The Interaction of Anesthetic Agents and Adrenergic Drugs to Produce Cardiac Arrhythmias

Ronald L. Katz, M.D., and Ralph A. Epstein, M.D.†*

DRUGS which stimulate structures innervated by adrenergic nerves are referred to as adrenergic drugs or sympathomimetics. In this review these terms will be used interchangeably. Catecholamines such as epinephrine, norepinephrine, isoproterenol and dopamine are adrenergic agents possessing a catechol nucleus (3,4-dihydroxybenzene) and amine group. Some of the adrenergic agents are commonly injected subcutaneously or applied topically to provide local hemostasis during plastic, gynecological, otolaryngological and neurological surgery—their value in these situations is well established. These agents are also injected intravenously or intramuscularly to increase arterial blood pressure. In some situations the rationale for this use is in doubt; there are many, including the present authors, who feel that vasopressors rarely are required during well-conducted general anesthesia.

Some sympathomimetics are capable of producing cardiac arrhythmias in unanesthetized patients. In the presence of certain inhalation anesthetics (cyclopropane or halogenated hydrocarbons) the dose of sympathomimetic that will produce cardiac arrhythmias may be decreased significantly. The clinical significance of this problem was emphasized in a recent review in which numerous cases of anesthetic–adrenergic cardiac arrhythmias and arrests were reported.[1]

* Associate Professor of Anesthesiology.
† Postdoctoral Research Trainee, U.S.P.H.S. GM 00056-09.
Received from the Department of Anesthesiology, Columbia University, College of Physicians and Surgeons, and the Anesthesiology Service, The Presbyterian Hospital in the City of New York, New York, N. Y. Supported by U.S.P.H.S. Grant GM-09069.

Anesthetics

As early as 1895, Oliver and Schäfer[2] noted that the intravenous injection of adrenal extract in a dog anesthetized with chloroform produced ventricular fibrillation. Levy and Lewis in 1911[3] reported that the intravenous injection of epinephrine during chloroform anesthesia would produce ventricular tachycardia and ventricular fibrillation in the cat. Levy's studies of this problem are classics of pharmacology.[3-6] Much of our understanding of the problem came about through work carried out by members of the Departments of Anesthesia, Physiology and Pharmacology at the University of Wisconsin. Meek *et al.*[7] stated that "Cardiac irregularities have repeatedly been studied in anesthesia but seldom under controlled conditions. Usually little attention has been given to accurate concentration of the anesthetic agent, the adequacy of the oxygen supply, the degree of carbon dioxide accumulation or the exact depth of anesthesia." A standardized preparation for study of the interaction of anesthetics and sympathomimetics was developed because, "It is not enough in judging an anesthetic merely to note that the heart shows no irregularities of rhythm. The normal pacemaker may be approaching an inhibition sufficient to allow escape phenomena, or ectopic centers may be on the point of exhibiting activity should an additional stimulus appear. This reasoning has suggested to us that the condition of the automatic tissue in the heart might be tested by a standard injection of adrenaline. This drug is well known to be a stimulant to cardiac tissue, either directly or by way of sympathetic nerve endings. It is known to stimulate not only the S-A node but specialized tissue in the ventricle. The direct

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

effect on the S-A node is of course generally masked by reflex vagal effects. The basis of our method has been to find a dose of adrenaline in the normal animal produced only reflex vagal inhibition of the pacemaker with or without escape of the A-V node, bundle, or ventricles, but never with tachycardia or fibrillation. Under anesthesia the same dose of adrenaline was repeated and the cardiac irregularities noted. Stimulation of ectopic pacemakers to faster rates has been interpreted as meaning that the anesthesia had sensitized or made the automatic tissue more irritable."

The term "sensitized" which they used has become firmly entrenched in the literature. Although we know today it is inaccurate, it is widely used for lack of a better term. The test was carried out as follows: a test dose of 10 μg./kg. (0.01 mg./kg.) diluted in 5 ml. of normal saline solution was injected intravenously at the rate of 1 ml. every 10 seconds. In the unanesthetized dog ventricular tachycardia did not occur. Ventricular arrhythmias were noted, but the endpoint chosen was ventricular tachycardia. On another day the test dose was repeated in the same dog, this time during cyclopropane anesthesia. Ventricular tachycardia was usually observed. Epinephrine also produced ventricular tachycardia during chloroform inhalation but less often. It was noted that during ether inhalation epinephrine did not produce ventricular tachycardia. In fact the frequency of ventricular arrhythmia was less than in the unanesthetized animal. Ether was therefore considered to have a protective action. There have since been numerous studies of the interaction of anesthetics and sympathomimetics; the basic technique described has been modified; many investigators have chosen smaller doses of epinephrine and have used ventricular ectopic beats rather than ventricular tachycardia as the endpoint.

Since the pioneering work of the Wisconsin group it has become standard practice in the study of a new inhalation anesthetic to determine whether the injection of epinephrine during inhalation will produce cardiac arrhythmias. Meek *et al.*[7] studied chloroform, cyclopropane and ether. Other agents studied since then include trichloroethylene, halothane, methoxyflurane, ethyl chloride and fluroxene.[8–13] In many of these studies two or more agents were compared. By pooling the results of the various studies it has been possible to devise a general order of sensitization in the dog. In order, of decreasing sensitization we have: trichloroethylene, ethyl chloride, cyclopropane, halothane, chloroform, methoxyflurane and fluroxene. It should be pointed out that this ranking has been determined by comparing different studies not necessarily carried out in a similar fashion. No study in which all of these agents were compared in the same animal, in the same laboratory and by the same technique has been reported. It is conceivable that the above order might be modified if such a study were carried out.

The studies noted above have been criticized as not necessarily applicable to man. There are many discussions of whether findings in the cat or the dog bear any relationship to man. But it has been demonstrated that an injection of epinephrine that produces arrhythmias during inhalation of an anesthetic in the cat or dog will do so in man.[2, 10, 14–17] It is of particular interest that in one study the mean dose of epinephrine required to produce cardiac arrhythmias during cyclopropane inhalation in the cat was 0.9 μg./kg.; in man, 0.5 μg./kg.[10] In the dog, during cyclopropane anesthesia, the dose was 0.25–1.0 μg./kg.[13] Thus, despite species differences, cat, dog and man respond in a similar fashion qualitatively and quantitatively. However, the order of sensitization found in the dog probably does not apply to man. For example, although trichloroethylene is a more potent sensitizer than cyclopropane in the dog, the reverse is true in man.[16, 19]

Adrenergic Drugs

Let us now consider which of the sympathomimetics are capable of producing cardiac arrhythmias in the presence of the anesthetics listed above. It is pertinent first to discuss briefly the sympathomimetics in terms of the alpha and beta adrenergic receptors. It is well known that sympathomimetics produce varying effects: vasodilation, vasoconstriction, cardiac acceleration, augmentation of myocardial contractile force, bronchial muscle relaxation,

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

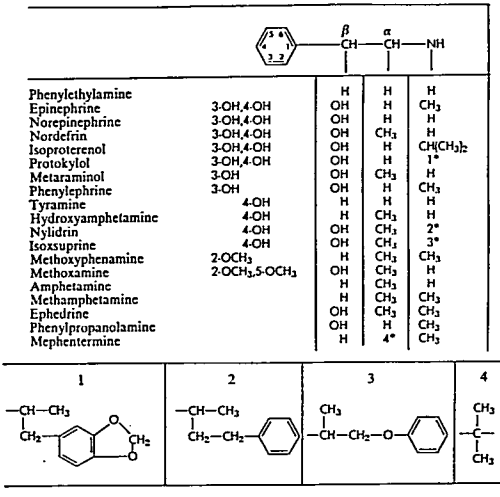

FIG. 1. Structural formulas of sympathomimetics. (From Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, third edition, Macmillan.)

contraction of the nictitating membrane, dilation of the pupil, excitation of the uterus, relaxation of the uterus and intestinal relaxation. In 1948, Ahlquist[20] explained the variation in the effects of sympathomimetics by hypothesizing the presence of two types of adrenergic receptor, alpha and beta. Some effects of sympathomimetics are blocked by drugs such as phentolamine, phenoxybenzamine, or ergot alkaloids, while other effects are not. The actions thus blocked are called alpha-adrenergic effects, the blocking drugs are called alpha-adrenergic blockers. Powell and Slater, in 1958,[21] reported that dichloroisoproterenol (DCI) was capable of blocking the effects of sympathomimetics which were not blocked by alpha adrenergic blockers. Since then, numerous similar agents have been termed beta-adrenergic blockers, the actions blocked are beta-adrenergic effects. Vasoconstriction is an alpha-adrenergic effect, whereas beta effects include vasodilation, increased heart rate and increased myocardial contractile force.

The arrhythmias produced by adrenergic agents initially were attributed to alpha-adrenergic stimulation. However, subsequent studies suggested that cardiac arrhythmias were due to beta-adrenergic stimulation (evidence for this will be discussed below). If we know that the beta adrenergic stimulating action produces cardiac arrhythmias, and if we know the structure–activity relationships of various compounds, it should be possible from the structural formula to predict whether an agent is a stimulator and therefore whether it will produce arrhythmias in the presence of anesthetics. The basic structure of adrenergic agents is shown in figure 1. Important modifications for enhancing beta-adrenergic stimulating activity include an alcoholic hydroxyl on the side chain in the beta position, and N-alkyl substitution with a methyl group or derivatives in which the hydrogens of the methyl groups are replaced by other methyl groups.[22]

Exogenous Administration

Orth *et al.*,[23, 24] in dogs anesthetized with cyclopropane, studied many sympathomimetics in doses approximately equal in pressor activity to 0.01 mg./kg. of epinephrine. Epinephrine, norepinephrine, epinine, kephrine and cobefrin regularly produced ventricular tachycardia while ephedrine, propadrine, ben-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

zedrine, paredrine, synephrine and neosynephrine did not. They further noted that a catechol nucleus (3,4-dihydroxybenzene) and a primary or secondary amino group were required to produce ventricular tachycardia.

Of the commonly-used sympathomimetics, epinephrine and norepinephrine produce arrhythmias during anesthesia, if given in sufficiently large doses.[1] Although methoxamine (Vasoxyl), ephedrine, mephentermine (Wyamine) and phenylephrine (Neosynephrine) are usually considered not to produce arrhythmias during inhalation of halogenated hydrocarbons or cyclopropane, arrhythmias occasionally have been observed both in animals and in man.[18, 25–28]

This may be related to the magnitude of increase in blood pressure produced by these agents. It is possible to produce arrhythmias in animals anesthetized with cyclopropane merely by elevating the arterial blood pressure markedly.[18, 29] In addition, dosage is a critical factor. In cats made hypotensive with halothane, the continuous intravenous infusion of 10 μg./kg./min. of dopamine elevated arterial pressure significantly without producing cardiac arrhythmias.[20] However, when larger doses were given, cardiac arrhythmias could be produced. In summary, it would seem safe to use methoxamine, ephedrine, mephentermine or phenylephrine provided that doses which increase arterial pressure above normal levels are avoided.

