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Mechanisms for Cardiac Dysrhythmias during Anesthesia

John L. Atlee, III, M.D., Zeljko J. Bosnjak, Ph.D.†*

CONTENTS

CARDIAC DYSRHYTHMIAS may occur in 60% or more of patients undergoing anesthesia and surgery when continuous methods are used for surveillance.[1–3] The incidence may be even higher in patients with major organ system disease, altered physiologic states, or receiving certain drugs. While some dysrhythmias have a minimal impact on cardiovascular function, this does not mean that they should be ignored. Indeed, a deviation from the normal and regular beating of the heart, particularly when a new occurrence, could be the only sign of some physiologic or pharmacologic derangement. Dysrhythmias that adversely affect circulatory function, or are likely to initiate dangerous ventricular tachydysrhythmias, require immediate treatment.

The effectiveness of remedial or more definitive measures in anesthetized patients will depend, in large part, on knowledge of how anesthetic and adjunct drugs affect electrical properties of the heart. We note that there has been no review of this topic in ANESTHESIOLOGY for nearly 20 yr,[4] despite a number of advances in the field. Hence, this review, the purposes of which are to: 1) bring anesthesiologists up to date on the current views regarding cellular mechanisms for cardiac dysrhythmias; 2) consider reported effects of anesthetics and adjunct therapy on electrical properties of the heart; 3) discuss these as they relate to the potential for dysrhythmias during anesthesia; and 4) suggest directions for further research. The review has two major sections. The first considers normal and abnormal electrical activity of the heart, and the second discusses anesthetic and adjunct drug effects on these.

ABBREVIATIONS

ACh:	Acetylcholine
AP:	Action potential
APD:	Action potential duration
APD_{90}:	Action potential duration at 90% repolarization
AV:	Atrioventricular
CCB:	Calcium channel blocker
CNS:	Central nervous system
CV:	Cardiovascular
DAD:	Delayed afterdepolarizations
EAD:	Early afterdepolarizations
ECG:	Electrocardiogram
LMP:	Loss of membrane potential
MDP:	Maximum diastolic potential
NDMR:	Nondepolarizing muscle relaxants
RMP:	Resting membrane potential
SA:	Sinoatrial
SCh:	Succinylcholine
TMP:	Transmembrane potential
TTX:	Tetrodotoxin

* Professor of Anesthesiology.

† Professor of Anesthesiology and Physiology.

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Address reprint requests to Dr. Atlee: Medical College of Wisconsin, MACC Bldg.-Anesthesiology, 8701 West Watertown Plank Road, Milwaukee, Wisconsin 53226.

Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: benzodiazepines; droperidol; etomidate; fentanyl; meperidine; methohexital; midazolam; morphine; thiopental. Anesthetics, local: bupivacaine; lidocaine. Anesthetics, volatile: enflurane; halothane; isoflurane. Heart: action potentials; arrhythmias; conduction; electrocardiography. Neuromuscular relaxants: atracurium; d-tubocurarine; gallamine; metocurine; pancuronium; succinylcholine; vecuronium. Pharmacology: Amiodarone; calcium channel blocking drugs; histamine. Sympathetic nervous system: β-adrenergic blocking drugs; catecholamines.

Some readers may wish to read only the brief overview of mechanisms, and then proceed to the second section, referring back to more detailed portions of the first section as needed for definition of terms and clarification of concepts.

Overview of Mechanisms for Dysrhythmias

Cardiac dysrhythmias are considered disorders of impulse initiation, propagation, or both.[5] Both normal and abnormal cellular electrophysiologic mechanisms may contribute to these disorders.[6] For example, cells found in the sinoatrial (SA) node exhibit spontaneous, sustained rhythmic activity (automaticity) and serve as the primary pacemaker for the heart. Cells found in several regions of the atria, the atrioventricular (AV) junction, and specialized ventricular conduction system also normally exhibit automaticity, which is usually suppressed by, or slower than that of, the SA node. The emergence of these secondary (subsidiary, latent) pacemakers, which could be due to slowing of SA node discharge by drugs or disease, is considered altered normal automaticity.[7] In contrast, atrial and ventricular muscle cells do not normally exhibit automaticity, but may do so when depolarized by disease or various other maneuvers.[7] Automaticity, so induced, is considered abnormal.[7] Additionally, sustained rhythmic activity may be dependent on prior impulses, in which case it is termed triggered activity or automaticity.[8] Finally, conduction *via* fibers of the atrial and ventricular specialized conduction system is normally quite fast. When these fibers become depolarized under pathophysiological circumstances, conduction may be slowed or even blocked. Either could contribute to re-entrant excitation.[9] The basis for these normal and abnormal electrophysiologic mechanisms, namely cellular mechanisms for dysrhythmias, are discussed in more detail below.

Normal Electrical Activity of the Heart

Action Potential. Most cardiac fibers are normally electrically quiescent. The level of cell membrane potential during electrical quiescence is termed the resting membrane potential (RMP). The cardiac action potential (AP) describes the changes in transmembrane potential (TMP) that occur with excitation, or, in the case of cells exhibiting automaticity, following slow spontaneous depolarization to some threshold potential for excitation. Depolarization in cardiac fibers, as in nerve, is due to the net inward movement of positive charges. The converse, repolarization, is due to the net outward movement of positive charges. The cardiac AP and the major ionic currents currently believed responsible for generation of the AP can be viewed in relation to figure 1, which depicts an AP for a quiescent (not exhibiting automaticity) Purkinje

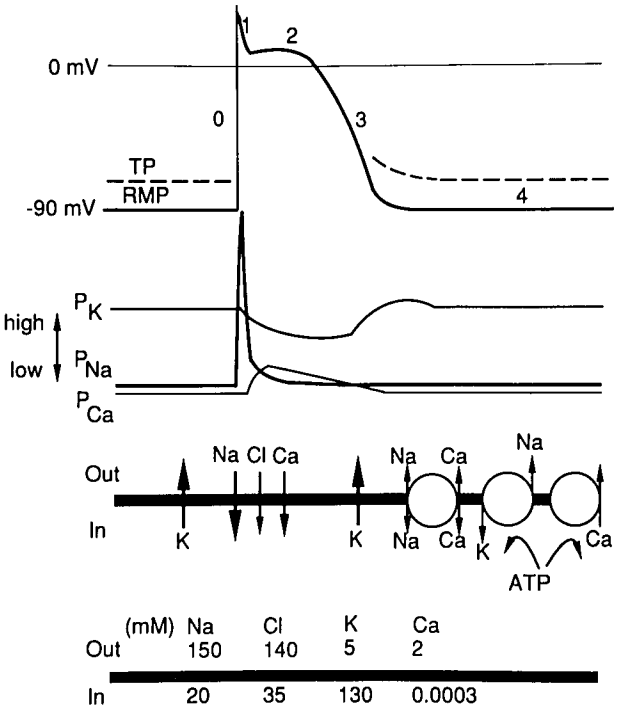

FIG. 1. Schematic representation of different phases of cardiac Purkinje action potential. These are shown in relationship to ionic permeability (P) across the cell membrane, along with ion exchange mechanisms and ionic concentrations outside (out), and inside (in) the cell. The five distinct phases of the action potential are the result of the selective membrane permeability to individual ions, ionic concentrations, and active and passive exchange mechanisms.

fiber. Note that the AP has five distinct phases: phase 0—rapid depolarization; phase 1—initial rapid repolarization; phase 2—plateau; phase 3—final rapid repolarization; phase 4—electrical diastole (diastolic depolarization in automatic fibers). The entire AP in cardiac fibers lasts several hundred milliseconds, in contrast to several milliseconds in nerve.

During phase 4, the cell is quite permeable to K^+ (K^+ conductance is high), but relatively impermeable to other ions, including Na^+, Ca^{2+}, and chloride (Cl^-).[10] The cell membrane is virtually impermeable to large, intracellular, anionic protein molecules. As a consequence of the foregoing, as well as the Na^+-K^+ exchange pump,[11] the intracellular Na^+ and K^+ concentrations are low and high, respectively, and the inside of the cell is negative with respect to the outside (fig. 1). The Na^+-K^+ exchange pump, which depends on energy supplied by the hydrolysis of adenosine triphosphate (ATP), transports three Na^+ out of the cell for two K^+ into the cell.[11] Depending on the membrane voltage and on the Na^+ and Ca^{2+} concentrations inside and outside the cells, the Na-Ca exchange mechanism (fig. 1) can provide a mechanism that may move Ca^{2+} or Na^+ into or out of cardiac cells. In parallel with the Na-Ca

TABLE 1. Comparison of Resting Membrane Potentials and Action Potentials of Cells in Different Regions of the Mammalian Heart*

Parameter	SA† Nodal Cell	Atrial Muscle Cell	AV† Nodal Cell	Purkinje Fiber	Ventricle Muscle Cell
Resting potential (mV)	−50–−60	−80–−90	−60–−70	−90–−95	−80–−90
Action potential					
Amplitude (mV)	60–70	110–120	70–80	120	110–120
Overshoot (mV)	0–10	30	5–15	30	30
Duration (ms)	100–300	100–300	100–300	300–500	200–300
V_{max}† (V/s)	1–10	100–200	5–15	500–700	100–200
Conduction velocity (m/s)	<0.05	0.3–0.4	0.1	2–3	0.3–0.4
Fiber diameter (μm)	5–10	10–15	5–10	30–50	10–16

* Data from Reference 10, p 190.

† Sinoatrial (SA), atrioventricular (AV), maximum velocity (rate of rise) of action potential (phase 0) upstroke (V_{max}).

exchange carrier an ATP-dependent calcium-transport system (fig. 1) also exists in cardiac sarcolemma.‡

Phase 0 depolarization in fast response fibers, fibers with a high RMP (atrial and ventricular muscle, Purkinje fibers; table 1) is largely dependent on the fast inward current carried by sodium ions (Na^+). In slow response fibers (SA and AV node cells), depolarization during phase 0 is largely dependent on the slow inward current carried mainly by calcium ions (Ca^{2+}). Regardless of cell type (fast or slow response), RMP is predominantly determined by potassium ion (K^+) permeability.[6,10] Automatic cells, strictly speaking, do not have a RMP, since they slowly depolarize during diastole (phase 4). The term maximum diastolic potential (MDP) refers to the maximum level of transmembrane potential attained during diastole in these fibers.

Both the fast inward (Na^+) and slow inward (Ca^{2+}) currents move through membrane protein channels that are specific (Na^+) or selective (Ca^{2+}) for the two ionic species. These channels have time and voltage-dependent gating characteristics, discussion of which can be found elsewhere.[12] The Ca^{2+} channel is not important for the generation of the upstroke (phase 0) of the AP in fast response fibers. Ca^{2+} supplied by it does, however, contribute to the excitation-contraction process (recently reviewed by Rusy and Komai[13]) as well as to abnormal electrical activity caused by loss of membrane potential (*vide infra*). Current moving through the Ca^{2+} channel, which has slower activation and inactivation gating characteristics than the Na^+ channel, also helps to maintain the AP plateau (phase 2).[12]

Repolarization occurs during phases 1 and 3 of the cardiac AP (fig. 1). The important repolarizing current is supplied by K^+.[14] Several different K^+ currents are believed involved (*i.e.*, instantaneous rectifier—i_{k1}; plateau-delayed rectifier—i_k; transient or early outward current—i_{to}, i_{eo}).[14] Importantly, most K^+ channels exhibit inward-going rectification. This means that as the transmembrane potential becomes more and more negative during repolarization, K^+ conductance (as a result K^+ current) increases. Conversely, as the transmembrane potential becomes more positive during depolarization, K^+ conductance decreases. Inward-going rectification enhances the outward movement of K^+ during repolarization, thereby accelerating repolarization by further increasing K^+ conductance. The regenerative increase in K^+ conductance partly explains all-or-none repolarization.[14,15] The latter means that during the AP-plateau phase a large repolarizing current will result in full repolarization to resting or maximum diastolic potential levels. A smaller (subthreshold) repolarizing current, on the other hand, will return the AP to its plateau level of potential. Finally, it should be noted that outward currents involved in repolarization can also be generated by the Na^+-K^+ exchange pump.[14,16]

Refractoriness. One characteristic of cardiac as opposed to nerve fibers is prolonged refractoriness.[6] During the cardiac AP plateau, fibers cannot be re-excited, regardless of stimulus strength—that is, they are absolutely refractory (fig. 2). The reason is that both the Na^+ and the Ca^{2+} inward current channels are Na^+ and Ca^{2+} inactivated during the AP plateau, and repolarization must occur before they can reopen. In fast response fibers, restoration of the normal RMP is usually sufficient for full recovery of excitability, but there is a period between the end of absolute refractoriness and full recovery of excitability when the fibers are relatively refractory (fig. 2). During the relative refractory period, the stimulus required to elicit an AP is larger than normal. The resulting AP may be too small to propagate, or it may propagate slowly. In slow response or depressed fast response fibers (*vide infra*), the relative refractory period may extend several hundred milliseconds beyond full repolarization.

Automaticity. Whether from a normal or abnormal level of membrane potential (normal or abnormal automaticity), automaticity must result from a net reduction in the

‡ Caroni P, Carafoli E. An ATP-dependent Ca^{2+} pumping system in dog heart sarcolemma. Nature 283:765–767, 1980.

outward movement of positive charges.[6,17] This could be either by a progressive decrease in outward current, increase in inward current, or both. In Purkinje fibers, the pacemaker current (i_f) is likely to be an inward current carried by Na^+ and Ca^{2+} that is inactivated at levels of membrane potential above (less negative than) −50 mV.[17] The pacemaker current is carried by a channel that is not the same as the Na^+ (fast inward) channel.[17] Additionally, in Purkinje fibers, K^+ currents involved in repolarization may affect the pacemaker current.[17] In the SA node, and possibly with abnormal forms of automaticity in depressed fast response fibers,[7] i_f is likely involved only when the level of membrane potential is more negative than about −50 mV.[17] Instead, automaticity in the SA node is thought to result from an imbalance between slowly decaying i_k and slowly recovering Ca^{2+} inward currents.[17] Regardless of the ionic mechanism(s) for automaticity (normal or abnormal), the rate of automaticity is affected by changes in MDP, threshold potential (TP), and the rate of spontaneous diastolic (phase 4) depolarization (fig. 3).

