA) node. They are 2-3 times larger than the surrounding the atrial muscle fibers, but they are connected to the atrial fibers with intercalated discs. The membranes of these fibers

allow some Na^+ to enter naturally so their resting potential is only -55 to -60 mV. In these cells, the membrane is more permeable to K^+ causing a very negative state. This increase in negativity inside causes the membrane to become less permeable to K^+ and allows more influx of Na^+, the potential eventually reaches the threshold potential necessary for excitation. It is in this way that action potential is initiated in the cell. It occurs on the average about 60-80 times a minute.

Once the impulse has spread through the atrial syncytium, it reaches the atrioventricular (AV) node, in approximately 0.15 seconds, connecting the atrial syncitium to the ventricular syncytium. A bundle of large fibers -- the bundle of His -- then transports the impulse into the Purkinjie fibers that connect to the cardiac muscular fibers. The specialized conducting fibers transmit impulses at a faster velocity (1.5-4.0 meters/second) than regular heart muscle fibers, allowing an almost immediate transmission of the impulses throughout the ventricle. This insures that the ventricle contracts as a unit. In summary: an impulse begins in the SA node and travels throughout the atrium reaching the AV node. Then specialized conduction fibers (that carry impulses faster than normal heart cells) spread the impulse to all the fibers of the heart, thus causing two contractions of two functional units, the atrium and the ventricle.[1]

There are two drugs often used in coronary care: isoproterenol and propranolol.

Isoproterenol

A derivative of epinephrine, it is a very potent beta adrenergic

stimulator. It is useful in the treatment of bradycardia due to sinus arrest. It increases stroke volume, work, and heart rate, thus increasing cardiac output. It also dilates the vascular bed, thus lowering the blood pressure, augmenting venous return, and improving peripheral blood flow. It increases the discharge rate of pacemakers and generally improves the conduction of the SA and AV junctional fibers.[6] These effects are results of the beta adrenergic stimulation. It activates the beta receptor sites of coronary vessels.[7] The metabolic O_2 requirement usually is increased in the heart cells after administration of isoproterenol. It has been shown that despite reduced or unchanged levels of systemic arterial pressure, the degree of coronary vasodilation exceeded the augmentation of metabolic requirement.[10]

Propranolol

A beta adrenergic blocking drug, it blocks the beta mimetic action of adrenergic drugs and hormones and their associated effects. It is a competative inhibitor that blocks the attachment of the beta-mimetic drug effector sites. It lowers heart rate and cardiac output associated with stroke volume.[6] It inhibits the neuronal uptake of NE. It inhibits both the chronotropic and inotropic effects of sympathetic stimulation in the heart. It has been shown that propranolol does not contract the coronary arteries, suggesting that the vascular beta receptors don't play an important role in the coronary response to nervous stimulation or NE.[7] The propranolol-induced blockade lowers the myocardial O_2 requirement. It has also been shown that it unmasks the alpha receptor causing vasoconstriction, and limiting coronary blood flow by increasing

the coronary artery resistance.[8] Propranolol has not been shown to cause coronary vasodilation in dogs.[9]

METHODS

Two dogs were anesthetized with Nembutal (16 mg/kg body weight). Respiration was maintained manually, and the heart was exposed through a left thoracotomy and suspended in a pericardial cradle. A ligature was passed under a branch of the left anterior descending coronary artery (LAD) and the associated vein. The ends of this ligature were passed through a rather rigid plastic tube and secured by a hemostat so that no apparent pressure was applied to the artery. The chest was closed and a chest tube was secured and attached to underwater drainage. The tube containing the ends of the ligature was exteriorized and sealed with an additional hemostat to maintain a closed chest. A catheter was passed into the right femoral artery so that arterial pressure could be measured throughout the experiment by a pressure transducer, and recorded by a physiograph. Self retaining electrodes were placed on each leg and five safety pins were secured on the 4th intercostal space between the midaxillary and left parasternal lines. Each EKG recording consisted of the standard leads (I, II, III, aVR, aVL, aVF) and five chest leads (taken by moving the chest lead -- an alligator clip -- to each of the five safety pins on the chest).