Although it is widely believed that only the catecholamines are capable of producing arrhythmias, this is not so. One example is metaraminol (Aramine), which though not a catecholamine, is capable of producing arrhythmias.[25] The problem of correlating structure–activity relationships, alpha and beta stimulating activity, and arrhythmic properties is complicated in that sympathomimetics may act directly or indirectly.[31] Some agents work directly on receptors. The indirect-acting agents, in varying degrees, cause the release of catecholamines. Therefore, in addition to the presence of a catechol nucleus and alpha- or beta-adrenergic stimulating properties, one must know whether an agent releases catecholamines, thus producing arrhythmias. It is probable that the arrhythmic actions of metaraminol, ephedrine and dopamine may in some measure be attributable to release of catecholamines.

Cardiac arrhythmias may be caused by the intramuscular or subcutaneous injection of sympathomimetics, as well as by intravenous administration. However, studies in the dog[12, 32] demonstrated that the amount of epinephrine required to produce an arrhythmia is over 100 times greater if given intramuscularly or subcutaneously. In man the intravenous dose of epinephrine required to produce arrhythmias was less than the intramuscular or subcutaneous dose.[10, 14–17]

Catecholamines may also produce arrhythmias when inhaled. The insufflation of isoproterenol in asthmatic patients anesthetized with halothane may produce cardiac arrhythmias.[33] In some cases acidosis may be a contributing factor.

Endogenous Release

We have mentioned the release of catecholamines by sympathomimetics. Hypercarbia, which causes release of catecholamines, may lead to cardiac arrhythmias. Price and his associates[17, 136] showed that the inhalation of carbon dioxide during cyclopropane anesthesia produced cardiac arrhythmias. The threshold Pa_{CO_2} required varied from 44 to 72 torr (mean 58). The higher the concentration of cyclopropane the smaller the increase in Pa_{CO_2} required to produce arrhythmias; stellate ganglion block prevented or abolished the arrhythmias. In studies of halothane, the Pa_{CO_2} required to produce cardiac arrhythmias ranged from 60 to 140 torr (mean 92).[34]

The mechanism by which anesthetics and carbon dioxide produce cardiac arrhythmias recently has been studied.[35] The inhalation of halopropane plus 10 per cent carbon dioxide produced ventricular arrhythmias in 99 per cent of animals studied. Transection of the brain between the pons and midbrain and removal of structures above the pons did not block the arrhythmias. However, transecting the spinal cord at C1 and removing the pons and medulla blocked the arrhythmias. In addition, reserpine pretreatment (0.1 mg./kg. intraperitoneally) for one day, which reduces cerebral and myocardial catecholamines with

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

little or no effect on adrenal catecholamines, did not prevent the arrhythmias; neither did acute bilateral adrenalectomy. A combination of these procedures, however, prevented the arrhythmias. Arrhythmias were also abolished by reserpine pretreatment (0.1 mg./kg. intraperitoneally) for seven days, which depletes myocardial and adrenal catecholamines. Thus, it is clear that the sympathetic nervous system and catecholamine release are involved in the production of arrhythmias. Respiratory acidosis stimulates vasomotor areas in the brain stem, resulting in an increased sympathetic outflow and myocardial and adrenal catecholamine release.

Catecholamines may also be released during surgical operation. Adrenal manipulation, common during renal surgery, may result in the release of catecholamines and the development of arrhythmias in normal patients. In patients with pheochromocytoma manipulation and the release of catecholamines may produce bizarre cardiac arrhythmias because of the large amounts of catecholamines present.

Succinylcholine produces cardiac arrhythmias when injected during inhalation of anesthetics.[36-38] In a study of the mechanism by which this occurs,[33] the injection of succinylcholine produced a rise in blood pressure and cardiac arrhythmias in nine of 20 decerebrate cats inhaling 1 per cent halopropane. After injection of the alpha-adrenergic blocking agent, dibenamine (5 mg./kg.), succinylcholine produced a fall rather than a rise in blood pressure. However, the arrhythmia was not prevented. The injection of the beta-adrenergic blocking agent pronethalol (5 mg./kg.) prevented the succinylcholine-induced arrhythmia, as did hexamethonium, a ganglionic blocking agent. Therefore, it appears that the arrhythmia produced by succinylcholine is due to its ganglionic stimulating action leading to the release of catecholamines.[33, 38] Schoenstadt and Whitcher[37] suggested that choline (produced by the hydrolysis of succinylcholine to succinylmonocholine and choline) sensitizes the patient to subsequent doses of succinylcholine. This explained the prevention by hexafluorenium of arrhythmias following repeated injections of succinylcholine. They also reported that thiopental could prevent these arrhythmias. Another factor in succinylcholine-induced arrhythmias may be the release of potassium succinylcholine. It is also known that the injection of gallamine during cyclopropane anesthesia may produce cardiac arrhythmias.[39] Although this action has long been attributed to the atropine-like action of gallamine, recent evidence suggests that gallamine has a sympathomimetic action which may be attributable to the release of catecholamines.[40]

Mechanisms of Arrhythmia

Although more than 70 years have passed since the first demonstration of the interaction of sympathomimetics and anesthetics, the mechanisms responsible for the arrhythmia still are not understood fully. The following section will discuss the electrophysiologic effects of the anesthetic agents and sympathomimetics, followed by a discussion of the roles of: (1) increased arterial blood pressure; (2) increased heart rate; (3) release of potassium from the liver—all of which may be induced by catecholamines. Then we will consider briefly the effects of central nervous system ablations and sympathetic denervation, the site of origin of the arrhythmias, and finally, the role of the alpha- and beta-adrenergic systems will be discussed.

Electrophysiology

Before discussing the electrophysiologic effects of anesthetics and sympathomimetics, a review of fundamental principles of electrophysiology seems in order.[41-53] If a microelectrode is placed inside a cardiac cell and another electrode outside, the interior will be found to be negative with respect to the exterior. The magnitude of the transmembrane potential of a quiescent atrial or ventricular muscle fiber is −90 mv. and remains constant until excitation occurs. Following stimulation or the arrival of a propagated impulse the transmembrane potential decreases (smaller negative value). If the transmembrane potential is reduced from the resting level to a critical level or threshold potential of −65 to −70 mv., an action potential may be recorded. Changes produced in the canine ventricle are shown in figure 2A. The phases of the action

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

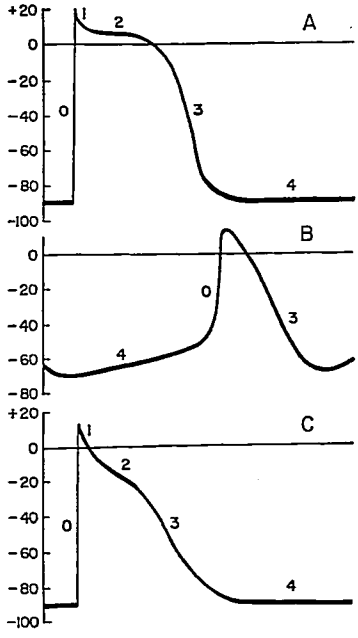

FIG. 2. Schematic records of transmembrane action potentials recorded from ventricle (*A*), sinoatrial node (*B*), and atrium (*C*). Sweep velocity in *B* one-half that in *A* and *C*. Ordinate scale to mv. See text for discussion. (From Hoffman and Cranefield.[6])

potential are designated 0, 1, 2, 3, 4. When the cell is excited there is a rapid decrease in membrane potential (depolarization, phase 0) with a reversal of polarity so that at the end of excitation the inside of the cell is 20 to 30 mv. positive with respect to the outside. Depolarization is followed by a prolonged period of repolarization, during which the transmembrane potential returns to the resting level. There is first a period of rapid repolarization (phase 1), followed by a period of slower repolarization (phase 2 or plateau). This is followed by a period of more rapid repolarization (phase 3) during which the resting level of membrane potential is restored. Phase 4, the diastolic period, is characterized by electrical quiescence.

The events described for the ventricle and seen in figure 2*A* are similar to those occurring in the atrium (fig. 2*C*). However, in the sinoatrial node the action potential is somewhat different (fig. 2*B*). The maximum diastolic potential, reached at the end of phase 3, is less than that of the ventricle cell (−70 mv. for the sinoatrial node and −90 mv. for the ventricle). In addition, phase 4 of the sinoatrial node action potential is characterized by slow depolarization (phase 4 diastolic depolarization). When the membrane potential decreases to a critical level (the threshold potential, approximately −50 mv. in figure 2*B*), depolarization occurs. Cells which show spontaneous phase 4 diastolic depolarization are capable of self-excitation and are known as automatic cells. The property of self-excitation is referred to as automaticity. Automa-

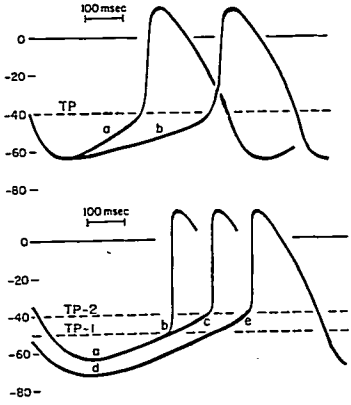

FIG. 3. Diagram representing the important mechanisms responsible for changes in frequency of a pacemaker fiber. The upper diagram shows a decrease in rate caused by a decrease in the slope of phase 4 from *a* to *b* and thus an increase in the time required for the transmembrane potential to reach the threshold potential (TP). The lower diagram shows rate changes associated with a change in the level of the threshold potential from TP-1 to TP-2 and an increase in cycle length from *a-b* to *a-c*; also shown is a change in rate due to an increase in resting potential (compare *a-c* and *d-e*). (From Hoffman and Cranefield.[6])

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

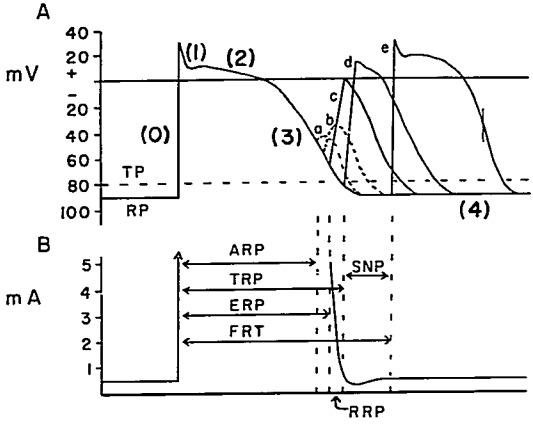

FIG. 4. In *A* are shown a normal transmembrane action potential and the responses to a series of stimuli applied during and after the end of repolarization. In *B* are shown the approximate durations of the absolute refractory period (ARP), total refractory period (TRP), effective refractory period (ERP), full recovery time (FRT), supernormal period (SNP), and relative refractory period (RRP). In *A* the responses shown as dotted lines (*a* and *b*) are graded responses which do not propagate. Response *c* is the earliest propagated response and thus defines the end of the effective refractory period. Response *d* is elicited at a time when transmembrane potential is close to the level of the threshold potential (TP) and thus occurs during the supernormal period. Response *e* is elicited after the end of repolarization and is normal in terms of rising velocity and amplitude. It thus defines the end of the full recovery time. The changes in threshold shown in the bottom half of the figure are related to an arbitrary scale of current strength. The curve shows the onset of inexcitability coincident with phase 0 of the transmembrane action potential, the gradual decrease in threshold during phase 3 of repolarization, a period of supernormal excitability associated with the terminal phase of repolarization and the restoration of full excitability after the end of phase 3 of the transmembrane action potential. (From Hoffman.[4])

ticity is found in the cells of the sinoatrial node and adjacent venous tissue, in certain specialized tracts of atrial fibers, and in the His–Purkinje system. These cells were once called pacemaker cells. However, since there is only one pacemaker at any moment, the term automatic cell is more appropriate. An automatic cell which is not normally the pacemaker may, under certain conditions, become the pacemaker; thus these cells are sometimes called latent pacemakers. The vast majority of cells which perform the contractile work of the heart do not show spontaneous diastolic depolarization during phase 4 and therefore are not automatic cells. These cells are referred to as nonspecialized, in contrast to automatic cells which are called specialized cardiac cells. In most automatic cells excitation results from the arrival of a propagated action potential before phase 4 depolarization has reached the threshold potential. In nonautomatic cells excitation also results from the arrival of a propagated action potential.