Impulse Propagation. The speed of impulse propagation (conduction) is dependent on the properties of the current source (*e.g.*, rate of rise of the AP, AP overshoot, AP amplitude) and current sink (*e.g.*, longitudinal cellular resistance,[6] axial currents, and propagation velocities.[18,19] The relation between the current source and sink determines whether electrotonic effects (local, nonpropagated) or successful impulse propagation will result following excitation of adjacent cells. For example, excitation of adjacent fast response fibers with high RMP's, AP amplitudes and overshoots (table 1), is likely to result in successful impulse propagation. In contrast, excitation, of adjacent slow response fibers (or depressed fast response fibers) are more likely to result in electrotonic effects. This is because slow response APs have lower RMPs, AP amplitudes, and overshoots (table 1). Finally, with regard to impulse propagation, the excess of activation current over that just required to produce successful propagation is termed the safety factor of conduction.[6] Based on the foregoing considerations, fast response fibers have a high safety factor of conduction, whereas slow or depressed fast response fibers have a low safety factor of conduction.

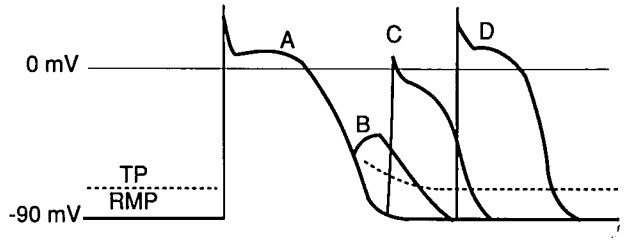

FIG. 2. A cardiac Purkinje fiber action potential is shown schematically along with responses obtained by stimulation given at different stages of repolarization. During the absolute refractory period (A) the fiber cannot be re-excited and the earliest response (B) occurs at the beginning of relative refractory period. These early responses do not propagate since they arise from low levels of membrane potential. During the later part of the relative refractory period, response C will propagate, although slowly because of its smaller rate of rise and amplitude. Finally, response D is applied following complete repolarization and has a normal rate of rise, conduction and amplitude.

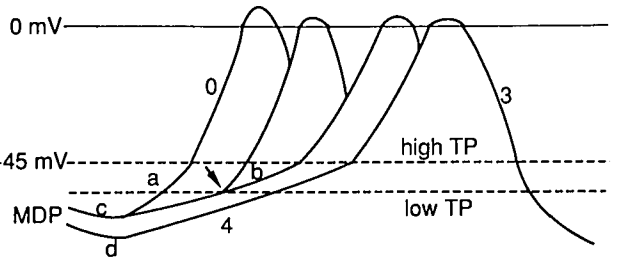

FIG. 3. Schematic representation of mechanisms that can alter automaticity of the SA node. A decrease in the slope of phase 4 depolarization from *a* to *b* slows the rate of automatic discharge by increasing the time to reach threshold potential (TP). An increase in TP from high to low level of membrane potential (more negative) increases the rate of discharge (*arrow*) by decreasing the time to reach the TP. In addition, automatic discharge can be slowed by an increase in maximum diastolic potential (MDP) from *c* to *d*.

Abnormal Electrical Activity of the Heart

Abnormal electrical phenomena include conduction of the depressed fast response, abnormal automaticity, triggered activity/automaticity, and re-entry of excitation. These result when normal electrophysiologic processes are disrupted by pathophysiological states. The latter could be the result of major organ system disease or due to the effects of hypoxia, ischemia, drugs, or electrolyte imbalance. Before we can consider these abnormal mechanisms, however, we must first discuss loss of membrane potential (LMP).

Cellular Mechanisms for Dysrhythmias. A common mechanism underlying some abnormal electrophysiological phenomena, and one that may contribute to dysrhythmias (notably, re-entry) is LMP in fast response fibers. In essence, with LMP, these fibers with a normally high level of RMP (table 1) become partially depolarized (less negative RMP). As a result, there is reduced Na^+ channel availability; that is, at low levels of RMP, there are fewer Na^+ channels that can be activated and a smaller Na^+ current.[20] Consequently, with LMP, conduction is slower. This is because AP upstroke velocities, overshoots, and amplitudes are reduced, and more similar to those of slow response fibers (table 1).§ Since the pathophysiologic pro-

§ Cells in transitional zones between working atrial myocardium and the SA and AV nodes (transitional cells)[3] may have RMPs intermediate between those of cells of the SA and AV nodes. Likely, this is not due to LMP *per se*, but rather, it is a normal phenomenon. Regardless, conduction is probably slower in these cells due to reduced Na^+ channel availability.

cesses responsible for LMP are not likely to be uniform, with LMP there is likely to be varying depression of the fast response, and uneven conduction and refractoriness.[21,22] Thus, depressed fast response APs create conditions that are favorable for re-entry of excitation. Finally, LMP in fast response fibers can be the cause for abnormal forms of automaticity.[7]

Conduction of the depressed fast response is likely to be slow, but variably so. Depending on Na^+ channel availability, conduction velocities may only slightly decrease from those reported for normal fast response fibers, or be more similar to those for slow response fibers (table 1). As already mentioned, depressed fast response conduction may be conducive to re-entry, but it could also be responsible for heart block.

Altered Normal Automaticity and Abnormal Automaticity. These two are distinguished from one another.[7] With the former, the ionic mechanism for automatic discharge remains normal, except that the kinetics or magnitude of the ionic current(s) may be altered. The result is acceleration or deceleration of normal pacemaker discharge. Circumstances or manipulations that might alter normal automaticity at different pacemaker sites are discussed in more detail elsewhere.[3,7] Abnormal automaticity, on the other hand, is due to an ionic mechanism that is substantially different from that for normal automaticity in the same fiber type (*e.g.*, Purkinje fibers), or it may be observed in fibers that do not normally exhibit automaticity (*e.g.*, atrial and ventricular muscle).[7] Depolarization of Purkinje, atrial, or ventricular muscle fibers by disease or other interventions, can accelerate existing spontaneous activity or induce abnormal automaticity in previously quiescent fibers.[23–26] Abnormal automaticity has been observed in subendocardial fibers surviving experimental myocardial infarction.[27,28] Interestingly, abnormal automaticity in depolarized Purkinje fibers was not affected by lidocaine, but was blocked by verapamil (fig. 4).[24] The latter provides indirect evidence for a role of the slow inward current in the genesis of abnormal automaticity.

Triggered Activity/Automaticity. This is abnormal, rhythmic activity of the heart that is dependent on prior impulses for its initiation. It stands in contrast to abnormal automaticity, just discussed. Two forms of triggering are distinguished: that occurring following delayed afterdepolarizations—triggered activity; and that following early afterdepolarizations—triggered automaticity.[8]

Delayed Afterdepolarizations (DAD). DAD are oscillations in the TMP that occur following full repolarization of the AP (*i.e.*, during phase 4), and they are caused by that AP.[8,23,29] Often, as shown in figure 5 (all panels), they are preceded by hyperpolarization of the membrane, that is, the level of TMP just prior to the DAD is more negative than it was prior to the AP that triggered the DAD. A triggered AP or rhythm results when the DAD reach

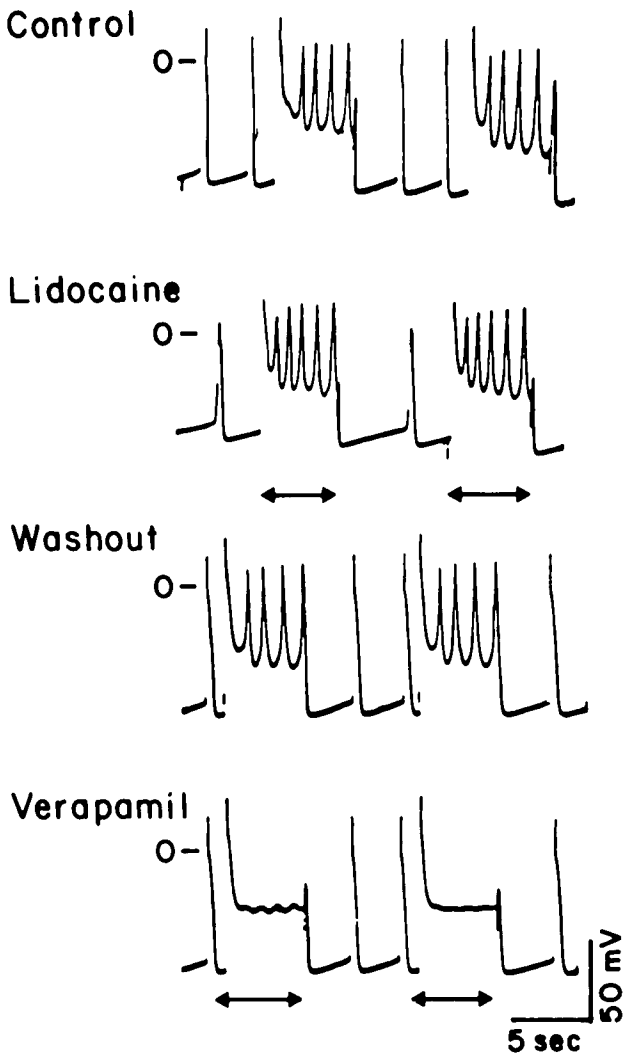

FIG. 4. Automaticity at two levels of membrane potential in a canine cardiac Purkinje fiber. During the interval between the arrowheads, the fiber was depolarized from −85 mV to −50 mV using current injection across a sucrose gap. Lidocaine (3 mg/l) slowed the spontaneous discharge rate and reduced the amplitude of action potentials (AP) arising from −85 mV, but it did not affect AP's or automaticity at −50 mV. After washout of lidocaine, exposure to verapamil (3×10^{-6} M) suppressed automaticity at −50 mV but not at −85 mV (From reference 24, used with permission.)

threshold for an AP or sustained rhythmic activity (fig. 5, panel D). DAD occur under a variety of conditions in which there appears to be excessive accumulation of intracellular Ca^{2+} stores, termed calcium overload.[8] Abnormalities in the sequestration and release of Ca^{2+} may also contribute to DAD, and toxic levels of digitalis are a recognized cause for DAD and triggered activity in a variety of fast response fibers.[8,30–32] DAD and triggered activity have been observed in most cardiac fiber types, and under a wide variety of conditions, all of which likely involve increased intracellular Ca^{2+}. In addition to toxic

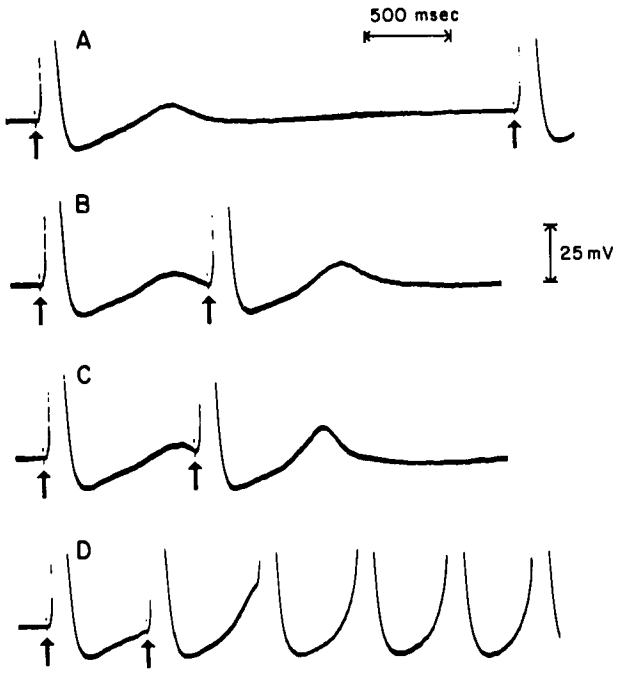

FIG. 5. Triggered activity in a fiber of the monkey mitral valve. The records were taken at a high gain to show the afterpotentials; as a result, much of the action potential (AP) proper is off scale. In *A*, *B*, and *C* the fiber is driven at a slow regular rate, one stimulus being applied every 2.8 s. Premature stimuli are applied at 1 s, 0.92 s, and 0.6 s after the drive in *B*, *C*, and *D*. The earlier the premature impulse arises, the greater is the amplitude of the delayed afterdepolarization (DAD). In *D* the DAD following the premature impulse reaches threshold (probably not at the site from which the record was taken) and gives rise to sustained, nondriven activity at a rate of about 2 per s. Note that in all cases driven and premature AP are followed by afterhyperpolarizations, that is, the transmembrane potential becomes more negative following the AP than it was just before the AP. Calibrations: 25 mV and 500 ms (From reference 23, used with permission.)

digitalis, these are: exposure to catecholamines,[33–37] Purkinje fibers surviving 1–4 days following experimental myocardial infarction,[38,39] a number of altered ionic environments,[8] and Purkinje fibers exposed to lysophosphatidylcholine.[40] In contrast to early afterdepolarizations (*vide infra*), DAD increase in amplitude (or the likelihood that they will trigger APs or sustained rhythmic activity) with increased paced rates or increasing prematurity of stimulated APs.[8] Further discussion of DAD and triggered activity, including postulated ionic mechanisms and possible involvement in clinical dysrhythmias, can be found elsewhere.[3,8]

Early Afterdepolarizations (EAD). EAD are oscillations in the TMP that occur during the plateau and repolarization phases of the AP (fig. 6).[8,23,29,41] It has been suggested that there are at least two types of EAD based on their location within the AP: 1) low membrane potential EAD, occurring at TMP between 0 and −30 mV (mid-to-late portion of AP plateau); 2) high membrane potential EAD, occurring at TMP more negative than −50 mV, but prior to completion of repolarization.[8,41,42] Since these two types of EAD occur at different levels of TMP, they likely involve different ionic mechanisms.[3,8] Possibilities include a time-dependent, Na^+ "window current,"[43,44] slow inactivation of the Na^+ fast inward current,[45–47] Ca^{2+} slow inward and transient inward currents,[41] and outward (K^+) currents during repolarization.[8,41] In general, EAD and EAD-triggered sustained rhythmic activity are more likely to occur at slow heart rates.[42] EAD-triggered sustained rhythmic activity is conceptually difficult to distinguish from abnormal forms of automaticity.[8,29] Hence, triggered automaticity is probably the preferred term for triggered sustained rhythmic activity following EAD.[8,29] Further discussion of EAD can be found elsewhere.[3,8]

Re-entry of Excitation. Re-entry occurs when the propagating AP does not die out following excitation of cardiac tissue.[9,48] Rather, the AP persists to re-excite atrial or ventricular tissue at the end of their refractoriness. The criteria for re-entry were first formulated by Mines.[49,50] First, there must be an area of unidirectional block. Second, the re-entrant circuit must be defined, that is, movement of the excitatory wavefront must be observed to pass through the pathway, to return to its site of origin, and then again follow the same pathway. Third, to rule out a focal origin (*e.g.*, automatic or triggered) for sustained re-excitation, one must be able to terminate re-excitation by interrupting the circuit at some point. Circus movement re-entry, the type of re-entry envisioned by Mines, requires an anatomic obstacle (fig. 7). Garrey was the first to consider that differences in refractory periods could create the temporal barriers for conduction (*i.e.*, slowed conduction) required to sustain circus movement.[51] However, despite a widely held clinical notion to the contrary, circus movement re-entry involving an anatomical obstacle is not an established mechanism for many clinical tachydysrhythmias.[9,48] In addition to circus movement re-entry involving an anatomic obstacle, other models for

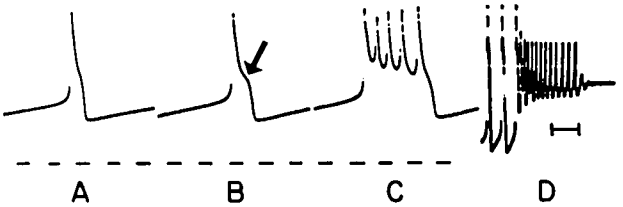

FIG. 6. Early afterdepolarization (EAD) and triggered activity. Action potentials (AP) are from a spontaneous active canine Purkinje fiber exposed to normal Tyrode solution. *A:* Normal AP. *B:* An EAD is seen (*arrow*). *C:* Four nondriven AP occur at a membrane potential corresponding to that of the EAD. *D:* Record obtained from a different fiber shows a series of three normal AP followed by a train of activity at a low membrane potential followed in turn by quiescence at a low level of membrane potential (From reference 29, used with permission of the American Heart Association.)

