ELECTROCARDIOGRAPHIC CHANGES IN RESPONSE TO EPINEPHRINE IN THE AWAKE AND HALOTHANE ANESTHETIZED DOG: EFFECT OF TREATMENT WITH LIDOCAINE AND XYLAZINE

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CHAPTER I

INTRODUCTION

Halothane anesthesia, introduced in the 1950's, is today a widely used general anesthetic in both veterinary and human medicine. With the use of halothane, however, there is a risk of cardiac arrhythmias developing during surgical procedures. One of the factors implicated in the genesis of arrhythmias is the administration of epinephrine (1). To prevent the genesis of fatal arrhythmias, a lidocaine bolus or infusion may be given to the patient (2).

Lidocaine, a local anesthetic, has been shown to be effective in the treatment of epinephrine induced cardiac arrhythmias under halothane (2). The possible mechanism of action is a decrease in the alterations of action potential durations in various regions of the heart induced by halothane and epinephrine. The ionic effects of lidocaine include a delayed closure and reactivation of fast sodium channels (4), increasing outward potassium current seen during spontaneous depolarization (5), and possible alterations with the slow inward calcium current (6).

Xylazine hydrochloride, a potent sedative, also possesses local anesthetic activity (7). There are investigators, however, which report xylazine and halothane will result in epinephrine arrhythmias in the dog (8). A complicating factor in this study, however was the presence of thiamylal as a preanesthetic agent, which by itself may result in arrhythmias.

The basic assumption in this study is that as local anesthetics, both lidocaine and xylazine would have similar mechanisms of action and thus similar effects on the cardiac action potential. This in turn would affect the response to epinephrine under halothane anesthesia.

The nature of these changes should be reflected by changes in the electrocardiogram, namely, changes in interval duration, wave amplitude and heart rate. This study will also compare the dose of epinephrine necessary to induce arrhythmia in lidocaine and xylazine treatment groups.

CHAPTER II

CARDIAC ACTION POTENTIAL

The ionic mechanisms underlying the cardiac action potential ultimately leading to contraction are multiple and do not seem to have an exact counterpart in nerve. These ionic movements are basically the same in the entire heart, but there are variations. These variations are related to the two basic types of tissue contained within the heart. One is nodal tissue which is characterized by clusters of cells supported by collagen and containing a paucity of myofibrils (9, 10). This is in contrast to the more regular pattern of the atrial and ventricular cells, which contain abundant myofibrils. The nodal tissue, which is part of the conductive tissue of the heart can be subdivided, as well, into basically two types, based on their electrophysiologic properties. Those tissues which can be classified as automatic typically do not have a stable resting membrane potential, but undergo a process of spontaneous depolarization to reach threshold potential (10). Typifying the automatic tissue is that of the sinoatrial node (SA) which normally controls heart rate by its intrinsic rate of spontaneous depolarization (9). Also known as the pacemaker, its action potential has a characteristic slow upstroke and low conduction velocity. Although composed of nodal tissue with action potential characteristics similar to that of the sinus node, the AV (atrioventricular) node does not normally possess automaticity. Cells which are not automatic are those comprising the atrial/ventricular muscle and bundle of His Purkinje fiber system. These cells are

characterized by a high resting potential and rapid conduction velocities. Throughout this discussion, the technique drawn upon to analyze the ionic basis of the cardiac action potential is the widely used method of voltage clamping. This technique utilizes a procedure of applying a steady voltage across the cellular membrane and measuring the resultant current flow through the membrane. The theory behind this technique is that a sensing electrode also placed through the membrane, senses the change in ionic currents as a result of the applied voltage, and alters the applied current so as to maintain the membrane potential current constant. The result is an equal and opposite current produced to oppose that of the ionic movement. This technique, however, only measures the total ionic flow and does not provide information concerning individual ionic currents responsible for that current. In order to analyze the specific ion effects, individual ion concentration can be raised or lowered in the extracellular fluid or a specific ion free solution can be used (11).

The characteristics of the cardiac action potential are long duration (up to 500 msec) and, in at least the Purkinje fiber system, consist of five phases. Each of these phases is associated with specific ionic movements and as previously mentioned, though all may not have an exact counterpart in nerve, some phases do share common mechanisms. The investigations concerning the Purkinje fibers will be reviewed first, followed by that of the sinoatrial node (9).

Purkinje Fiber System

The Purkinje fiber system is normally responsible for the initiation of ventricular depolarization and is a network consisting of large specialized conducting cells, passing just beneath the endocardium (12).

The network arises from the atrioventricular bundle and divides into the right and left bundle branches at the base of the interventricular septum. In this manner, electrical activation is rapidly propagated through the ventricles.

Ionic Mechanisms

The cardiac cell membrane, as in the nerve, is selectively permeable to the ions, K^+, Na^+, Ca^{++} and Cl^-. To describe the movements between intracellular and extracellular fluids, a conceptual model of these passing through channels has been proposed (11). The ability of these ions to move across the membrane depends upon the driving force or electrochemical gradient and the ability of the ions to pass through the membrane (conductance) (11). The ability of the sarcolemma to undergo sequential changes in ion conductances results in five phases of the action potential, each with its own characteristics (20).

Phase 4 - Resting Potential. The resting potential or phase 4 of the action potential is similar in mechanism in the cardiac cell to that of other excitable cells. Thus, the basis for the resting potential can be discovered, in terms of the electrochemical gradient for potassium that exists across the sarcolemma. In the resting state this gradient is such that there is a higher intracellular potassium concentration than that of the extracellular fluid space. This electrochemical gradient is maintained by a sarcolemmal transport system, the Na^+/K^+ pump (10). In this system, the small amount of sodium that enters the cell is exchanged for potassium by a Mg^{++} - dependent ATPase enzyme. Energy is needed here because both sodium and potassium are moved against concentration gradients (11, 20).

In the resting myocardial cell, the sarcolemma is more permeable to

the potassium ion, so K^+ has a tendency to move out of the cell down its concentration gradient. As these ions pass out of a cell, a positive charge is carried to the outside of the cell, which results in an electrical gradient across the sarcolemma in which the outside is positively charged (13).

The Nernst equation can be used to describe the differences in electrical potential and is:

$$Em = \frac{RT}{ZF} \ln \frac{Ci}{Ci}$$

$$= 61.5 \log \frac{Co}{Ci} \text{ (for } Na^+, K^+ \text{ and a body temperature of } 37^oC),$$

where Em is the membrane potential, R is the gas constant, T is the absolute temperature , Z is the valence, F is the Faraday constant and Co and Ci are the ion concentrations outside and inside of the cell, respectively (9).

For K^+ where $[K^+]_o$ = 4mM and $[K^+]_i$ = 140 mM, Em = -95 mV, which is very close to the actual Em of -80 mV to -95 mV. Variations in $[K^+]_o$, as can occur, especially during ischemia and/or infarction can alter Em. For example, increasing $[K^+]_o$ will result in depolarization, while decreasing $[K^+]_o$ will reduce Em or result in hyperpolarization. This theoretical concept fits well until $[K^+]_o$ gets $\leq$ 3mM, when the predicted hyperpolarization is greater than the actual Em. The reason is that as $[K^+]_o$ < 3mM, sodium diffusion into the cell becomes more important in determining membrane potential (background sodium current) (10).

Phase 0 - Upstroke. As a depolarization occurs the myocardial cell changes its permeability to Na^+ and K^+. In the presence of the background sodium current, potassium conductance decreases. Should the stimulus result in the threshold potential being reached, a regenerative current is

established. Depolarization during the upstroke of the action potential in most regions of the heart is determined largely by the rate of diffusion of sodium ions across the sarcolemma, creating the fast inward current (11). A decrease in the membrane permeability to potassium also contributes significantly to the upstroke of the action potential (9). According to the Nernst equation for sodium, a positive membrane potential of +41 mv would be predicted based on a 140 mM sodium concentration in the extracellular fluid and a 30 mM concentration in the intracellular fluid space:

$$Em = 61.5 \log \frac{140}{30} \frac{(Co)}{(Ci)} \text{ or } 37^{\circ}C \text{ body temperature}$$

The positive potential of +41 mM is not reached, however, due to a residual permeability to potassium and chloride (10).

The dependence of the upstroke on the fast inward sodium channel is demonstrated when tetrodotoxin (TTX), a poison from Japanese puffer fish, is applied to the cell. As a selective inhibitor of the sodium channel, TTX abolishes this current (13). The premise that sodium is the ion involved, can be established by replacing the perfusing medium sodium with an impermeant ion like choline - the sodium current does not appear (10).

Just as the activation of the sodium channels is a rapid process, closure of these channels is also a rapid process. Although both of these processes occur with extreme rapidity, recovery of these channels or the ability to be reactivated is much slower and not only depends on the membrane voltage level but on the time elapsed from the preceding action potential (10).

That the recovery or ability of the cell to respond to a second action potential can be seen to be voltage dependent, can be demonstrated by changing the level of the resting membrane potential prior to stimulation.

If this resting membrane potential is high (-90 mV) rapid depolarization causes the sodium channel to open rapidly and widely. If, however, the membrane is already in a partially depolarized state, (-80 mV to -70 mV), then a similar stimulus produces a more slowly rising action potential. The amplitude and Vmax are less because the sodium channels open less widely. It may also be thought of as a voltage dependent reduction in the available sodium carrier (10). Recovery can take up to 100 msec and can be prolonged by prior depolarization and drugs, such as quinidine (10).

Another current involved in this initial phase is an outward potassium current. In neurons, potassium conductance is high immediately following depolarization, allowing positive charges to be carried out of the cell initiating repolarization. In cardiac cells, however, potassium conductance decreases. This tends to keep the cell in a depolarized state, by preventing the positive ions from repolarizing the cells. This is known as anomalous rectification (14).

Phase 1 - Early Repolarization. Following the upstroke of the action potential there is a brief period of rapid repolarization often called phase 1 of the action potential. This early repolarization is due mainly to a fall in conductance to sodium (10).

Phase 2 - Plateau. The plateau is characterized by a steady membrane potential at or near zero for well over 100 msec. It is generally accepted that there are at least two, and possibly three, ionic currents responsible for the plateau phase of cardiac muscle action potentials. The ions responsible for these currents are sodium and calcium and the currents generated are known as slow inward currents (I_{si}) (15).

The slow inward sodium channel is kinetically and pharmacologically

distinct from the fast inward sodium channel (11, 13). It has a less negative activation potential (-35 mV) and a lower inactivation potential. The contribution of sodium ions to the action potential differs among atrial, ventricular and Purkinje fibers and varies between species (11). For example, in ventricular muscle of the dog and cat, changing the sodium concentration does not greatly affect the slow inward current (17, 18). However, in Purkinje and ventricular fibers of the guinea pig (19, 20), the cow (84) and the rat, the slow sodium current plays a significant role.

The slow inward calcium current has a threshold of -55 mV, is time and voltage dependent and has its maximum effect at -10 mV. Separate conduction pathways for the calcium and sodium ions are indicated by the evidence manganese and lanthanum ions preferentially block the Ca^{++} channels (22). A third slow inward current is a sodium/calcium slow channel. In this instance some bound sodium is required for this channel to be operative (13).

The role of the calcium that enters the cell during the slow inward current is involved in the release of intracellular calcium stores from the sarcoplasmic reticulum. It is this calcium which interacts with the myofibrillar protein, troponin C, to initiate muscle contraction (9).

Phase 3 - Repolarization. This phase of the action potential is the return of the Em to those levels characteristic of the resting cell. The ionic mechanism underlying the process is an increase in membrane permeability to potassium and a decrease in sodium and calcium permeability to resting values (9, 11).

Sinoatrial Node

Unlike cells of the atria or the Purkinje fibers, the nodal cells do not have a stable membrane potential. Instead, nodal cells demonstrate spontaneous depolarization (10).

As in the Purkinje cell, there are currents in the sinoatrial node that are time and voltage dependent. The characteristics of the sinoatrial node action potential are its Em threshold ≃ -35 V/sec (compared to 80-300 V/sec for atrial fibers) (10).

The mechanism(s) responsible for the spontaneous depolarization of nodal cells may be a decreasing outward K^+ current, an increase in the background sodium current, or an increase in the slow inward calcium current (9). The most recent view of spontaneous depolarization is that it is a result of an increase in the calcium current with a subsequent decrease in the potassium current (15). At threshold there is a further increase in the permeability of the membrane to calcium and a decrease in membrane permeability to potassium. Sodium ions to not seem to play an important role in either spontaneous depolarization or in phase 0 of the action potential. These conclusions are based on the results obtained after using pharmacological agents such as Verapamil and tetrodotoxin (TTX) (23, 14). Verapamil, a slow calcium channel inhibitor, will suppress phase 0 of the sinus node, while TTX has a minor effect of suppressing phase 0 of the sinus node action potential (11). Finally, decreasing $[Na^+]_o$ will not decrease the slope of spontaneous depolarization, as occurs in Purkinje fibers. Repolarization of the SA node is brought about by a decrease in membrane permeability to calcium with an increase in permeability to potassium (15).

Atrium

The atrial action potential is similar to the action potential of the Purkinje fibers except the duration is shorter. Diastolic potential is constant, hence, there is no pacemaker activity. Phase 0 is rapid and is followed by a brief phase 1. Phase 2 is abbreviated and often merges into phase 3 repolarization. The terminal portion of phase 3 tends to return to diastole at a slower rate than in Purkinje fibers (10).

AV Node

The AV node, a region of slow conduction, is reflected in action potentials of low amplitude and slow rate of rise. Spontaneous depolarization, once thought to be prominent, is now believed to be absent in these fibers, so the AV node has little or no pacemaker activity. The resting potential is -80 mV with an overshoot amplitude of +5 to +10 mV (9).

Ventricle

The ventricular action potential is similar to that described for the Purkinje fibers, although the duration and amplitude are less than that for the His Purkinje system. Spontaneous diastolic depolarization is not seen in the normal working myocardial cell (9).

CHAPTER III

THE ELECTROCARDIOGRAM

The wave of electrical activation which arises in the SA node spreads through the heart, first through the atria and then the ventricles. This conduction takes place throughout cardiac muscle and is made possible by sites of low electrical resistance at junctional complexes between adjacent cardiac muscle cells known as the intercalated discs (24).

In the atrial musculature, the conduction velocity is approximately 0.3 m/sec and is slowed to 0.2 m/sec in the region of the AV node. This allows the atrial musculature to depolarize and contract before the ventricles begin to depolarize. Conduction velocity is accelerated to 4 m/sec in the Purkinje system, until the termination of those fibers is reached, where velocity is again slowed to approximately 0.4 m/sec (9).

The organization of the Purkinje fiber system varies somewhat between species. In the dog, the Purkinje system passes along the subendocardial surface of the interventricular septum. Terminal branches arise within the septum, prior to termination within the subendocardial musculature (9).

The first deflection of the electrocardiogram is the P wave, which represents atrial depolarization. No manifestation of sinoatrial nodal depolarization is evident for the electrical potential differences are not of sufficient magnitude. The duration of the P wave depends on both the size of the atria and the conduction velocity (25). Occasionally, a wave of opposite polarity, low voltage and long duration follows the P wave.

This is the atrial repolarization or atrial T wave (Ta or Tp). The action potential of the atria has a very short plateau, hence, repolarization (Tp) develops directly after the P wave (24). There is no isoelectric interval such as the ST segment. Spread of activation to the AV node and the delay of conduction is reflected in the PR segment of the ECG. The PR segment is that time from the end of the P wave to the next deflection from the baseline. This segment is isoelectric because the mass of tissue involved is too small to generate surface voltage (24).

After the impulse has traversed the Purkinje fiber system, ventricular activation begins, producing the QRS complex of the electrocardiogram (24). The amplitude of the QRS complex is much greater than that of the P wave due to the mass of tissue involved. The process of ventricular activation can be divided into three phases, septal activation, apical activation, then activation of the base of the heart (24).

Following the QRS complex, the ECG returns to or near the baseline until the last wave, T, is inscribed. This is the ST segment, and is a time when all regions of the heart are in a depolarized state. The isoelectric segment reflects an absence of potential difference within the ventricles at this time. The long duration of this segment reflects the plateau (phase 2) of the cardiac action potential (9, 24).

The ST segment usually starts with a slowly rising phase, which develops into the T wave. This is due to an asynchrony of fiber repolarization. The longer the plateau, the more isoelectric is ST. Any shift in the ST segment will reflect changes in the local properties of fibers. This can be either due to damage or to changes in heart rate (24). For example, ST is depressed at higher rates and elevated during slower heart rates. The repolarization of the ventricles produces the T wave and corresponds to

phases 2 and 3 of the cardiac action potential. The duration of the T wave is longer than that of the QRS complex, because repolarization is not as rapidly propagated as depolarization. The T wave is determined largely by local factors that may influence the duration of the action potentials in each region of the ventricles.

Coinciding with the T wave is what is referred to as the vulnerable period of ventricular repolarization (9). It has been shown experimentally that stimulation during this time is more likely to result in lethal ventricular arrhythmias. The underlying mechanism of the arrhythmias seen during this time is probably reentry due to slowed conduction and unidirectional block (see section on arrhythmias).

Another interval usually measured in the electrocardiogram is the QT duration (24). The end of the T wave represents the time whan repolarization of the ventricle is completed. The QT duration must, therefore, depend upon the factors: the amount of asynchrony which may be calculated from the QRS, and the longest action potential duration of the myocardial fibers. The duration of the QT depends mainly on the heart rate, and also on the factors which may change the rate. Heating, for example, shortens the QT interval, whereas, an increase in sympathetic activation increases the QT duration (9, 24).