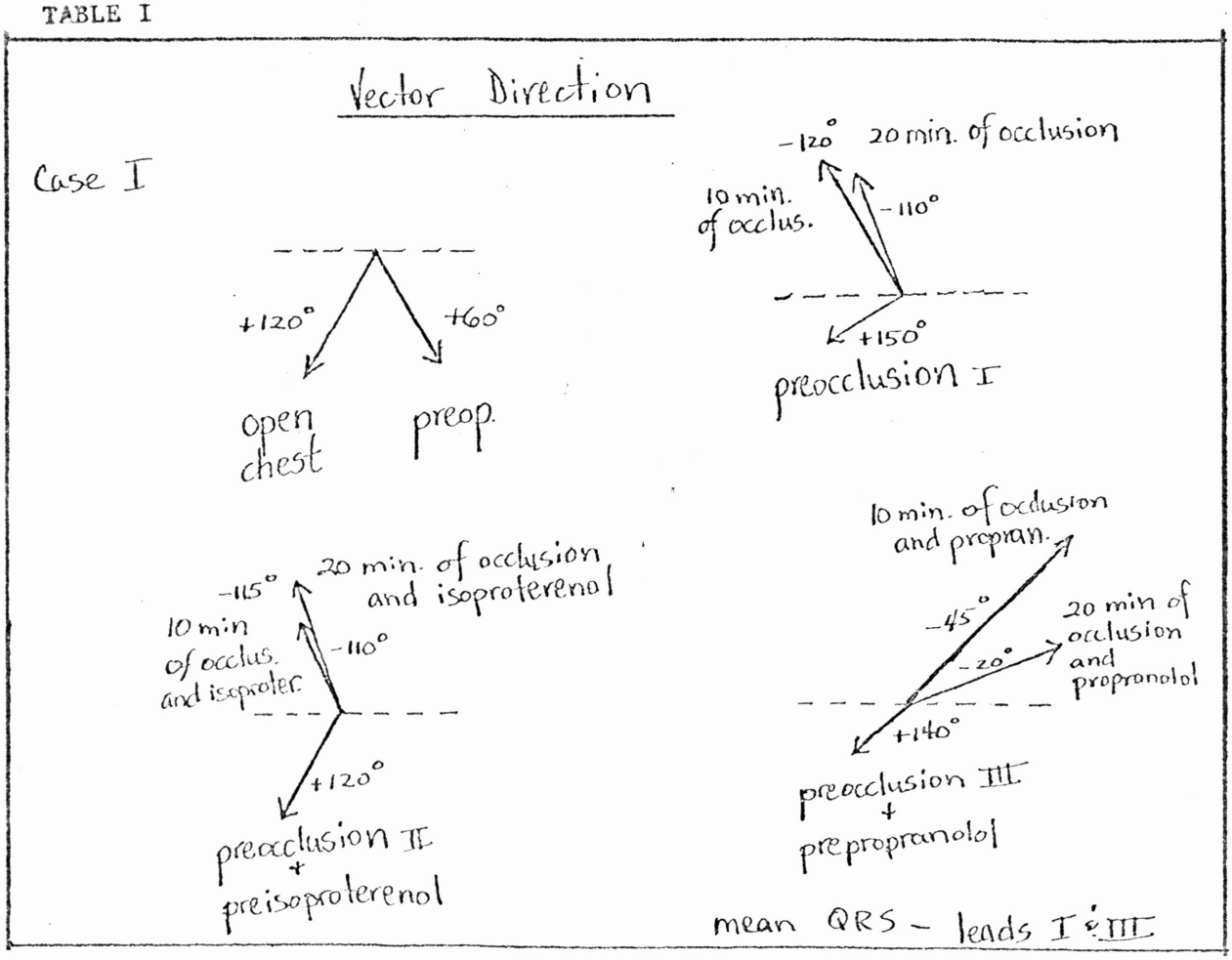
The LAD artery was occluded by pulling the ligature taut and securing it with a hemostat thus pinching the artery between the ligature and the tube. There were three occlusions that lasted 20 minutes with an hour of reperfusion allowed between each successive occlusion. The first occlusion has no simultaneous pharmacologic intervention. In the second, isoproterenol

(0.25 Mg/kg) was administered IV at the time of the occlusion. In the third, propranolol (1 mg/kg) was administered IV at the onset of the final occlusion. An EKG was taken before each occlusion and 10 and 20 minutes into the occlusion time. The 20 minute EKG was taken before the artery's ligature was released.