The rate of firing of an automatic cell depends upon: (1) the slope of phase 4 depolarization; (2) the level of the threshold potential; (3) the maximum level of membrane potential attained at the end of the repolarization (the maximum diastolic potential). In figure 3, upper diagram, the lesser slope of phase 4 diastolic depolarization in *b* results in a longer time to reach threshold potential; thus a slower rate than seen in *a*. In the lower diagram it can be seen that decreasing the threshold potential from −50 mv. to −40 mv. also slows the rate of firing (compare time of *a–b* with *a–c*). An increase (larger negative value) in maximum diastolic potential (from *a* to *d*) will also slow the rate (compare *a–c* with *d–e*). Any factor which changes the rate of firing of automatic cells can cause arrhythmias. A decrease in automaticity of the normal pacemaker may permit the escape of a latent pacemaker, while an increase in automaticity of a latent pacemaker may permit it to assume the pacemaker role. In general, most

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

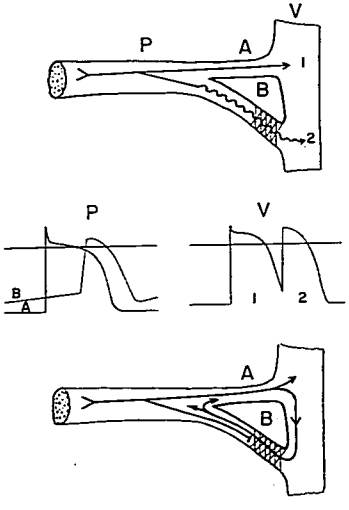

FIG. 5. Diagrammatic representation of arrhythmias due to delayed conduction and unidirectional block. The upper drawing represents a peripheral part of the Purkinje system (P) and attached ventricular muscle (V). In the branch A, conduction proceeds at normal velocity and the action potential is shown by trace *A*. In branch B, conduction velocity is reduced and unidirectional block is present in the hatched area. The locally recorded action potential is shown by trace *B*. The action potential in branch A elicits the ventricular action potential number 1; the slowly propagating action potential in B initiates the second ventricular action potential, number 2. The lower drawing shows, by the direction of the arrows, a possible mechanism for production of a self-sustaining arrhythmia. Here the direction of unidirectional block is opposite to that in the upper drawing. (From Hoffman.[4])

changes in rate are due to a slowing of the firing rate of the pacemaker and the escape of some other automatic sinoatrial nodal fiber.

Excitability is the ability of a cardiac fiber to generate an action potential in response to stimulation. Excitability can be related to the level of membrane potential at the time of stimulus application. It can be seen in figure 4*A* that during repolarization a stimulus applied before the membrane potential has reached approximately −50 mv. will not result in a response. This period is referred to as the absolute refractory period (fig. 4*B*). When the membrane potential reaches −50 to −55 mv., a small response can be produced. However, the action potential elicited is unable to excite adjacent fibers and does not propagate (curves *a* and *b* in figure 4*A*). The first propagated response (curve *c* of figure 4*A*) defines the end of the effective refractory period (fig. 4*B*). The completion of repolarization and the first normal response to stimulation define the end of the full recovery time (figs. 4*A*, *B*).

The greater the membrane potential (larger negative value) at the time of stimulation, the greater the amplitude and rising velocity of the action potential produced by stimulation (fig. 4*A*). In addition, the amplitude and rising velocity of the action potential determine its ability to excite adjacent tissue and propagate. The relationship between excitability and level of membrane potential can be described not only in terms of response to stimulation but in strength of stimulus required to elicit a response. The greater the membrane potential the smaller the stimulus required; there is an exception, however. Just before complete repolarization (end of phase 3) the strength of stimulus required to produce a response is less than that required after return of the membrane potential to the resting level (phase 4). This is the supernormal period (fig. 4*B*). It should be pointed out that the relationship between excitability and responsiveness and the level of membrane potential does not hold strictly for fibers of the sinoatrial and atrioventricular nodes. Here the duration of refractoriness may outlast recovery of the resting level of membrane potential.

Since excitation of cardiac fibers can result from either automatic activity or impulse conduction, arrhythmias can be considered in terms of alteration in automaticity (discussed above) and/or alterations in conductivity. Although conduction in the heart usually is described as all-or-none, decremental conduction occurs, defined as "a type of conduction in which the properties of the fiber change along its length in such a manner that the action potential becomes progressively less effective as a stimulus to the unexcited portion of the fiber

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

ahead of it. The change may progress to the point where conduction fails completely or the properties may again become more favorable to propagation. Since the efficiency of the action potential as a stimulus depends upon its amplitude, upon its rate of depolarization, upon the extent to which the depolarization caused by it reaches ahead, and upon the threshold of the fiber, a progressive change in any of these factors might cause decremental conduction."[45] Decremental conduction in the sinoatrial or atrioventricular node can explain intermittent failure of conduction which is not the result of refractoriness. Impaired conduction is known to be responsible for arrhythmias; in the His–Purkinje system a decrease in transmembrane potential (*i.e.*, partial depolarization) due to phase 4 depolarization, or incomplete repolarization, may cause partial or complete decrement. It should be clear that phase 4 diastolic depolarization, which is responsible for normal automaticity, can also be a cause of delay or failure of conduction. The interrelationship between automaticity and conduction in Purkinje fibers and the role of alterations in automaticity and conduction in the genesis of cardiac arrhythmias have been described clearly by Singer *et al.*[51] Figure 5 is an example of an arrhythmia due to delayed conduction.

The electrical phenomena described above can be explained in terms of ionic movement, for the cell membrane separates media of different ionic composition. The concentration of potassium inside the cell (cat heart muscle) is 151 mEq./l.; that outside 4.8 mEq./l.; sodium inside is 6.5 mEq./l. and outside 159 mEq./l.[45] These gradients are due to active transport mechanism(s) and a differential membrane permeability to ions and account for the transmembrane potential. The resting membrane is more permeable to potassium than to sodium ions. Depolarization of the membrane to the critical threshold level increases the permeability of the membrane to sodium and permits an influx of sodium ions. The greater the depolarization the greater the permeability to sodium and the greater the sodium influx. The increase in sodium conductance has been interpreted as the activation of a sodium carrier system. During the rapid upstroke of the action potential (phase 0) in both automatic and nonautomatic fibers, there is an absolute increase in sodium conductance and an absolute decrease in potassium conductance (fig. 6). An increase in permeability to sodium dur-

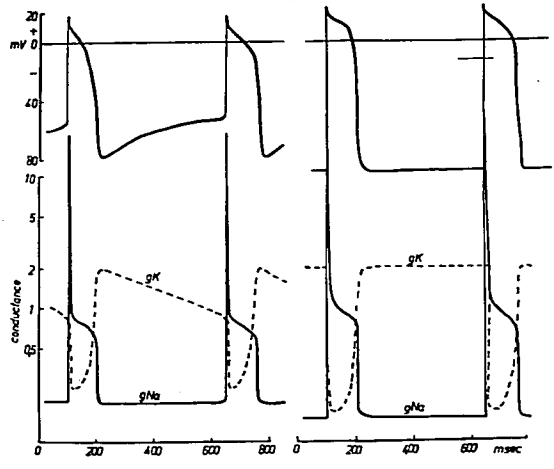

FIG. 6. Schematic diagram of the estimated sodium and potassium conductances (lower tracings) underlying the action potential and pacemaker potential (upper tracing). Left, in a sinus fiber; right, in a rabbit ventricular fiber. (From Trautwein.[53])

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

ing diastolic depolarization (phase 4) can occur if sodium conductance increases relative to potassium conductance. The relative increase in sodium conductance is believed by some to be due to the reduction of potassium conductance during diastole (fig. 6); thus, the depolarizing current during phase 4 may be carried by sodium ions.

Repolarization of cardiac cells is less well understood. During repolarization there is a decrease in sodium conductance, an increase in potassium conductance (fig. 6); sodium leaves the cell and potassium enters.

Electrophysiologic Effects of Catecholamines [45, 48, 49, 51, 53]

Catecholamines do not significantly affect threshold potential or maximum diastolic potential; however, they increase the slope of spontaneous diastolic depolarization (phase 4) of automatic cells. (Most experiments carried out on sinoatrial node or Purkinje fibers.) Since automatic cells differ in their sensitivity to catecholamines, there may be a shift in pacemaker site. With sufficient amounts of catecholamines, automaticity may be so enhanced that multiple pacemakers may develop, resulting in arrhythmia. It has also been reported that catecholamines may produce oscillatory changes in membrane potential during phase 4, delaying repolarization. Thus, epinephrine may produce arrhythmias by increasing the slope of phase 4 depolarization, by delaying repolarization, or by producing oscillation of membrane potential.

In contrast to the striking effects of catecholamines on automaticity, there are only minor effects on excitability. The effect is diphasic, with a brief (1–5 minutes) initial increase in excitability (diastolic threshold decreased 10–25 per cent) followed by a longer period (up to 30 minutes) of decreased excitability (threshold increased 25–50 per cent). With small doses, only the increase in excitability may be seen, but a long-lasting decrease follows larger doses. The increase in excitability may be related to a transient increase in serum potassium, which produces a slight depolarization (a decrease in membrane potential, a smaller negative value), thus decreasing the difference between resting membrane and threshold potential, thereby increasing excitability. The decreased excitability is associated with hypokalemia. There may also be a direct effect of catecholamines, since changes in excitability can be produced by sympathetic stimulation which does not affect serum potassium. The depression of excitability appears to be a direct effect on the cardiac fibers.

The effects of sympathomimetics on the refractory period and duration of cardiac action potential are small and inconsistent. It is generally accepted that changes in refractory period, like those in resting excitability, are of minimal importance in the production of arrhythmias.