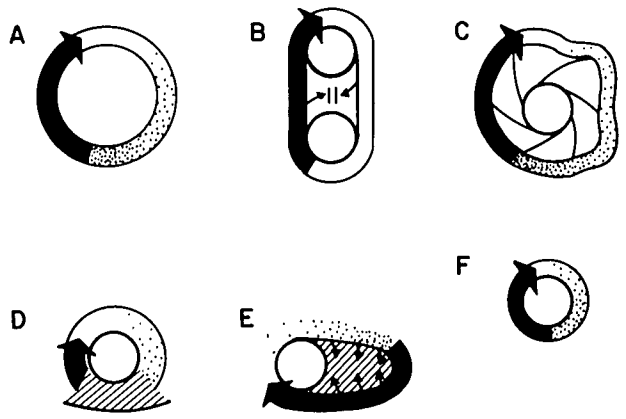

FIG. 7. Schematic representation of various types of circus movement re-entry. The arrows represent the crest of the circulating wave front, and in its wake are the areas of absolute refractoriness (*black zones*) and relative refractoriness (*stippled zones*). *A:* Circus movement around a gross anatomical obstacle, as introduced by Mines. *B:* Circus movement around the orifices of two veins, separated by a zone of bidirectional block, as suggested by Lewis to be responsible for atrial flutter. *C:* Model of circus movement, introduced by Moe and coworkers, in which the impulse is thought to circulate in a loop composed of bundles having a greater conduction velocity than the tissue around it. *D* and *E:* Types of circus movement based on the combination of an anatomical obstacle and an adjacent area of diseased tissue exhibiting depressed conduction (*hatched zones*). *F:* Circus movement around a relatively small obstacle has become possible because of shortening of the refractory period and a decrease in conduction velocity, resulting in a shortening of the wavelength of the impulse. See text for further discussion. (From Allessie MA, Lammers WJEP, Bonke IM, Hollen J: Intra-atrial re-entry as a mechanism for atrial flutter induced by acetylcholine and rapid pacing in the dog. *Circulation* 70:123–135, 1984, used with permission.)

re-entry include linear re-entry (fig. 8),[52] reflection (fig. 9),[53,54] and the leading circle concept (fig. 10).[55] None of these last three models require an anatomical obstacle, and none will be discussed further. The interested reader can find more complete discussion elsewhere.[3,9] However,

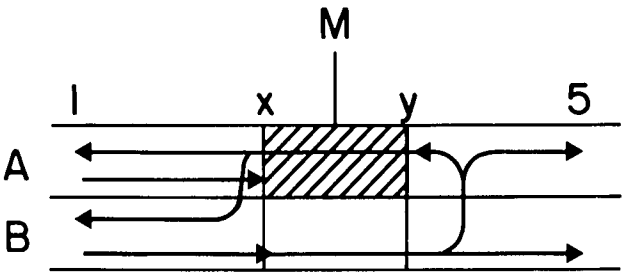

FIG. 8. Schematic representation of re-entry in a linear bundle with a region of asymmetrical depressed tissue, as proposed by Schmitt and Erlanger.[52] The shaded area is a zone of unidirectional block. The impulse propagating from left to right blocks at x in region *A* but conducts slowly in *B* beyond this area. There the impulse crosses over to *A via* lateral connections and propagates slowly back through the depressed zone (y to x) to re-excite the left part of the bundle. (From reference 52, used with permission.)

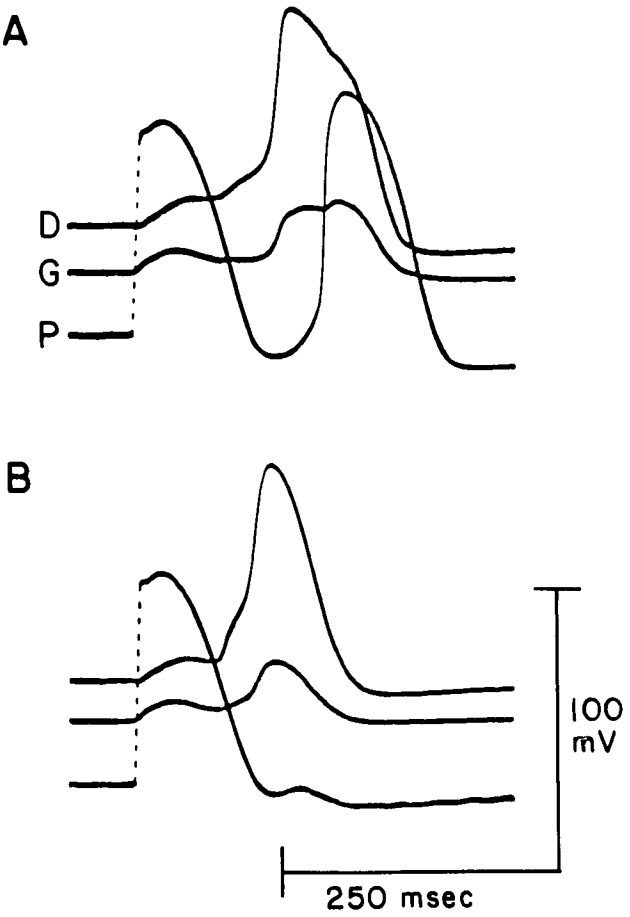

FIG. 9. Reflection. Transmembrane potentials recorded from a strip of feline epicardial ventricular muscle placed in a three-compartment tissue bath. Proximal (P) and distal (D) segments were superfused with normal Tyrode solution. The middle segment, 1 mm in width, was superfused with a solution containing 35 mM K^+ ("inexcitable gap," G). The preparation was stimulated at the proximal end with a basic cycle length of 1 s. In panel *A*, the distal element is activated with sufficient delay to allow reflection across the inexcitable gap, and re-excitation of the proximal segment occurs. In panel *B* reflection also occurs but produces only a subthreshold depolarization at the end of repolarization. (From reference 54, used with permission.)

remaining to be discussed are mechanisms for unidirectional block of conduction and slowed conduction, both of which are required for any form of re-entrant excitation.

Unidirectional Block of Conduction. Unidirectional block of conduction may be due to regional differences in recovery of excitability and to differences in cellular connections.[9] These can result from nonuniform refractoriness or recovery of excitability due to geometrical factors or from asymmetrical depression of conduction and excitability. When an impulse propagates through tissue with uneven refractoriness (*i.e.*, temporal dispersion of refractoriness), there can be failure of propagation (unidirec-

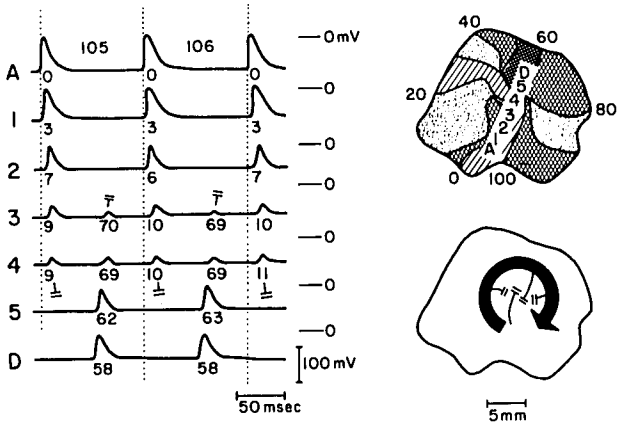

FIG. 10. Leading circle concept. Activation maps during steady-state tachycardia induced by a premature stimulus in an isolated rabbit left atrium (*upper right*). On the left are transmembrane potentials (AP) recorded from seven fibers located on a straight line through the center of the circus movement. The numerals under the action potentials (AP) indicate their timing in relation to the preceding AP in *A*. Note that the central area is activated by centripetal wavelets and that the fibers in the central area show double responses of low amplitude. Both responses are unable to propagate beyond the center, thus preventing the impulse from short-cutting the circuit. On the lower right the activation pattern is schematically indicated, showing the leading circuit and the converging centripetal wavelets. Block is indicated by double bars. (From reference 55, used with permission.)

tional block) in regions with the longest refractory periods. These regions will be available for re-excitation if the impulse can propagate *via* alternate pathways (that are not refractory) and return to excite a former site of unidirectional block that is no longer refractory. While the foregoing is unlikely to occur in normal myocardium, even at fast heart rates, this may not be the case with premature excitation. The latter could be spontaneous (*e.g.*, automatic, triggered) or externally applied (*e.g.*, premature paced stimuli) impulses. Re-entry caused by premature stimulation is facilitated by fast heart rates (similar to DAD-induced triggered activity), because refractory periods in the re-entrant circuit are shortened.[56] Additionally, with fast heart rates, repolarization is enhanced by electrotonic current flow to nonexcited cells from cells that have just been excited.[57,58] In atria, the degree of temporal dispersion of refractoriness required for unidirectional block following premature stimulation can be quite small, in contrast to the ventricles where refractory periods are longer, even at fast heart rates.[9] In addition to temporal dispersion of refractoriness, the dimension of the area of unidirectional block is also important, since re-entry will not occur if the site(s) of prolonged refractoriness are small, even with large temporal dispersion of refractoriness.[59] Temporal differences in recovery of excitability, as the consequence of the activation sequence of a prior impulse, and without differences in duration of refractoriness, may also provide transient unidirectional block.[59] Geometrical factors, including the Purkinje fiber-ventricular muscle junction,[60–63] branching sites of Purkinje fibers, or junctions of separate muscle bundles with a low safety factor for conduction,[18,19,64] may also provide the substrate for unidirectional block and re-entry.[9] Finally, unidirectional block of conduction can be due to asymmetrical depression of conduction and excitability,[9] which is the basis for linear re-entry in the model proposed by Schmitt and Erlanger in 1929 (fig. 8),[52] or in Purkinje fibers subjected to asymmetric crushing or cooling.[65]

For re-entry to occur, there must be slow conduction in an alternate pathway, which allows tissue proximal to a site of unidirectional block to recover from refractoriness.[9] Re-entry would, therefore, be facilitated when conduction was depressed.[23] As discussed earlier, conduction in fast response fibers is dependent on the magnitude of the Na^+ fast inward current during phase 0. Inactivation of this current by LMP (*vide supra*) can be a cause for slow conduction. Furthermore, in both depressed fast response and slow response fibers, refractoriness may extend well beyond repolarization.[6,66] This could also be conducive to re-entry if prolonged refractoriness was the mechanism for unidirectional block of conduction.[9]

Postulated Mechanisms for Clinical Dysrhythmias

As previously stated, cardiac dysrhythmias are conceptually considered disorders of impulse initiation, propagation, or both. Altered normal or abnormal cellular electrophysiologic mechanisms may be responsible for dysrhythmias. However, the involvement of one or another of these cellular mechanisms in clinically encountered dysrhythmias is not indubitable; for as recently said by Rosen: "studies in the single cell tell us what it can do, not what it does do"¶ under normal or pathophysiologic circumstances in the intact heart.[67] The criteria used by clinical cardiac electrophysiologists to establish mechanisms for tachycardia are discussed elsewhere.[3,7–9] Based on that discussion, likely or possible mechanisms for clinical rhythm disturbances are provided in table 2.

Anesthetic/Adjunct Drug Effects on Electrical Activity of the Heart

Noteworthy among the causes for cardiac dysrhythmias during anesthesia and surgery, and almost unique to this circumstance, are the involvement of altered physiologic states, autonomic imbalance, and the adverse effects of drugs and drug interactions.[3] Comprehensive discussion of these is beyond the scope of this review, the focus of which will be on effects of contemporary anesthetics and

¶ Statement attributed by Rosen[67] to Chandler McC. Brooks.

TABLE 2. Likely or Possible Cellular Mechanisms for Clinical Dysrhythmias

Altered Normal Automaticity
Sinus bradycardia; sinus tachycardia; sinus dysrhythmia; wandering atrial pacemaker; AV junctional escape rhythm; idioventricular escape rhythm.
Abnormal Automaticity
Some VT within 3 days of AMI; some automatic (non-paroxysmal) atrial tachycardia; accelerated idioventricular rhythm.
Triggered Activity/Automaticity
VT due to reperfusion of ischemic myocardium (DAD); exercise-induced VT in patients without CAD (DAD); accelerated AV junctional rhythm (DAD); PMVT/torsades de pointes in patients with QT prolongation (EAD); automatic (nonparoxysmal) atrial tachycardia with digitalis (DAD).
Re-entry
AV reciprocating tachycardia in patients with accessory AV pathways; PSVT due to SA node, atrial, or AV node re-entry; some VT with myocardial ischemia/infarction; atrial flutter, atrial/ventricular fibrillation (possibly with other mechanisms).