RESULTS

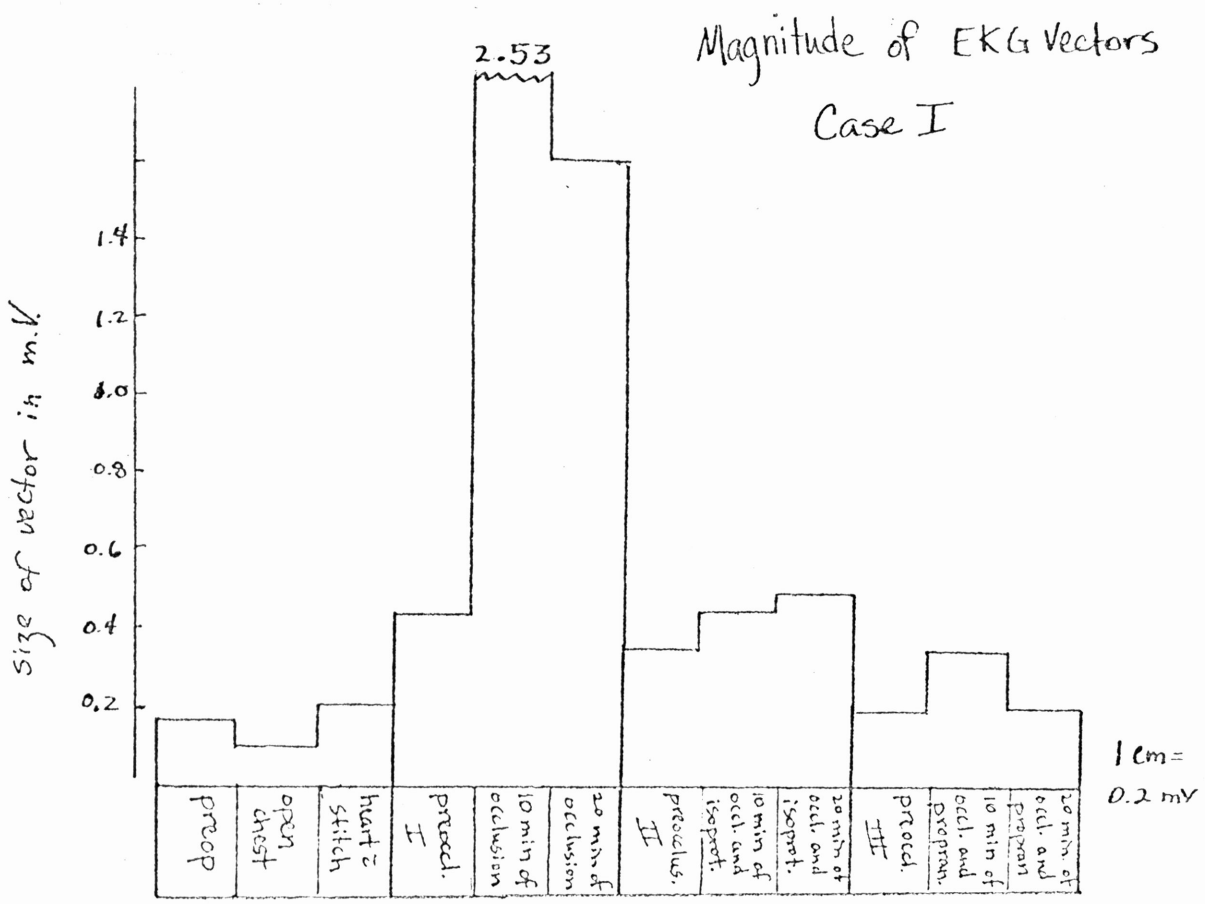
Case I: The first mean QRS vector was directed in a manner that would be expected for a normal heart. Once the chest had been opened and a stitch placed under the coronary artery, a shift of +60 degrees was observed. Once the artery was sealed, the vector swung into the fourth quadrant, approximately perpendicular to the preocclusion vector. The

TABLE I



large size of the vector as well as the direction of the change reflects apparent myocardial damage of the left ventricle in the area served by the artery which was occluded. After 20 minutes of occlusion, the vector shifted another 10 degrees and the magnitude was considerably less. After releasing the ligature and waiting an hour, the preocclusion II vector shifted back to the control and the magnitude was just slightly elevated. When isoproterenol was administered and the artery again occluded, the mean QRS vector shifted about the same amount as in the occlusion without medication, but the magnitude was more than 5 times less than the previous occlusion. Note however, that the vector shift after20 minutes of occlusion