The ionic basis for the action of catecholamines is not well understood. An increase in the resting sodium conductance has been assumed to account for some of the membrane effects of epinephrine.

Electrophysiologic Effects of Anesthetics

There are relatively few studies concerning the electrophysiologic effects of anesthetics on the heart. Smith *et al.*[54] studied the effects of cyclopropane and halothane on refractory periods, conduction times and diastolic thresholds (excitability) and concluded that anesthetic-induced arrhythmias involved more factors than these. Chloroform increased the threshold for electrical stimulation (*i.e.*, decreased excitability) of cat papillary muscle.[55] More strikingly, chloroform increases the degree of nonuniformity of recovery of muscle excitability during the relative refractory period.[56] Arrhythmias may be produced by nonuniform recovery of excitability, permitting reentry.[56–58]

Dresel and Duncan [59] studied the effects of chloroform and cyclopropane on the dose of epinephrine required to induce automaticity in cat papillary muscle (ordinarily without automaticity). Chloroform decreased the concentration required to induce automaticity, by 50 per cent. This might account for the effect of chloroform in decreasing the dose of epinephrine required to produce arrhythmia (see discussion of increasing automaticity in genesis

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

of arrhythmia). However the effect of chloroform on epinephrine-induction of automaticity was not very large when compared to the effect on decreasing the arrhythmic dose of epinephrine. Furthermore, cyclopropane had no effect on the concentration of epinephrine required to induce automaticity. This may have been the result of difficulty in delivering sufficient concentrations, since the authors suggested that cyclopropane might have been too insoluble in tissues to be effective.

Levy *et al.*[60] studied the effects of cyclopropane on transmembrane potentials of isolated rabbit atria and on ventricular membrane potentials in the intact dog, both nonautomatic tissues. In the atrial studies the rates of repolarization of phases 1 and 2 increased with no change in resting membrane potential or action potential amplitude. Electrical excitability decreased (increased threshold voltage required) in the right atrial preparation, but increased in the left preparation. In ventricular muscle *in situ*, there were no changes in the transmembrane potential which could not be attributed to changes in heart rate. In both preparations cyclopropane had no effect on resting potential or action potential amplitude.

Davis *et al.*[61] found in isolated canine Purkinje fibers (automatic tissue) that cyclopropane increased the rate of repolarization during phase 2, decreased the rate of depolarization during phase 3 and decreased overall the time required to repolarize to −60 mv. Resting potential, magnitude of action potential, overshoot, total action potential duration and diastolic depolarization were not changed, taking into account the possible effect of hypoxia induced by substituting cyclopropane for oxygen in the perfusion system. The decrease in time required to repolarize to −60 mv. may be interpreted as a decrease in functional refractory period, which might explain in part the arrhythmogenic action of cyclopropane. The increase in rate of repolarization during phase 2 and the decrease in repolarization during phase 3 produced by cyclopropane are similar to effects of increasing calcium ion concentration. Davis *et al.*[62] subsequently found that reducing calcium reversed the effect of cyclopropane while increasing calcium increased the effect on repolarization of Purkinje fibers. They also reported that the combination of cyclopropane and increased calcium increased the rate and magnitude of diastolic depolarization. Thus a concentration of calcium (which does not change the rate of diastolic depolarization) in the presence of cyclopropane (which also does not affect diastolic depolarization) increases the rate and magnitude of diastolic depolarization. It would be helpful to know whether the increase in diastolic depolarization produced by epinephrine is further facilitated by cyclopropane. This could account for cyclopropane–epinephrine arrhythmias, since increased automaticity will produce arrhythmias directly and also increase the possibility of conduction defects (see above).

Studies of halothane demonstrate that this agent has no significant effects on the rabbit atrial membrane potential.[63] In studies of the rabbit sinoatrial node the velocity of diastolic dpolarization was reduced to two-thirds of control by 1 per cent halothane and to less than 50 per cent of control by 2 per cent halothane.[64] In addition, 2 per cent halothane decreased the difference in mv. between maximum diastolic potential and threshold potential; this added to the increase in slope of diastolic depolarization produced by epinephrine, could account for the halothane–catecholamine arrhythmias. Although the separate electrophysiologic effects of halothane and catecholamines could account for the arrhythmias, combined effects could offer additional mechanisms.

In a study of the interaction of cyclopropane and epinephrine on sodium transport in the toad bladder [65]: (1) epinephrine increased sodium transport; (2) cyclopropane increased sodium transport; (3) the combination of epinephrine and cyclopropane exceeded the estimated additive effect of the two drugs. It should be recalled that during depolarization of the myocardial cell, sodium enters and the depolarizing current during diastole is carried by sodium ions. It would be of interest to know whether cyclopropane likewise increases sodium transport in the heart and whether the synergistic effects of cyclopropane and epinephrine on sodium transport in the heart are similar to those in the toad bladder. Such

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

studies would shed light on the ionic mechanisms responsible for anesthetic–catecholamine arrhythmias.

Arterial Blood Pressure

Levy[6] felt that ventricular fibrillation produced by chloroform–epinephrine in the cat had no relation to the height of arterial blood pressure since a rise was not absolutely necessary for the appearance of the arrhythmia. He noted, however, that compression of the aorta, which increased central arterial pressure, produced ventricular extrasystoles. Furthermore, when the circulation was depressed by blood loss or other causes, cardiac arrhythmias disappeared. Levy therefore concluded that a certain pressure, approximately 100 torr or greater, favored the development of ventricular extrasystoles and fibrillation.

Moe et al.[29] carefully studied cyclopropane–epinephrine arrhythmias and the effect of arterial blood pressure. A regulator produced a sudden increase or decrease in aortic pressure or set the pressure of various levels to compare the responses to epinephrine at different pressures. A dose of epinephrine which did not produce cardiac arrhythmias at a steady pressure produced arrhythmias if the pressure was elevated. Also, a sudden rise of pressure was not necessary for the production of arrhythmias. By maintenance of an elevated arterial pressure (with the regulator) a dose of epinephrine which had not produced an arrhythmia now caused ventricular tachycardia without further significant change in pressure. The threshold dose of epinephrine required to produce arrhythmias at different pressures was also determined. In some cases preventing the rise in arterial pressure permitted eight times the threshold dose of epinephrine to be given without producing arrhythmias. A facilitating role of arterial pressure in the production of arrhythmias has also been reported by others.[35, 66, 67] On the other hand, Murphy *et al.*[66] showed that epinephrine could produce arrhythmias in dogs anesthetized with cyclopropane in the absence of a rise in arterial pressure.

Dresel *et al.*,[18] studying the effect of continuous infusion of epinephrine (0.063 to 3.0 μg./kg./min.) in cyclopropane-anesthetized dogs, found that the arrhythmia produced could be converted to normal sinus rhythm by lowering the blood pressure with a pressure regulator and reinduced by again raising the pressure. They felt as did Moe *et al.*[29] that the level of blood pressure reached rather than the extent of the pressure rise is important in the induction of arrhythmias. These workers also studied the separate and combined roles of blood pressure, heart rate, and sympathomimetic amines in the production of arrhythmias. Tachycardia induced by stimulation of the atrial appendage caused bigeminy in only three of 31 dogs. An increase in blood pressure comparable to that produced by an arrhythmic dose of epinephrine, but achieved by rapid infusion of blood and dextran, reduced bigeminy in only one of nine experiments. When the increase in blood pressure was combined with tachycardia, bigeminy was induced in six of 14 experiments. However, the combination of epinephrine, an increase in blood pressure, and an increase in heart rate regularly produced cardiac arrhythmias.

Katz[68] found that the injection of isoproterenol decreased arterial pressure but was capable of producing cardiac arrhythmias in 28 of 36 animals. However, a facilitating role of hypertension could be demonstrated. In five animals a dose of isoproterenol which decreased blood pressure and did not produce arrhythmias was given. When the same dose of isoproterenol was injected and the aorta constricted, so as to increase pressure or prevent the decrease, arrhythmia were now seen in four of five animals, and persisted for more than 60 seconds. However, releasing the clamp after 20 or 30 seconds produced an immediate fall in blood pressure and restoration of normal sinus rhythm.

Much of the argument concerning the importance of a rise in arterial blood pressure in the production of arrhythmias is a semantic one. It is clear that a rise in arterial blood pressure is not absolutely necessary.[66, 68] Nevertheless, a rise in pressure does facilitate the production of the arrhythmia. It seems reasonable to state that an increase in blood pressure is important in producing cardiac arrhythmias but not absolutely essential. The role of blood pressure may vary with the ex-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

perimental conditions, amount of epinephrine used, and the depth of anesthesia.[69]

It is possible to abolish cardiac arrhythmias produced by sympathomimetic amines in animals inhaling halothane by lowering blood pressure with trimethaphan (Arfonad).[26] Concomitant with the fall in pressure, cardiac arrhythmias disappeared. Knowing the role of the blood pressure, we developed a technique for preventing arrhythmias in patients undergoing operation for removal of pheochromocytoma.[33] During the manipulation of the adrenal gland and the consequent release of catecholamines, the arterial blood pressure threshold at which arrhythmias occur was established, the pressure then maintained below this level with the continuous infusion of sodium nitroprusside at a rate of 0.1–1.0 mg./min. It was possible to abolish virtually all arrhythmias. The arrhythmia threshold level was invariably higher than the patient's blood pressure prior to manipulation of the adrenal gland.

It is likely that an elevated pressure increases the possibility of producing arrhythmias by stretching cardiac muscle. Stretch increases automaticity, decreases the amount of epinephrine required to induce automaticity, decreases the resting potential (to a smaller negative number), increases the slope of phase 4 depolarization, and produces multifocal pacemaker activity.[41, 45, 70, 71]

Heart Rate

In addition to the work of Dresel *et al.*[18] discussed above, Vick[72] has demonstrated clearly the importance of an increased heart rate in the genesis of the anesthetic–epinephrine arrhythmias, producing arrhythmias in chloroform-anesthetized dogs by the continuous infusion of 1–5 μg./kg./min. of epinephrine. The bigeminy thus produced could be converted to regular rhythm by vagal stimulation, which slowed the atrial rate. If during the vagal stimulation the atrium or ventricle was driven at a rate equal to that at which the arrhythmia formerly occurred, the arrhythmia was restored. In another experiment, after producing a stable arrhythmia by the infusion of epinephrine, the rate of infusion was gradually decreased until regular rhythm returned; then the atrium was driven at a rate approximately that at which the arrhythmia had occurred. The arrhythmia could again be produced at the lower rate of infusion of epinephrine. As will be pointed out below, a beta-adrenergic blocking agent is capable of preventing anesthetic–catecholamine arrhythmias; whether due to the effect of the beta blocker on the heart or whether attributable to prevention of the increase in heart rate is not clear. This could be determined in an experiment in which (1) an arrhythmia was produced; (2) a beta-adrenergic blocking agent was injected to abolish the arrhythmia; and then (3) the heart driven at the rate at which the arrhythmia had been produced previously.