Various Influences Upon the ECG

Effects of Anoxia, Hypoxia and CO_2

If the CO_2 of perfusing fluid is increased, leaving the electrolyte composition constant, the T wave is heightened. Reduction of coronary flow produces the same changes (26). Under severe oxygen lack, the T wave is

flattened and the ST segment is slightly depressed. The changes occurring in the cellular action potential resulting in the ECG changes are a shortening of the action potential duration followed by a decrease in the resting membrane potential of the ischemic cells (24).

Autonomic Influences

Stimulation of the vagus nerve decreases propagation velocity, and therefore, lengthens the PQ and QRS duration. Vagal stimulation will shorten QT while sympathetic stimulation lengthens this interval. The amplitude of the QRS is increased by vagus nerve stimulation and decreased by sympathetic activation. The influence on the T wave is harder to isolate, but it is generally assumed that the vagus nerve augments while the sympathetic system depresses the T wave (11, 24).

Ions

The influence of ions on the heart are best exemplified by changes in the QRS and T wave, the QRS is prolonged in hyperkalemia whereas, in a human heart, a severe deficiency of Na^+ will prolong the duration (9). The QT interval is rather insensitive to changes in plasma Na^+, K^+, Cl^- and HCO_3^-, although hypocalcemia will prolong the interval (9). Hypercalcemia will prolong QT even further while if $[K^+]_i/[K^+]_o$ rises, QT may be prolonged (9, 24).

CHAPTER IV

CARDIAC ARRHYTHMIAS

Arrhythmias or abnormal rhythms, have been classed into three categories relating them to alterations in the physiology of the heart, and to certain drug effects. As with any classification scheme, the possibility of overlapping causes can be expected (27, 28).

Triggered Activity

One of the causes of cardiac arrhythmias is known as triggered activity (29). Triggered activity is sustained by a locally evoked potential or from a distant action potential by after depolarization (30). Such activity can be initiated by acetylstrophanthidin or ouabain in Purkinje fibers (31). An afterdepolarization can be produced when repolarization results in hyperpolarization. Following the hyperpolarization, a transient diastolic depolarization occurs - a delayed afterdepolarization (30, 32). The amplitude of the afterdepolarization depends upon the rate of action potential production in the fibers. By increasing the rate and thus the amplitude of the afterdepolarization, threshold may be reached, resulting in one or a burst of impulses or triggered activity (30, 33). The evidence to suggest the current responsible for the afterdepolarization triggered activity is the slow inward Ca^{++} current is that catecholamine application may result in afterdepolarization (34-36).

Automaticity

Automaticity is a property seen in the SA node and the rest of the specialized conduction tissue of the myocardium (9, 30). Since the automatic firing rate of the SA node is the greatest this area suppresses the formation of impulses from the other cells (37). Any condition which will suppress the activity of the SA node or enhance activity of ectopic, or latent pacemakers can result in arrhythmias (28). If the sinus node fails to excite the rest of the heart, a latent pacemaker may take over primary pacemaker activity (38). An example of this occurs with strong vagus nerve stimulation, which will inhibit sinus node automaticity as well as other atrial pacemakers (39). Since vagal effects on the Purkinje system are minimal, spontaneous diastolic depolarization may still occur, which can result in impulse initiation. If the impulses arise in specialized atrial fibers or in Purkinje fibers with maximum diastolic potentials of -60 mV or greater, the response seen is that of the fast type - a response associated with the fast inward channel (39). If the maximum diastolic potential is less than -60 mV (Em $\rightarrow$ 0) and arise in the AV junctional or AV valve leaflets (slow fibers), the response is characteristic of slow conduction (39).

Enhanced automaticity resulting in a pacemaker shift may result from one or two reasons. One is the enhanced activity resulting from sympathetic activation (40). Since catecholamines enhance activity in all conducting fibers, and activation may not be uniform, shift of pacemaker site is possible (41). In situ sympathetic stimulation can result in a shift of pacemaker site allowing the latent pacemakers to assume primary pacemaker function (38). These conditions can result in atrial or ventricular tachycardias.

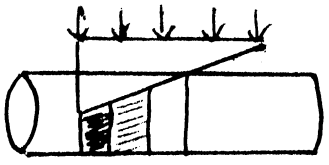
Pathological conditions such as infarction/ischemia can result in local changes in fiber automaticity (39). Evidence exists that Purkinje fibers and normal atrial myocardial cells depolarized to -40 mV exhibit enhanced automaticity under pathological conditions similar to that seen in ischemia/infarction. Automaticity in ventricular muscle fibers has not yet been shown, but depolarization as a result of injury has been produced.

Reentry

Lately there is an increasing body of evidence used to explain arrhythmias in terms of reentry. The concept of reentry depends on the abnormal excitation of the heart from an impulse which does not die out after propagation (42). Normally, an impulse initiated from the SA node which excites tissue in atria and ventricles eventually will die out when it encounters refractory tissue. For reentry to occur, the impulse must remain somewhere in the heart to reexcite after the refractory period. Since the refractory period can be as long as 500 msec, the reentry impulse must remain for this period within a pathway functionally isolated from the rest of the heart (43). Because the conduction velocity of the impulses in atrial or ventricular tissue is between 0.5 to 4 msec, a functional pathway could not exist in the heart to allow this to occur. The reentrant impulse must conduct at a slow velocity, which would not need a long conduction pathway (44). For example, a velocity of 0.02 msec would only use a pathway of 6 mm in a refractory period of 300 msec. Other mechanisms that would result in reentry are shortening of the refractory period, or re-excitation due to heterogeneities in refractory period in adjacent fibers. Such an example would exist in catecholamine administration or halothane anesthesia (42).

Reentry Due to Slow Conduction and Unidirectional Block

Functional pathways do exist in the ventricles which will allow reentry in the presence of slowed conduction. Reentrant pathways can exist in the areas where Purkinje fibers are in loops - areas of contact with other Purkinje fiber bundles and areas in contact with the ventricular myocardium (29, 42). Under normal circumstances, an impulse initiated from the SA node will invade the Purkinje system and ventricular muscle and then die out after encountering refractory tissue. For reentry to occur in the ventricle, an area of slowed conduction and unidirectional block must exist (42). The concept of unidirectional block is important in reentry phenomena and implies that conduction is blocked completely in one direction. The mechanism of unidirectional block can occur in any bundle of tissue which sustains an injury and results in an asymmetric depression in action potential amplitude and decremental conduction (9). This is illustrated below:



(darker shading indicates a greater degree decremental conduction)

(NOTE: Wedge shaped block to indicate asymmetric pressure to myocardial strand to result in asymmetric depression of cellular function).

Assuming: In the tissue from 0-2 and 8-10, normal propagation occurs and the action potential is capable of activating up to 2 units of

tissue. Between 2-3, damage is enough to completely block an impulse. Between 3-8, degree of compression dictates ability to conduct impulses.

If an action potential starts at 0, it can spread to 2, then to 4 where depressed conduction occurs. It is delayed up to point 8, where it emerges again as a normal action potential. An action potential starting at 10, conduction starts to slow at 8 down to 6. At 6, depressed conduction starts until the impulse finally reaches the area of complete block, and goes no further.

After the impulse leaves the area, if it encounters tissue that is ready to be reexcited, a premature or reentrant beat will be initiated. This can result in a continuous circling of impulses resulting in repetitive ventricular activation. This type of unidirectional block is similar to the mechanism of reflection, which may occur in unbranched bundles such as the His bundle.

Reentry may result from excitation by a premature impulse entering the conducting system. If the cells are reactivated prematurely before complete recovery is possible, unidirectional block and slowed conduction may also result. (The safety margin of conduction is lower in partially refractory tissue) (45, 46).

Reentry Due to Summation

Summation, or the process where two stimuli can combine to produce an action potential of greater amplitude, can also occur in myocardial tissue (42).

In depressed cardiac fibers that demonstrate slow response action potentials, the degree of activation of individual current during the depolarization phase is dependent in part on the strength of the depolari-

zing stimulus. After a weak stimulus produces a submaximal response, further depolarization can result in an increased amplitude, if done during the initial phases of the action potential. If both ends of a Purkinje fiber bundle are activated simultaneously, summation may occur in an area of depressed conduction, resulting in an action potential of greater amplitude than either response along. The impulse can then be conducted out of a branch of the fiber system, but at a very slow velocity. The time it takes to get out of the depressed area, which may be up to 300 msec, will put this impulse in tissue whose refractory periods are over (or nearly over), thus resulting in premature beats.

Reentry Due to Alterations in Refractoriness

Unidirectional block and slowing of conduction resulting from local alterations in refractoriness of tissues can also produce reentry (45).

In the ventricles, there is a point along the conducting branches which has the maximum action potential duration and refractoriness, and is called the gate. This gate, under normal conditions determines the effective refractory period for that part of the ventricular conduction system. Thus, when a premature impulse enters the bundle before the end of the effective refractory period at the gate, it will not reach excitable ventricular muscle (42).

Localized disease or ischemia can result in alteration of the refractory periods of the gate or fibers in the terminal Purkinje fiber region. Conditions for reentry are then established for producing premature systoles. The current thought, however, relating alterations in refractory period to premature beats, deals with the action potential duration/effective refractory period ration. There is evidence that if

the action potential duration in one area of cardiac muscle is shorter than in an adjacent area, conditions are produced for a flow of depolarizing current (boundary current). This current flows from the area of longer action potential duration to an area of short action potential duration, which should speed up the conduction of the adjacent area (47).

Any of the above conditions necessary for reentry can occur as a result of changes in local factors, such as acid base balance or from pharmacological interventions. Changes such as this include halothane sensitization which alters the action potential durations and refractory periods of the Purkinje fiber and ventricular fiber systems (48). The mechanism for these changes is believed to be a result of an increased potassium conductance (48).

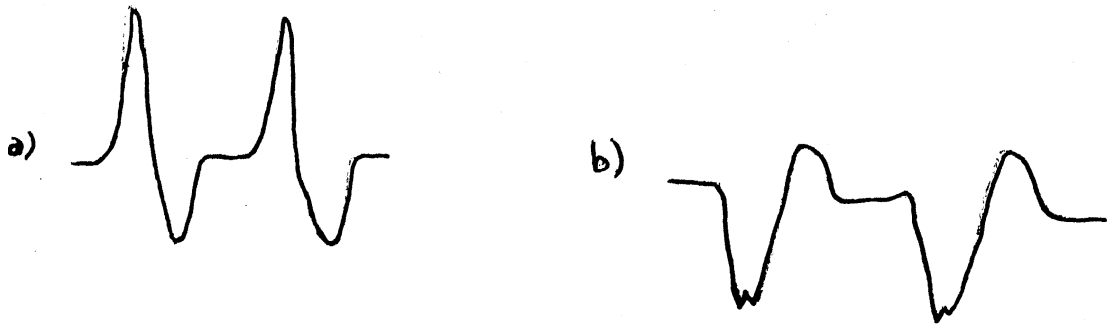
Premature Systoles

There are various theories concerning the underlying causes of premature systoles. There is a body of evidence, however, to suggest that premature systoles can be explained by reentry (9). Moe (49) has demonstrated reentry as an underlying cause for arrhythmias of the atria and possibly for those occurring in the ventricles. These arrhythmias range from atrial flutter/fibrillation to premature ventricular depolarizations and ventricular tachycardia (49). Associated with premature beats is a classification scheme which is related to their origin and certain electrocardiographic changes (50).

Classification. Supraventricular: Supraventricular premature beats are those beats which arise either from the atria or the region around the AV node. In atrial premature beats the P wave occurs earlier than

normal, is positive in leads II, III and aVF. The P wave is usually abnormal in size and/or configuration due to its discharge from an ectopic pacemaker. The QRS complex, however, is usually normal for the pattern of ventricular activation is usually unaffected. Those beats arising from around the AV node or junctional region are characterized by normal or nearly normal QRS complexes preceded by an inverted P wave in leads II, III and aVF. This occurs for atrial activation is usually in a retrograde manner.

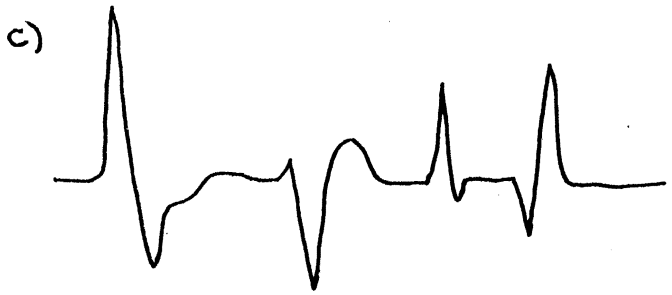
Ventricular: Premature ventricular beats are those usually arising from the fibers of the ventricles. The ectopic focus may originate from any part of the ventricle, the closer to the bundle of His, the more normal the QRS-T complex. Reentry can explain many of the electrocardiographic changes usually associated with premature ventricular systoles. Circus movements may occur in the peripheral ventricular conducting system, whereas, summation may occur in the peripheral Purkinje system. The characteristic ECG finding is a widened, slurred QRS complex. [a] Reentry by reflection, however, may occur anywhere in the A-V conducting system, from the His bundle to the distal Purkinje twigs. This would result in a premature ventricular depolarization with an aberrant QRS complex. [b] This is illustrated in a and b below:



There is general agreement that those premature depolarizations which have a fixed relation to the preceding P wave, are caused by the preceding impulse and may be reentrant (42).

Reentry by circus movement or reflection, would result in a normal activation sequence at first. During the QRS complex and QT interval, the impulse would be conducting slowly in a depressed pathway. This depressed conduction is silent, most likely because the wave front is small and travels at low velocities. Emerging from the reentrant pathway, an abnormal QRS complex would be inscribed. The R-R' interval is, therefore, determined by the time of conduction through the pathway. Fixed coupling would occur if the pathway is fixed and conduction always occurs at the same speed (42, 45).

Reentry by summation also may be predicted to be characterized by fixed coupling if certain assumptions are made. These include a constant conduction velocity of the summating and summated impulses, as well as a constant time for summation. These constant interval beats are known as unifocal ectopic beats, those arising from one ectopic focus. When these intervals vary and the forms vary, they are identified as multifocal. c) This is illustrated in c below:



Premature beats may occur in groups of 2 or more, each resulting from continuation of conduction through a reentrant loop. Two are referred to as a pair, three as a run and four or more as a tachycardia (50). Resetting of the cardiac rhythm or a compensatory pause between is also usually associated with premature systoles. Although the sinus node continues at its normal rate, it encounters refractory AV nodal tissue during the premature contraction. This refractory state of the AV node results from a partial but incomplete retrograde conduction from the premature ventricular contraction. Thus, although the P waves are occurring at their normal rates, the P wave that may precede the premature contraction is unrelated to the abnormal QRST complex.

Occurrence of premature contractions is dependent upon origin of ectopic pacemakers. Whereas atrial ectopic beats rarely occur in a normal dog, ventricular premature contractions may occur as a result of stress or anxiety. Detweiler et al. (12) considers presence of premature ventricular contractions as pathologic.

Hemodynamics. Cardiac arrhythmias pose their threat to life when they involve disturbances in the hemodynamics of circulation. The extent of hemodynamic disturbance in any arrhythmia depends upon the prematurity, frequency and site of origin of the ectopic impulses (51).

Postextrasystolic Potentiation. The first beat to occur after a pause from a premature beat may show an increased contractility. This is manifested as an augmented stroke volume with a shorter period of isometric contraction. It has been held that the degree of potentiation is related to the degree of prematurity of the ectopic beat and the strength of the nonpotentiated contractions.

Frequency of Premature Beats. Only those occurring in couples or groups will significantly reduce the cardiac output. Ventricular premature beats may reduce the stroke volume by as much as 25 percent. The hemodynamic effects of PVC's depend upon several factors, the most important being the degree of prematurity. These beats are less effective than normal sinus beats, because being premature, the ventricles are not completely filled with blood at this time. One important point is that the energy expenditure of premature beats is not decreased to the same extent as the decrease in work. Therefore, their frequent occurrence lowers the efficiency of the heart and may lead to heart failure.

Data obtained in dogs indicate that coronary blood flow is reduced about 12 percent by premature contractions. A reduction of as much as 25 percent may occur if the frequency is increased. This in turn contributes to impaired ventricular performance during these arrhythmias.

CHAPTER V

HALOTHANE

In the 1950's, a series of nonexplosive, fluorinated hydrocarbon anesthetics were developed. Among these is halothane, an anesthetic that is in widespread use today in veterinary and human medicine (52). The effects of halothane, as with some other general anesthetics, upon the cardiovascular and respiratory systems is a dose dependent depression of a number of functions. The literature concerning these effects is extensive and conclusions are variable among authors, though many investigators relate a depression of these systems with increasing alveolar anesthetic gas concentrations (53-59).

Generally, halothane anesthesia results in relaxation of vascular smooth muscle and a decrease in myocardial contractility (60). These influences are presumably mediated by direct effects of the anesthetic on the muscle, although mediation through neural and humoral mechanisms remains a possibility. The evidence is that some effect on the regulatory mechanisms is present, but the data is difficult to interpret clearly. For example, evidence favoring a direct action is the hypotension which results when halothane is administered to the body of a dog in a cross circulation preparation. If halothane is administered only to the head, the resting arterial pressures are changed only slightly (61, 62). Halothane has also been shown to result in vasodilatation when applied to strips of aorta, probably working through increasing levels of cyclic AMP (3).