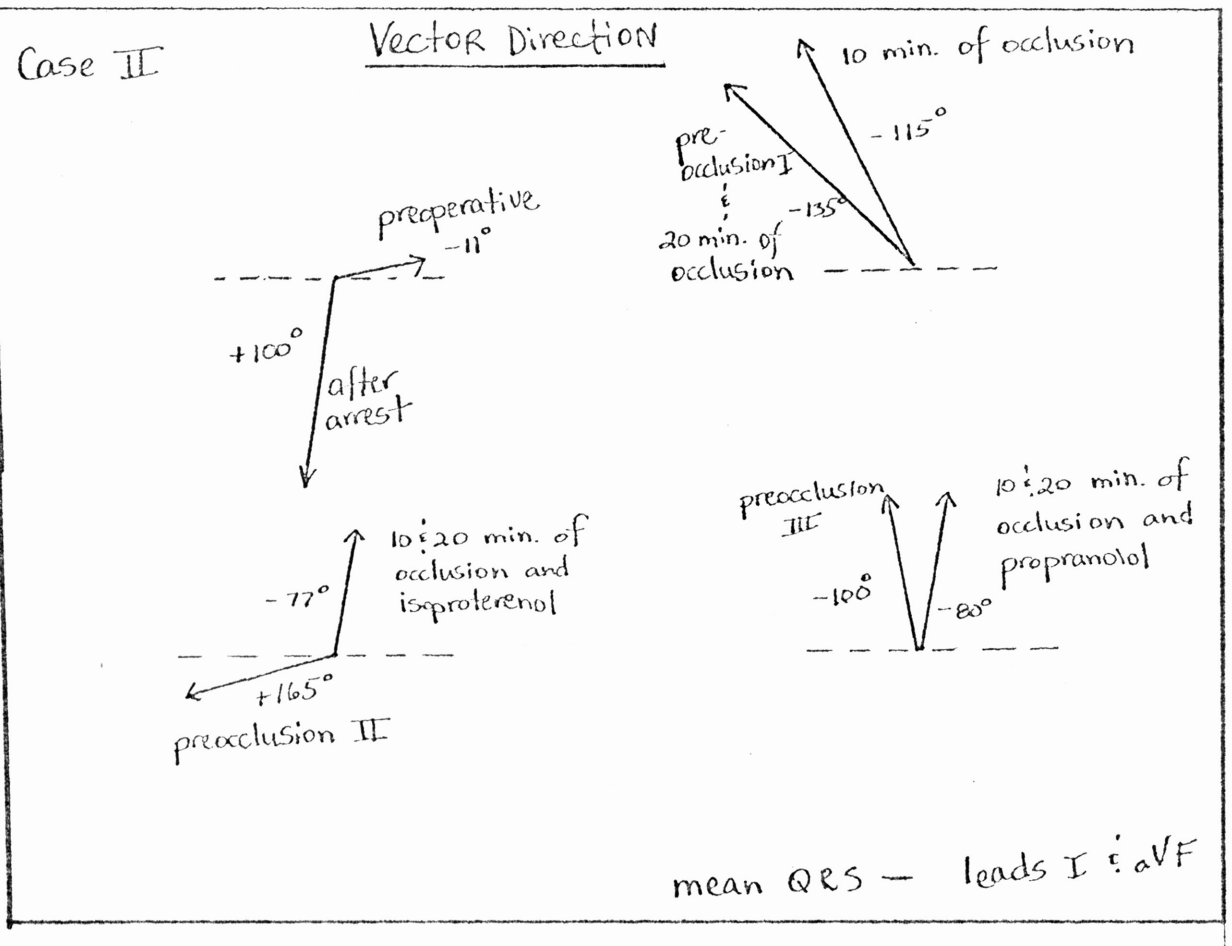
TABLE II



was predictably about 10 degrees, but the magnitude, instead of being smaller was larger. The blood pressure dropped from 140 mm Hg to 100 mm Hg. After waiting one hour after the release of the artery, the preocclusion III reading was even closer to control than the other two preocclusion readings. Propranolol then was given and the artery occluded. After 10 minutes of occlusion, the vector shifted almost 180 degrees to a -45 degrees and the magnitude increased. After 20 minutes of occlusion, the vector was at -20 degrees or a 200 degree shift and the magnitude was smaller than that of 10 minutes, but larger than the preocclusion reading.