Release of Potassium from the Liver

The injection of epinephrine produces hyperkalemia due to the release of potassium from the liver,[73] greater in animals anesthetized with cyclopropane than in those anesthetized with pentobarbital or ether or the unanesthetized.[74] This raises the possibility that hyperkalemia might be a factor in epinephrine or cyclopropane–epinephrine arrhythmias. Excluding the liver from the circulation has protected against cyclopropane–epinephrine arrythmias in a large percentage of dogs.[75, 76] Furthermore, the injection of potassium and epinephrine, during cyclopropane anesthesia, produced arrhythmias in ten of 19 protected animals. In another study of dogs anesthetized with cyclopropane the injection of epinephrine increased plasma potassium and produced cardiac arrhythmias. When the animals were fed a low-potassium diet for 2–3 weeks, the epinephrine-induced hyperkalemia was reduced and 11 of the 20 dogs studied no longer developed ventricular tachycardia.[77] However, others[135] have found that: (1) there is no correlation between the absolute rise in plasma potassium and arrhythmias; (2) exclusion of the liver, although eliminating the hyperkalemic response to epinephrine, does not prevent arrhythmias. In addition, other sympathomimetic agents with little or no hyperkalemic action are capable of producing arrhythmias in cyclopropane-anesthetized dogs.[49, 74] It appears then that epinephrine is capable

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

of releasing potassium from the liver, that this facilitates the production of arrhythmias, but that hyperkalemia is not essential for the production of arrhythmias.

Sympathetic and Central Nervous System

The role of the sympathetic and central nervous systems in the production of anesthetic–sympathomimetic arrhythmias has been disputed. Procedures reported to afford some protection against arrhythmias include: lumbar sympathectomy [78]; denervation of the carotid sinuses and section of the afferent aortic nerve fibers [79]; decerebration or thoracic sympathectomy [80]; partial abdominal evisceration, partial abdominal denervation, or bilateral adrenalectomy [81, 137]; stellate ganglionectomy [82]; adrenalectomy.[83] However, it has been demonstrated clearly that arrhythmias can be produced in decerebrate, spinal and reserpinized animals,[35] in animals with denervated hearts,[5, 84] and in the heart-lung preparations.[29, 85, 86] These apparent inconsistencies were explained by Dawes [69] as follows: "Under the particular experimental conditions, the removal of even a small part of the continuous secretion of sympathomimetic amines or even the operative procedure alone is sufficient to upset the very delicate balance of the numerous factors which influence the outcome, so that the test dose of adrenaline is no longer effective in precipitating ventricular fibrillation."

Site of Origin of Arrythmia

The site of origin of cyclopropane–epinephrine arrhythmias has also been disputed. Based on electrocardiographic interpretation, it was suggested that the arrhythmia could not be due to a focus of increased ventricular automaticity,[18] instead that the arrhythmia originated in the atrioventricular node or upper bundle of His.[87–89] This was based on the observations that: (1) vagal stimulation abolished the arrhythmia and the vagus is not believed to innervate the ventricle distal to the bundle of His; (2) injection of acetylcholine into the left circumflex coronary artery (which reaches the atrioventricular node) abolished the arrhythmia, while injection into the left anterior descending coronary artery (which does not reach the atrioventricular node) did not. Moore *et al.*[90] pointed out the difficulties of proposing mechanisms to explain arrhythmias solely on the basis of electrocardiographic evidence. In studies recording electrograms from several sites in the hearts of intact animals as well as transmembrane potentials from isolated Purkinje and attached ventricular muscle fibers, they concluded that the arrhythmia originated in the ventricle distal to the bundle of His and that increased automaticity produced by epinephrine was the cause of the arrhythmia.

Alpha and Beta Adrenergic Receptors

We stated above that stimulation of beta-adrenergic receptors rather than alpha-adrenergic receptors was responsible for the cardiac arrhythmias produced by sympathomimetics, a matter now discussed in greater detail. The cardiac arrhythmias produced by catecholamines originally were attributed to alpha-adrenergic stimulation because the injection of alpha-adrenergic blocking agents prevented the anesthetic–catecholamine arrhythmias.[29, 67, 91, 92] However, subsequent studies revealed that the antiarrhythmic action of alpha-adrenergic blockers was not specific but indirect, attributable in part to the ability to prevent the catecholamine-induced rise in arterial pressure. Another effect of alpha-adrenergic blockers is a nonspecific myocardial depressant action (quinidine-like) which may also account for an antiarrhythmic action.

Following the introduction of the beta-adrenergic blocking agent dichloroisoproterenol [21] DCI was found to be an effective antiarrhythmic agent against anesthetic–adrenergic arrhythmia.[18, 93] However, others [94] reported that DCI could also block digitalis-induced arrhythmias and that this activity was independent of beta-adrenergic block. Similar results were reported with pronethalol by Lucchesi [95] who felt that the antiarrhythmic action of this agent was independent of beta-adrenergic block. Furthermore, pronethalol had a quinidine-like action which, by interference with depolarization of cardiac muscle, might account for the antiarrhythmic activity.[52, 96, 97] In addition to its quinidine-like action, pronethalol has local anesthetic activity approximately twice as

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

great as that of procaine and equal to that of lidocaine[98–100]; both local anesthetics are known to be antiarrhythmic agents. The recently developed agent propranolol also possesses local anesthetic activity similar to that of lidocaine.[98] Thus, the specificity of the antiarrhythmic activity of beta-adrenergic blocking agents has been questioned.

One way to settle the controversy was to separate the local anesthetic and/or quinidine-like effect of these agents from their beta-adrenergic blocking properties, then to compare antiarrhythmic abilities. This was accomplished with 1-(0-allylphenoxy)-isopropylamino-2 propanol-hydrochloride (H 56/28) which has been resolved into its optical isomers.[30, 101] Both the dextro and levo forms of this agent have local anesthetic activity equal to that of lidocaine. However, the beta-receptor blocking activity of the levo form is approximately 40 to 60 times greater than that of the dextro form. The dextro form had little antiarrhythmic activity against anesthetic-catecholamine arrhythmias, whereas the levo form had a long-lasting antiarrhythmic action. It was concluded, therefore, that beta-adrenergic receptor blockade is the important factor in preventing anesthetic–catecholamine arrhythmias, also that the brief antiarrhythmic action of the dextro form was secondary to its local anesthetic activity. These results with H 56 /28 differ from those of Luchessi,[102] who found that dextro-pronethalol with only 1/40 the beta-blocking activity of the levo form, protected against hydrocarbon–epinephrine arrhythmias. He therefore concluded that beta-adrenergic receptor inhibition was not the mechanism by which this compound prevented hydrocarbon–epinephrine arrhythmias. Thus, various beta-adrenergic blockers may differ in mechanisms of antiarrhythmic action. Propranolol differs from pronethalol but is similar to H 56/28. Levo-propranolol, with 60–100 times the beta-adrenergic blocking activity of the dextro isomer, was at least ten times more active in preventing halothane–catecholamine arrhythmias.[103] Further support for the role of beta-adrenergic receptors in the genesis of the anesthetic–catecholamine arrhythmias is evident in that arrhythmias produced by the injection of epinephrine, norepinephrine, isoproterenol or ethylnorepinephrine during cyclopropane inhalation could not be prevented consistently by the alpha-adrenergic blocking agent dibenamine.[68] When an antiarrhythmic effect occasionally was seen, it was often attributable to prevention of the increase in blood pressure. Pronethalol, however, consistently blocked the cyclopropane–catecholamine arrhythmias. In the heart-lung preparation alpha blockade did not prevent catecholamine–anesthetic arrhythmias whereas beta blockade did.[56] From the available evidence it seems reasonable to conclude that the anesthetic–catecholamine arrhythmias are due to stimulation of beta-adrenergic receptors.

The electrophysiologic effects of beta-adrenergic blocking agents have recently been determined[48, 52, 104] and may aid in understanding the mechanism of prevention of cardiac arrhythmias. Unfortunately (as pointed out above), these agents have actions in addition to beta-adrenergic blockade, which makes it difficult to determine whether a given effect is due to beta block or some other action. Development and study of more specific beta-adrenergic blockers will clarify the situation. However, it has been possible to separate the effect into specific (*i.e.*, beta-adrenergic block) and nonspecific action (*i.e.*, sypmpathomimetic, anticholinergic, quinidine-like, local anesthetic[46, 104]) by studying the effects of small yet effective doses of beta-adrenergic blockers and comparing them with the effects of catecholamine depletion or cardiac denervation. It is reasonably clear that an important effect of beta-adrenergic block which can account for an antiarrhythmic action is the decrease in automaticity of the His-Purkinje system. There is a decrease in the spontaneous firing rate of automatic cells which is attributable to a reduction in the rate of spontaneous phase 4 depolarization. There is no depression of atrioventricular conduction or intraventricular conduction, ventricular refractoriness, or excitability of atrial or ventricular muscle. When larger doses of beta blockers are given, conduction can be depressed, and diastolic membrane potential reduced. These effects probably result from a nonspecific direct action on the cardiac cell rather than beta blockade.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

Effects of Other Drugs

Other drugs given may influence the ease with which cardiac arrhythmias are produced. The major mechanism by which the action of catecholamines is terminated is through uptake into the adrenergic neuron. Cocaine conspicuously increases and prolongs action of the catecholamines by preventing reuptake. Reserpine modifies the action of catecholamines by depleting the body of catecholamines, thus producing supersensitivity to these agents. Fleming[105] showed in the reserpinized cat that the dose of epinephrine required to produce cardiac arrhythmias was reduced strikingly. In a patient on long-term reserpine therapy, we observed bizarre cardiac arrhythmias during halothane anesthesia and the injection of what we considered to be a safe dose of epinephrine.[33] We believe this to be attributable to reserpine-induced supersensitivity. Reserpine, like cocaine, also increases the likelihood of producing arrhythmias by preventing the uptake of catecholamines. Bretylium and guanetidine also decrease the dose of catecholamines required to produce cardiac arrhythmias in animals anesthetized with halogenated hydrocarbons or cyclopropane.[23] This may be an acute denervation supersensitivity phenomenon or due to a decrease in uptake (and thus termination of action) of catecholamines.

Monoamine oxidase (MAO) is responsible for the enzymatic destruction of many sympathomimetics. Patients on MAO inhibitors may have an increased and prolonged response to sympathomimetics which are metabolized by MAO or release catecholamines metabolized by MAO. Hypertension, arrhythmias and death have been reported in these patients following the injection of catecholamine releasing sympathomimetics during anesthesia or following the ingestion of cheese, wine or other food containing tyramine, a sympathomimetic which releases catecholamines.[106–108]

Safe Intravenous Use of Sympathomimetics

As stated earlier, we believe that the intravenous injection of a sympathomimetic is rarely necessary during general anesthesia. When such is necessary, and an action mainly on the myocardium is desired, ephedrine or mephentermine usually can be given without producing cardiac arrhythmias. If a peripherally-acting vasopressor is required, it is less likely that methoxamine or phenylephrine will produce arrhythmias. Another potentially useful sympathomimetic is dopamine, which in addition to being a precursor of norepinephrine and a releaser of catecholamines, has considerable activity of its own. It has a pronounced myocardial stimulant action but does not produce peripheral vasoconstriction. Goldberg and his associates believe that dopamine may be of value in the treatment of certain patients in shock.[109–113] In two such patients treated with isoproterenol and metaraminol cardiac arrhythmias resulted, but dopamine produced a satisfactory therapeutic effect without arrhythmias.[111] In another study[30] injection of a dose of dopamine which in hypotensive cats elevated the arterial blood pressure significantly, did not produce cardiac arrythmias. Clinical studies are planned in order to determine whether it is safe to use dopamine in hypotensive patients anesthetized with cyclopropane and halothane. If it is necessary to inject epinephrine, norepinephrine or metaraminol intravenously in an anesethetized patient, it would seem wise to discontinue cyclopropane or halogenated hydrocarbons in favor of nitrous oxide or ether.