The effects on respiration are also disputed, these disputes being due in part to lack of effective experimental controls. The primary effect of halothane, as with most inhalation anesthetics, is respiratory depression (53, 54). In studies in various animals, it has been found that $PaCO_2$ usually rises, the extent of the rise depending on the type of premedication, and whether there is controlled or spontaneous ventilation (63-65). In man and in dogs (55, 64) an improvement in cardiovascular performance was associated with spontaneous ventilation, and attributed to lack of positive thoracic pressure, or more likely, an increased $PaCO_2$ (55, 65). In dogs, the $PaCO_2$ did not exceed 40 mmHg, except when the halothane concentration was three times minimum alveolar concentration.

Halothane Anesthesia and Cardiac Arrhythmias

It has been well documented from the original study in 1956 by Raventos (52), that halothane anesthesia can result in cardiac arrhythmias. There are a number of factors which can result in arrhythmias, ranging from changes in cardiovascular system parameters such as blood pressure to the electrophysiology of the heart.

One of the factors implicated in the genesis of arrhythmias during anesthesia is surgical manipulation (66). Another factor implicated in the genesis of arrhythmias is the $PaCO_2$. As mentioned previously, with spontaneous ventilation, there is generally a higher $PaCO_2$ than if ventilation was controlled (64, 65, 67). What is important about the $PaCO_2$ is that there is apparently a threshold, dependent upon the anesthetic used, which would allow the production of arrhythmias (67). The mechanism has been debated, with direct CNS stimulation as one possible cause and the release of endogenous catecholamines as the alternative (23). Comparing

the effects of various anesthetics it was found that with pentobarbital raising the $PaCO_2$ and allowing the pH to fall to values around 7.0, provides protection against epinephrine induced arrhythmias. This result is in agreement with those found with cyclopropane in dogs (67). This protection is dependent upon maintenance of a state of acidosis, for if arterial pH was kept constant, protection was not afforded. Artificially increasing H^+ concentration in animals via acid infusions, was found to protect against epinephrine induced arrhythmias in spite of a normal end tidal $PaCO_2$. The proposed mechanism(s) for protection might include: 1) a reduced vasopressor response to systemically administered catecholamines during acidosis and/or 2) a direct inhibition of metabolism during acidosis (67).

Other investigators have found a threshold for $PaCO_2$ induced arrhythmias during anesthesia. With cyclopropane, for example, the threshold $PaCO_2$ varied from 44mm to 72mm of mercury, depending upon the anesthetic concentration. For halothane, the $PaCO_2$ threshold ranges from 60mm to 140mm of mercury (66).

Role of Heart Rate and Blood Pressure

It has been documented by various investigators that change in heart rate and blood pressure play a role in the genesis of arrhythmias (1). The response to epinephrine generally consists of an immediate pressor effect with an increase of heart rate, followed by a depressor effect, widening of pulse pressure and a decrease in heart rate (68, 69).

It was reasoned since the first studies relating cardiac arrhythmias with blood pressure under chloroform, that a change in aortic pressure was at least one of the criteria necessary for production of ventricular

extrasystoles (66). It was later found, that this change, although not absolutely necessary, would facilitate the production of the arrhythmia. Moe et al. (70) reasoned that blood pressure, heart rate and the sympathomimetic amines in some combination were important factors. Heart rate is also an important factor in arrhythmia production. Vick and Dresel have found that cardiac arrhythmias produced by epinephrine infusion could be terminated by vagal stimulation (71). If a lower infusion rate was used, but the atria were paced at the higher rate, arrhythmias appeared.

Halothane acts on the sinoatrial node to produce a slower rate of rise on the phase 4 spontaneous depolarization and a decreased overshoot amplitude. This is manifested as a slower sinus rhythm and thus heart rate (48). Halothane also depresses conduction velocity, which is manifested by increased interval duration of the surface electrocardiogram (72). In the Purkinje and ventricular fiber systems, halothane results in a decrease in the Vmax, overshoot amplitude and action potential duration (48). The effective refractory period is also shortened in these areas, but not to the same extent (73, 74).

Considering the experimental evidence, the production of arrhythmias by halothane is most likely due to reentry of impulses and not from enhanced automaticity (75). Reentry requires a slowed conduction and/or unequal distribution of effect on the refractory period (29, 73). These conclusions come from experiments on ouabain toxicity and ventricular escape time (75). It was found that when ventricular tachycardia was induced in dogs with ouabain, halothane exposure converted this to sinus rhythm. In the same experiments, strong vagal stimulation produced

cardiac standstill. Vagal escape time and rate of the escape beats was lower in dogs anesthetized with halothane than in dogs anesthetized with sodium pentobarbital (75).

CHAPTER VI

EPINEPHRINE

The influences of the sympathetic nervous system are attributable to many of the problems seen in cardiac arrhythmias.

Innervation

The innervation of the heart is supplied by thoracic nerves, T_1 -T_5, whose postganglionic fibers richly innervate the sinus and AV nodes. Adrenergic innervation of the atrial musculature is also quite extensive, though not to the same extent as in the nodal areas (33). Ventricular innervation is also extensive, but the density of the innervation varies markedly in different regions. The Purkinje network appears to have only limited innervation (22).

β Receptor Activation

It was postulated in 1906 that the catecholamines released from the nerve terminals, reacted with a receptor to result in a physiological effect (76). Since then, these receptors have been classified as α and β and attempts to encompass all known effects have been made (77). When dealing with the cardiovascular system, α receptor stimulation results in arteriolar constriction and little direct effect on the heart. There is not much evidence to suggest α receptors exist in the heart resulting in a decreased heart rate and decreased contractility (38). Beta receptor stimulation results in arteriolar vasodilation, with an increased heart

rate, strength of contraction and conduction velocity. The density of the beta receptor has been the subject of many investigations (78). It has been suggested that the β receptor has protein binding sites with crucial sulfhydryl groups, located on the outer membrane surface (38).

Activation of β receptors by epinephrine results in a series of reactions eventually leading to the physiological response. Studies indicate that the formation of cyclic AMP may be the link between β receptor stimulations and the physiological response (79). Beta receptor stimulation has been shown to increase the activity of the membrane bound enzyme, adenylate cyclase, which in turn catalyzes the formation of cyclic AMP from ATP. Beta receptor antagonists such as propranolol can block its activation (80, 81).

Electrophysiology

The catecholamines, whether endogenous or exogenous, elicit a wide variety of effects depending upon the types of cardiac muscle fiber studied.

Sinus Node

The sinoatrial node exhibits spontaneous phase 4 depolarization and by changing the slope of depolarization, the rate of firing will change (1).

Catecholamines increase the slope of phase 4 depolarization and therefore, shorten the cycle length between spontaneous action potentials (38). The primary effect of catecholamines is to enhance inward calcium current (38). Calcium influx is also enhanced by shifting the threshold potential for the current to more negative levels (82, 83, 84).

A secondary effect of catecholamines is to accelerate deactivation of the outward potassium current which is responsible for repolarization (38, 9, 73). The electrophysiological effects are an increased Vmax and overshoot amplitude of the action potential (38).

Purkinje Fibers

Beta receptor stimulation enhances the spontaneous depolarization seen in Purkinje cells (38). Overall effects of catecholamines on the Purkinje fiber system include an acceleration of repolarization with a shorter action potential duration. The frequency of spontaneous depolarization is increased, with no direct effect on phase 0 (9, 38). The plateau phase of the action potential is also increased to a more positive value (85). Enhancement of spontaneous depolarization is thought to be due to an increase in the slow inward calcium current, with a shift in the threshold potential to more negative levels (9, 82, 83). Evidence suggests this may also be mediated by cyclic AMP (86). As in nodal fibers there is no effect on the rapid inward sodium current, neither increasing the current nor altering the threshold potential (9, 73). Catecholamines also cause a more rapid and complete deactivation of the outward potassium current in Purkinje fibers (73).

Atrium

Beta receptor stimulation has little effect on the action potential of the normal working atrial myocardium (38, 87). Repolarization may be accelerated in some species (dog, cat) but not in others (rabbit, guinea

pig, rat) (88). No effect is seen on Vmax in normal cells (38). In some specialized atrial fibers, spontaneous depolarization may be induced or enhanced (89).

AV Node

Beta receptor stimulation of the AV node improves speed of and increases Vmax in the cells of the upper and middle nodal regions. There appears to be no effect on the cells of the lower nodal region (9, 38).

Ventricle

There are very few effects of neurogenic amines on resting membrane potential of ventricular muscle, Vmax of phase 0 or the overshoot amplitude of the spike potential (38, 41). Repolarization may be either slightly prolonged or accelerated, while spontaneous diastolic depolarization is not enhanced. The effects result in shortening of the relative refractory period (38, 41, 90).

Electrocardiographic Changes

The increased conduction velocity in the AV node is manifested as a shortening of the PR interval in the ECG (38, 91). Changes in the ST segment and T wave are also seen, probably resulting from variations in the ventricular muscle action potential (38, 92).

Arrhythmias due to enchanced automaticity may occur in response to catecholamines (29). This is usually manifested in an increased firing of the sinus node resulting in tachycardia. By the increased rate, the sinus node can control initiation of ectopic pacemakers in the atria or ventricles. This is true in normal canine hearts, where the Purkinje

fibers rarely initiate impulses greater than 80-100 per minute after maximum activation. However, in infarcted tissue, the response may be higher, thus initiating and sustaining ventricular ectopic beats (29, 39).

Several mechanisms are proposed for catecholamine effects on the heart which will result in reentry of impulses (29, 42, 80). These effects are manifested by changes in the refractory period, particularly of the ventricular fibers. With the nonuniform distribution of nerve fibers on the ventricular muscle, a disparity of the spread of effect and of ventricular recovery can occur, leading to reentry. These conditions can be potentiated in instances where a nonuniform recovery of cells already exists, such as in myocardial ischemia or in subjects anesthetized (exposed) with halothane (73, 93). Slow response action potential development can also be envisioned in extensive myocardial damage, where $[K^+]_o$ may obtain levels which result in complete inactivation of the fast sodium channel (93).

CHAPTER VII

ACETYLCHOLINE

The effects of the neurotransmitter, acetylcholine, on the nodal cells and Purkinje cells are related to its effects on the ionic currents (9, 15).

Sinus Node

The greatest effect of the parasympathetic neurotransmitter is on the SA and AV nodes (41). The effects of acetylcholine on the SA node is a decrease in calcium influx along with an increase in the potassium conductance (94-97, 98). This is manifested as prolongation of the effective refractory period (9, 99), hyperpolarization and a slowing of the rate of closure of potassium channels. Inhibition of the release of norepinephrine from sympathetic nerve terminals and an increase of cyclic GMP are the probable mechanisms of acetylcholine's actions (22, 100-102). Atrial contractility is decreased as well by acetylcholine application and the increase in cyclic GMP (2, 103). Through the cyclic GMP mechanism, it has been shown acetylcholine can antagonize the effects of the catecholamine, isoproteranol (101). Under conditions of low resting potassium conductance, acetylcholine tends to hyperpolarize the cells increasing Vmax and the amplitude of the action potential (9). Vagal stimulation has the potential of inducing atrial arrhythmias due to an unequal distribution of nerve terminals, resulting in nonuniform recovery times (41).

Purkinje Fibers

Acetylcholine has little or no effect on the His Purkinje system or the ventricles. High concentrations can shorten action potential duration, again possibly due to increased potassium conductance (9, 15).

AV Node

Acetylcholine is known to slow conduction in the AV node, in the AN and N (upper nodal and nodal) regions. Repolarization is accelerated and the amplitude of the action potential may be reduced (9).

CHAPTER VIII

LIDOCAINE

Lidocaine hydrochloride, a local anesthetic, is a widely used drug for use in the treatment of ventricular arrhythmias (104-106). On the studies of lidocaine as a local anesthetic or antiarrhythmic, its quarternary derivatives, QX314 and QX572 are extensively used because of their permanent positive charge at body pH (6).

The mode of action on nerve or myocardial cells is believed to be exerted on the fast sodium channels, which control the influx of sodium ions (4, 107). Evidence for this is derived from its application to the nerve or cardiac cell membrane, resulting in a decrease in Vmax (or the rate of rise of the action potential) which is primarily controlled by fast sodium influx (106, 108, 109). More specifically, the effects of the local anesthetic appears to be on the 'inactivation' aspect of sodium permeability (4, 109). Evidence indicates that anesthetic molecules combine with 'open' sodium channels, delaying closure as well as reactivation of these channels (4, 109).

As an antiarrhythmic agent, lidocaine's effectiveness depends on its effects upon conduction, refractoriness and automaticity of cardiac fibers (106). Lidocaine was first used as an antiarrhythmic in 1950 by Southwirth (110). Although not very effective in the treatment of supraventricular arrhythmias, it seems to be the drug of choice in the treatment of ventricular arrhythmias (106). There appear to be conflicting views as to the effects of lidocaine on the cardiac action potential.

According to Bigger and Mandel, there is little or no effect on action potential Vmax until toxic concentrations and it speeds conduction across the papillary muscle - Purkinje fiber junction (108). Singh and Vaughan-Williams (111), however, have reported that lidocaine in concentrations less than 10 µg/ml has a myocardial depressant effect. It should be noted that these depressant effects are dependent upon $[K^+]_o$, being more prominent as $[K^+]_o$ was increased. These depressant effects were similarly noted by Rosen, Merker and Pippenger (2). Rosen et al. (2) showed that with lidocaine infusion, there was a decrease in action potential amplitude and Vmax, with an acceleration of repolarization in Purkinje fibers. The voltage time course of repolarization is accelerated as a result of the effect on phases 2 and 3 of the action potential. Below therapeutic concentrations of 1 µg/ml, control action potential parameters were again attained (5, 112).

Effect on Action Potential Duration, Refractoriness and Conduction of Premature Impulses

Lidocaine shortens the action potential duration and effective refractory period of Purkinje fibers (109), the magnitude of effect is dependent upon the location of the fiber (113). Lidocaine shortens these parameters in the fibers whose action potential duration is the longest (106).

Effects on Automaticity

Lidocaine suppresses spontaneous diastolic depolarizations and automatic impulse initiation which occurs at membrane potentials between -90mv and -60mv (106). At normal therapeutic concentrations, there is no

effect on impulse initiation by the sinus node, so the latter may be restored as the dominant pacemaker (114, 115). Effects of lidocaine on those potentials occurring at -60 mv (slow wave potentials) are uncertain. Evidence, however, indicates that when the membrane potential is -60 mv, the phase 4 spontaneous depolarization is quite resistant to lidocaine (106). This may be, in part, why some ventricular arrhythmias are not abolished by lidocaine (116).

Ionic Basis of Effect

Phase 0

The effect on this phase of the action potential has been attributed to changes in the time dependent activation of the sodium channels. As a result, action potential amplitude and Vmax are decreased (117). This effect on Vmax not only depends on $[K^+]_o$ but also on the rate of stimulation (106).

Phase 4

Lidocaine modifies phase 4 of the action potential by changing the outward potassium current which is initiated when the diastolic potential is restored (106). Phase 4 depends, in part, upon the outward potassium current, which is increased in the presence of lidocaine (5). This leads to a slower rate of depolarization and slower impulse initiation in ectopic pacemakers (106). This effect on various heart tissues may be related to lidocaine's ability to result in a potassium efflux when applied to the tissue (106). Kabel (116) showed that lidocaine resulted in a larger K^+ efflux from Purkinje and ventricular fibers than from atrial fibers.

The basis for this difference is unknown but it may be due to the nature of the action potential itself in these tissues (116) and the role of the potassium current in the generation of spontaneous depolarization (118). Anomalous rectification occurs in all of the tissues studied but at present there is insufficient knowledge of the process to obtain significance (119).

Phase 2 and Phase 3

When lidocaine is added to the superfusate, the voltage level of phase 2 becomes more negative and action potential duration was decreased (6). Although the effect is more marked, addition of the derivative had similar effects (6, 109).

The possible mechanism of lidocaine's effect on the phase 2 plateau voltages can be interaction from within the membrane on the secondary inward current (isi) or interaction with the repolarizing potassium current. It should be noted that the effect on action potential does not correspond well with the potassium efflux in ventricular and Purkinje fibers (108, 114). The action potential durations of Purkinje fibers are shortened to a greater extent than fibers of the ventricle, yet potassium efflux is greater in the ventricle (108). A correspondence is not necessarily expected since the ionic currents in the tissues may not carry the same significance (114).

Basis of Antiarrhythmic Action

The effectiveness of lidocaine as an antiarrhythmic agent depends upon its modification of action potential duration and effective refractory period (106).