AMI = acute myocardial infarction; AV = atrioventricular; CAD = coronary artery disease; DAD = delayed afterdepolarization; EAD = early afterdepolarization; PMVT = polymorphous VT; PSVT = paroxysmal supraventricular tachycardia; QT = QT interval of surface electrocardiogram; SA = sinoatrial; VT = ventricular tachycardia.

adjunct drugs on electrical properties of the heart that could affect the genesis of dysrhythmias. Similar effects of older or less commonly used agents were considered by Katz and Bigger.[4] Finally, we discuss interactions between the anesthetics and other drugs that have established dysrhythmic potential, including catecholamines, histamine, calcium channel, and β-adrenergic blockers.

Inhalation Anesthetics. Halothane, enflurane, and isoflurane slow the rate of sinoatrial (SA) pacemaker discharge by both direct and indirect effects on SA node automatically.[68,69] Clinically, any direct depressant effect of the inhalation anesthetics on SA node function may be altered by the effects of other drugs and autonomic compensatory mechanisms.[68-70]

Little is known of the effects of the volatile anesthetics on subsidiary pacemaker function. Data of Reynolds *et al.*[71] and Morrow and Logic[72] support the notion that halothane depresses automaticity in pacemakers of the ventricular specialized conducting system (Purkinje fibers). Comparable data are not available for enflurane and isoflurane.** Finally, there are no data for the effects of any of these agents on normal mechanisms for automaticity in subsidiary atrial or AV junctional pacemakers.

** Pruett and coinvestigators (personal communications) have obtained preliminary data which suggest that enflurane and isoflurane enhance normal automaticity in Purkinje fibers.

Halothane shortens AP duration and refractoriness in normal Purkinje fibers.[71,73,74] Halothane prolongs His-Purkinje and ventricular conduction times[69,75] and shortens ventricular refractory periods[76] in the intact dog heart. Enflurane, like halothane, produces comparable prolongation of His-Purkinje and ventricular conduction times in dogs.[69,77] Its effect on Purkinje fiber AP characteristics or *in vivo* ventricular refractoriness have not been reported. Neither have those of isoflurane. One study suggests that increasing level of isoflurane (without awake control) has no effect on ventricular specialized conduction times in dogs.[78] Another more recent study, also in dogs, but with a conscious control and higher system resolution (±1 ms *vs.* ±5 ms), indicates that isoflurane does prolong ventricular specialized conduction times compared to awake.[69]

Halothane and enflurane cause similar dose-dependent prolongation of AV nodal conduction time and refractoriness,[75,77,79] but atrial refractoriness appears less affected by increasing halothane.[77,79] Blitt *et al.* found no effect of increasing isoflurane on AV nodal conduction time,[78] and there are no reports for the effect of increasing isoflurane on supraventricular refractory periods.

More recently, the effects of halothane, enflurane, and isoflurane on supraventricular conduction and refractoriness have been contrasted to awake in chronically instrumented dogs.[80] Compared to awake, AV nodal conduction time is prolonged in anesthetized dogs by about 20% with 1.6 MAC enflurane and halothane.[69] The prolongation was less, however, with isoflurane[69] (fig. 11). Another report indicates that enflurane, halothane, and isoflurane (1.2 and 1.6 MAC) increase atrial and AV nodal refractoriness compared to awake.[81] While no data exist for anesthetic effects on specialized cardiac conduction and refractoriness in man, animal studies suggest that none of the contemporary inhalation anesthetics are likely to be a cause for second or third degree AV block in the absence of intrinsic conduction system disease or drugs that prolong AV conduction time.

Data are now appearing which suggest that the potent inhalation agents have dysrhythmic and antidysrhythmic actions against abnormal cardiac electrophysiologic mechanisms. This is not entirely unexpected, since previous reports had demonstrated protective effects for: 1) halothane against ouabain-induced dysrhythmias;[82] 2) halothane, enflurane, and chloroform against ventricular fibrillation in rats with proximal LAD coronary artery occlusion;[83,84] and 3) all three contemporary inhalation agents against ventricular fibrillation in a canine acute LAD coronary artery occlusion/reperfusion model.[85] Recent data obtained by Turner *et al.* support the contention that halothane has dysrhythmic and antidysrhythmic actions in canine Purkinje fibers surviving 1 day after experimental myocardial infarction.[74] The prodys-

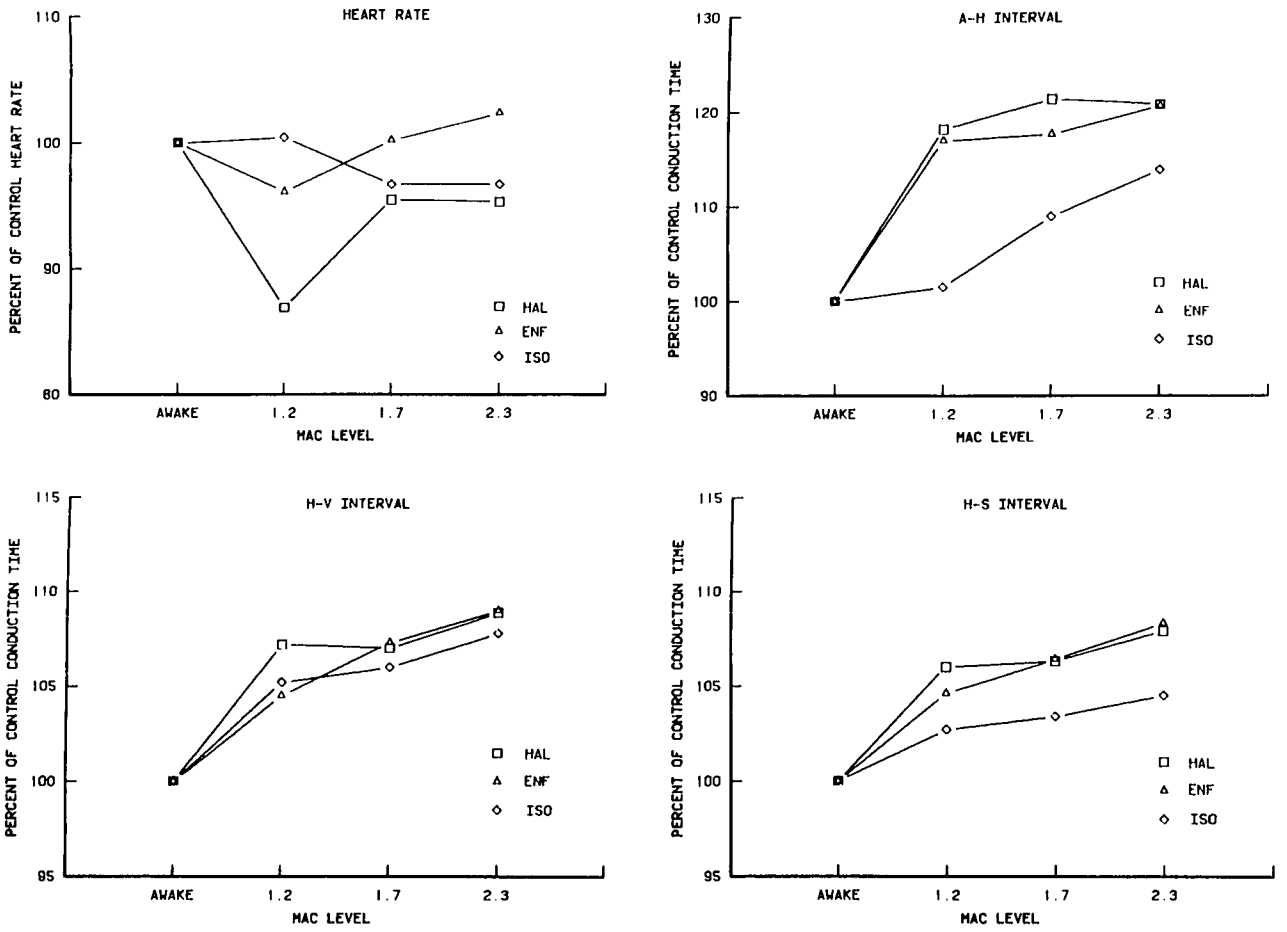

FIG. 11. Halothane (HAL), enflurane (ENF), and isoflurane (ISO) effects on heart rate and AV nodal (A-H interval), His-Purkinje (H-V interval), and ventricular conduction times (H-S interval) in the absence of autonomic blockade. Values for each anesthetic level are shown as percent of the awake (control) values. (From reference 69, used with permission.)

rhythmic action of halothane increased the range of premature responses that are conducted slowly enough into the ischemic (distal) region to produce unstimulated responses that could re-excite the nonischemic (proximal) region (fig. 12). Since these responses possibly were due to a re-entrant mechanism,[86] halothane may have acted to facilitate re-entry in the experiments of Turner *et al.*[74] On the other hand, in these same experiments,[74] halothane opposed spontaneous rhythmic activity likely due to an abnormal mechanism for automaticity (fig. 13, panels A and B), as well as DAD-induced triggered activity (fig. 13, panels B and C).

We speculate as to the mechanism for these dysrhythmic and antidysrhythmic effects of halothane.[74] Comparable studies have not been reported for enflurane or isoflurane. Voltage clamping studies support the premise that halothane directly reduces both the Ca^{2+} slow inward and Na^{+} fast inward currents.[87,88] All three contemporary volatile anesthetics depress the rate of depolarization of myocardial slow AP, presumably due to an effect on the Ca^{2+} slow inward current.[89-91] Furthermore, preliminary results indicate a depressant effect of these agents on the peak Ca^{2+} current in enzymatically dispersed ventricular and Purkinje fibers (fig. 14).[92] It has been shown that calcium channels are heterogeneous in various cell types, including those from cardiac tissue.[93] The two types of cardiac Ca^{2+} channels differ in time course and are called "T" and "L" for transient time course and long lasting, respectively. The current flowing through T channel is considerably smaller with a quick decay as compared to L-channel current. In the ventricular cell, T-channel current probably contributes little to Ca^{2+} influx. However, it may be significant for pacemaker depolarization and action potential initiation, which more critically depend on the inward T-channel current at more negative potentials.[93] Differential sensitivity of these channels to the calcium channel blockers is discussed later in this review.

The Ca^{2+} slow inward current is one of the currents involved in the genesis of abnormal forms of automatic-

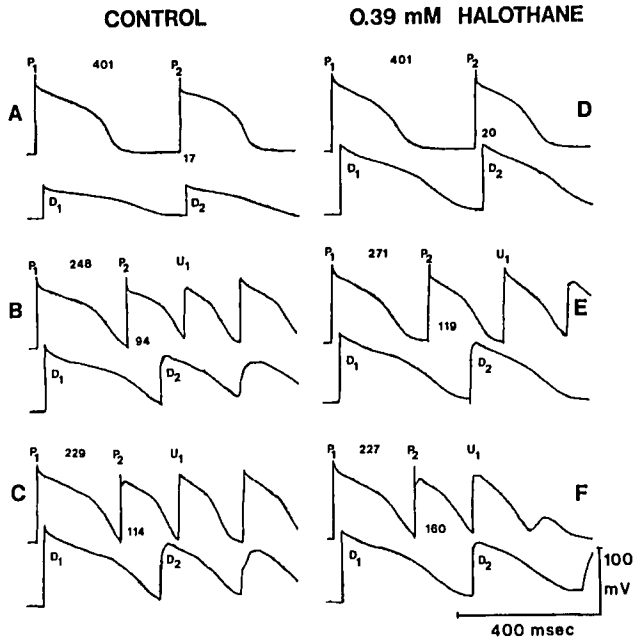

FIG. 12. Effects of halothane on the generation of unstimulated repetitive response (U1) in an infarction preparation. The top tracings in each panel are from the proximal fiber, and the bottom tracings are from the distal Purkinje fibers. *A, D:* Responses of single proximal (nonischemic) and distal (ischemic) fibers to a drive stimulus (P1, D1) and a subsequent late premature impulse (P2, D2) applied at a coupling interval of 401 ms. *B, E:* Latest premature impulse producing U1. *C, F:* Earliest premature impulse inducing U1. The repetitive response zone increased from a control "width" of 19 ms (248–229 ms, B–C) to 44 ms (271–227 ms, E–F) in the presence of halothane. (From reference 74, used with permission.)

ity.[7,17] It is possible that any of the contemporary volatile anesthetics oppose such activity by their depressant effects on the Ca^{2+} slow inward current. In contrast, while the mechanisms for DAD-induced triggered activity could involve the Ca^{2+} slow inward current, a transient inward current carried predominantly by Na^{+} is more likely involved.[3,8] The transient inward current is thought to be generated by a change in membrane conductance regulated by the intracellular Ca^{2+} concentration.[94] This elevated intracellular Ca^{2+} concentration may initiate an electrogenic Na-Ca exchange (3:1 ratio) resulting in a net inward current. For instance, DAD first appear or become larger during interventions known to increase intracellular Ca^{2+} (*e.g.*, digitalis, ischemia).[8,29] Thus, the potent volatile anesthetics might oppose the transient inward current and DAD-induced triggered activity (*e.g.*, Turner *et al.*[74]) by decreasing intracellular Ca^{2+} availability. This could be through inhibition of the Ca^{2+} slow inward current or by affecting Ca^{2+} release from the sarcoplasmic reticulum.[13]

Bosnjak *et al.* have examined anesthetic effects on intracellular Ca^{2+} availability by determining their effects on calcium transients and contractile force in guinea pig papillary muscle.[95,96] Representative findings for the effects of halothane, enflurane, and isoflurane are shown in figure 15. At least at low concentrations of the anesthetics, the decrease in the intracellular Ca^{2+} transient is consistent with reduced Ca^{2+} entry *via* the slow inward channel. At high concentrations, it appears that myocardial depression with isoflurane involves factors other than a reduction in the Ca^{2+} slow inward current, such as decreased affinity of troponin-C for Ca^{2+} or reduced myofibrillar responsiveness to Ca^{2+},[97] or depression of the sarcoplasmic reticulum.[91] These findings suggest that isoflurane has a less depressant effect on intracellular Ca^{2+} accumulation (hence, generation of the transient inward current—*vide supra*) than enflurane or halothane. This could mean that isoflurane might be shown less effective than enflurane and halothane against DAD-induced triggered activity.