Safe Use of Epinephrine for Local Hemostasis

The vast majority of anesthetic–adrenergic arrhythmias can be summed up as resulting from too much epinephrine in too high a concentration, given too rapidly into a highly vascular area. Epinephrine can be injected safely subcutaneously with trichloroethylene, halothane or cyclopropane provided certain precautions are taken as to dose, concentration and mode of administration.[10, 16, 114] Concentrations from 1:100,000 to 1:200,000 and a dose in adults not in excess of 10 ml. of 1:100,000 in any given ten-minute period nor 30 ml. per hour, are recommended. Avoidance of hypoxia and hypercarbia is important in the prevention of arrhythmias. The margin of safety with cyclopropane is less than with other agents since, with 30 ml. of 1:60,000

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

epinephrine, cardiac arrhythmias were observed with cyclopropane but not with trichloroethylene or halothane.[16, 19, 114] Our studies as well as those of others[33, 115] suggest that methoxyflurane and fluroxene behave in a fashion similar to that of halothane and trichloroethylene.

Despite the careful detailing of the precautions necessary for the safe use of epinephrine, arrhythmias and cardiac arrest in anesthetized patients receiving epinephrine continue to be reported.[10] It is clear that epinephrine still is not always used with the precautions suggested. It may be that a different approach is required. A valuable new agent would be one that produced hemostasis following subcutaneous injection but not cardiac arrhythmias when given in the presence of halogenated hydrocarbons or cyclopropane. Phenylephrine was tried but has been abandoned. Phenylalanine-2-lysine-8-vasopressin (PLV-2) was found to be an effective local vasoconstrictor and not productive of cardiac arrhythmias when injected intravenously or subcutaneously in patients anesthetized with cyclopropane, halothane or trichlorethylene.[10, 116-119] However, at present PLV-2, although used in Europe, is not available for use in the United States. In addition to PLV-2 there are related polypeptides with similar or greater vasoconstrictor action that will not produce cardiac arrhythmias when injected intravenously during cyclopropane anesthesia.[120, 121]

Treatment of Cardiac Arrhythmias

Faced with an anesthetic–sympathomimetic arrhythmia, the most logical and physiologic treatment is elimination of the cause.[122] This often can be accomplished by eliminating the anesthetic agent and hyperventilating the lungs with oxygen. If catecholamines were the result of respiratory acidosis, hyperventilation and restoration of a normal *p*H should abolish the arrhythmia. If due to catecholamine injection, cessation of injection should usually restore a normal sinus rhythm. If produced by adrenal manipulation and release of catecholamines, cessation of the manipulation should abolish the arrhythmia.

There may be situations, however, in which it is not possible to discontinue surgical manipulations or to change the anesthetic management rapidly. In addition, the deleterious cardiovascular effects produced by the arrhythmia may require a more-rapid restoration of a normal sinus rhythm than can be achieved by these means. It is in these *rare* situations that antiarrhythmic drugs may be useful. While our previous comments on the mechanism of production of anesthetic–adrenergic arrhythmias might suggest that the beta-adrenergic blockers are the best agents to use, we do not believe this to be the case. The beta-adrenergic blocking agents modify many functions of the body. Beta-adrenergic blocking agents impair the ability to respond to catecholamines. Thus, the reflex responses to stress, of great importance in the maintenance of homeostasis, will be diminished. Since the release of catecholamines is a major factor in counteracting the depressant cardiovascular effects of anesthetics,[123] beta blockers may cause hypotension in anesthetized patients.[124]

Bronchodilation is a function of beta-adrenergic receptors, and their blockage therefore increases airway resistance in both normal and asthmatic subjects,[125, 126, 128] leading to bronchospasm. Furthermore, patients with bronchospasm who require the injection of isoproterenol will have a diminished response in the presence of beta-adrenergic blockade.

Coronary blood vessels contain alpha receptors which mediate vasoconstriction and beta receptors which mediate vasodilation.[127] Beta-adrenergic block has been reported to reduce coronary blood flow.[128] In the presence of beta-adrenergic blockade, catecholamines produce coronary vasoconstriction.[129] Blocking of beta-adrenergic receptors is therefore potentially dangerous. In addition, it does not seem wise to depress the ability of the myocardium to increase its contractile force in response to catecholamines. Since patients in frank or incipient congestive heart failure may depend upon the catecholamine stimulus for adequate myocardial function, beta-adrenergic blockade may precipitate or worsen congestive failure.[130-133] Although there is insufficient clinical experience upon which to draw final conclusions, our opinion, based on laboratory and clinical studies, is that the beta-adrenergic

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

blocking agents are not best or safest agents for the treatment of cardiac arrhythmias.

If an antiarrhythmic agent is required, lidocaine is an effective antiarrhythmic agent which in the doses used clinically increases blood pressure slightly and has little or no effect on myocardial contractile force.[134] The duration of action is brief, ten to 20 minutes, but this should provide sufficient time to correct the underlying abnormality responsible for the arrhythmia.

Summary and Conclusions

Anesthetics and sympathomimetics interact to produce cardiac arrhythmias. Possible mechanisms have been discussed. The use of catecholamines for local hemostasis is safe provided minimal doses are used and hypercarbia and hypoxia are avoided. It is also possible to use sympathomimetics as vasopressors safely, although this is rarely necessary. Work is in progress in an attempt to find agents capable of producing local hemostasis and vasopressor effects without production of cardiac arrhythmias.

References

1. Katz, R. L., and Katz, G. J.: Surgical infiltration of pressor drugs and their interaction with volatile anesthetics, Brit. J. Anaesth. 38: 712, 1966.
2. Oliver, G., and Schäfer, E. A.: The physiological effects of extracts of the suprarenal capsules, J. Physiol., Lond. 18: 230, 1895.
3. Levy, A. G., and Lewis, T.: Heart irregularities resulting from the inhalation of low percentages of chloroform vapour, and their relationship to ventricular fibrillation, Heart 3: 99, 1911–12.
4. Levy, A. G.: Sudden death under light chloroform anesthesia, J. Physiol. 42: 3, 1911.
5. Levy, A. G.: The exciting causes of ventricular fibrillation in animals under chloroform anaesthesia, Heart 4: 319, 1912–13.
6. Levy, A. G.: The genesis of ventricular extrasystoles under chloroform; with special reference to consecutive ventricular fibrillation, Heart 5: 299, 1913–14.
7. Meek, W. J., Hathaway, H. R., and Orth, O. S.: The effects of ether, chloroform and cyclopropane on cardiac automaticity, J. Pharmacol. Exp. Ther. 61: 240, 1937.
8. Bamforth, B. J., Siebecker, K. L., Kraemer, R., and Orth, O. S.: Effect of epinephrine on the dog heart during methoxyflurane anesthesia, ANESTHESIOLOGY 22: 169, 1961.
9. Israel, J. S., Criswick, V. G., and Dobkin, A. B.: Effect of epinephrine on cardiac rhythm during anesthesia with methoxyflurane (Penthrane) and trifluoroethyl vinyl ether (Fluoromar), Acta Anaesth. Scandinav. 7: 7, 1962.
10. Katz, R. L.: Epinephrine and PLV-2: Cardiac rhythm and local vasoconstrictor effects, ANESTHESIOLOGY 26: 619, 1965.
11. Morris, L. E., Noltensmeyer, M. A., and White, J. M.: Epinephrine-induced cardiac irregularities in the dog during anesthesia with trichloroethylene, cyclopropane, ethyl chloride and chloroform, ANESTHESIOLOGY 14: 153, 1953.
12. Raventos, J.: The action of Fluothane: a new volatile anaesthetic, Brit. J. Pharmacol. 11: 394, 1956.
13. Waters, R. M., Orth, O. S., and Gillespie, N. A.: Trichloroethylene anesthesia and cardiac rhythm, ANESTHESIOLOGY 4: 1, 1943.
14. Anderson, N., and Johansen, S. H.: Incidence of catecholamine-induced arrhythmias during halothan anesthesia, ANESTHESIOLOGY 24: 51, 1963.
15. Johnstone, M.: Adrenaline and noradrenaline during anaesthesia, Anaesthesia 8: 32, 1953.
16. Matteo, R. S., Katz, R. L., and Papper, E. M.: The injection of epinephrine during general anesthesia with halogenated hydrocarbons and cyclopropane in man. 1. Trichlorethylene, ANESTHESIOLOGY 23: 360, 1962.
17. Price, H. L., Lurie, A. A., Jones, R. E., Price, M. L., and Linde, H.: Cyclopropane anesthesia. II. Epinephrine and norepinephrine in initiation of ventricular arrhythmias by carbon dioxide inhalation, ANESTHESIOLOGY 19: 619, 1958.
18. Dresel, P. E., MacCannell, K. L., and Nickerson, M.: Cardiac arrhythmias induced by minimal doses of epinephrine in cyclopropane-anesthetized dogs, Circulation Res. 8: 948, 1960.
19. Matteo, R. S., Katz, R. L., and Papper, E. M.: The injection of epinephrine during general anesthesia with halogenated hydrocarbons and cyclopropane in man. 3. Cyclopropane, ANESTHESIOLOGY 24: 327, 1963.
20. Ahlquist, R. P.: A study of the adrenotropic receptors, Amer. J. Physiol. 153: 586, 1948.
21. Powell, C. E., and Slater, J. H.: Blocking of inhibitory adrenergic receptors by a dichloro analog of isoproterenol, J. Pharmacol. Exp. Ther. 122: 480, 1958.
22. Lands, A. M.: The pharmacological activity of epinephrine and related dihydroxyphenylalkylamine, Pharmacol. Rev. 1: 279, 1949.
23. Orth, O. S., Leigh, M. D., Mellish, C. H., and Stutzman, J. W.: Action of amines in cyclopropane, ether and chloroform anes-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