The effects upon the action potential duration/effective refractory period and conduction velocity are seen best in examples of ischemic or infarcted tissue (47, 106). In these tissues, the pH is likely to be lower from acidosis, anoxia or metabolites and the $[K^+]_o$ is likely to be higher (120, 121). Action potential duration is shorter in infarcted tissue due in part to an increase in potassium conductance related to the local elevated potassium concentration (121). In normal fibers, the action potential duration is shortened in response to lidocaine, also thought to be related to an increased potassium conductance (109). The selective depression of conduction velocity in damaged tissues can be related to the pH and ionic effects (4, 107, 112). Thus, in ischemic or infarcted tissue with partially depolarized cells, lidocaine has a greater depressant effect on conduction velocity. By further slowing reentrant impulses, which are usually already slowed, lidocaine can thus create a bidirectional block, where once existed a one-way block. The effects of lidocaine on the effective refractory period may be related to the recovery kinetics of the rapid inward current. Lidocaine delays the time for recovery of the channels for i_{na}, thus delaying the time during and after the action potential when a new action potential may be initiated. The refractory period is thus prolonged relative to the action potential duration (↓APD/ERP ratio). By slowing the time dependent recovery lidocaine might be expected to have little effect on slow or normal heart rates. A way that disparity of action potential duration/effective refractory period may result in reentry is through the development of boundary currents (120). The shorter action potential duration in the ischemic zone sets up a potential difference with a flow of depolarizing current from the normal to the ischemic zone. The slow conduction in the ischemic zone

enhances this mechanism. By decreasing action potential duration in only the normal tissue, the action potential durations in both zones are nearly equal, diminishing the differences in potential in the latter part of the action potential. By increasing effective refractory period to a greater extent in the ischemic zone any current would encounter refractory tissue and would less likely propagate. This may be the mechanism in lidocaine's ability to raise the arrhythmia threshold dose of epinephrine under halothane. By decreasing the disparity in action potential duration between fibers induced by halothane, the heart is thus protected (this effect is present despite the observation that lidocaine decreases conduction further in the presence of halothane). Although it might be expected, it has been reported that there is no evidence of electrocardiographic changes of P-R, QRS, QT or R-R intervals (104). This may not be expected due to lidocaine's effect on conduction. These conduction changes may not be of sufficient magnitude to be apparent in the surface ECG (104).

CHAPTER IX

XYLAZINE (ROMPUN ^{R})

In 1962, in Germany, Bayer A.G. Leverkusen (122) synthesized a new drug to be used in the chemical restraint of horses, xylazine hydrochloride. Chemically it is (2-(2,6 dimethyl phenylamino) -4-H-5,6 dihydro 1,3 thiazine) and is used today as a sedative preanesthetic, analgesic and muscle relaxant (123-125). The pharmacology of uptake and excretion has not yet been reported for large animals, but results have been obtained for rats by Duhn et al. (126). It was found that following an intravenous injection the drug was distributed to the central nervous system, kidneys, pancreas, liver and thyroid. Seventy percent of the dose was excreted in the urine with 8% in the unchanged form. The remainder was excreted in the bile, with excretion being completed within 10-15 hours. Following I.M. administration, within 10 minutes, 67 percent of the dose was absorbed with free and conjugated metabolites excreted in the urine (127). Peak excretion took place within 2 hours and the drug was undetectable after 10 hours. Xylazine administration is associated with various changes in hematologic and blood chemistry parameters (122). Within the first hour postinjection, blood glucose increases while plasma insulin, RBC, PCV and Hb parameters fall. All levels return to normal within 24 hours (128, 129).

Cardiorespiratory Changes

Following administration of xylazine to animals, several changes occur in the cardiovascular and respiratory systems which must be considered when using this agent as a preanesthetic.

The effects of xylazine on respiration have been investigated by several authors with the overall conclusion that no significant changes occur (130, 131).

In sheep, blood gas values showed no significant changes in PHa, $PaCO_2$, or PaO_2, except in two cases where a slight increase in $PaCO_2$ occurred following a 3-5 minute period of apnea (130).

The initial cardiovascular event seen with administration (IM or IV) is a pressor response, accompanied by increases in both heart rate and myocardial contractility (132). This sympathomimetic response lasts for 1-3 minutes and is followed by a longer period (up to 60 minutes) of hypotension, bradycardia and fall in cardiac output. This period is accompanied by an increase in sensitivity of the baroreceptors to changes in blood pressure (133). The initial sympathomimetic phase has been attributed to a few possible factors. One is central stimulation of the cardiac nerves, as determined by monitoring the splanchnic and cardiac nerves (68, 133). Another is the release of catecholamines, since after adrenalectomy, the blood pressure response will be decreased by 50% or more (68, 134). The other possibility is the Anrep effect, which attributes the increased cardiac contractility to an increased end diastolic ventricular fiber stretch resulting from an increased arterial pressure (135). Evidence for this last hypothesis comes from pharmacological studies using α and β blocking agents, phentolamine and propranolol. In those animals

treated with phentolamine, the hypertensive phase was decreased, while in those treated with propranolol, the hypertensive phase was potentiated and the subsequent hypotension was reduced (7). Evidence suggests possible α and β receptor activity. The α agonist activity has been related to its ability to contract rabbit atria, guinea pig vas deferens and the cat nictitating membrane (7). The decrease in blood pressure is associated with decreased aortic flow, even in the presence of an increased peripheral resistance (134). Xylazine has also been shown to depress contractions in guinea pig atria, which is not abolished by atropine, phentolamine, propranolol or hexamethonium (7).

That xylazine results in changes in conduction is evidenced by the presence of cardiac arrhythmias such as atrioventricular conduction block, especially prominent in horses (69, 125). It was also shown to be present in dogs after administration of atropine, casting some doubt on their origin as being due to an increased vagal tone (134). One possibility is that xylazine is acting on the heart as a local anesthetic - membrane stabilizing agent (7). As mentioned previously, those antiarrhythmic agents classified as local anesthetic - membrane stabilizing agents can result in a depressed conduction, and possibly decreased contractility. That xylazine possesses a local anesthetic effect is shown by its effects on the neuromuscular junction and frog sciatic nerve preparation. Aziz and Martin (7) showed xylazine blocked the neuromuscular junction in a manner similar to d-tubocurarine, yet neostigmine did not angatonize xylazine's effects. They also showed that a complete blockage of the action potential occurred with concentrations of .075% and higher concentrations produced a more rapid block with a longer recovery time. As the blockage occurred, there was a decrease in conduction

velocity of the compound action potential. Results similar to these were obtained with 0.5% procaine (7). These effects could possibly have a beneficial application to the protection of the heart from the cardiac stimulating effects of epinephrine under halothane anesthesia.

Muir et al. (8) have suggested, however, that the effect of xylazine is not to protect the heart from the arrhythmogenic properties of epinephrine under halothane, but enhancement of the sensitivity of the halothane exposed heart to epinephrine. Data to support their hypothesis was obtained by comparing the effects of epinephrine in groups of dogs receiving xylazine/thiamylal/halothane or acetylpromazine/thiamylal/halothane combinations. Although acetylpromazine allowed a greater dose of epinephrine to be given, the presence of thiamylal needs to be questioned in light of the evidence that thiamylal also sensitizes the heart to epinephrine (8). This data is in contradiction to that found by Kerr et al. (136), who found the use of xylazine in horses as a preanesthetic resulted in less respiratory depression and a greater cardiovascular stability during general anesthesia with halothane. Kerr et al., also found less potentiation of the cardiovascular depression associated with halothane. There were differences in heart rate associated with each treatment but these may have been due to a greater respiratory depression in the acetylpromazine treated animals (136).

This thesis attempts to examine the arrhythmogenic properties of epinephrine in dogs under halothane anesthesia and the protection afforded by treatment with lidocaine or xylazine. The basic assumption in this study is that since lidocaine and xylazine possess structural and functional similarities, their effects on the response of the myocardium to epinephrine would be similar.

CHAPTER X

MATERIALS - METHODS

Six mongrel dogs, of both sexes (4 males, 2 females) and various weights (7.5 $\pm$ 0.8 S.E. kilograms) were obtained from the Oklahoma State University animal care unit. Upon arrival and for at least three consecutive days a lead II electrocardiogram was run for each animal to screen for any abnormalities. Any animal showing premature ventricular contractions or any ectopic rhythm was discarded from the study. Serum electrolytes and enzymes (SGOT, SGPT) were determined upon arrival. CBC and the direct test for heartworms were run on each animal for three consecutive days or until baseline hematological values were obtained. Canine distemper and rabies vaccine were also given to each dog. Daily body temperatures were taken and recorded.

All animals were housed singly in cages, and fed standard laboratory chow and water ad libitum. Each animal was handled and brought into the laboratory daily for at least one week prior to experimentation. In the laboratory they were placed in the restraining cradle and the ECG was recorded. Blood values (CBC and enzymes) were determined prior to initiation of the second phase of the experiment.

NOTE: One dog (#5) was treated for pulmonary congestion with chloramphenicol for 3 days. This occurred eight days before experiments were begun.

Experimental Procedure

The basic experimental design consisted of injecting various doses of epinephrine (2µg to 18µg total dose in increments of 2µg) under two conditions and three treatments. The conditions were either anesthetized with halothane or awake. The treatments were injections of lidocaine, xylazine or saline administered through an indwelling catheter. Drugs to be given were chosen on a random basis, with each dog receiving all treatments. Individual trials were separated by at least 72 hours throughout the procedure, the lead II ECG was recorded, and the blood gases were monitored.

Drugs/instrumentation

The halothane[1] used was delivered through a Fluotec[R] vaporizer. Lidocaine hydrochloride[2], without epinephrine, was given as a 4 mg/kg I.V. bolus followed by a 1 mg/min infusion in a saline drip. Xylazine[3] was given in a dose of 1.0 mg/kg I.V. and the saline group received a 2 ml injection of saline. Each of these groups had a normal saline infusion of 1 ml/min. The epinephrine[4] for injection was prepared daily in a 1:100,000 dilution. The ECG was recorded on a polygraph[5],

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[1] Fluothane[R] , Ayerst Laboratories

[2] Xylazine HCl without epinephrine, Astra Pharmaceutical

[3] Rompun HCl, Bayvet Corp., Kansas

[4] Epinephrine Injection, Haver-Lockhart

[5] Grass Instruments, Model F polygraph, Quincy, Massachusetts

while the dogs were in a cradle allowing the legs to move freely. Body temperature was maintained with a circulating hot water pad[6]. Blood gases were analyzed on a Corning 175 blood gas machine[7].

Procedure

Group 1: Halothane

Each animal was brought into the laboratory fifteen minutes prior to each trial. Induction of anesthesia was accomplished with a mask and 5% halothane/25% N20/70% O_2 until a surgical level of anesthesia was reached. After incubation was accomplished (approx. 5 minutes after start of anesthesia), N_2O was discontinued. Thirty minutes were allowed to expire, with the animals breathing spontaneously, before the control period recordings were taken. Anesthesia was delivered through a semi-closed rebreathing system with 1% halothane/O_2 during this period. Following this, blood gases were determined. The control period recording and subsequent recording periods were five minutes in duration. After the control time, lidocaine, xylazine or saline was injected. Five minutes later, bolus injections of epinephrine were given. The initial dose was 2µg, with 2µg being added to subsequent doses until one of the following criteria were met:

1. multiple ectopic ventricular beats;

or 2. multifocal ectopic ventricular beats;

or 3. a final dose of 13 µg/kg epinephrine;

or 4. intervention with any drug to resuscitate the animal.

---

[6]Gaymar T Pump

[7]Corning 175 automatic pH/blood gas analyzer

(For example, it was necessary to intervene with atropine in cases of cardiac arrest when heart would not respond to external massage).

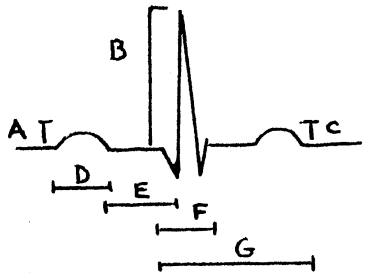
The arrhythmias were selected because of their close relationship to the development of ventricular fibrillation. The dose of epinephrine (13µg/kg) chosen was the highest reported dose given under halothane anesthesia. The dogs were allowed to recover in the cradle then returned to their cages.

Group 2: Awake

The same procedure was followed as in group 1, except for the anesthesia. In this group the equilibration period was twenty minutes.

Data Analysis

Data were analyzed for heart rate and selected intervals and amplitudes. (see diagram).



a = P amplitude (mv)

b = R amplitude

c = T amplitude

d = P duration (seconds)

e = PR segment

f = QRS interval

g = QT interval

Heart Rate

Heart rate data were analyzed in 10 second intervals at -10 sec, +10 sec, +20 sec, +30 sec, +40 sec, +50 sec, +60 sec, +2 min, +3 min, +4 min (e.g., +30 sec interval was +30 to +40 seconds). Waveforms were counted and multiplied by six. The analysis consisted of analysis of variance

and factor analysis[8].

The analysis of variance divided the data into three categories, one of which was the effect of the three drug treatments (lidocaine, xylazine or saline) on the heart rate. If there was a significant difference (up <.05), the computed last significant difference values were then used to distinguish among groups. The second analysis was determination of the effect of condition (anesthetized or awake) upon the heart rate. The third determination was a test of interaction. If a significant result appeared here, this was taken to mean under one condition the magnitude of effect was not parallel to that seen in the other condition. Each of these three categories were analyzed by dose of epinephrine, taking the time intervals into account. The results here were then utilized for factor analysis.

For the amplitude and interval data the absolute numbers as well as the change in interval and amplitude from the control or preinjection values were analyzed by analysis of variance. A correlation procedure was then made for all the variables.

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[8]Data was analyzed on the Oklahoma State University computer, or IBM 158, using the SAS (Statistical Analysis System) package for ANOVA, FACTOR and Corr, as designed by J. Barr and J. Goodnight.

CHAPTER XI

RESULTS

Heart Rate

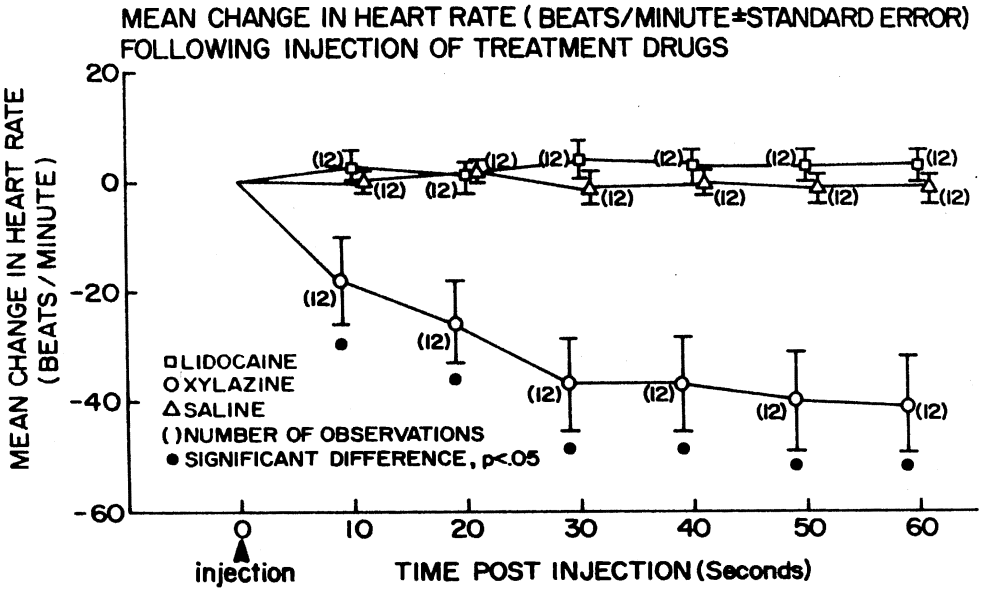
The heart rate data was analyzed for differences among the three treatment groups (lidocaine, xylazine and saline) and the two conditions (anesthetized, awake) in response to individual doses of epinephrine (range 2μg to 18μg) and injection of the treatment drugs. Actual heart rate, change and percent change in heart rate were analyzed in this manner. (NOTE: This procedure was followed for the interval and amplitude data as well.) When a significant difference was indicated between the treatment groups, the least significant division was used to determine which groups were different (all determinations significant at $p < .05$ level).

For actual heart rate, analysis of variance showed significant differences between treatment drugs, during the control or preinjection period and when epinephrine (all doses) were administered. The differences were found between 1) the lidocaine and xylazine and 2) the saline and xylazine groups. There was no difference between the lidocaine and saline groups. There was no significant drug x condition interaction for the control period. There was a significant drug condition interaction with epinephrine administration.

Epinephrine doses of 2μg to 18μg resulted in differences between all three treatment groups. Factor analysis, on the other hand, gave

slightly different results. First, the control or preinjection rate for all three groups were not significantly different. Epinephrine doses of 2μg to 10μg and 16μg to 18μg resulted in differences between 1) the lidocaine and xylazine groups and 2) the xylazine and saline groups. There was no difference between the lidocaine and saline treatment groups. For epinephrine doses 12μg and 14μg, the difference was between 1) the lidocaine and xylazine and 2) the lidocaine and saline groups. There was no difference between the saline and xylazine groups. In all instances, the xylazine group had the lowest mean heart rate of the three groups. The interaction of drug and condition after administration of epinephrine was a factor of nonparallel response under the awake or anesthetized conditions. The data was classified by drug type and epinephrine levels to compare the anesthetized and awake condition. The analysis of variance showed the difference to be significant and the results were similar to those found for effects of treatment, with the anesthetized group having the lowest mean heart rate. However, factor analysis showed no significant difference between conditions.

The next analysis was on the change and the percent change in heart rate. Since these analyses represent a change from the preinjection time (time=0), any significant differences automatically include differences at the measured time intervals. Time intervals measured were from time=0 or preinjection to +240 seconds, and were 10 seconds in duration. Analysis showed that after +60 seconds there were no differences between the three treatments or the two conditions, $p > .05$. For both the change and percent change in heart rate, injection of xylazine slowed the heart rate (mean rate) to a greater extent over the 60 second time interval ($p < .01$) than either the lidocaine or saline injections ($p > .05$) (Figures 1 and 2).