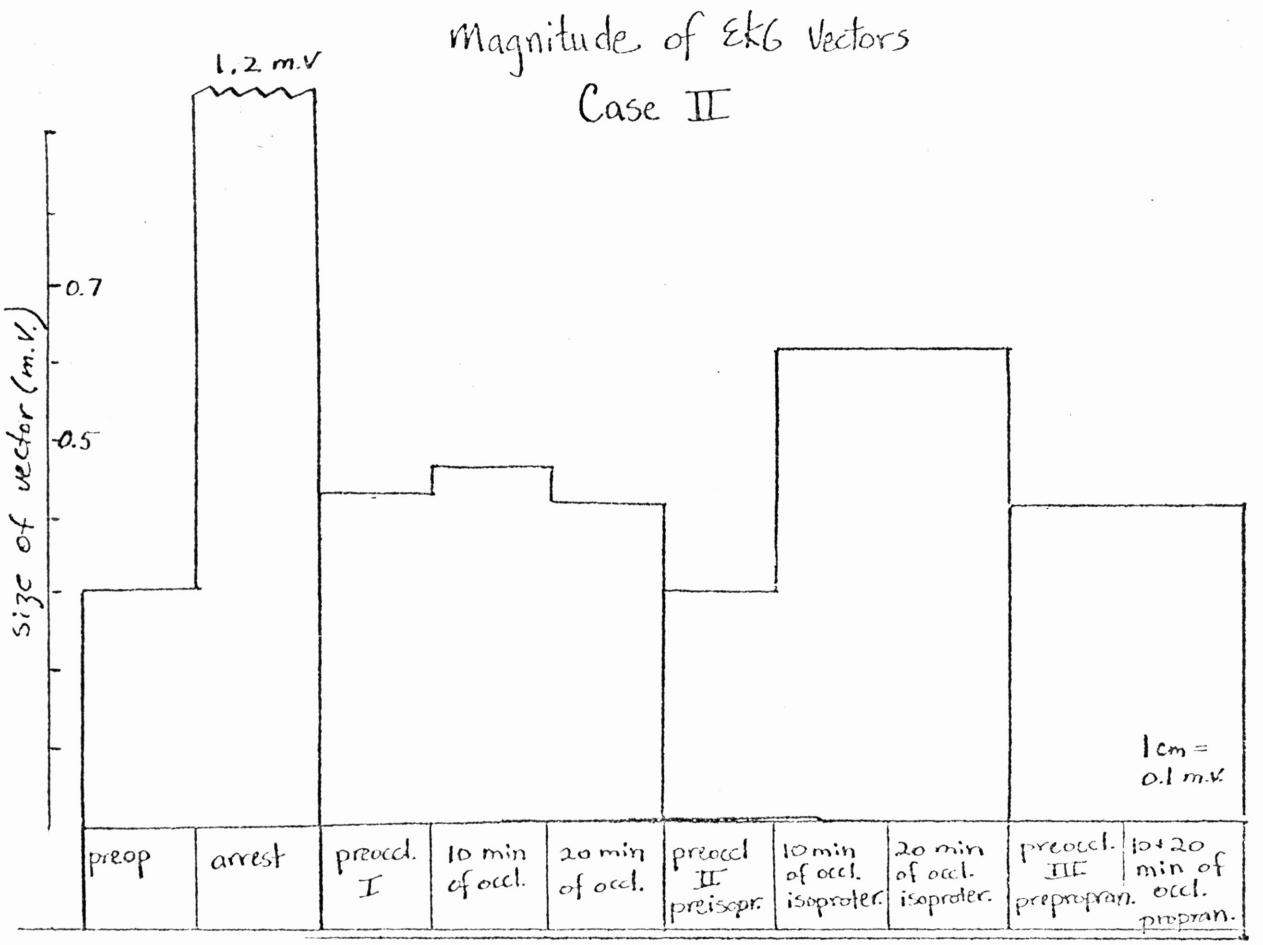
Case II: The heart arrested for a few minutes and the EKG was taken after the return of a beat (initiated by intracardiac epinephrine). This problem indicated an overall ischemia with a vector magnitude considerably