Finally, in the study by Turner *et al.*,[74] halothane promoted re-entry. It did this by increasing regional differences in AP duration. The mechanism for increased AP

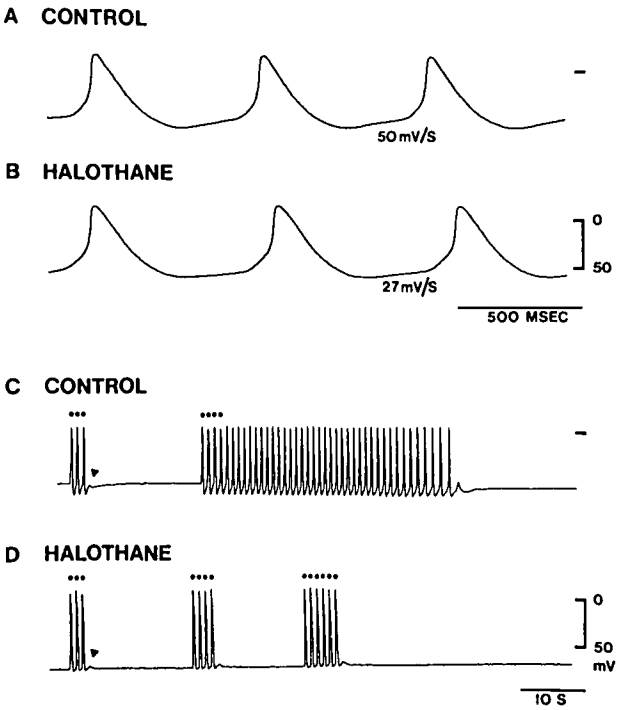

FIG. 13. Responses of single ischemic fibers to 0.39 mM halothane in two small infarction preparations. The upper panels (*A, B*) show reduction of the slope of spontaneous phase 4 diastolic depolarization by halothane (mV/s) in an ischemic Purkinje fiber with a low maximum diastolic potential. The lower panels (*C, D*) show abolition by halothane of triggered activity induced by extracellular stimuli in a fiber exhibiting delayed afterdepolarizations (*arrows*). The action potentials indicated by dots were initiated by stimuli applied at 1-s intervals. (From reference 74, used with permission.)

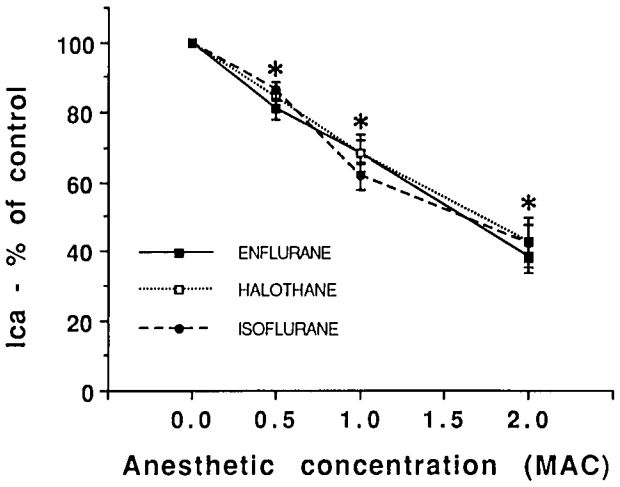

FIG. 14. Dose-dependent depression of peak calcium currents by all three anesthetics at three different doses in voltage-clamped ventricular cells. Whole-cell voltage clamp experiments were performed in freshly isolated canine ventricular cells obtained by enzymatic dissociation. The cells were voltage-clamped with patch pipettes at room temperature. Na^+ inward current was eliminated by replacing extracellular Na^+ with tetraethylammonium chloride. Outward K^+ current was eliminated by substituting cesium glutamate for K^+ in the pipette solution. The effects of all three inhalational anesthetics were tested in the same cardiac cell. Whole-cell calcium current was activated by depolarizing (200 ms pulse) the cell from a constant holding potential of −80 mV to the command (test) potential in 10-mV increments. In these cells, essentially the same magnitude of the I_{Ca} is obtained if the holding potential is held at −40 mV. Since only a long-lasting (*L*) current is activated from a holding potential of −40 mV, this is an indication that calcium *L* channel current is decreased in the presence of inhalational anesthetics. Asterisks indicate significant change in the I_{Ca} from the preceding anesthetic concentration.[92]

duration by halothane in ischemic fibers could be an effect on the Ca^{2+} slow inward current or K^+ repolarization currents. Shortening of the AP duration in nonischemic fibers may be due to an inhibitory effect of halothane on the Na^+ "window current."[43,44],†† This possibility is suggested by the results of preliminary work‡‡ in which the effects of halothane, tetrodotoxin, and veratridine were tested on the AP duration of Purkinje fibers, from two regions of the canine left ventricle. The results of this study suggest that regional differences in AP duration produced by halothane in normal Purkinje fibers, which are similar to those produced by lidocaine,[98] could be mediated by an effect of halothane on the Na^+ "window current."

There are no data for the effects of nitrous oxide (N_2O) on electrical properties of the heart, despite the widespread use of N_2O to supplement anesthesia with other agents. Nor are there reports of how N_2O might alter the cardiac electrophysiologic actions of other drugs, except that a recent report suggests that the addition of N_2O to narcotic-based or inhalation anesthesia can provoke AV junctional rhythms.[99] We offer no explanation for these observations in the absence of more complete data for the effects of anesthetic drugs on dominant and subsidiary pacemakers.

In summary, concerning the dysrhythmic potential of the contemporary volatile anesthetics, we suggest the following. First, with the possible exception of isoflurane, any of these agents appear conducive to bradycardia and AV conduction disturbances. This would be due to their direct depressant action on the slow response (SA and AV nodes) or depressed fast response (atrial or ventricular muscle, Purkinje fibers). Second, in depressed fibers (*e.g.*, with myocardial ischemia/infarction), halothane (possibly, enflurane, and isoflurane) is conducive to re-entrant excitation (increased temporal dispersion of refractoriness). In contrast, halothane (possibly enflurane and isoflurane) is expected to oppose abnormal automaticity and DAD-triggered sustained rhythmic activity. The latter effect might explain halothane's effectiveness against ouabain-induced ventricular dysrhythmias.[82] Third, there are no data for anesthetic effects on EAD or EAD-induced triggered automaticity. The latter may be the mechanism for

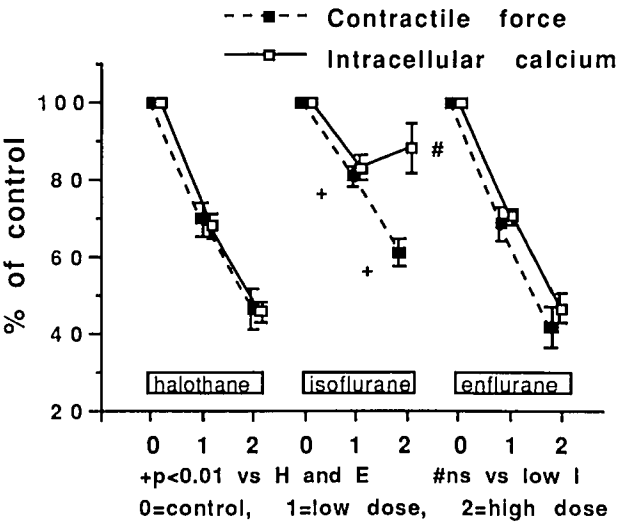

FIG. 15. The effects of 1 and 2 MAC halothane, isoflurane, and enflurane on the peak intracellular calcium transients and the peak contractile force in papillary muscle (N = 13) of the guinea pig. Data are shown mean ± SE.[96]

†† The Na^+ "window current" is a small TTX- and lidocaine-sensitive inward current that persists during the action potential plateau[45] (see also Colatsky T. Circ Res 50:17–27, 1982). The persistance of Na^+ current during the plateau may be due to peculiar Na^+ channel phenomena such as delayed opening and reopening or bursting rather than a second type of Na^+ channel distinct from the "fast" Na^+ channel.

‡‡ Turner LA, Bosnjak ZJ, Marijic J, Kampine JP. Sodium actions of halothane on Purkinje fibers. 9th World Congress of Anaesthesiologists, Washington D.C., May 1988.

torsades de pointes tachycardia in patients with idiopathic or acquired long QT syndrome.[100] We note that halothane, enflurane, and isoflurane have been shown to prolong the QTc interval (QT interval corrected for heart rate) independent of changes in autonomic tone in chronically instrumented dogs.[101] Whether any of the anesthetics can be shown to affect EAD-induced triggered automaticity remains to be seen.

Local Anesthetics. A number of clinical reports in the mid to late 1970s and early 1980s documented cases of sudden cardiovascular (CV) collapse with nearly simultaneous seizures, but not antecedent hypoxia following inadvertent intravascular injections of typical clinical doses of bupivacaine or etidocaine.[102–108] Many of the cases were parturients and there was a rather high incidence of fatalities, apparently because CV collapse was resistant to conventional methods for resuscitation. These reports stimulated extensive animal investigation that has increased our understanding of mechanisms for cardiotoxicity with local anesthetics.

In adult sheep, the dose of bupivacaine (iv infusion) necessary to cause CV collapse in the presence of hypoxia and acidosis was about half that required for lidocaine.[109] Additionally, the mean dose of bupivacaine causing cardiovascular collapse was significantly lower in pregnant ewes (5 ± 1 mg/kg) than in nonpregnant ewes (9 ± 1 mg/kg).[109] In normocarbic cats, subconvulsant doses of bupivacaine produced nodal and ventricular dysrhythmias, whereas convulsant doses of lidocaine did not.[110] Cardiotoxicity with bupivacaine in dogs included increased atrial conduction time and AV nodal refractoriness, decreased left ventricular contractility, ventricular tachydysrhythmias, and electromechanical dissociation.[111] In isolated rat hearts, bupivacaine was more potent than lidocaine in decreasing the atrial rate and delaying atrioventricular conduction.[112] In isolated guinea pig hearts, bupivacaine was 6–10 times more potent than lidocaine in decreasing heart rate, contractility, and myocardial oxygen consumption.[113] In *in vitro* studies, acidosis and hypoxia enhanced the bradycardic effects of bupivacaine more than lidocaine.[114–116] Additionally, hypercapnic acidosis and hypoxia slowed SA node rate in neonatal and adult guinea pig hearts, the effect of which was additive to that produced by lidocaine and bupivacaine.[114] However, neither hypoxia nor acidosis alone appear sufficient to alter local anesthetic-induced depression.[115] Finally, combined hypoxia and acidosis caused a greater reduction in sinus rate in neonatal compared to adult guinea pig hearts.[116]

Kotelko *et al.* examined the cardiovascular effects of equipotent doses of lidocaine and bupivacaine for neural blockade following intravascular injection into chronically instrumented sheep.[117] While animals convulsed with both drugs, serious dysrhythmias were seen only with bupivacaine, and transient ST-T changes or sinus tachycardia with lidocaine. In a subsequent study by this same group (also in sheep), bupivacaine cardiotoxicity was enhanced by hypercarbia, acidosis, and hypoxia.[118] Thus, evidence from both *in vitro* and *in vivo* animal studies suggests that hypoxia and acidosis, which could result from CNS and circulatory depression with bupivacaine, would increase the likelihood of serious dysrhythmias following inadvertent intravascular injection of bupivacaine.

The contrasting dysrhythmic effects of bupivacaine and lidocaine can be explained by the modulated receptor hypothesis.[119,120] According to this hypothesis, different local anesthetics (also, class 1 antidysrhythmic drugs[120]) block Na^+ channels by binding to a common receptor site. Bupivacaine, and possibly lidocaine, may also exert a weak Ca^{2+} channel blocking action, based on their ability to depress myocardial slow APs.[121,122] Drug affinity for the Na^+ channel receptor site is determined by the state of the channel, which could be resting, open, or, inactivated. Rate constants defining association and dissociation of a drug from its receptors are different for each channel state and different drugs. In ventricular myocytes, Na^+ channels are blocked by local anesthetics in the open and inactivated states; the resting state displays the least affinity for local anesthetics.[120] Lidocaine, a smaller and less lipid soluble molecule than bupivacaine, rapidly blocks Na^+ channels in both open and inactivated states. Lidocaine, compared to bupivacaine, binds more loosely and exhibits less block of the Na^+ channels at faster heart rates (use-dependence). Bupivacaine has also been shown to block Na^+ channels in the inactivated state much more avidly than lidocaine, and has a low affinity for open and rested Na^+ channels.[119] Because bupivacaine is so tightly bound to inactivated Na^+ channels, the half-life for recovery from block during the resting state is much longer. Consequently, at fast heart rates, Na^+ channel block by bupivacaine can accumulate. This could explain the greater occurrence of cardiac conduction and rhythm disturbances with bupivacaine at doses that produce comparable neurotoxic symptoms to lidocaine. Therefore, increased potency of bupivacaine compared to lidocaine at physiologic heart rates may be due to its higher affinity for inactivated cardiac Na^+ channels, as well as to qualitative difference in its kinetics of interaction with these channels.

Two recent studies have examined electrophysiologic mechanisms for dysrhythmias with bupivacaine[124,125] Wheeler *et al.* determined the effects of toxic levels of bupivacaine and lidocaine in an isolated preparation (canine) that included the SA node and right atrium, and in some cases the AV node and interventricular septum as well.[124] In the absence of dysrhythmias, spontaneous rate was similarly depressed by increasing doses of bupivacaine and lidocaine. The most prominent dysrhythmia with either drug was SA block, with bupivacaine more potent (15:1). SA block could be reversed with norepinephrine.

Sinus dysrhythmia, retrograde conduction block and irregular AV nodal rhythms were observed with both drugs at concentrations similar to those that produced SA block. Records obtained from atria that retained a regular rate and rhythm during local anesthetic perfusion are illustrated in figure 16. These illustrate a variety of compound AP contours that could reflect varying dependence of the AP upstrokes of SA and transitional cells along the crista terminalis on the Na^+ fast inward current.[124] Compound AP contours could also be due to electrotonic effects following excitation of adjacent slow-response or depressed fast-response fibers. Finally, spontaneous AV nodal and septal activity were typically present during atrial quiescence due to SA block, and septal tissue could be driven during atrial quiescence. The latter finding, if clinically applicable, suggests ventricular pacing might be effective for temporary rate support during severe bradycardia or cardiac asystole due to local anesthetic toxicity.