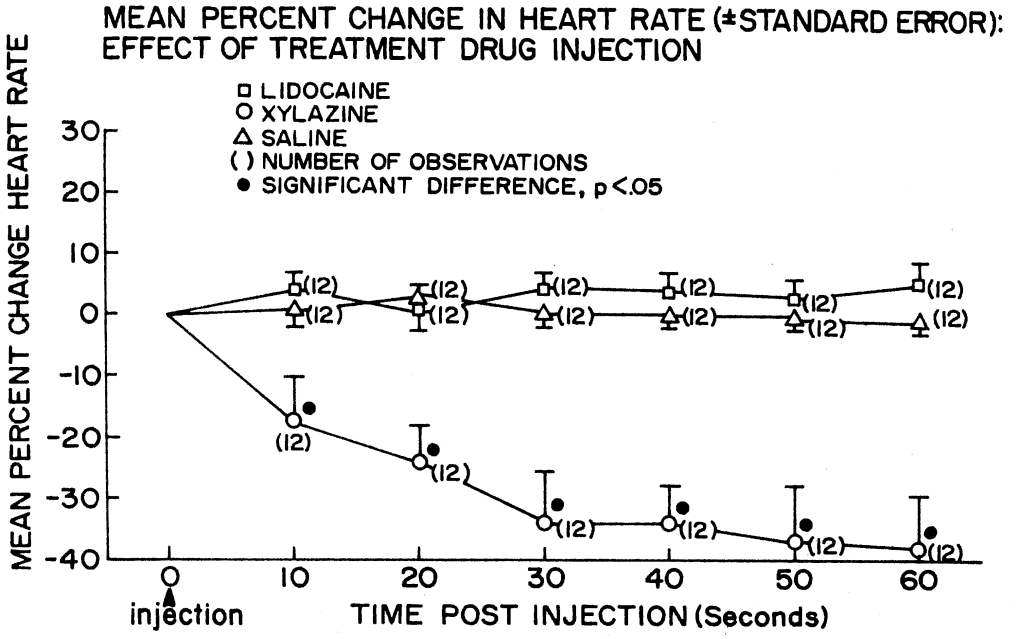
A significant difference between treatment drugs ($p < .05$) is marked with (.). To determine difference between groups, the least significant difference for the times indicated are:

@ 10 seconds 14.6
@ 20 seconds 13.6
@ 30 seconds 16.4
@ 40 seconds 15.9
@ 50 seconds 16.8
@ 60 seconds 15.4

Treatment Drugs

Lidocaine	4 mg/kg bolus followed by 1 mg/min infusion
Xylazine	1 mg/kg I.V. followed by saline infusion
Saline	2 ml normal saline followed by saline infusion

Figure 1: Mean Change in Heart Rate (Beats/Minute ± Standard Error) following injection of Treatment Drugs.



For determination of significantly different groups, ($p < .05$), use the least significant difference values:

@ 10 seconds 13.3
@ 20 seconds 11.9
@ 30 seconds 14.4
@ 40 seconds 14.1
@ 50 seconds 15.3
@ 60 seconds 13.9

Treatment Drugs

Lidocaine	4 mg/kg bolus followed by 1 mg/min infusion
Xylazine	1 mg/kg I.V. followed by saline infusion
Saline	2 ml normal saline followed by saline infusion

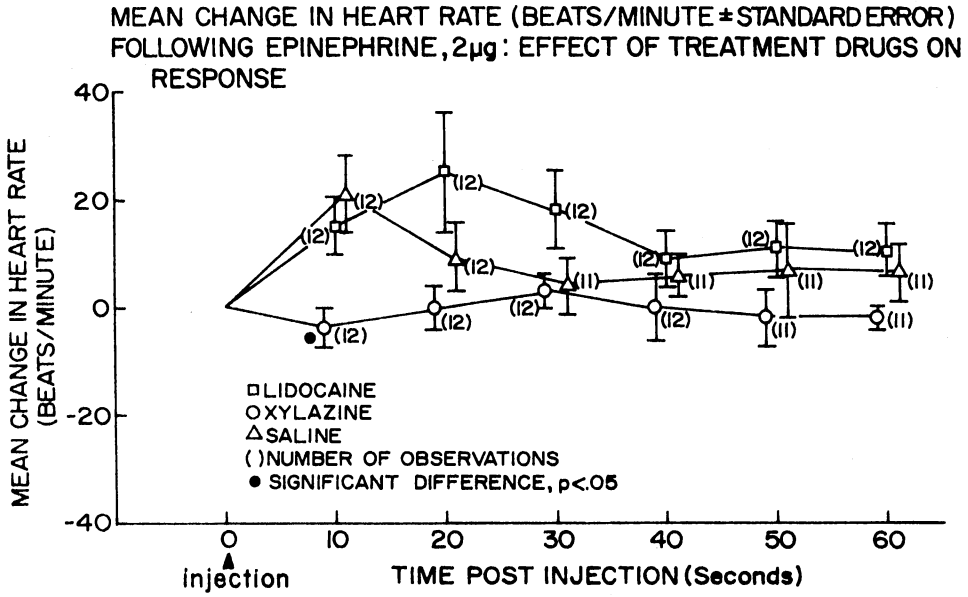
Figure 2: Mean Percent Change in Heart Rate (± Standard Error): Effect of Treatment Drug Injections.

Injection of epinephrine, 2μg, resulted in an increase for change and percent change of heart rate over time for the lidocaine and saline groups, with a decrease in heart rate (mean change of -4.6 beats/minute) for the xylazine group (Figures 3 and 4). For doses of epinephrine, 8μg to 14μg, differences were found between 1) the lidocaine and saline groups and 2) the xylazine and saline groups ($p < .05$) with no significant difference between the lidocaine and xylazine groups. Condition affected the heart rate (a lower mean heart rate and response for the anesthetized group) at all doses of epinephrine (Figure 5). Factor analysis confirmed the results of the analysis of variance.

Intervals

Analysis of variance on differences between treatment groups using raw data, showed differences in all intervals measured ($p < .01$). For the treatments, these differences were for the P wave duration, PR segment duration, and QRS interval. For the P wave and PR segment duration the 1) lidocaine and saline and 2) the xylazine and saline groups were significantly different. The injection of lidocaine or xylazine prolonged these intervals with respect to the saline treatment group. For the QRS interval, there were differences between all three groups with the xylazine group having the longest mean duration. There were no significant variations with respect to time. Condition affected the response, the anesthetized group having the longer duration (Figure 6-12).

Injections of epinephrine (see table for actual doses) resulted in a decrease in mean interval duration for the lidocaine treatment groups, an increase in mean interval duration for the xylazine treatment group and a decrease then increase in mean interval duration for the saline



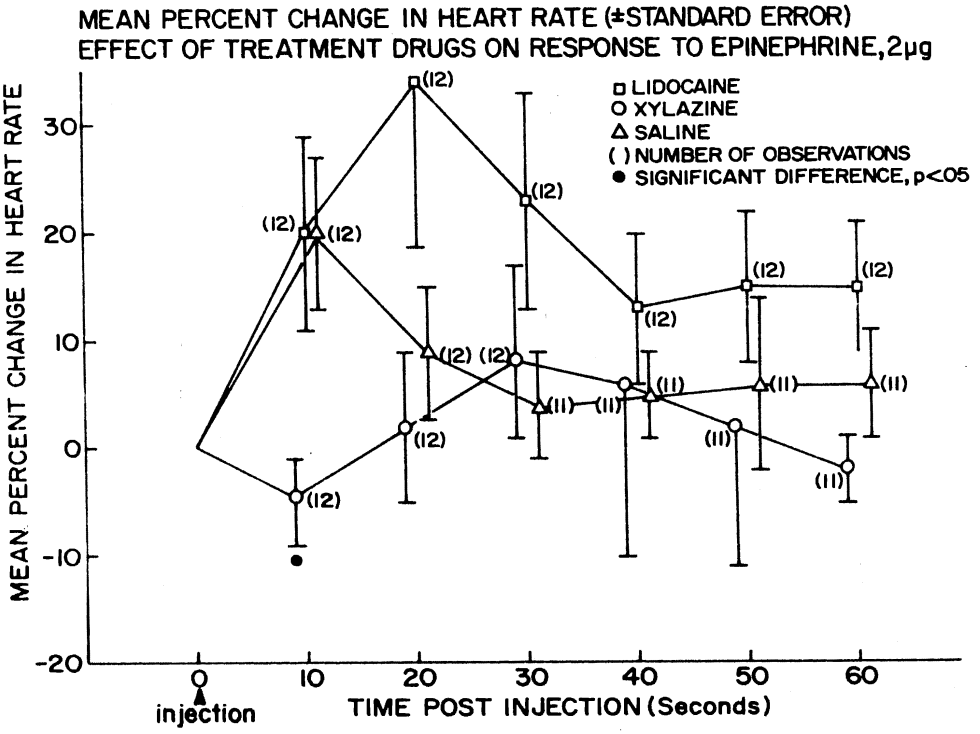
Least significant difference values, for determination of significantly different groups ($p < .05$):

@ 10 seconds 16.7

Treatment Drugs

Lidocaine	4 mg/kg bolus followed by 1 mg/min infusion
Xylazine	1 mg/kg I.V. followed by saline infusion
Saline	2 ml normal saline followed by saline infusion

Figure 3: Mean Change in Heart Rate (Beats/Minute ± Standard Error) in Response to 2µg Epinephrine: Effect of Treatment Drug.



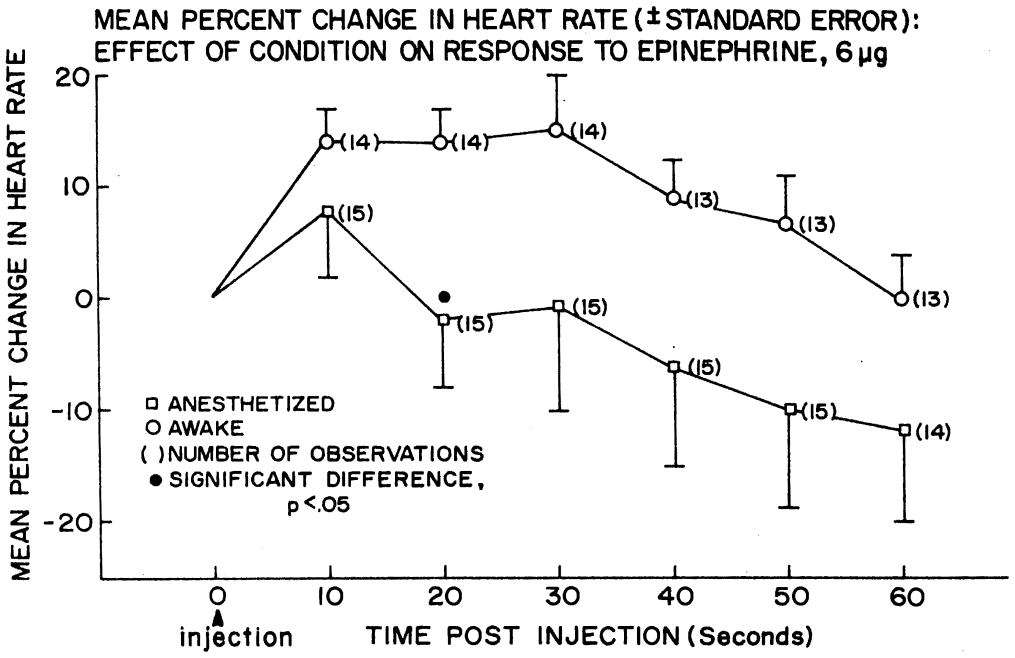
For determination of significantly different groups ($p < .05$), use the least significant difference values:

@ 10 seconds 22.0

Treatment Drugs

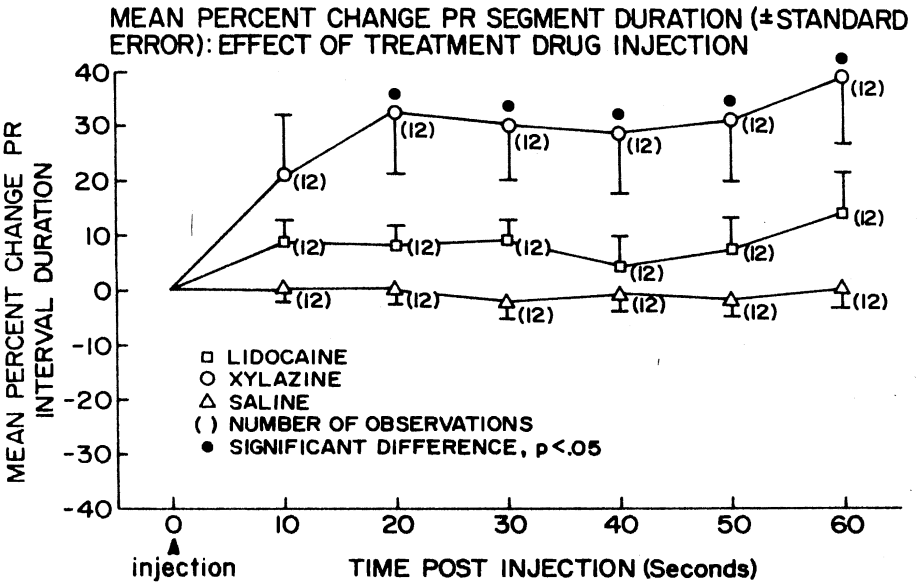
Lidocaine	4 mg/kg bolus followed by 1 mg/min infusion
Xylazine	1 mg/kg I.V. followed by saline infusion
Saline	2 ml normal saline followed by saline infusion

Figure 4: Mean Percent Change in Heart Rate (± Standard Error): Effect of Treatment Drugs on Response to Epinephrine, 2µg.



Significant difference between conditions ($p < .05$) was at +20 seconds.

Figure 5: Mean Percent Change in Heart Rate (± Standard Error): Effect of Condition on Response to Epinephrine, 6µg.



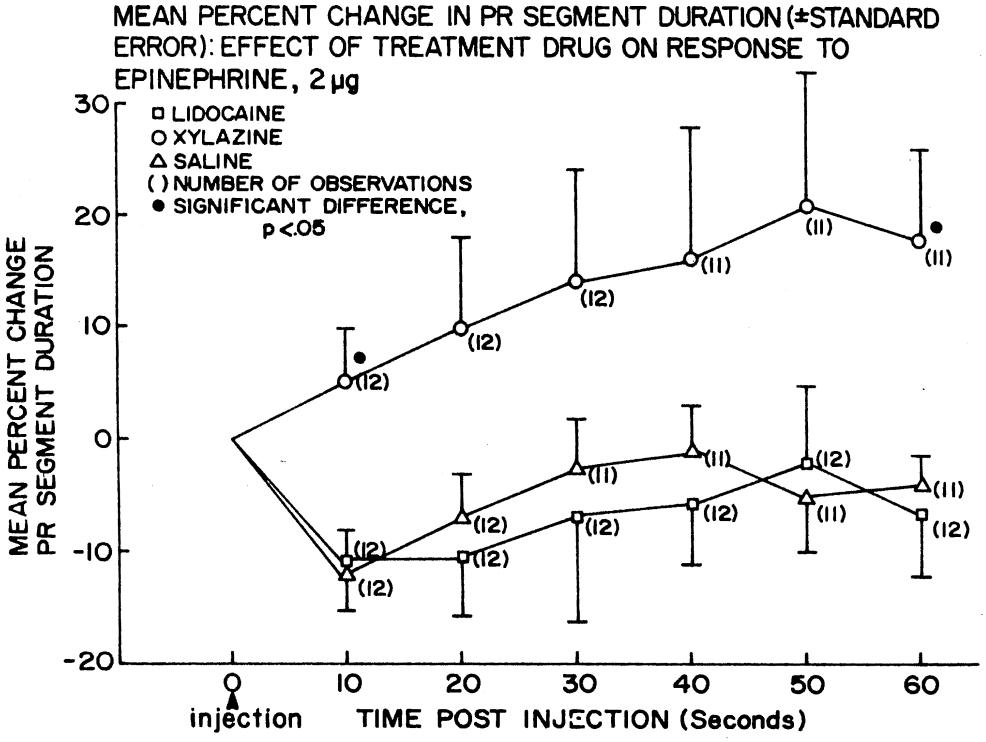
For determination of significantly different groups ($p < .05$), use the least significant difference values:

@ 20 seconds 21.08
@ 30 seconds 20.7
@ 40 seconds 20.6
@ 50 seconds 21.2
@ 60 seconds 24.9

Treatment Drugs

Lidocaine	4 mg/kg bolus followed by 1 mg/min infusion
Xylazine	1 mg/kg I.V. followed by saline infusion
Saline	2 ml normal saline followed by saline infusion

Figure 6: Mean Percent Change PR Segment Duration (± Standard Error): Effect of Treatment Drug Injection.