TABLE III



greater then any of the others, shifted into the 3rd quadrant. One hour after the arrest, the preocclusion I EKG indicated that there was some damage to the left ventricle (probably from the stitch), but the magnitude was almost back to the original preoperative vector's. The occlusion of the artery caused a 30 degree shift and an increase in magnitude. After 20 minutes, the vector had shifted back to the preocclusion I vector in both magnitude and direction. After one hour of reperfusion, the vector had swung back 60 degrees and the magnitude was back to control. When isoproterenol was administered and the artery occluded, the vector shift was over 90 degrees and the magnitude almost doubled. The blood pressure dropped from 80 mm Hg to 60 mm Hg. Preocclusion II vector recovered 30

TABLE IV



degrees and the magnitude dropped, although not quite back to normal. After occlusion and admisistration of propranolol, the vector swung 20 degrees, but the magnitude did not change.

DISCUSSION

Since observations were carried out on the same heart and at the same epicardial site, influence of variation of coronary arterial distribution among different animals is eliminated, and each dog can serve as its own control. The shift of 60 degrees which occurred after the chest was opened remained the same after the stitch EKG with only a small increase in the magnitude. This probably is due to a combination of two factors: a relocation of the heart and some left ventricular damage incurred from the stitch's insult on the heart. The direction indicated that when the heart was in the pericardial cradle, its axis was shifted about 60 degrees. The increase in magnitude after the stitch may be a reflection of a small amount of myocardial damage. The vector changes seen in the results of the first occlusion in both cases indicated significant myocardial damage in the area of incurred infarct, and showed that the vector changes indeed manifest themselves in a predictable manner. The return of the vector to near preocclusion I state after one hour of reperfusion indicated that the one hour time set was long enough to allow the heart to regain almost all the previous perfusion. There is substantial evidence, based on histological, electron microscopic, and histochemical studies, that immediate symptoms of irreversable damage do not occur within 20 minutes of coronary occlusion.[10] The decrease in magnitude between 10 and 20 minutes of occlusion could indicate localized compensation

from localized vasodilation or the opening of a small amount of circulation. The likely overall vasodilation from the ischemia caused by the heart's arrest may override any localized effects from the ischemia caused by the infarct. This might explain why there was no change between the 10 and 20 minutes of occlusion time in the second case. The fact that there was no increase in damage indicated in the EKG during the last 10 minutes of occlusion may indicate that there was some perfusion, but not as much as in the first case.

In both cases, the damage from an infarct accompanied by propranolol was less than that accompanied by isoproterenol. In the non-arrested heart, the occlusion without medication was the largest. In the previously arrested heart, the first occlusion was not nearly as significant as in case I. This could be due to residual effects of epinephrine given to start the heart again, as well as an overall residual vasodilation from the compensation for the arrest. Hypertrophy from the damaged area should be considered, but it is likely that after 20 minutes of occlusion, not enough damage is done to cause a significant hypertrophy. In the case where the heart was arrested, the overall hypertrophy would affect the entire heart, but the experiment only takes the changes into consideration.

The isoproterenol was shown to increase the myocardial infarct size somewhat. This might be explained by several things. An increased myocardial O_2 requirement of the cells probably is the most significant, however, the decrease in the blood pressure should also be considered. The myocardial effects are likely due to the isoproterenol effect on the myocardial cells in the heart not involved in the infarct. By increasing

the O_2 requirement of the cells, the cells bordering the ischemic area also become ischemic, thus causing an increase in the infarct size. Propranolol lowers the O_2 requirement of the myocardial cells, thus decreasing the ischemic zone and, therefore, the infarct size. The propranolol also may overcome any residual isoproterenol left from the previous injection.

This study was done on dogs, but the results might be extrapolated to cover the human heart. Dogs generally have more collateral circulation than humans, and the dogs that were used in this study showed some improvement between the 10 and 20 min of occlusion. However, if the effects of these drugs are indeed in the cells surrounding the infarct, the change in O_2 requirement could significantly alter the infarct size. The changes in vessel size from the beta stimulation or blockade seems to be overridden by the localized effects in the infarct zone.

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