Moller and Covino evaluated the cardiac electrophysiologic effects of bupivacaine and lidocaine in a rabbit Purkinje fiber ventricular muscle preparation.[125] Of interest were electrophysiologic alterations that might contribute to re-entrant dysrhythmias. Two protocols were used: one to determine the effect of increasing level of the two drugs during prolonged exposure, and the other to model the clinical situation following inadvertent intravascular injection. High concentrations of bupivacaine (not lidocaine) reduced MDP in Purkinje fibers, but not

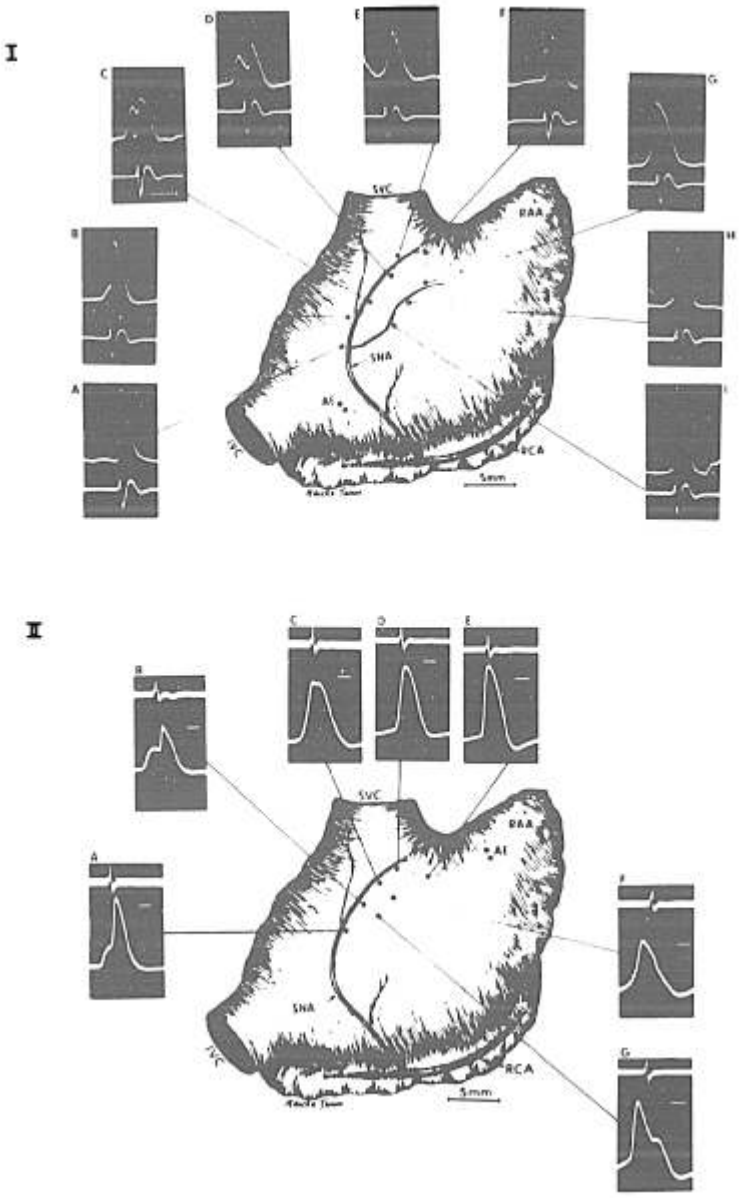

FIG. 16. Action potentials recorded along the crista terminalis near sinus node in two spontaneously beating perfused right atria. *I:* Lidocaine 25 μg/ml. The lower traces in these panels represent the atrial bipolar electrogram (AE). *II:* Bupivacaine 2.5 μg/ml. The upper traces in these panels are the AE.

SVC = superior vena cava; RCA = right coronary artery; SNA = sinus node artery; RAA = right atrial appendage. The horizontal bar in each panel marks 0 mV. (From reference 124, used with permission.)

ventricular muscle. Both bupivacaine and lidocaine reduced AP upstroke velocity and amplitude in Purkinje and ventricular muscle fibers, but reductions were greater with bupivacaine. Both drugs produced comparable shortening of the AP duration (APD) and increases in effective refractory period to APD ratio. However, while Purkinje fiber to ventricular muscle (P-M) conduction time was increased by both local anesthetics, bupivacaine (3 and 5 μg/ml) produced P-M block in 90–100% of preparations, while P-M block occurred in only one preparation with lidocaine (20 μg/ml). Finally, recovery of excitability and return to control values for P-M conduction time with bupivacaine took four to eight times longer than with lidocaine. These alterations in electrical properties of Purkinje and ventricular muscle fibers were interpreted by Moller and Covino as conducive to re-entrant ventricular dysrhythmias.

Two studies have tested the hypothesis that a central, neurogenic action also contributes to local anesthetic cardiotoxicity.[126,127] Heavner[126] injected saline and local anesthetics (bupivacaine, lidocaine, procaine) at approximately equipotent neural blocking doses into the right lateral cerebral ventricle of chronically instrumented cats. Additional cats were given iv bupivacaine (1.1 and 1.4 mg/kg) to determine whether electrocardiographic ECG changes following intracerebroventricular (ICV) infusion of bupivacaine were due to a direct cardiac action following systemic absorption. No dysrhythmias (sinus tachycardia excluded) were observed after the ICV infusion of saline or with iv bupivacaine. One of six (lidocaine, cumulative dose to 9.6 mg), five of seven (procaine, cumulative dose to 9.6 mg), and ten of ten cats (bupivacaine, cumulative dose to 0.7 mg) developed ventricular dysrhythmias following ICV infusion. Heavner speculated on the similarity between these CNS effects of local anesthetics and digitalis, and suggested that a common neuroexcitatory mechanism could involve central adrenergic stimulation.[126]

Thomas *et al.* considered concomitant cardiovascular (CV) and CNS toxicity with bupivacaine or lidocaine.[127] Equal molar amounts of either drug were injected into one of three discrete, medullary vasomotor centers in adult chloral hydrate-anesthetized rats. At any of these areas, both local anesthetics produced bradycardia and hypotension. In addition, when injected at the nucleus tractus solitarius, ventricular dysrhythmias were observed in 55% of animals. In all animals with lidocaine, dysrhythmias spontaneously reverted to sinus rhythm. With bupivacaine, dysrhythmias reverted to sinus rhythm in one-half of the animals, but were fatal in others. Several explanations were offered for these findings: 1) the modulated receptor hypothesis (*vide supra*) explains both CV and CNS toxicity with the local anesthetics; 2) convulsions with the local anesthetics might alter blood-brain barrier permeability, and enhance their uptake into CV regulatory centers; 3) the antidysrhythmic action of lidocaine might oppose centrally stimulated dysrhythmias due to lidocaine toxicity; and 4) greater accumulation of bupivacaine in the brain during convulsions might explain the nearly simultaneous CNS and CV toxicity.

Controversy exists regarding the management of bupivacaine or other local anesthetic cardiotoxicity. Without question, avoidance of intravascular injection and limiting the dose of agents used are the most effective preventive measures. Diazepam has been suggested as a preventive or treatment measure for CNS and CV toxicity with bupivacaine,§§ and also lidocaine.[128,129] Gregg *et al.*[130] examined the effect of diazepam on bupivacaine-induced cardiotoxicity in chloral hydrate-anesthetized rats. They found a higher incidence of toxicity (ventricular and supraventricular tachydysrhythmias) in rats pretreated with diazepam. Furthermore, in rats pretreated with diazepam or its vehicle, there was significantly worse respiratory and metabolic acidosis. Finally, in no treatment group did hypoxia appear to be a factor in dysrhythmogenesis. The conflicting results of Gregg's group may be due to species' differences, an effect of chloral hydrate, or their criteria for toxicity.[130] Regardless, none of the forementioned studies establish that diazepam (or other benzodiazepines) are effective against or will prevent local anesthetic cardiotoxicity. A dose-response relationship will have to be established, and studies cannot be confounded by the presence of other drugs.

Two reports from Kasten and Martin concern the management of cardiotoxicity following massive doses of bupivacaine.[131,132] The first showed that bretylium was effective against inducible ventricular tachycardia in bupivacaine-treated dogs.[131] In the second, protocols for resuscitation following bupivacaine cardiotoxicity were examined.[132] Resuscitation included open-chest cardiac massage, 100% O_2, and bicarbonate for any acidosis. Cardiovascular collapse following bupivacaine (cumulative dose 67 ± 24 mg/kg) occurred either as sustained ventricular tachycardia or, more commonly, bradycardia with electromechanical dissociation. All animals could be resuscitated "easily and consistently" with bretylium (ventricular tachycardia) or epinephrine and atropine (electromechanical dissociation). While the doses of epinephrine and atropine used by Kasten and Martin[132] for resuscitation were much greater than those recommended for cardiopulmonary resuscitation,[133] one recent report suggests that higher-than-recommended doses of epinephrine (4–5 mg over 2 min *vs.* 0.5–1.0 mg over 5 min) may be effective for some resuscitations.[134]

§§ deJong RH, Davis NL. Treating bupivacaine arrhythmias: Preliminary report. Reg Anesth 6:99–103, 1981.

Intravenous Anesthetics and Adjuncts. Thiopental has little effect on RMP and AP amplitude in ventricular septal muscle.[135] It increases AP duration and decreases the height of the AP plateau and the rate of depolarization during phase 0.[135] In addition, thiopental prolongs the AP and reduces the rate of rise of slow channel-mediated AP in canine papillary muscle.[136] These results have been interpreted to indicate that thiopental reduces the Ca^{2+} slow inward current, and possibly K^+ permeability. Very high concentrations of thiopental severely depress TMP, reduce spontaneous rate and resting AP amplitude, increase AP duration, and ultimately abolish the AP.[137] Despite its overall depressant effect, thiopental had an initial, but transient, stimulatory effect on the above-mentioned AP parameters.[137]

In rabbit papillary muscle, intracellular Ca^{2+} influences thiopental-induced spontaneous activity.[138] It was suggested that spontaneous activity is caused by a mechanism similar to that responsible for delayed DAD.[138] Further, it was hypothesized that despite its negative inotropic effect and inhibition of slow APs, thiopental permits accumulation of Ca^{2+} in the sarcoplasmic reticulum at high rates of stimulation, which could lead to increased influx of extracellular Ca^{2+}.[138] Despite direct reduction of Ca^{2+} influx by thiopental *via* the Ca^{2+} slow inward current, the amount of intracellular Ca^{2+} available for contraction is not markedly diminished.[139] One additional report also suggests that thiopental may induce DAD.[140] If thiopental does induce DAD, then this may explain in part its reported effect (thiamylal as well[141]) to potentiate epinephrine-induced, ventricular dysrhythmias with cyclopropane,[142] halothane,[143] and enflurane and isoflurane.[144]

Fentanyl is thought to reduce heart rate *via* a central mechanism that leads to decreased sympathetic and increased vagal efferent tone.[145] In animals, about 90% of the bradycardia seen with fentanyl use resulted from enhanced vagal activity, and 10% from decreased sympathetic efferent tone.[146] In this respect, fentanyl is similar to other opiates, except meperidine, that can cause tachycardia.[147] Tachycardia with meperidine may be related to its structural similarity to atropine or to reflex-caused increase in heart rate with hypotension. The centrally mediated increase in vagal tone produced by fentanyl can be reversed by naloxone, which implicates the involvement of central opiate receptors as mediators for this effect.[148] Premedication with atropine is expected to reduce bradycardia with any of the opiates. In addition to indirect actions, fentanyl directly reduces SA node rate, potentiates the action of ACh, and may inhibit acetylcholinesterase activity.[149]

Morphine may also have direct negative chronotropic (SA node) and dromotropic (AV node) actions.[150] These actions may, in part, explain reduced vulnerability to ventricular fibrillation with morphine.[150] In addition to direct effects, it was demonstrated that endogenous endorphins can attenuate β-adrenergic stimulation and possibly contribute to reduced ventricular dysrhythmias.[151] Based on similar actions to morphine, a reduced incidence of ventricular dysrhythmias following tracheal intubation in adults and children given fentanyl[152] may be due to fentanyl's central vagal actions, or to attenuation of sympathetic effects.

Droperidol, which may be used in fixed combination with fentanyl (Innovar® Janssen, Piscataway, NJ), has *in vitro* electrophysiologic properties similar to quinidine and procainamide.[153] Droperidol prevents epinephrine-halothane induced ventricular tachycardia and ventricular fibrillation following coronary artery ligation in cats.[154] Finally, droperidol (220–600 μg/kg) with fentanyl (30–50 μg/kg) increases both antegrade and retrograde refractoriness in the accessory pathway of patients with Wolff-Parkinson-White syndrome.[155]

Succinylcholine (SCh) can be associated with all manner of dysrhythmias, which could be due to its direct or indirect actions, or other factors (airway manipulation under light anesthesia). The mechanism for bradycardia and dysrhythmias with SCh[156,157] is not established. Bradycardia after a single dose of SCh most likely results from stimulation of cardiac muscarinic receptors, which are most prominent in the SA and AV nodes. SCh also stimulates presynaptic nicotinic receptors, thereby causing the release of norepinephrine. The net effect could be a small and variable increase or decrease in heart rate.[158] Other drugs used during the course of anesthesia could alter or intensify the action of SCh.[159,160] Enhanced vagal activity is also likely involved in bradysrhythmias following repeat doses of SCh.[156,161,162] While Schoenstadt and Whitcher[163] have suggested that choline produced by hydrolysis of the initial dose of SCh "sensitized" the heart to repeat doses of SCh, in a more recent study, repeat doses of SCh produced only an increase in heart rate.[164] Concerning a mechanism for bradycardia and dysrhythmias with repeat doses of SCh, Nigrovic has suggested the following.[158] Activation by SCh of presynaptic nicotinic receptors causes the release of norepinephrine. Activation of these, as well as postsynaptic muscarinic receptors following a single dose of SCh, results in opposing actions, with little effect on heart rate. With a repeat dose of SCh, cardiac muscarinic receptors would be stimulated but presynaptic receptors would remain desensitized, with bradycardia the result. We question why the two receptors should be so differently affected. Nevertheless, and regardless of the mechanism for SCh-induced bradycardia, protection is likely afforded by pretreatment with iv atropine. Drugs such as thiopental[163,165] or intramuscular atropine[166] should not be relied upon for protection.