thesia, J. Pharmacol. Exp. Ther. 67: 1, 1939.
24. Orth, O. S., Stutzman, J. W., and Meek, W. D.: Relationship of chemical structure of sympathomimetic amines to ventricular tachycardia during cyclopropane anesthesia, J. Pharmacol. Exp. Ther. 81: 197, 1944.
25. Catenacci, A. J., DiPalma, J., Anderson, J. P., and King, W. E.: Serious arrhythmias with vasopressors during halothane anesthesia in man, J.A.M.A. 183: 662, 1963.
26. Loehning, R. W., and Czorny, V. P.: Halothane-induced hypotension and the effects of vasopressors, Can. Anaesth. Soc. J., 7: 304, 1960.
27. Stephen, C. R., Margolis, G., Fabian, L. S., and Bourgeois-Gavardin, M.: Laboratory observations with Fluothane, ANESTHESIOLOGY 19: 770, 1958.
28. Wyant, G. M., Merriman, J. E., Kilduff, C. J., and Thomas, E. T.: The cardiovascular effects of halothane, Can. Anaesth. Soc. J. 5: 384, 1958.
29. Moe, G. K., Malton, S. D., Rennick, B. R., and Freyburger, W. A.: The role of arterial pressure in the induction of idioventricular rhythms under cyclopropane anesthesia, J. Pharmacol. Exp. Ther. 94: 319, 1948.
30. Katz, R. L., Lord, C. O., and Eakins, K. E.: Anesthetic–dopamine cardiac arrhythmias and their prevention by beta adrenergic blockade, J. Pharmacol. Exp. Ther. 158: 40, 1967.
31. Burn, J. H., and Rand, M. J.: The action of sympathomimetic amines in animals treated with reserpine, J. Physiol. 144: 314, 1958.
32. Hall, K. D., and Norris, F. H., Jr.: Fluothane sensitization of dog heart to action of epinephrine, ANESTHESIOLOGY 19: 631, 1958.
33. Katz, R. L.: Unpublished data.
34. Black, G. W., Linde, H. W., Dripps, R. D., and Price, H. L.: Circulatory changes accompanying respiratory acidosis during halothane (Fluothane) anesthesia in man, Brit. J. Anaesth. 31: 238, 1959.
35. Katz, R. L.: Neural factors affecting cardiac arrhythmias induced by halopropane, J. Pharmacol. Exp. Ther. 152: 88, 1966.
36. Craythorne, N. W. B., Turndorf, H., and Dripps, R. D.: Changes in pulse rate and rhythm associated with the use of succinylcholine in anesthetized children, ANESTHESIOLOGY 21: 465, 1960.
37. Schoenstadt, D. A., and Whitcher, C. E.: Observations on the mechanism of succinylcholine-induced cardiac arrhythmias, ANESTHESIOLOGY 24: 358, 1963.
38. Williams, C. H., Deutsch, S., Linde, H. W., Bullough, J. W., and Dripps, R. D.: Effects of intravenously administered succinylcholine on cardiac rate, rhythm and arterial blood pressure in anesthetized man, ANESTHESIOLOGY 22: 947, 1961.
39. Walts, L. F., and Prescott, F. S.: The effect of gallamine on cardiac rhythm during general anesthesia, Anesth. Analg. 44: 265, 1965.
40. Brown, B. R., and Crout, J. R.: The sympathomimetic effect of gallamine on the heart, ANESTHESIOLOGY 29: 179, 1968.
41. Dudel, J., and Trautwein, W.: Das Aktionspotential und Mechanogram des Herzmuskels unter dem Einfluss der Dehnung, Cardiologia 25: 344, 1954.
42. Hoffman, B. F.: The genesis of cardiac arrhythmias, Prog. Cardiov. Dis. 8: 319, 1966.
43. Hoffman, B. F.: The electrophysiology of heart muscle and the genesis of arrhythmias. *In* Dreifus, L. S., and Likoff, W. (editors): Mechanisms and Therapy of Cardiac Arrhythmias. New York, Grune and Stratton, 1966.
44. Hoffman, B. F.: The possible mode of action of antiarrhythmic agents. *In* Briller, S. A., and Conn, H. L. (editors): The Myocardial Cell. Philadelphia, University of Pennsylvania Press, 1966.
45. Hoffman, B. F., and Cranefield, P. F.: The Electrophysiology of the Heart. New York, McGraw Hill Book Co., 1960.
46. Hoffman, B. F., and Cranfield, P. F.: The physiological basis of cardiac arrhythmias, Am. J. Med. 37: 670, 1964.
47. Hoffman, B. F., Kao, C. Y., and Suckling, E. E.: Refractoriness in cardiac muscle, Am. J. Physiol. 190: 473, 1957.
48. Hoffman, B. F., and Singer, D. H.: Appraisal of the effects of catecholamines on cardiac electrical activity, Ann. N. Y. Acad. Sci. 139: 914, 1967.
49. Siebens, A. A., Hoffman, B. F., Enson, Y., Farrell, J. E., and Brooke, C. McC.: Effects of 1-epinephrine and 1-norepinephrine on cardiac excitability, Am. J. Physial. 175: 1, 1953.
50. Singer, D. H., Lazzara, R., and Hoffman, B. F.: Transmembrane potentials of cardiac cells and their ionic basis. *In* Briller, S. A., and Conn, H. L. (editors): The Myocardial Cell. Philadelphia, University of Pennsylvania Press, 1966.
51. Singer, D. H., Lazzara, R., and Hoffman, B. F.: Interrelationships between automaticity and conduction in Purkinje fibers, Circulation Res. 21: 537, 1967.
52. Singer, D. H., Yeh, B. K., Seberlay, B. J., and Hoffman, B. F.: Beta blockade and the specialized conduction system of the heart, Circulation 30: (suppl. 3) 160, 1964.
53. Trautwein, W.: Generation and conduction of impulses in the heart as affected by drugs, Pharmacol. Rev. 15: 277, 1963.
54. Smith, S. L., Webb, W. R., Fabian, L. W., and Hagaman, V. D.: Cardiac excitability

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

in ether, cyclopropane and halothane anesthesia, ANESTHESIOLOGY 23: 766, 1962.
55. Garb, S., and Chenoweth, M. B.: Studies on hydrocarbon–epinephrine induced ventricular fibrillation, J. Pharmacol. Exp. Ther. 94: 12, 1948.
56. Han, J., and Moe, G. K.: Nonuniform recovery of excitability in ventricular muscle, Circulation Res. 14: 44, 1964.
57. Han, J., Garcia de Jalon, P., and Moe, G. K.: Adrenergic effects on ventricular vulnerability, Circulation Res. 14: 516, 1964.
58. Wallace, A. G., and Mignone, R. J.: Physiologic evidence concerning the re-entry hypothesis for ectopic beats, Amer. Heart J. 72: 60, 1966.
59. Dresel, P. E., and Duncan, D. G.: Induction of automaticity in cat papillary muscles by sympathomimetic amines, J. Pharmacol. Exp. Ther. 133: 70, 1961.
60. Levy, J. V., Ichiyanagi, K., and Frederickson, E. L.: Effect of cyclopropane on myocardial contraction and membrane potentials, ANESTHESIOLOGY 24: 185, 1963.
61. Davis, L. D., Temte, J. V., Helmer, P. R., and Murphy, Q. R.: Effects of cyclopropane and of hypoxia on transmembrane potentials of atrial, ventricular and Purkinje fibers, Circulation Res. 18: 692, 1966.
62. Temte, J. V., Helmer, P. R., and Davis, L. D.: Effects of calcium and cyclopropane on Purkinje fibers, ANESTHESIOLOGY 28: 354, 1959.
63. Awalt, C. H., and Frederickson, E. L.: The contractile and cell membrane effects of halothane, ANESTHESIOLOGY 25: 90, 1964.
64. Hauswirth, O., and Schaer, H.: Effects of halothane on the sino-atrial node, J. Pharmacol. Exp. Ther. 158: 36, 1967.
65. Anderson, N. B.: Synergistic effect of cyclopropane and epinephrine on sodium transport in toad bladder, ANESTHESIOLOGY 28: 438, 1967.
66. Murphy, Q., Crumpton, C. W., and Meek, W. J.: The effect of blood pressure rise on the production of cyclopropane–epinephrine induced cardiac arrhythmias, ANESTHESIOLOGY 10: 416, 1949.
67. Nickerson, M., and Nomaguchi, G. M.: Mechanism of dibenamine protection against cyclopropane–epinephrine cardiac arrhythmias, J. Pharmacol. Exp. Ther. 95: 1, 1949.
68. Katz, R. L.: The effects of alpha and beta adrenergic blocking agents on cyclopropane–catecholamine cardiac arrhythmias, ANESTHESIOLOGY 26: 289, 1965.
69. Dawes, G. S.: Experimental cardiac arrhythmias and quinidine-like drugs, Pharmacol. Rev. 4: 43, 1952.
70. Innes, I. R., and Sanders, H. D.: Effect of tension on inductoin of automaticity by epinephrine in papillary muscle, Circulation Res. 15: 380, 1964.
71. Vick, R. L.: Effects of increased transmural pressure upon atrial and ventricular rhythms in the dog heart-lung preparation, Circulation Res. 13: 39, 1963.
72. Vick, R. L.: Effects of altered heart rate on chloroform–epinephrine cardiac arrhythmia, Circulation Res. 18: 316, 1966.
73. D'Silva, J. L.: The action of adrenaline on serum potassium, J. Physiol., Lond. 86: 219, 1936.
74. O'Brien, G. S., Murphy, Q. R., and Meek, W. J.: The effect of sympathomimetic amines on arterial plasma potassium and cardiac rhythm in anesthetized dogs, J. Pharmacol. Exp. Ther. 109: 453, 1953.
75. Davis, L. D., Helmer, P. R., and Murphy, Q. R.: Role of potassium in cyclopropane–epinephrine ventricular tachycardia, ANESTHESIOLOGY 25: 54, 1964.
76. O'Brien, G. S., Eid, C. H., Murphy, Q. R., Jr., and Meek, W. J.: Effects of elimination of hepatic circulation on cyclopropane–epinephrine ventricular tachycardia and arterial serum potassium in dogs, J. Pharmacol. Exp. Ther. 112: 374, 1954.
77. Steffenson, J. L., and Murphy, Q. R.: Effect of low potassium diet on cyclopropane–epinephrine ventricular tachycardia and arterial plasma potassium in dogs, Proc. Soc. Exp. Biol. Med. 98: 155, 1958.
78. Papilian, V., Russu, I. G., and Antonescou, C.: Le sympathique et la syncope adrenalino-chloroformique, C. R. Soc. Biol. (Paris) 118: 471, 1935.
79. Bouckaert, J. J., and Heymans, C.: Syncope adrenalino-chloroformique et sinus carotidiens, Compt. Rend. Soc. Biol. 105: 878, 1930.
80. Allen, C. R., Stutzman, J. W., and Meek, W. J.: The production of ventricular tachycardia by adrenalin in cyclopropane anesthesia, ANESTHESIOLOGY 1: 158, 1940.
81. Stutzman, J. W., and Pettinger, F. L.: Mechanism of cardiac arrhythmias during cyclopropane anesthesia, ANESTHESIOLOGY 10: 374, 1949.
82. Allen, C. R., Hoefflich, E. A., Cooper, B. M., and Slocum, H. C.: Influence of the autonomic nervous system upon spontaneous cardiac arrhythmias during cyclopropane anesthesia, ANESTHESIOLOGY 6: 261, 1945.
83. Hoff, H. E., and Nahum, L. H.: The nature of ventricular fibrillation following electric shock and its prevention by acetyl-β-methyl choline chloride, Am. J. Physiol. 110: 675, 1935.
84. Bardier, E., and Stillmunkes, A.: The adrenaline-chloroform syncope, Arch. Int. Pharmacodyn. 27: 375, 1923.
85. Fawaz, G.: The mechanism by which N:N-dibenzylchloroethylamine protects animals against cardiac arrhythmias induced by sympathomimetic amines in presence of

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

cyclopropane or chloroform, Brit. J. Pharmacol. 6: 492, 1951.