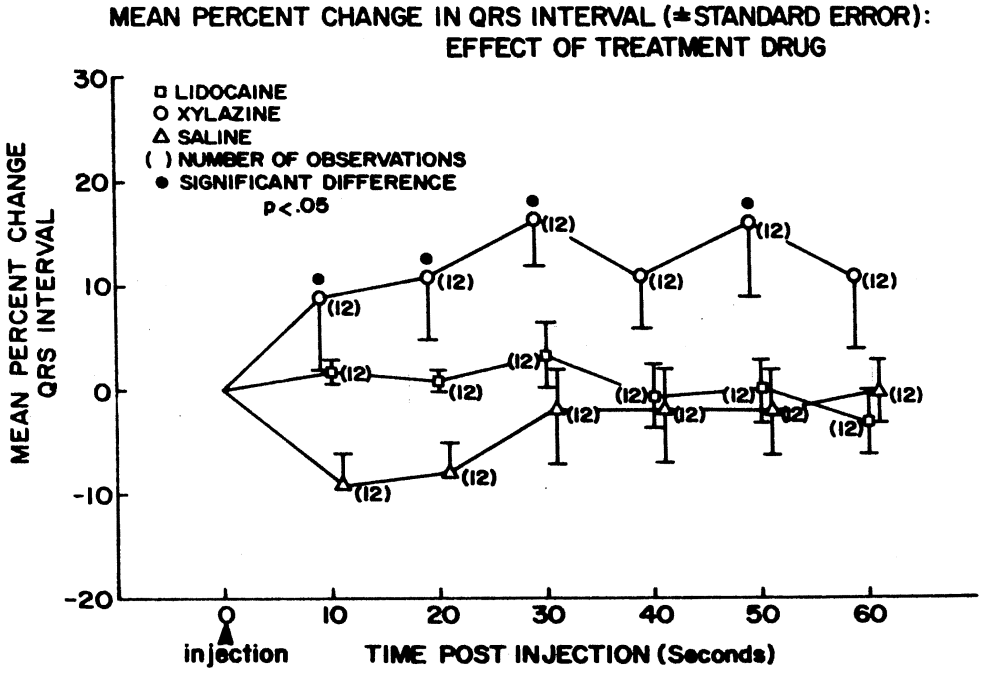
For determination of significantly different groups ($p < .05$), use the least significant difference values:

@ 10 seconds 12.9
@ 60 seconds 19.5

Treatment Drugs

Lidocaine	4 mg/kg bolus followed by 1 mg/min infusion
Xylazine	1 mg/kg I.V. followed by saline infusion
Saline	2 ml normal saline followed by saline infusion

Figure 7: Mean Percent Change in PR Segment Duration (± Standard Error): Effect of Treatment Drug on Response to Epinephrine, 2µg.



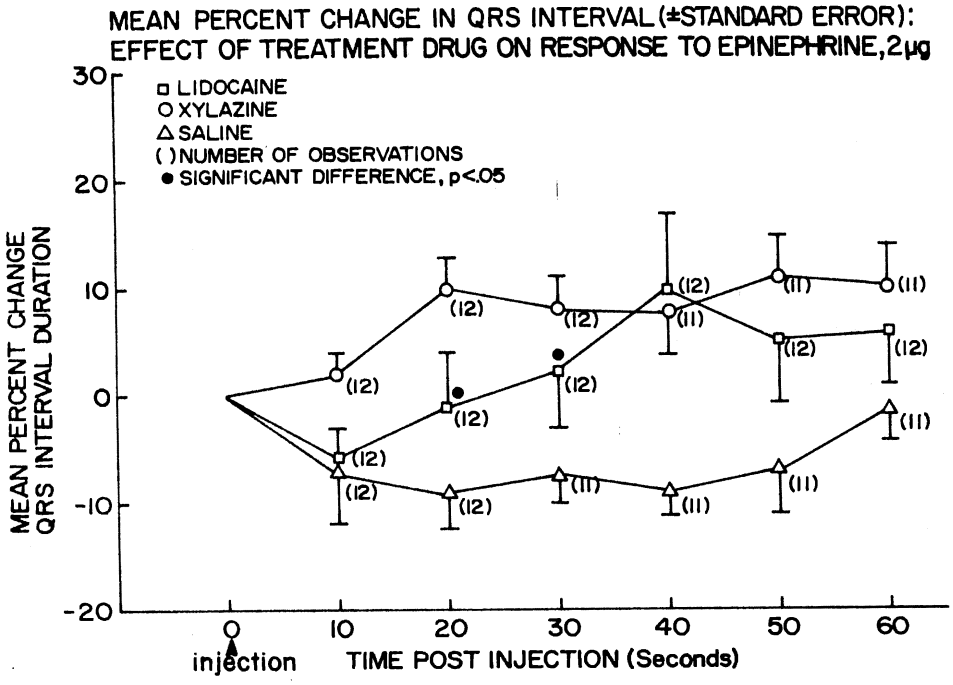
For determination of significantly different groups ($p < .05$), use the least significant difference values:

@ +10 seconds 13.1
@ +20 seconds 12.4
@ +30 seconds 13.2
@ +50 seconds 15.0

Treatment Drugs

Lidocaine	4 mg/kg bolus followed by 1 mg/min infusion
Xylazine	1 mg/kg I.V. followed by saline infusion
Saline	2 mg normal saline followed by saline infusion

Figure 8: Mean Percent Change in QRS Interval (± Standard Error): Effect of Treatment Drug.



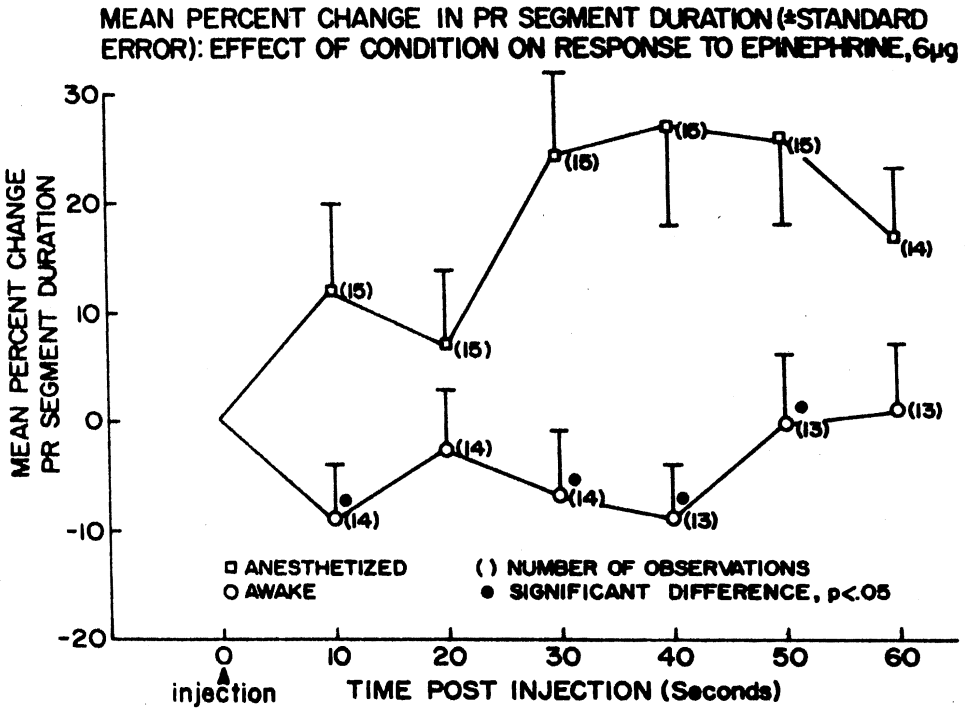
For determination of significantly different groups ($p < .05$), use the least significant difference values:

@ 20 seconds 12.9
@ 30 seconds 12.9

Treatment Drugs

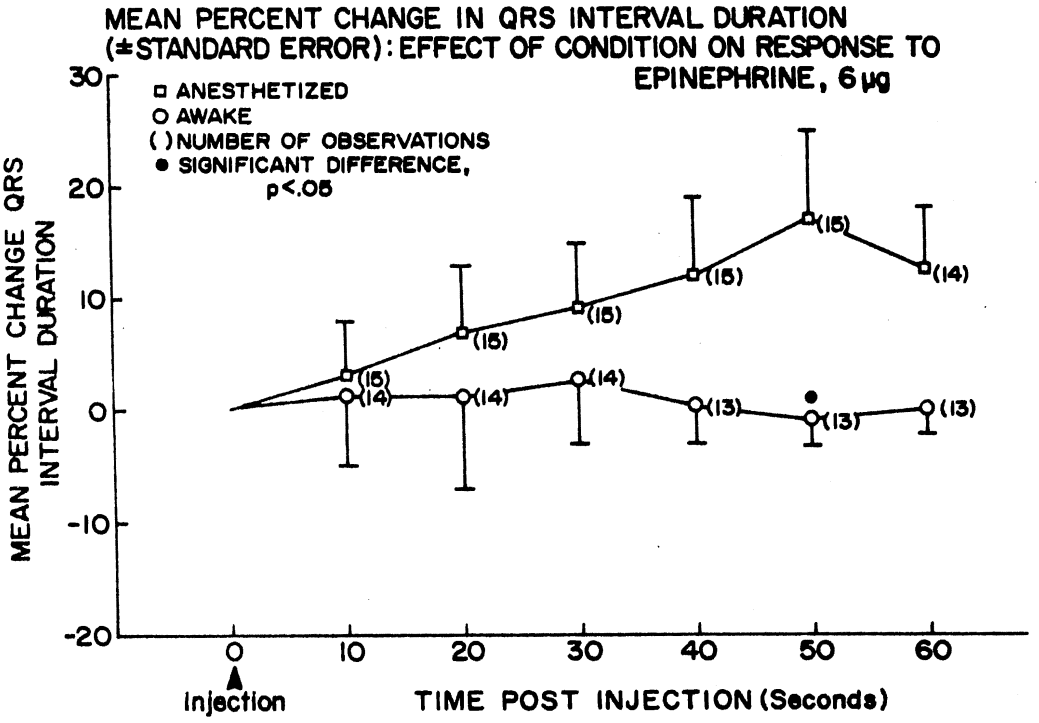
Lidocaine	4 mg/kg bolus followed by 1 mg/min infusion
Xylazine	1 mg/kg I.V. followed by saline infusion
Saline	2 ml normal saline followed by saline infusion

Figure 9: Mean Percent Change in QRS Interval (± Standard Error): Effect of Treatment Drug on Response to Epinephrine, 2µg.



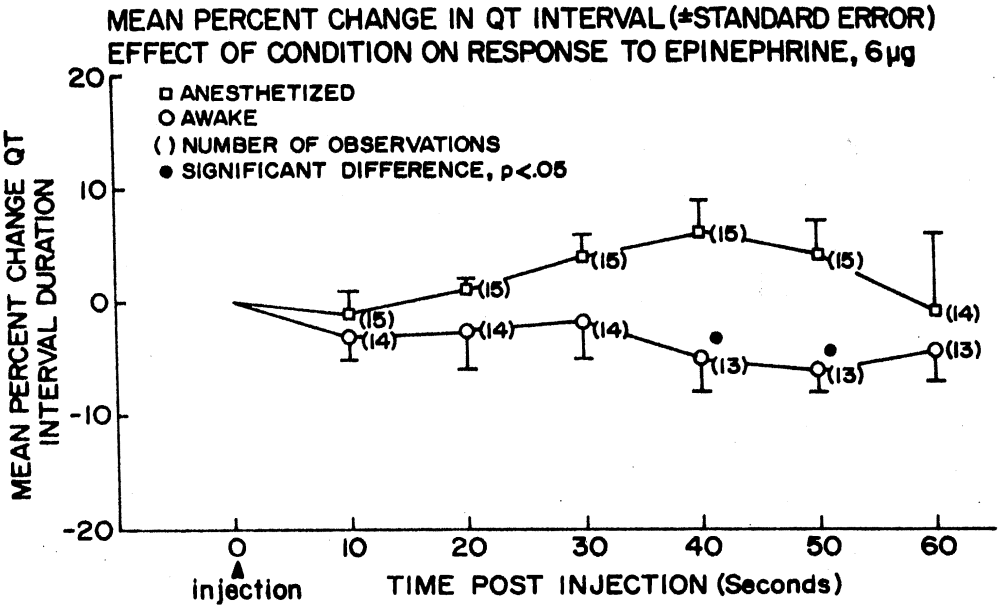
Significant difference ($p < .05$), between conditions occurred at +10, +30, +40, +50 seconds.

Figure 10: Mean Percent Change in PR Segment Duration (± Standard Error): Effect of Condition on Response to Epinephrine, 6µg.



Significant difference ($p < .05$) between conditions occurred at +50 seconds.

Figure 11: Mean Percent Change in QRS Interval (± Standard Error): Effect of Condition on Response to Epinephrine, 6µg.



Significant difference ($p < .05$) between conditions occurred at +40, +50 seconds

Figure 12: Mean Percent Change in QT Interval (± Standard Error): Effect of Condition on Response to Epinephrine, 6µg.

treatment group. (This is the mean duration averaged over 60 seconds.) Condition affected the mean duration response to epinephrine with a significant prolongation of all intervals in the anesthetized state with increasing epinephrine doses. The awake group response was a decrease in interval duration.

For the change in interval significant differences existed between 1) the lidocaine and xylazine treatments and 2) between the saline and xylazine treatments for doses of epinephrine up to 10μg. The mean change in response to epinephrine or drug treatment was a significant prolongation of intervals for the xylazine group, with usually a decrease in interval duration in response to the other two drugs and epinephrine (Figures 6-9). Again conditions affected the mean response overall with the anesthetized group having the longer interval duration (Figures 10-12).

For the change in interval after 10μg the differences existed between the 1) lidocaine and saline groups and between 2) the xylazine and saline groups with no difference between the lidocaine and xylazine treatments.

Analyses of the percent change in interval duration resulted in the same significant differences as the change in interval duration. Factor analyses confirmed the results of the original analysis.

Amplitudes

The only significant changes occurred with the R amplitude. When the treatment drugs were injected, xylazine administration resulted in a significant increase in R amplitude above control of lidocaine treatment values. Injection of epinephrine resulted in a decrease in R ampli-

tude for the xylazine group (either a negative change or a smaller positive change), the change significantly different from either the lidocaine or saline group, which had an increase in amplitude.

For percent change in amplitude, there was no significant difference found from the analysis of variance or factor analysis.

Correlation

A correlation was run on the actual (raw) data. Although there was a significant correlation between some of the parameters measured, the only consistently significant correlation was a negative correlation between heart rate and interval duration ($p < .05$).

CHAPTER XII

DISCUSSION

In the present study, anesthesia was induced with halothane and nitrous oxide in oxygen. In association with a more potent anesthetic (i.e., halothane) nitrous oxide provides a means for a rapid induction and allows for less of the more potent anesthetic to be used (64, 137, 138). Although addition of nitrous oxide to halothane will result in an increased peripheral resistance and mean arterial pressure (139, 141) discontinuation of nitrous oxide will allow return of these parameters to control levels (140). The nitrous oxide used for induction of anesthesia in the present study, therefore, is assumed to have had no effect on the other treatments.

Halothane Anesthesia and Cardiac Arrhythmias

There are several factors to consider in the genesis of arrhythmias under halothane anesthesia. One factor is the $PaCO_2$ and associated with this is the mode of ventilation (55, 65, 67). In both man and dogs, spontaneous ventilation is usually associated with increased PCO_2 levels, which may lead to cardiac arrhythmias after reaching a threshold value. The threshold for halothane anesthesia has been shown to be approximately 60mmHg. In those animals where blood gases were monitored at the onset of arrhythmia, the PCO_2 values did not exceed 40mmHg. Since this measurement was not available in all dogs, it is possible a high PCO_2 might have been a factor in the development of the arrhythmia.

The role of blood pressure cannot be determined since arterial pressure was not recorded. By analysis of the heart rate on that dose of epinephrine where an arrhythmia was produced (i.e., final dose) it can be seen that heart rate possibly played a role in the genesis of those arrhythmias.

A possible explanation for the arrhythmias in the lidocaine and saline groups may be the critical rate for arrhythmiogenesis was reached. Except for the individual cases where cardiac arrest occurred (these are included in the analysis), the arrhythmias were usually preceded by an increased heart rate. For the dogs receiving xylazine it is possible that a change in blood pressure was one of the underlying causes of the arrhythmias. The reason heart rate may not play a role is that first, under halothane anesthesia, heart rate was initially significantly slower compared to the awake group. Secondly, the response to low doses of epinephrine under xylazine and halothane was that of a negative change or a smaller positive change in heart rate, as compared to the other treatments. The results in this section of the experiment compare to what is known about the response to epinephrine under halothane. It is known that the heart is less responsive to epinephrine under halothane, although the overall sympathetic response is still maintained (142). This can be seen in data comparing the two conditions and the response to epinephrine. In analyzing the change of heart rate, it was shown the halothane group had a lower mean change in heart rate in response to epinephrine, independent of treatment group. When analyzed by treatment, the xylazine group had the lowest mean response of the three treatments. The reason blood pressure may therefore be more important deals with the α sympathomimetic actions of xylazine, accompanied possibly by an increased sensitivity of

the baroreceptors (7, 133). The effects of lidocaine on heart rate at higher doses of epinephrine are statistically similar to the response of the xylazine group. It has been reported that the depressant effects of lidocaine of Vmax are rate dependent (105). Stimulation of heart rate, especially by epinephrine, will increase the effect of lidocaine. The possible mechanism of this may be related to its property of prolonging the effective refractory period relative to action potential duration (113). The effect on the sodium channels (prolonging the time for reactivation) may also be part of its mechanism. Since xylazine has local anesthesia properties (133), perhaps it is through the action on the sodium channel that its effect is mediated. The time delay in reactivation of the sodium channel may be the mechanism involved in xylazine's production of second degree atrioventricular block. This is a common arrhythmia in horses following xylazine administration (136). This effect, however, occurred at low doses of epinephrine. Another possible mechanism might be that which is proposed for halothane, which is increasing the outward potassium current (73, 74). This may account for halothane's depression of the response to epinephrine at all dosage levels.