It is well established that susceptible patients may be at risk for exaggerated K^+ release following SCh.[167] If of

sufficient magnitude, this could be the cause for severe ventricular dysrhythmias. Predisposing conditions include extensive burns, peritonitis, massive trauma, closed-head injury, ruptured cerebral aneurysms, spinal cord injury, and possibly renal failure.[167-169] The vulnerability to exaggerated K^+ release might reflect a proliferation of extrajunctional cholinergic receptors that are not normally present in large numbers in muscle because their synthesis is suppressed by neural activity.[170] A number of studies, both in animals and man, have attempted to establish the time interval for increased susceptibility to exaggerated K^+ release following SCh and reliable measures to prevent such release.[171-181] After careful consideration of these, we are of the opinion that neither the time interval for increased susceptibility or reliable preventive measures have been established. Therefore, it would seem more prudent to avoid SCh altogether in patients that might be susceptible to exaggerated K^+ release.

There are no well-established, strong dysrhythmic associations for any of the nondepolarizing muscle relaxants (NDMR). All are competitive antagonists at postjunctional cholinergic receptors at the motor end plate. Although these receptors have certain features in common with nicotinic receptors located in autonomic ganglia, they are not identical.[182] Thus, it should not be surprising that NDMR, which vary in potency as neuromuscular blockers, also vary in potency as ganglionic blockers. In addition to ganglionic blockade (tubocurarine-moderate, metocurine-modest), potentially adverse CV effects may result from block of cardiac muscarinic receptors (gallamine-moderate, pancuronium-modest) or drug-induced release of histamine (tubocurarine-moderate, metocurine-modest, atracurium-slight).[170] Vecuronium at clinical dose ranges should not produce ganglionic blockade, histamine release, or cardiac muscarinic blockade.[170] With the exception of pancuronium, there are no reports of the electrophysiologic actions of any of the NDMR. An increase in heart rate with gallamine or pancuronium likely involves block of the cardiac muscarinic receptors,[183,184] but there may be a direct blocking action on the vagus itself.[185] The latter was not thought to be a ganglionic blocking action or blockade of axonal conduction, but rather an affect at the pre- or postganglionic nerve terminal.[185] These vagolytic actions of gallamine and pancuronium should also facilitate AV nodal conduction, which has been confirmed for pancuronium in dogs anesthetized with halothane.[186]

Jacobs *et al.* have examined the *in vitro* cardiac electrophysiologic effects of pancuronium.[187] Recordings were made from quiescent and spontaneously active papillary muscle fibers during superfusion with pancuronium, pancuronium with epinephrine, verapamil, or propranolol. Pancuronium prolonged AP duration and increased resting potential, AP magnitude, and the rate of rise of phase 0 of the AP. These effects are consistent with the nonspecific effects of pancuronium on the Na^+, Ca^{2+}, and K^+ currents, but their physiologic significance is uncertain.[187] Additionally, pancuronium induced automaticity (normal) in 12% of fibers. With epinephrine, normal or abnormal forms of automaticity were induced in 80% of fibers. In three driven fibers with a reduced level of membrane potential, there were DAD and what appear to be triggered AP. Abnormal automaticity and DAD could be abolished with verapamil, but not consistently with propranolol. Jacobs *et al.* speculated that these findings might explain certain clinical instances of tachycardia and ventricular dysrhythmias with pancuronium.[187] In light of the above, it is perhaps surprising to note that pancuronium has been reported not to affect the dose of epinephrine for ventricular dysrhythmias with halothane.[188]

Finally, a number of recent clinical reports indicate that vecuronium, particularly with large doses of opiates or reflex vagal stimulation, may be associated with severe bradycardia and even asystole.[189-194] In patients about to undergo coronary artery surgery, Inoue *et al.* found that the combination of etomidate, vecuronium, and a small dose of fentanyl led to the greatest reduction in heart rate.[195] When thiopental was substituted for etomidate, the reduction in heart rate was significantly less. Bradycardia responded to atropine, but often after a short period (5–10 min) of AV junctional rhythm.[195]

Drug Interactions. The ability of some anesthetic agents to reduce the dose of catecholamines for cardiac dysrhythmias (compared to awake) is a classic example of an adverse drug interaction.[3] This phenomenon, still widely but inaccurately[4,196,197] referred to as "sensitization," has been the subject of numerous case reports and extensive investigations since the pioneering work in 1895 of Oliver and Shafer.[198] The interaction of older anesthetics with catecholamines has been reviewed by Katz *et al.*[4,196,197] The estimated dose of epinephrine (submucosal injection) required to produce ventricular dysrhythmias in 50% of patients (ED_{50}) was found by Johnston *et al.* to be 2.1 μg/kg for halothane, 6.7 μg/kg for isoflurane, and 10.9 μg/kg for enflurane.[199] However, with enflurane there was a wide variation in patient response to epinephrine, and the dose-response curve for epinephrine dysrhythmias with enflurane was significantly flatter than with other agents. This latter result with enflurane was confirmed in a subsequent study from the same institution.[200] Finally, lidocaine (0.5%) appeared to afford protection with both halothane[199] and enflurane.[200] These studies[201,202] do not establish the dose of epinephrine for ventricular dysrhythmias in anesthetized patients, nor do they suggest a safe dose of epinephrine. To be considered are: 1) variable systemic absorption following submucosal injection; 2) the absence of measured plasma catecholamine levels; and 3) the relatively limited number and select group of patients.

Katz *et al.* have suggested that a dose of 1.0 μg/kg of epinephrine should be safe with halothane.[201] The dysrhythmogenic dose of epinephrine in children may be higher.[202] It appears that as much as 10 μg/kg of epinephrine may be injected subcutaneously without the risk of ventricular dysrhythmias in normo- or hypocarbic children anesthetized with halothane, and without congenital heart disease.[202]

Based almost entirely on results of animal studies, there are many modifying factors that can affect the interaction of anesthetics with catecholamines. Among anesthetic induction agents, thiopental,[141,143] thiamylal,[141] and ketamine[203] have been shown to increase the likelihood of epinephrine-dysrhythmias with halothane. The thiopental effect extends to enflurane and isoflurane,[144] and persists for up to 4 h following a single iv induction dose.[143,144] No explanation has been offered for this long-lasting action of thiopental. We speculate that it might be due to an effect of residual thiopental that has accumulated in myocardium and/or the CNS. Among the local anesthetics only cocaine[203] increases the likelihood of epinephrine dysrhythmias, presumably by blocking intraneuronal reuptake of catecholamines. Drugs such as the tricyclic antidepressants and MAO inhibitors, which similarly affect catecholamine reuptake or biodegradation process, may also increase the likelihood of the anesthetic-epinephrine interaction. However, at least with imipramine, this is likely to be so following acute,[204] but not chronic[205] administration. Nitrous oxide favors the development of epinephrine-dysrhythmias in halothane-anesthetized dogs.[206] Acute,[203,207,208] but not chronic[208] aminophylline facilitates halothane-epinephrine dysrhythmias in dogs. A critical increase in arterial pressure or heart rate is required for epinephrine-induced ventricular bigeminy in vagotomized dogs anesthetized with halothane.[209] The likelihood of epinephrine dysrhythmias with halothane or isoflurane may be increased by simultaneously administered vasopressors.[210] Fasting has been shown to reduce the dose of epinephrine for ventricular dysrhythmias in halothane-anesthetized rats.[211]

Lidocaine, bupivacaine, and etidocaine at several dose levels afforded about equal protection against epinephrine dysrhythmias in halothane-anesthetized dogs.[212] Metoprolol (β_1-selective),[213] prazosin (α_1-selective),[213] and propranolol (β nonselective)[214] oppose epinephrine dysrhythmias in halothane-anesthetized dogs. The nonselective α- and β-adrenergic blockers were also effective against epinephrine dysrhythmias with cyclopropane, but β blockers had a more consistent and specific effect.[4] Verapamil[215] and diltiazem[216] increase the dose of epinephrine for ventricular dysrhythmias with halothane. Clinical experience suggests that epinephrine-anesthetic dysrhythmias are less likely to occur in children.[202,217,218] Finally, several drugs used during anesthesia have been experimentally shown not to affect epinephrine dysrhythmias with halothane. At present, these include pancuronium,[188] d-tubocurarine,[188] and etomidate.[219] Neither do exogenous prostaglandins (PGE, and $PGF_2\alpha$) or inhibitors of prostaglandin synthesis (indomethacin) affect the dose of epinephrine for dysrhythmias with halothane.[207]

Studies of adrenergic mechanisms for catecholamine-anesthetic dysrhythmias have been flawed by the use of nonselective α- and β-adrenergic blocking drugs.[198,214,220] While such experimentation supports the widespread clinical use of β-adrenergic blockers for suppressing hypertensive episodes and dysrhythmias in response to catecholamines during anesthesia,[221,222] it should not be interpreted as suggesting the mechanism for catecholamine-anesthetic dysrhythmias. A nonselective β-blocker would block the presynaptic β_2 receptor, which when stimulated by epinephrine facilitates the release of norepinephrine.[223] Similarly, a nonselective α blocker would block the presynaptic α_2 receptor, which has an autoinhibitory effect on the release of norepinephrine.[224] Certainly, an adrenergic mechanism for anesthetic-catecholamine dysrhythmias must consider the contribution of each of the subtypes of adrenoreceptors to dysrhythmia formation.[213] Maze and Smith examined the relative contributions of the α_1- and β_1-adrenergic receptors to the genesis of halothane-epinephrine ventricular dysrhythmias in dogs.[213] The effect of prazosin (α_1-selective blocker) was significantly greater than that of metoprolol (β_1-selective blocker) in increasing the dysrhythmic dose of epinephrine. Additionally, the increase in the epinephrine dysrhythmia threshold with prazosin could not be specifically ascribed to a blood pressure-lowering effect, since sodium nitroprusside had no effect on the dysrhythmic epinephrine dose determined without adrenergic blockers. This suggests that while both α_1 and β_1 adrenoreceptors are important for epinephrine-halothane ventricular dysrhythmias, the α_1 adrenoreceptors might be more involved. Other experiments by this same group demonstrated a good correlation between the dysrhythmogenic dose of epinephrine and α-adrenergic, but not β-adrenergic responsiveness,[225] as well as correlation between increasing α_1-adrenergic blockade (droperidol, doxazosin) and epinephrine-dysrhythmia thresholds in halothane-anesthetized dogs.[226] Maze *et al.* speculated that the antidysrhythmic action of droperidol or doxazosin was on the basis of blockade of myocardial α_1-adrenergic receptors.[226] In a companion editorial to this report, Dresel[227] cautioned that while cardiac α_1 stimulation may be involved with epinephrine-induced dysrhythmias with halothane alone, this might not be the case in other models for anesthetic-epinephrine dysrhythmias, especially those in which thiopental was used for the induction of anesthesia.[141-144]

Hyashi *et al.* have examined the role of α- and β-adrenoreceptors with epinephrine dysrhythmias during halothane or pentobarbital anesthesia in dogs.[228] Isopro-

terenol or phenylephrine (up to 4 and 200 μg/kg, respectively) failed to induce dysrhythmias with either anesthetic. However, with halothane there was a synergistic, dysrhythmic action between isoproterenol and phenylephrine. Furthermore, at a systolic pressure of 140 mmHg, the dysrhythmic dose of isoproterenol in the presence of phenylephrine was significantly lower than in the presence of angiotensin II (pressor effect not mediated by α_1 receptors). At systolic pressures of 150 mmHg or higher, there was no significant difference between the dysrhythmic dose of isoproterenol in the presence of phenylephrine or angiotensin II. Finally, increased heart rate *per se* did not affect the dysrhythmogenic interaction between isoproterenol and phenylephrine. These results suggest that the α_1 receptors may contribute to dysrhythmias at low levels of systolic blood pressure (140 mmHg), but not at higher levels.

In summary, work to date concerning the catecholamine-anesthetic interaction has been largely descriptive and focused on autonomic involvement, with little attention paid to cellular electrophysiologic mechanisms. Given our increased understanding of these mechanisms, as well as improved technology to study their basis (voltage[229] and patch clamp[230] methods), it should be possible to determine cellular and subcellular mechanisms for "sensitization" with anesthetics.

Other drug interactions that may be the cause for dysrhythmias during anesthesia include those accompanied by the release of histamine and other vasoactive substances, and involving calcium channel and β-adrenergic blockers, or amiodarone. While digitalis may be a cause for dysrhythmias, it has no special dysrhythmic associations with any of the contemporary volatile anesthetics; in fact, anesthetics may oppose digitalis-induced dysrhythmias.[82] Histamine is among the chemical mediators released by mast-cell degranulation during anaphylaxis and with anaphylactoid reactions. Also released are prostaglandin D_2 and leukotrienes,[231] although their involvement with dysrhythmias accompanying anaphylactic or anaphylactoid reactions is unknown. Histamine can by itself produce dysrhythmias.[232,233] Possibly, this effect of histamine involves stimulation of adenylate cyclase,[233] which would enhance Ca^{2+} entry into the cell, as well as Ca^{2+} uptake by the sarcoplasmic reticulum. Until recently, there have been no studies of dysrhythmic interactions between histamine and any of the anesthetics. Stowe *et al.* compared the cardiac effects of histamine and epinephrine during exposure to halothane isolated perfused guinea pig hearts.[234] Alone, histamine increased sinus rate and atrial-septal conduction time (ASCT). Halothane caused dose-dependent depression of sinus rate, prolonged ASCT and intraventricular conduction time (IVCT), and produced AV block with junctional bradycardia. Halothane antagonized the effects of histamine on sinus rate, but enhanced those of histamine on ASCT. Histamine with halothane greatly increased the incidence of junctional tachycardia with AV dissociation (histamine: 0%; histamine plus halothane: 48%). Epinephrine, similar to histamine, increased sinus rate. Unlike histamine, it did not increase ASCT. Halothane antagonized the inotropic and chronotropic effects of epinephrine, but increased the incidence of ventricular tachycardia (6–28%) and premature ventricular beats (0–40%) compared to epinephrine alone. Finally, histamine with epinephrine, halothane with epinephrine, and halothane with epinephrine and histamine were more dysrhythmogenic (about equally so) than any drug alone. However, the types and incidence of specific rhythm disturbances varied among these various drug combinations. If these findings apply to man, there appears to be some potential for ventricular dysrhythmias when epinephrine is used to treat anaphylactic/anaphylactoid reactions during halothane anesthesia.