85. Somani, P., and Lum, B. K. B.: Blockade of epinephrine- and ouabain-induced cardiac arrhythmias in the dog heart-lung preparation, J. Pharmacol. Exp. Ther. 152: 235, 1966.

87. Dresel, P. E.: Cyclopropane–epinephrine arrhythmias. *In* Price, H. L., and Cohen, P. J. (editors): Effects of Anesthetics on the Circulation. Springfield, Illinois, Charles C Thomas, 1964.

88. Dresel, P. E., and Sutter, M. C.: Factors modifying cyclopropane–epinephrine cardiac arrhythmia, Circulation Res. 9: 1284, 1961.

89. MacConnell, K. L., and Dresel, P. E.: On the site of origin of cyclopropane–adrenaline arrhythmias, Canad. J. Physiol. Pharmacol. 42: 157, 1964.

90. Moore, E. N., Morse, H. T., and Price, H. L.: Cardiac arrhythmias produced by catecholamines in anesthetized dogs, Circulation Res. 15: 77, 1964.

91. Acheson, G. H., Farah, A., and French, G. N.: Some effects of dibenzyl-β-chlorethylamine (dibenamine) on the mammalian heart, J. Pharmacol. Exp. Ther. 97: 455, 1949.

92. Nickerson, M.: The pharmacology of adrenergic blockade, Pharmacol. Rev. 1: 27, 1949.

93. Schull, L. G., Berry, G., and Villarreal, P.: Prevention and correction of ventricular arrhythmias by dichloroisoproterenol in dogs anesthetized with cyclopropane, ANESTHESIOLOGY 22: 444, 1961.

94. Lucchesi, B. R., and Hardman, H. F.: The influence of dichloroisoproterenol (DCI) and related compounds upon ouabain and acetylstrophanthidin-induced cardiac arrhythmias, J. Pharmacol. Exp. Ther. 132: 372, 1961.

95. Lucchesi, B. R.: Action of nethalide upon experimentally induced cardiac arrhythmias, J. Pharmacol. Exp. Ther. 145: 286, 1964.

96. Rosati, R. A., Alexander, J. A., Wallace, A. G., Sealy, W. C., and Young, W. G., Jr.: Failure of beta-adrenergic blockade to alter ventricular fibrillation thresholds in the dog, Circulation Res. 19: 721, 1966.

97. Sekiya, A., and Vaughan Williams, E. M.: A comparison of anticirculatory actions and effects on intracellular cardiac potentials of pronethalol, disopyramide, and quinidine, Brit. J. Pharmacol. 21: 473, 1963.

98. Morales-Aguilera, A., and Vaughan Williams, E. M.: The effects on cardiac muscle of beta-receptor antagonists in relation to their activity as local anesthetics, Brit. J. Pharmacol. 24: 332, 1965.

99. Murmann, W., Saccani-Guelfi, M., and Gamba, A.: Pharmacological properties of 1-(4-nitrophenyl)-2-isopropylaminoethanol (INPEA). A new beta-adrenergic receptor antagonist, Boll. Chimicofarm. 105: 292, 1966.

100. Samani, P., and Lum, B. K. B.: The antiarrhythmic actions of beta adrenergic blocking agents, J. Pharmacol. Exp. Ther. 147: 194, 1965.

101. Lord, C. O., Katz, R. L., and Eakins, K. E.: Antiarrhythmic properties of stereoisomers of a beta-adrenergic blocking agent (H56/28), ANESTHESIOLOGY 29: 288, 1968.

102. Lucchesi, B. R.: The effects of pronethalol and its dextro isomer upon experimental cardiac arrhythmias, J. Pharmacol. Exp. Ther. 148: 94, 1965.

103. Howe, R., and Shanks, R. H.: Optical isomers of propanolol, Nature 210: 1336, 1966.

104. Wallace, A. G., Schaal, S. F., Sugimoto, T., Rozear, M., and Alexander, J. A.: The electrophysiological effects of beta-adrenergic blockade and cardiac denervation, Bull. N. Y. Acad. Med. 43: 1119, 1967.

105. Fleming, W. W.: Supersensitivity of the cat heart to catecholamine-induced arrhythmias following reserpine pretreatment, Proc. Soc. Exp. Biol. Med. 111: 484, 1962.

106. Horowitz, D., Lovenberg, W., Engelman, K., and Sjoerdsma, A.: Monoamine oxidase inhibitors, tyramine and cheese, J. A. M. A. 188: 1108, 1964.

107. Mason, A.: Fatal reaction associated with tranylcypromine and methamphetamine, Lancet 1: 1073, 1962.

108. Stark, D. C. C.: Effects of giving vasopressors to patients on monoamine oxidase inhibitors, Lancet 1: 1405, 1962.

109. Goldberg, L. I., and Sjoerdsma, A.: Effects of several monoamine oxidase inhibitors on the cardiovascular actions of naturally occurring amines in the dog, J. Pharmacol. Exp. Ther. 127: 212, 1959.

110. Horowitz, D., Fox, S. M., III, and Goldberg, L. I.: Effects of dopamine in man, Circulation Res. 10: 237, 1962.

111. MacCannell, K. L., McNay, J. L., Meyer, M. B., and Golberg, L. I.: Dopamine in the treatment of hypotension and shock, New Engl. J. Med. 275: 389, 1966.

112. McDonald, R. H., Jr., and Goldberg, L. I.: Analysis of the cardiovascular effects of dopamine in the dog, J. Pharmacol. Exp. Ther. 140: 60, 1963.

113. McDonald, R. H., Jr., Goldberg, L. I., McNay, J. L., and Tuttle, E. J., Jr.: Effects of dopamine in man: Augmentation of sodium excretion, glomerular filtration rate and renal plasma flow, J. Clin. Invest. 43: 1116, 1964.

114. Katz, R. L., Matteo, R. S., and Papper, E. M.: The injection of epinephrine during general anesthesia with halogenated hydro-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024

carbons and cyclopropane in man. 2. Halothane, ANESTHESIOLOGY 23: 597, 1962.
115. Jacques, A., and Hudon, F.: Effect of epinephrine on the human heart during methoxyflurane anaesthesia, Can. Anaesth. Soc. J. 10: 53, 1963.
116. Hügin, W.: Die Verträglichkeit von Octapressin mit verschiedenen Narkosen, Der Anaesthesist 11: 185, 1962.
117. Hunter, M. E., and Gordon, R. A.: Laboratory and clinical studies of 2-phenylalanine-8-lysine vasopressin (Octopressin), Can. Anaesth. Soc. J. 13: 40, 1966.
118. Shanks, C. A.: Intravenous Octapressin during halothane anaesthesia: A pilot study, Brit. J. Anaesth. 35: 640, 1963.
119. Shanks, C. A.: The compatibility of Octapressin with cyclopropane, trichloroethylene and halothane, N. Z. Med. J. 63: 156, 1964.
120. Berde, B., Boissonnas, R. A., Huguenin, R. L., and Sturmere, E.: Vasopressin analogues with selective pressor activity, Experientia 20: 42, 1964.
121. Katz, R. L.: Effects of oxytocin, vasopressin and their analogues on cardiac rhythm, Proceedings 23 Internat. Cong. Physiol. Science, p. 516, 1965.
122. Katz, R. L.: Clinical experience with neurogenic cardiac arrhythmias, Bull. N. Y. Acad. Med. 43: 1106, 1967.
123. Price, H. L.: General anesthesia and circulatory homeostasis, Physiol. Rev. 40: 187, 1960.
124. Jorfeldt, L., Löfström, B., Möller, J., and Rosen, A.: Propranolol in ether anesthesia, Acta Anaesth. Scandinav. 11: 159, 1967.
125. McNeill, R. S.: Effect of β-adrenergic-blocking agent, propranolol, on asthmatics, Lancet 2: 1101, 1964.
126. McNeill, R. S., and Ingram, C. G.: Effect of propranolol on ventilatory function, Am. J. Cardiol. 18: 473, 1966.
127. Zuberbuhler, R. C., and Bohr, D. R.: Responses of coronary smooth muscle to catecholamines, Circulation Res. 16: 431, 1965.
128. Parratt, J. R., and Grayson, J.: Myocardial vascular reactivity after beta-adrenergic blockade, Lancet 1: 338, 1966.
129. Gaal, P. G., Kattus, A. A., Kolin, A., and Ross, G.: Effects of adrenaline and noradrenaline on coronary blood flow before and after beta-adrenergic blockade, Brit. J. Pharmacol. 26: 713, 1966.
130. Braunwald, E., and Chidsey, C. A.: The adrenergic nervous system in the control of the normal and failing heart, Proc. Roy. Soc. Med. 58: 1063, 1965.
131. Epstein, S. E., and Braunwald, E.: Beta-adrenergic receptor blocking drugs, New Engl. J. Med. 275: 1106, 1175, 1966.
132. Gaffney, T. E., and Braunwald, E.: Importance of the adrenergic nervous system in the support of circulatory function in patients with congestive heart failure, Am. J. Med. 34: 320, 1963.
133. Stock, J. P. P., and Dale, N.: Beta-adrenergic receptor blockade in cardiac arrhythmias, Brit. Med. J. 2: 1230, 1963.
134. Harrison, D. C., Sprouse, J. H., and Morrow, A. G.: The antiarrhythmic properties of lidocaine and procaine amide. Clinical and physiologic studies of their cardiovascular effects in man, Circulation 28: 486, 1963.
135. Dresel, P. E., and Nickerson, M.: The role of potassium in epinephrine-induced cardiac arrhythmias, J. Pharmacol. Exp. Ther. 125: 142, 1959.
136. Lurie, A. A., Jones, R. E., Linde, H. W., Price, M. L., Dripps, R. D., and Price, H. L.: Cyclopropane anesthesia: cardiac rate and rhythm during steady levels of cyclopropane anesthesia at normal and elevated end-expiratory carbon dioxide tensions, ANESTHESIOLOGY 19: 457, 1958.
137. Stutzman, J. W., Murphy, Q., Allen, C. R., and Meek, W. J.: Further studies on the production of cyclopropane–epinephrine tachycardias, ANESTHESIOLOGY 8: 579, 1947.
138. Zaid, G., and Beall, G. N.: Bronchial response to beta-adrenergic blockade, New Eng. J. Med. 275: 580, 1966.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/29/4/763/617462/0000542-196807000-00021.pdf by guest on 19 April 2024