Halothane also depresses conduction velocity, which is manifested by increased interval duration of the surface electrocardiogram (72). In the present study the P wave, PR segment and QRS duration were prolonged in the anesthetized group as compared to the awake group. The P wave and PR segment represent a decreased atrioventricular conduction. Combined with xylazine, the effect of halothane on conduction velocity is enhanced. Lidocaine is known to decrease conduction velocity, although the decrease is not necessarily seen on the surface ECG (2). In combination with halothane, the conduction velocity may be depressed further

and may possibly be demonstrated by the electrocardiogram (48, 72).

Considering the experimental evidence the production of arrhythmias by halothane is most likely due to reentry of impulses (75). Reentry requires a slowed conduction and/or unequal distribution of effect on the refractory period, and these are changes known to occur in the myocardium upon exposure to halothane and/or epinephrine (73, 74, 84). Lidocaine's effectiveness as an antiarrhythmic might be its ability to equalize disparity between action potential duration and effective refractory period in these areas (47, 113, 143). Changes in response to epinephrine, seen in the ECG, are decreases in interval duration, except for the QT interval, which may be prolonged. Disparity in recovery due either to vagal or sympathetic stimulation, may be evidenced by changes in the QT interval and T wave form. (The T wave form, however, in the dog is extremely variable.) If this is any indication of disparity of recovery, the T interval did change in length depending on the dose of epinephrine. It should be stressed again that changes in QT interval to epinephrine are somewhat variable. In the lidocaine treatment group, QT interval duration usually decreases, while in the xylazine group it increases. This last observation has been correlated by some authors as evidence of an increased susceptibility to fatal ventricular arrhythmias (51). Another point of observation is the interrelation between various intervals. Using data from the correlation, it should be noted that at particular doses of epinephrine, one particular interval may be positively correlated to another interval and negatively correlated to a third. This may relate to alterations in refractoriness, which would allow reentry arrhythmias to occur (92).

The amplitude of the R wave may be useful in diagnosing disparity between areas in the ventricular conduction system (92). It has been shown that amplitude is increased by vagal and decreased by sympathetic stimulation. This is related to a lower and higher, respectively, synchronization of individual ventricular fibers, due to a changed conduction. It would seem in this instance, the xylazine group and epinephrine resulted in a decreased R wave amplitude. This is in contrast to the other two treatments and the results of the anesthetized group (as compared to the awake condition).

CHAPTER XIII

SUMMARY AND CONCLUSIONS

Electrocardiographic changes were monitored in response to graded doses of epinephrine in awake and halothane anesthetized dogs. The effects of treatment with lidocaine and xylazine on the response to epinephrine was characterized.

Halothane anesthesia generally resulted in a lowered heart rate and longer PR, QRS, and QT interval durations, when compared to the awake group. Injection of all doses of epinephrine (2μg to 18μg in increments of 2μg) prolonged interval duration and increased heart rate. The change in heart rate in response to the epinephrine was significantly lower ($p < .05$) in halothane anesthetized animals than in unanesthetized animals.

In combination with halothane, both lidocaine and xylazine prolonged interval durations in the electrocardiogram. Xylazine resulted in a change in heart rate and R wave amplitude in response to epinephrine, tending to block the epinephrine effect to a greater degree than lidocaine. Lidocaine had a similar blocking effect at doses of epinephrine greater than 10μg.

The characteristics of halothane or epinephrine induced cardiac arrhythmias are an increase in heart rate and prolonged QT interval. Halothane in combination with xylazine resulted in a diminished change in heart rate demonstrating its antiarrhythmic effect. However, xylazine prolonged the QT interval duration, an event associated with the produc-

tion of arrhythmias. In contrast, lidocaine resulted in a decrease in QT interval duration in response to epinephrine.

The mechanism of action of xylazine may be similar to that of lidocaine on the fast inward sodium current, although the time delay in reactivation may be greater than for the lidocaine group.

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APPENDIXES

TABLE I

ANALYSIS OF VARIANCE: EFFECT OF TREATMENT DRUGS (LIDOCAINE, XYLAZINE, SALINE) ON MEAN VALUES FOR HEART RATE, CHANGE HEART RATE AND PERCENT CHANGE IN HEART RATE

		Lidocaine			Xylazine			Saline		Least
Parameter	Injection	N	mean	Standard error	N	mean	Standard error	N	mean	Standard error	Significant Difference
Heart Rate	Preinjection	64	90.2	3.30	68	100.58	2.86	66	102.3	3.69	9.96
	Drug Treatment	84	93.3	2.96	84	71.2	2.8	84	101.5	2.8	8.21
Change in Heart Rate	Treatment Drug										
	+10 seconds	12	3.5	2.38	12	-18.5	8.33	12	1.0	0.67	14.6
	+20 seconds	12	1.5	2.46	12	-26	7.54	12	2.5	1.37	13.6
	+30 seconds	12	4.5	3.22	12	-37	8.55	12	-1.0	2.19	16.4
	+40 seconds	12	3.5	3.42	12	-37.5	8.35	12	0.5	1.37	15.9
	+50 seconds	12	3.5	2.80	12	-40	8.90	12	-1.6	1.82	16.8
	+60 seconds	12	4.0	2.50	12	-41.5	8.17	12	-1.0	1.62	15.4
	2µg epinephrine										
	+10 seconds	12	15	5.50	12	- 4.6	3.24	12	22	7.58	16.7
	8µg epinephrine										
	+10 seconds	10	10.8	7.93	8	- 0.75	3.29	9	32	9.11	22.8
	+40 seconds	9	11.4	7.14	8	0	5.66	6	-22	7.04	20.2
	+50 seconds	8	11.2	7.89	8	- 2.2	5.31	6	-22	8.29	20.7
	+60 seconds	8	20.2	11.99	8	- .82	5.40	6	-25	9.47	27.5
	10µg epinephrine										
	+50 seconds	7	4.2	7.60	8	- 5.2	5.37	5	-30	12.5	20.1
	+60 seconds	7	13.7	11.54	8	- 3.0	4.81	4	-21	9.0	23.1

TABLE I (Continued)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Least Significant Difference
Change in Heart Rate (Continued)	Treatment Drug										
	12µg epinephrine										
	+10 seconds	7	24.8	10.42	8	- 1.5	2.71	4	31.5	16.13	27.5
	+30 seconds	6	- 6.0	8.19	8	- 3.7	6.89	3	-38	2.00	20.9
	+40 seconds	6	-15.0	6.88	8	- 9.0	3.00	3	-46	8.00	14.9
	14µ epinephrine										
	+30 seconds	6	- 6.0	11.89	7	- 6.8	4.22	3	-42	6.00	19.0
	+40 seconds	6	-14.0	11.02	7	- 12.8	4.42	3	-46	8.71	24.4
Percent Change in Heart Rate	Treatment Drug										
	+10 seconds	12	4.66	3.14	12	- 17	7.32	12	1.07	0.72	13.3
	+20 seconds	12	1.95	2.77	12	- 24.6	6.45	12	2.8	1.51	11.9
	+30 seconds	12	4.72	3.14	12	- 34.7	7.55	12	- .09	1.38	14.4
	+40 seconds	12	3.96	3.36	12	- 34	7.32	12	.8	1.01	14.1
	+50 seconds	12	3.33	2.96	12	- 37	8.00	12	- .82	1.32	15.3
	+60 seconds	12	5.68	3.19	12	- 38.6	7.06	12	- .46	1.48	13.9
	2µg epinephrine										
	+10 seconds	12	20.8	9.32	12	- 6.8	4.81	12	21.5	7.67	22.0
	8µg epinephrine										
	+40 seconds	9	14.78	9.19	8	7.96	10.71	6	- 21.7	7.25	27.1
	+50 seconds	8	12.6	8.71	8	- 11.4	7.93	6	- 22.5	8.55	25.3
	+60 seconds	8	20.0	11.21	8	- 6.8	8.05	6	- 26.1	10.55	29.5

TABLE I (Continued)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Least Significant Difference
Percent Change in Heart Rate (Continued)	Treatment Drug										
	10µg epinephrine										
	+50 seconds	7	6.9	8.84	8	-10.00	8.50	5	-27.7	11.52	24.8
	+60 seconds	7	18.0	13.4	8	- 6.6	8.25	4	-20.7	9.27	30.4
	12µ epinephrine										
	+40 seconds	6	-14.4	7.26	8	-13.4	4.55	3	-46.5	6.83	17.1
	16µg epinephrine										
	+20 seconds	4	12.4	11.42	7	- 3.6	5.92	3	-33.7	6.87	20.2
	18µg epinephrine										
	+20 seconds	3	10.7	15.97	7	- 1.5	12.49	3	-41.5	4.81	28.3

N = number of observations making up average values
L.S.D. = least significant divisor - used to determine which groups are significantly different at the .05 level
Values above are mean values for the time interval and dose indicated. All values significant at the .05 level

TABLE II

ANALYSIS OF VARIANCE: MEAN VALUES FOR EFFECT CONDITION (ANESTHETIZED, AWAKE) ON HEART RATE, CHANGE IN HEART RATE AND PERCENT CHANGE IN HEART RATE

		Anesthetized			Awake		
Parameter	Injection	N	mean	Standard error	N	mean	Standard error
Heart Rate	Preinjection	94	93.8	1.56	104	101.8	3.35
	Treatment Drugs	126	85.3	1.93	126	92.0	3.13
	- lidocaine						
	- xylazine						
	- saline						
Change in Heart Rate	2µg epinephrine						
	+50 seconds	16	-2.2	2.76	18	12.0	6.35
	+60 seconds	16	-2.0	1.85	18	10.6	4.6
	4µg epinephrine						
	+60 seconds	15	-3.1	3.5	14	9.2	5.3
	8µg epinephrine						
	+20 seconds	14	-4.1	4.9	12	11.4	4.7
	+50 seconds	12	-14.2	5.3	10	1.2	7.3
	+60 seconds	12	-12.2	5.5	10	3.6	11.4
	10µg epinephrine						
	+20 seconds	12	-4.1	5.5	8	26.5	9.0
	+30 seconds	12	-12.2	5.6	8	11.7	6.0
	+40 seconds	12	-16.5	4.7	8	0.2	5.0
	+60 seconds	12	-11.5	4.4	7	14.7	10.7
	12µg epinephrine						
	+20 seconds	12	-13.8	5.9	7	13.5	9.4
	+30 seconds	11	-19.4	6.2	6	10.0	7.0
	+40 seconds	11	-27.3	5.8	6	-5.0	1.8
	14µg epinephrine						
	+20 seconds	10	-16.8	7.6	6	16.0	8.8
	+30 seconds	10	-27.3	5.9	6	8.0	5.2
	+40 seconds	10	-29.8	6.8	6	-5.0	6.4
	16µg epinephrine						
	+20 seconds	9	-14.6	5.6	5	17.5	9.0

TABLE II (Continued)

Parameter	Injection	Anesthetized N	Anesthetized mean	Anesthetized Standard error	Awake N	Awake mean	Awake Standard error
Percent Change in Heart Rate	2µg epinephrine						
	+60 seconds	16	-2.1	2.1	18	12.9	5.6
	4µg epinephrine						
	+60 seconds	15	-2.9	4.2	14	12.2	6.1
	6µg epinephrine						
	+20 seconds	15	-2.3	3.2	14	14.4	7.7
	8µg epinephrine						
	+20 seconds	14	-3.3	6.1	12	16.7	5.3
	+50 seconds	12	-16.3	5.9	10	7.02	8.7
	+60 seconds	12	-14.1	6.2	10	11.9	11.8
	10µg epinephrine						
	+20 seconds	12	-4.2	5.8	8	33.0	11.3
	+30 seconds	12	-11.5	6.4	8	16.4	9.6
	+40 seconds	12	-16.4	4.5	8	-.27	6.3
	+60 seconds	12	-12.1	4.9	7	19.4	14.6
	12µg epinephrine						
	+20 seconds	12	-14.5	6.3	7	14.5	10.5
	+30 seconds	11	-18.2	6.8	6	17.2	14.2
	+40 seconds	11	-27.2	5.8	6	-5.6	2.0
	14µg epinephrine						
	+20 seconds	10	-17.2	8.9	6	17.0	9.4
	+30 seconds	10	-28.5	5.9	6	9.0	6.5
	16µg epinephrine						
	+20 seconds	9	-16.8	6.1	5	14.8	7.3
	+30 seconds	9	-27.9	6.0	5	7.3	14.2

N = number of observations

Times shown are post injection of epinephrine or treatment injections (Lidocaine, Xylazine, Saline)

TABLE III

ANALYSIS OF VARIANCE: EFFECT OF TREATMENT DRUGS (LIDOCAINE, XYLAZINE, SALINE) ON MEAN INTERVAL DURATIONS

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Least Significant Difference
Pwave duration (seconds)	Preinjection	64	.0455	.0015	69	.0467	.0014	66	.0412	.0014	.0044
	Treatment Drug	84	.0465	.0013	84	.0480	.0012	84	.0414	.0011	.0037
	4µg epinephrine	84	.0444	.0012	68	.0531	.0016	68	.0430	.0011	.0039
	6µg epinephrine	80	.0467	.0013	56	.0536	.0013	63	.0402	.0011	.0038
	14µg epinephrine	39	.0466	.0020	49	.0554	.0012	21	.0530	.0025	.0047
	16µg epinephrine	28	.0423	.0020	49	.0542	.0015	21	.0532	.0023	.0047
PR segment duration (seconds)	Treatment Drug	84	.0465	.0013	84	.0484	.0021	84	.0402	.0012	.0045
	2µg epinephrine	84	.0427	.0014	81	.0545	.0024	80	.0379	.0013	.0049
	4µg epinephrine	84	.0428	.0013	68	.0571	.0028	68	.0433	.0017	.0056
	6µg epinephrine	80	.0474	.0017	56	.0603	.0032	63	.0414	.0017	.0062
	8µg epinephrine	65	.0440	.0017	56	.0561	.0030	50	.0481	.0021	.0067
	12µg epinephrine	45	.0506	.0022	55	.0643	.0033	24	.0581	.0033	.0090
	16µg epinephrine	28	.0454	.0029	49	.0740	.0034	21	.0615	.0038	.0082
QRS Interval duration (seconds)	Treatment Drug	84	.0437	.0012	84	.0458	.0009	84	.0382	.0009	.0028
	4µg epinephrine	84	.0418	.0011	68	.0485	.0010	68	.0349	.0007	.0029
	6µg epinephrine	80	.0439	.0013	56	.0480	.0012	63	.0361	.0009	.0036
	8µg epinephrine	65	.0414	.0013	56	.0500	.0009	50	.0404	.0013	.0035
	10µg epinephrine	49	.0403	.0016	56	.0495	.0010	34	.0470	.0021	.0045
	12µg epinephrine	45	.0411	.0018	55	.0507	.0011	24	.0447	.0018	.0042

TABLE III (Continued)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Least Significant Difference
QT interval duration (Continued) (seconds)	14µg epinephrine	39	.0418	.0018	49	.0507	.0009	21	.0442	.0016	.0043
	16µg epinephrine	28	.0375	.0007	49	.0517	.0010	21	.0452	.0022	.0039
QT Interval duration (seconds)	2µg epinephrine	84	.2146	.0029	81	.2469	.0028	80	.2021	.0052	.0109
	16µg epinephrine	28	.2175	.0058	49	.2482	.0032	21	.2450	.0040	.0127

N = number of observations
To Determine Difference Between Groups, Use Least Significant Divisor Mean
Values Averaged Over All Time Intervals (Time = 0 to Time = 60)

TABLE IV

ANALYSIS OF VARIANCE: EFFECT OF CONDITION (ANESTHETIZED OR AWAKE) ON MEAN INTERVAL DURATION IN RESPONSE TO TREATMENT DRUGS (LIDOCAINE, XYLAZINE, SALINE) AND EPINEPHRINE

		Anesthetized			Awake		
Parameter	Injection	N	mean	Standard error	N	mean	Standard error
Pwave duration (seconds)	Preinjection	95	.0463	.0013	104	.0428	.0011
	Treatment Drug	126	.0476	.0011	126	.0430	.0009
	4µg epinephrine	107	.0486	.0011	113	.0448	.0011
	6µg epinephrine	104	.0498	.0011	95	.0430	.0011
	10µg epinephrine	84	.0527	.0011	55	.0471	.0018
	14µg epinephrine	69	.0558	.0012	40	.0449	.0016
	16µg epinephrine	63	.0554	.0012	35	.0419	.0018
PR segment duration (seconds)	Treatment Drug	126	.0511	.0014	126	.0390	.0010
	2µg epinephrine	119	.0508	.0018	126	.0396	.0011
	4µg epinephrine	107	.0536	.0019	113	.0415	.0013
	6µg epinephrine	104	.0550	.0020	95	.0427	.0015
	12µg epinephrine	79	.0635	.0025	45	.0487	.0021
	16µg epinephrine	63	.0718	.0027	35	.0476	.0029
QRS interval duration (seconds)	Treatment Drug	126	.0464	.0009	126	.0387	.0007
	4µg epinephrine	107	.0441	.0010	113	.0395	.0008
	6µg epinephrine	104	.0455	.0011	95	.0394	.0009
	8µg epinephrine	93	.0467	.0011	78	.0406	.0009
	10µg epinephrine	84	.0487	.0012	55	.0409	.0013
	12µg epinephrine	79	.0490	.0012	49	.0409	.0012
	14µg epinephrine	69	.0487	.0012	40	.0421	.0011
	16µg epinephrine	63	.0477	.0012	35	.0437	.0014
QT Interval duration (seconds)	2µg epinephrine	119	.2274	.0036	126	.2154	.0034
	16µg epinephrine	63	.2453	.0029	35	.2268	.0052

TABLE V

ANALYSIS OF VARIANCE: EFFECT OF TREATMENT DRUGS (LIDOCAINE, XYLAZINE AND SALINE) ON MEAN CHANGE IN INTERVAL DURATION

		Lidocaine			Xylazine			Saline		Least
Parameter	Injection	N	mean	Standard error	N	mean	Standard error	N	mean	Stanrard error	Significant Difference (.05)
Change in Pwave duration	2µg epinephrine +20 seconds	12	-.0052	.0045	12	.0081	.0035	12	-.0030	.0028	.0107
	12µg epinephrine +40 seconds	12	-.0052	.0045	12	.0081	.0035	12	-.0030	.0028	.0107
	14µg epinephrine +50 seconds	5	-.0036	.0042	7	-.0037	.0021	3	.0123	.0023	.0074
	18µg epinephrine +40 seconds	3	.0070	.0075	7	.0010	.0005	2	.0195	.0095	.0135
PR segment duration	Treatment Drug +10 seconds	12	.0034	.0016	12	.0082	.0032	12	-.0001	.0003	.0061
	+20 seconds	12	.0035	.0017	12	.0131	.0042	12	0	.0005	.0079
	+30 seconds	12	.0034	.0019	12	.0128	.0040	12	-.0019	.0012	.0080
	+40 seconds	12	.0017	.0019	12	.0015	.0041	12	-.0009	.0010	.0080
	+50 seconds	12	.0030	.0018	12	.0119	.0044	12	-.0013	.0010	.0083
	+60 seconds	12	.0049	.0024	12	.0145	.0045	12	0	.0009	.0089
	2µg epinephrine +10 seconds	12	-.0056	.0021	12	.0024	.0021	12	-.0050	.0019	.0060
	+20 seconds	12	-.0062	.0029	12	.0034	.0027	12	-.0038	.0024	.0075
	+60 seconds	12	-.0049	.0037	11	.0090	.0037	11	-.0018	.0014	.0097

TABLE V (Continued)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Significant Difference (.05)
PR segment duration (Continued)	4µg epinephrine										
	+10 seconds	12	-.0055	.0032	11	.0059	.0025	11	.0041	.0034	.0088
	+20 seconds	12	-.0064	.0036	11	.0109	.0043	10	.0040	.0040	.0118
	6µg epinephrine										
	+10 seconds	12	-.0040	.0030	8	.0127	.0048	9	-.0062	.0024	.0092
	+20 seconds	12	-.0052	.0034	8	.0082	.0047	9	.0006	.0022	.0103
QRS Interval duration (seconds)	Treatment Drug										
	+10 seconds	12	.0008	.0006	12	.0028	.0029	12	-.0043	.0018	.0057
	+20 seconds	12	.0003	.0006	12	.0034	.0023	12	-.0039	.0018	.0052
	+30 seconds	12	.0018	.0013	12	.0063	.0017	12	-.0020	.0021	.0053
	2µg epinephrine										
	+20 seconds	12	-.0015	.0022	12	.0050	.0013	12	-.0044	.0026	.0063
	+30 seconds	12	.0002	.0027	12	.0039	.0015	11	-.0032	.0010	.0054
	+40 seconds	12	.0029	.0031	11	.0040	.0023	11	-.0039	.0011	.0069
	6µg epinephrine										
	+10 seconds	12	-.0041	.0018	8	.0053	.0027	9	.0024	.0026	.0069
	+50 seconds	11	-.0006	.0016	8	.0086	.0045	9	.0017	.0022	.0075
	8µg epinephrine										
	+60 seconds	8	-.0025	.0008	8	.0020	.0015	6	.0093	.0041	.0073

TABLE V (Continued)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Significant Difference
QRS Interval duration (seconds)	Treatment										
	10µg epinephrine										
	+20 seconds	7	-.0004	.0011	8	-.0031	.0027	5	.0088	.0038	.0081
	+50 seconds	7	.0014	.0012	8	.0002	.0033	5	.0136	.0048	.0099
	+60 seconds	7	.0002	.0011	8	-.0001	.0034	4	.0152	.0063	.0115
QT Interval duration	Treatment										
	+40 seconds	12	.0021	.0075	12	.0215	.0065	12	-.0013	.0014	.0176
	+50 seconds	12	.0042	.0056	12	.0235	.0068	12	-.0044	.0029	.0166
	+60 seconds	12	.0046	.0053	12	.0250	.0059	12	-.0029	.0031	.0155
	2µg epinephrine										
	+10 seconds	12	-.0144	.0056	12	.0123	.0064	12	-.0032	.0052	.0173
	+20 seconds	12	-.0152	.0060	12	.0141	.0064	12	-.0021	.0064	.0180
	+30 seconds	12	-.0122	.0063	12	.0168	.0065	11	-.0064	.0052	.0173
	+40 seconds	12	-.0106	.0065	11	.0148	.0098	11	-.0025	.0056	.0203
	+50 seconds	12	-.0112	.0064	11	.0106	.0076	11	-.0026	.0052	.0176
	8µg epinephrine										
	+20 seconds	10	-.009	.0047	8	.0025	.0072	8	.0103	.0038	.0148
QT Interval duration	10µg epinephrine										
	+30 seconds	7	-.0024	.0055	8	-.0070	.0066	5	.0352	.0094	.0194

TABLE V (Continued)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Significant Difference
QT Interval duration	10µg epinephrine										
	+40 seconds	7	-.0057	.0058	8	-.0010	.0047	5	.0444	.0114	.0225
	+50 seconds	7	-.0075	.0052	8	-.0046	.0062	5	.0354	.0119	.0247
	+60 seconds	7	-.0080	.0052	8	-.0040	.0062	4	.0322	.0135	.0243
	14µg epinephrine										
	+10 seconds	6	-.0065	.0060	7	.0104	.0051	3	-.0183	.0099	.0204

TABLE VI

ANALYSIS OF VARIANCE:EFFECTS OF CONDITION (AWAKE, ANESTHETIZED) ON RESPONSE TO EPINEPHRINE OR TREATMENT INJECTION (LIDOCAINE, XYLAZINE, SALINE)

:MEAN CHANGE INTERVAL DURATION: $p < .05$

Parameter	Injection	Anesthetized N	Anesthetized mean	Anesthetized Standard error	Awake N	Awake mean	Awake Standard error
P wave duration	2µg epinephrine						
	+10 seconds	18	.0037	.0022	18	-.003	.0022
	4µg epinephrine						
	+40 seconds	15	.0034	.0024	15	-.003	.0018
	6µg epinephrine						
	+10 seconds	15	.0024	.0019	14	-.004	.0018
	+30 seconds	15	.0024	.0022	14	-.0042	.0018
	+40 seconds	15	.0042	.0019	13	-.0023	.0014
	+50 seconds	15	.0050	.0023	13	-.0023	.0017
	+60 seconds	14	.0043	.0024	13	-.0028	.0018
	10µg epinephrine						
	+20 seconds	12	.0047	.0020	8	-.0032	.0012
	12µg epinephrine						
	+20 seconds	12	.0036	.0029	7	-.0051	.0019
	14µg epinephrine						
	+30 seconds	10	.0045	.0027	6	-.0076	.0031
	+40 seconds	10	.0065	.0029	6	-.0071	.0027
	+50 seconds	10	.0035	.0025	5	-.0084	.0028
	+60 seconds	9	.0052	.0020	5	-.0078	.0047
PR Segment duration	6µg epinephrine						
	+10 seconds	15	.0041	.0036	14	-.0045	.0028
	+30 seconds	15	.0086	.0043	14	-.0038	.0030
	+40 seconds	15	.0116	.0044	13	-.0047	.0024
	+50 seconds	15	.0119	.0038	13	-.0010	.0025

Table VI (Continued)

Parameter	Injection	Anesthetized N	Anesthetized mean	Standard error	Awake N	Awake mean	Standard error
PR segment duration	14µg epinephrine						
	+30 seconds	10	.0143	.0029	6	-.0008	.0071
	+40 seconds	10	.0162	.0036	6	.0018	.0066
	+50 seconds	10	.0018	.0033	5	.0010	.0081
	+60 seconds	9	.0177	.0024	5	-.0088	.0046
PR Segment duration	16µg epinephrine						
	+40 seconds	9	.0207	.0043	5	.0010	.0039
	+50 seconds	9	.0248	.0045	5	.0002	.0023
	+60 seconds	9	.0232	.0032	5	.0094	.0063
QRS Interval duration	6µg epinephrine						
	+50 seconds	15	.0058	.0028	13	-.0007	.0010
	+60 seconds	14	.0046	.0018	13	0	.0011
	14µg epinephrine						
	+20 seconds	10	.0018	.0014	6	-.0025	.0012
QT Interval duration	Preinjection						
	+30 seconds	18	-.002	.0046	18	.0016	.0060
	6µg epinephrine						
	+40 seconds	15	.0140	.0064	13	-.013	.0085
	+50 seconds	15	.0099	.0065	13	-.014	.0066
	8µg epinephrine						
	+40 seconds	13	.0126	.0076	10	-.015	.0087
	+50 seconds	12	.0205	.0081	10	-.017	.0086
	+60 seconds	12	.0225	.0076	10	-.013	.0078
	10µg epinephrine						
	+30 seconds	12	.0124	.0078	8	-.005	.0059

N = Number of Observations

Mean = Mean Value Averaged by Dog & Drug Treatment

All Values Significant at .05 level

TABLE VII

ANALYSIS OF VARIANCE:EFFECT OF TREATMENT DRUGS (LIDOCAINE, XYLAZINE, SALINE) ON MEAN PERCENT INTERVAL DURATION ($p < .05$)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Least Significant Difference
P wave duration	2µg epinephrine +20 seconds	12	-7.81	9.31	12	21.3	9.71	12	-5.8	6.19	(.05)
	12µg epinephrine +40 seconds	6	30.6	7.2	8	-3.7	4.7	3	21.4	24.4	
	14µg epinephrine +50 seconds	5	-7.6	9.0	7	-6.8	3.85	3	29.1	10.4	
PR segment duration	Treatment Drug +20 seconds	12	8.90	4.8	12	3.37	11.4	12	.208	1.4	21.08
	+30 seconds	12	9.02	4.9	12	30.98	10.8	12	-3.5	2.4	20.7
	+40 seconds	12	4.69	5.0	12	29.8	11.3	12	-1.6	2.4	20.65
	+50 seconds	12	8.87	5.0	12	31.7	11.9	12	-2.7	2.3	21.27
	+60 seconds	12	14.63	7.2	12	39.7	12.8	12	-.13	2.3	24.94
	2µg epinephrine +10 seconds	12	-10.2	3.8	12	5.17	5.2	12	-12.12	4.3	12.96
	+60 seconds	12	-7.47	5.9	11	18.13	8.8	11	-4.38	3.5	19.55
	6µg epinephrine +10 seconds	12	-7.65	5.4	8	31.81	13.1	9	-13.2	4.8	21.26
QRS Interval duration	Treatment Drug +10 seconds	12	1.94	1.43	12	9.94	7.1	12	-9.15	3.7	13.11
	+20 seconds	12	.879	1.49	12	11.12	6.05	12	-8.02	3.7	12.44

TABLE VII (Continued)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Least Significant Difference (.05)
	+30 seconds	12	3.53	2.85	12	16.90	4.9	12	-2.87	5.2	13.25
	+50 seconds	12	-.048	3.07	12	16.3	7.1	12	-5.02	4.8	15.08
	2µg epinephrine										
	+20 seconds	12	-1.84	5.06	12	10.83	3.30	12	-9.5	4.6	12.97
	+30 seconds	12	3.34	6.5	12	8.13	3.10	11	-8.27	2.5	12.65
	6µg epinephrine										
	+10 seconds	12	-8.97	3.7	8	14.02	7.2	9	7.60	8.2	18.25
	8µg epinephrine										
	+60 seconds	8	-.351	1.96	8	3.80	3.05	6	26.23	12.50	20.45
QRS Interval duration	10µg epinephrine										
	+20 seconds	7	-1.02	3.23	8	-5.41	4.8	5	21.91	9.5	17.32
	+50 seconds	7	4.23	3.41	8	2.08	6.4	5	36.25	14,0	24.31
	+60 seconds	7	-.46	3.14	8	1.05	6.5	4	40.58	18.9	27.48
QT Interval duration	Treatment Drug										
	+60 seconds	12	2.02	2.97	12	11.69	2.74	12	-1.05	1.40	7.32
	2µg epinephrine										
	+30 seconds	12	-5.06	2.6	12	7.47	3.0	11	-2.94	2.48	7.74
	+40 seconds	12	-4.22	2.7	11	7.37	4.6	11	-1.18	2.68	9.51
	+50 seconds	12	-4.59	2.7	11	5.19	3.4	11	1.40	2.58	7.99
	8µg epinephrine										
	+20 seconds	10	-4.14	2.18	8	1.81	3.07	8	8.45	3.66	8.44
	+30 seconds	10	-3.58	2.73	8	1.16	4.02	6	12.12	3.33	10.26

TABLE VII (Continued)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Least Significant Difference (.05)
	+40 seconds	9	-6.31	3.53	8	1.86	5.33	6	14.19	5.71	13.29
	+50 seconds	8	-5.82	4.51	8	3.05	5.83	6	14.35	5.77	14.59
	+60 seconds	8	-4.79	4.63	8	5.80	4.93	6	13.66	6.12	13.85
	10µg epinephrine										
	+40 seconds	7	-2.6	2.70	8	-.18	2.1	5	29.2	5.5	10.3
	+50 seconds	7	-3.3	2.46	8	-1.5	2.6	5	42.2	24.7	33.6
	+60 seconds	7	-3.5	2.55	8	-1.2	2.6	4	49.6	34.9	40.9
	14µg epinephrine										
	+10 seconds	6	-3.04	2.94	7	4.34	2.19	3	-7.04	3.73	8.89

N = Number of Observations

Mean = Mean Value Averaged over Dog and Condition

Least Significant Divisor is used to distinguish difference between groups at .05 level of significance.

TABLE VIII

ANALYSIS OF VARIANCE:EFFECT OF CONDITION (AWAKE OR ANESTHETIZED) ON RESPONSE TO TREATMENT DRUG OR EPINEPHRINE :PERCENT CHANGE INTERVAL DURATION:

Parameter	Injection	Anesthetized N	Anesthetized mean	Anesthetized Standard error	Awake N	Awake mean	Awake Standard error
PR Segment	6µg epinephrine						
	+10 seconds	15	12.18	8.95	14	-9.9	5.42
	+30 seconds	15	24.31	8.67	14	-7.0	6.85
	+40 seconds	15	27.7	9.70	13	-9.9	5.49
	+50 seconds	15	26.5	8.29	13	.06	6.20
	14µg epinephrine						
	+40 seconds	10	33.4	8.02	6	2.86	13.13
	+60 seconds	9	39.4	10.52	5	-17.4	9.01
	16µg epinephrine						
	+50 seconds	9	47.4	11.31	5	-.83	4.90
QRS Interval duration	6µg epinephrine						
	+50 seconds	15	17.4	8.15	13	-1.6	2.62
	16µg epinephrine						
	+30 seconds	9	5.93	2.41	5	-3.7	1.53
	+40 seconds	9	5.5	2.36	5	-4.0	2.34
	+50 seconds	9	5.2	2.35	5	-4.0	2.34
QT Interval duration	6µg epinephrine						
	+40 seconds	15	6.5	2.93	13	-5.6	3.38
	+50 seconds	15	4.8	2.98	13	-6.0	2.64
	8µg epinephrine						
	+40 seconds	13	7.9	3.9	10	-6.0	4.0
	+50 seconds	12	11.6	4.0	10	-7.5	3.6
	+60 seconds	12	12.5	3.8	10	-6.0	3.4
	18µg epinephrine						
	+60 seconds	6	8.07	2.40	4	-4.0	4.20

TABLE IX

ANALYSIS OF VARIANCE FOR EFFECT OF TREATMENT DRUG (LIDOCAINE, XYLAZINE, SALINE) ON R WAVE AMPLITUDE ($p < .05$)

Parameter	Injection	Lidocaine N	Lidocaine mean	Lidocaine Standard error	Xylazine N	Xylazine mean	Xylazine Standard error	Saline N	Saline mean	Saline Standard error	Least Significant Difference
R Wave Amplitude	8µg epinephrine	65	1.38	.062	56	1.29	.050	50	1.55	.084	.19
Change in R Wave Amplitude	Treatment Drug										
	+20 seconds	12	-.089	.042	12	.110	.052	12	-.051	.031	.11
	+30 seconds	12	-.059	.018	12	.141	.056	12	-.057	.037	.11
	+40 seconds	12	-.018	.025	12	.125	.043	12	-.018	.026	.09
	+50 seconds	12	-.007	.025	12	.125	.043	12	-.041	.026	.09
	+60 seconds	12	-.021	.032	12	.092	.045	12	-.075	.048	.12

VITA

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Master of Science

Thesis: ELECTROCARDIOGRAPHIC CHANGES IN RESPONSE TO EPINEPHRINE IN THE AWAKE AND HALOTHANE ANESTHETIZED DOG: EFFECT OF TREATMENT WITH LIDOCAINE AND XYLAZINE.

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