Calcium channel blockers (CCB: verapamil, diltiazem, nifedipine) do not directly antagonize the effects of Ca^{2+}; rather they inhibit the entry of Ca^{2+} into the cell or its mobilization from intracellular stores.[235] The effect of a CCB on AV nodal conduction or SA rate appears to be dependent in part on whether the agent delays recovery of activation of the slow (Ca^{2+}) channel.[235,236] Although nifedipine reduces the Ca^{2+} slow inward current in a dose-dependent manner, it does not affect the rate of recovery of the Ca^{2+} channel.[237] Hence, channel blockade by nifedipine and related dihydropyridines exhibits little dependence on heart rate (use-dependence).[235,238,¶¶] Con-

¶¶ There are currently believed to be a number of different types of voltage-dependent Ca^{2+} channels.[239] The best characterized subtypes are termed *L* (long lasting, large current), *N* (neurally located), and *T* (transient, tiny current), based on different electrophysiologic behavior and different drug sensitivity.[93,240–242] Only the *L*-type channels are inhibited by the CCB.[239] Tissue sensitivity to the CCB is quite variable, and the effectiveness of the CCB is related to the dependency of the tissue on the influx of Ca^{2+} and binding affinity of the drug.[239] The CCB are thought to bind with highest affinity to channels in the inactivated state. The voltage-dependency of the CCB is well known, and inhibition of the Ca^{2+} current is much greater when cells are depolarized. The binding constants for the CCB can increase when the cells are depolarized and the Ca^{2+} channel favors an inactivated state. Because the resting membrane potential (hence, percentage of inactivated channels) differs widely among cardiac fibers, the sensitivity to drugs also varies. Use dependence, which also contributes to tissue selectivity, means that inhibition of Ca^{2+} channels can vary with the frequency of stimulation, due to incomplete recovery of the channels from the inactivated state at fast stimulation rates (similar to Na channels). Tissues with low levels of membrane potential (*e.g.*, SA and AV node cells, depressed fast response fibers) that strongly rely on extracellular Ca^{2+} for normal function are most sensitive to the CCB. While the aforementioned factors account for selective CCB action, other factors (*e.g.*, different kinetic and conductive properties of the *L*-type channels in various tissues) may also be important.[239] In addition, while the CCB (diltiazem, nifedipine, verapamil) all bind to *L*-type channels, their structural differences probably account for the fact that they bind to different recognition sites on the α_1 subunit of the *L*-type Ca^{2+}

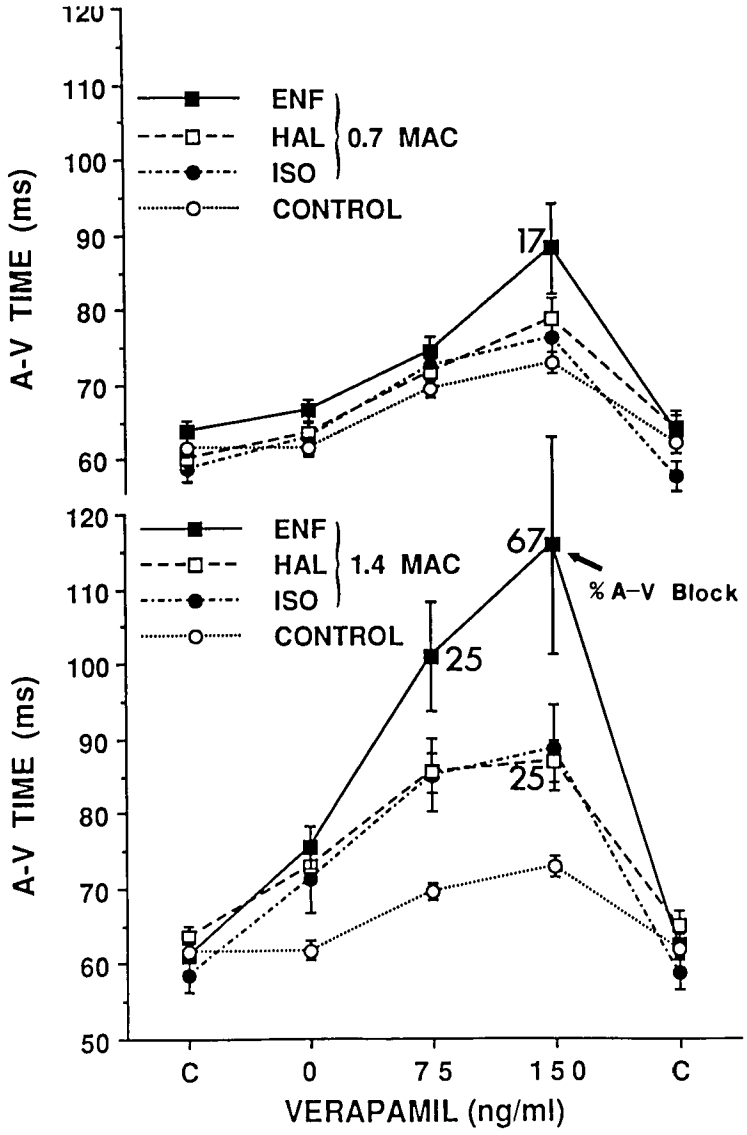

FIG. 17. Interactive effects of verapamil and anesthetics on atrioventricular (AV) conduction time. Numbers indicated the % of animals with AV block. N = 12 for each anesthetic group at both anesthetic levels. ISO = isoflurane; ENF = enflurane; HAL = halothane; MAC = minimum alveolar concentration; C = control; 0 = anesthetic alone. (From reference 258, used with permission.)

sequently, under clinical circumstances, nifedipine should not affect AV node conduction or reduce SA rate. Indeed, due to its blood pressure-lowering effect, there may be a baroreflex-mediated decrease in AV node conduction time and an increase in SA rate. Verapamil reduces the magnitude of the Ca^{2+} slow inward current, and also decreases the rate of recovery of the slow channel.[235,243] In addition, channel blockade caused by verapamil (to a lesser extent, diltiazem) is use dependent.[235] Heart block and dysrhythmias (sinus bradycardia/arrest/block, escape rhythms) with verapamil or diltiazem may occur with any of the volatile inhalation anesthetics,[244-249] and when these drugs are used with β-adrenergic blockers.[250-256] While the volatile inhalation anesthetics alter verapamil pharmacokinetics,[247] and have additive effects with verapamil on cardiac contractile function and conduction,[244-249] this does not appear to be the case with fentanyl-pancuronium and verapamil.[257] Finally, several *in vivo*[244-249] and *in vitro*[258] reports indicate that the combination of verapamil with enflurane is more likely to cause heart block than verapamil or diltiazem with halothane or isoflurane. The interactive effects of verapamil with the anesthetics on AV conduction time are shown in figure 17.[258]

β-Adrenergic blockers depress sinus rate and AV node conduction, but these effects are highly dependent on existing sympathetic tone. While there is the potential for

channels.[239] That all dihydropyridines bind at the same site and modulate the calcium channel function (either up- or down-regulation) has been challenged (Kamp TJ, *et al.* Circ Res 64:338-351, 1989). Future research concerned with anesthetics and mechanisms for dysrhythmias might well focus on differential effects of anesthetics and CCB on the various voltage-dependent Ca^{2+} channel subtypes, as well as their binding subunits.

bradycardia or heart block with any of the anesthetics (enflurane > halothane > isoflurane[259,260]), the danger is not excessive and continued treatment with β-adrenergic blockers is recommended prior to anesthesia.[259] In this regard, halothane has been shown to have no effect on the affinity of agonists or antagonists for myocardial β-adrenergic receptors.[261] Another study suggests that there may be only partial or noncompetitive antagonism between β-adrenergic antagonists and any of the volatile anesthetics at the SA node.[262]

Amiodarone, which prolongs AP duration and refractoriness in all cardiac tissues, has significant potential for adverse interactions with any of the anesthetics.[263–266] Side effects of amiodarone are dose dependent and include myocardial depression, peripheral vasodilation, atropine-resistant bradycardia, prolonged duration of action (half-life: 10–100 days), and sinus arrest.[266–269] Additionally, amiodarone alters digoxin pharmacokinetics,[269] which action may be responsible for sinus arrest and asystole with amiodarone in patients receiving digoxin.[264,270,271] As iv amiodarone*** may be an effective drug for dysrhythmias that fail to respond to conventional management, interactions of anesthetic drugs with amiodarone deserve further study.

Summary and Recommendations

Cardiac dysrhythmias are a potential, and sometimes real, cause for morbidity or mortality in patients undergoing anesthesia and surgery. Their actual incidence, causes, and associations, or how they might affect the outcome of the surgery, are not known. To determine these will require studies of large numbers of patients employing continuous (Holter) monitoring and epidemiologic methods.

Regardless of the specific rhythm disturbance, a dysrhythmia is of concern if it produces circulatory compromise, is sustained tachycardia, or is likely to initiate life-threatening ventricular dysrhythmias. Additionally, a new dysrhythmia should be viewed as a sign of some physiologic or pharmacologic derangement, and remedial action taken. While the latter may obviate the need for, or increase success with more specific measures, there is the danger of producing more serious dysrhythmias with specific drug or electrical therapy.

Mechanistically, dysrhythmias are considered disorders of impulse initiation, propagation, or both. Cellular mechanisms involve altered normal, as well as abnormal, mechanisms for impulse initiation and propagation. Abnormal mechanisms, which often involve loss of membrane potential, include abnormal automaticity, delayed afterdepolarizations with triggered activity, early afterdepolarizations with triggered automaticity, and re-entry of excitation. Anesthetics, adjunct drugs, or interactions involving anesthetics and other drugs may have pro- or antidysrhythmic effects on any of these dysrhythmia mechanisms. Cellular mechanisms that are likely to be affected by anesthetics or adjunct drugs are summarized in table 3. Currently, more data exist for the effects of local anesthetics (bupivacaine, lidocaine) and halothane on electrical properties of the heart. It will be necessary to provide similar data for enflurane, isoflurane, N_2O, and many of the iv anesthetics or adjuncts. Moreover, new methods, including voltage and patch clamping, should be used to further our understanding of anesthetic effects on electrophysiologic mechanisms. Finally, among the factors likely to influence dysrhythmias during anesthesia are the effects of altered physiologic states and autonomic imbalance. A major focus of future investigation

TABLE 3. Cellular Mechanisms for Dysrhythmias That Are Likely to be Affected by Anesthetics or Adjunct Drugs

Inhalation Anesthetics
Normal and abnormal forms of automaticity (decrease rate of discharge: E, H, I); oppose DAD-induced triggered activity (H, possibly E or I); oppose SV re-entry (E, H, I); facilitate ventricular re-entry in damaged fibers (H, possibly E or I).
Local Anesthetics
Normal automaticity (decrease rate of discharge: B, L); abnormal automaticity (NE); triggered activity/automaticity with DAD/EAD (unknown); SV re-entry (NE); oppose ventricular re-entry (L).
Intravenous Induction Agents
Normal and abnormal automaticity (direct effects unknown); DAD-induced triggered activity (possibly enhanced by T); re-entry (unknown).
Intravenous Narcotics
Normal automaticity (most decrease by indirect effects); abnormal automaticity, triggered activity/automaticity, and re-entry (unknown).
Muscle Relaxants
Normal automaticity (S, P, G, possibly V); abnormal automaticity (possibly P enhance); DAD-induced triggered activity (possibly P enhance); re-entry (unknown).
Miscellaneous Intravenous Agents
Normal automaticity (K, possibly D); abnormal automaticity and triggered activity/automaticity (unknown); SV re-entry and ventricular re-entry in damaged fibers (possibly D).

E = enflurane; H = halothane; I = isoflurane; DAD = delayed afterdepolarization; SV = supraventricular; poss. = possible effect based on similarity to drug with reported effects on same mechanism, or on other electrophysiologic actions; B = bupivacaine; L = lidocaine; NE = no effect; EAD = early afterdepolarization; T = thiopental; S = succinylcholine; G = gallamine; P = pancuronium; V = vecuronium; K = ketamine; D = droperidol.

*** Investigational use only.

will be study of the involvement of these with anesthetic-related dysrhythmias.

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References

1. Kuner J, Enescu V, Utsu F, Boszormenyi E, Bernstein H, Corday E: Cardiac arrhythmias during anesthesia. Dis Chest 52:580–587, 1967
2. Bertrand CA, Steiner NV, Jameson AG, Lopez M: Disturbances of cardiac rhythm during anesthesia and surgery. JAMA 216: 1615–1617, 1971
3. Atlee JL: Perioperative Cardiac Dysrhythmias: Mechanisms, Recognition, Management. 2nd Edition. Chicago, Year Book Medical Publishers, 1990, p 443
4. Katz RL, Bigger JT Jr: Cardiac arrhythmias during anesthesia and operation. ANESTHESIOLOGY 33:193–213, 1970
5. Hoffman BF, Cranefield PF: The physiological basis of cardiac arrhythmias. Am J Med 37:670–684, 1964
6. Fozzard HA, Arnsdorf MF: Cardiac Electrophysiology. The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 1–30
7. Gilmour RF Jr, Zipes DP: Abnormal automaticity and related phenomena. The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York. Raven Press, 1986, pp 1239–1257
8. Wit AL, Rosen MR: Afterdepolarizations and triggered activity. The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 1449–1490
9. Janse MJ: Reentry rhythms. The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 1203–1238
10. Sperelakis N: Origin of the cardiac resting potential. Handbook of Physiology. Section 2. The Cardiovascular System. Vol. I: The Heart. Edited by Berne RM. Bethesda, American Physiological Society, 1979, pp 187–267
11. Thomas RC: Electrogenic sodium pump in nerve and muscle cells. Physiol Rev 52:563–594, 1972
12. Brown AM, Yatani A: Ca and Na channels in the heart. The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 627–636
13. Rusy BF, Komai H: Anesthetic depression of myocardial contractility: A review of possible mechanisms. ANESTHESIOLOGY 67:745–766, 1987
14. Cohen IS, Datyner NB, Guntant GA, Kline RP: Time-dependent outward currents in the heart. The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 637–669
15. Noble D, Tsien RW: The repolarization process in heart cells. Electrical Phenomena in the Heart. Edited by De Mello WC. Orlando, Academic Press, 1972, pp 133–161
16. Eisner DA: The Na-K pump in cardiac muscle. The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 489–507
17. Baumgarten CM, Fozzard HA: The resting and pacemaker potentials. The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 601–626
18. Spach MS, Miller WT, Dolber PC, Kootsey JM, Sommer JR, Mosher CE Jr: The functional role of structural complexities in the propagation of depolarization in the atrium of the dog. Cardiac conduction disturbances due to discontinuities of effective axial resistivity. Circ Res 50:175–191, 1982
19. Spach MS, Miller WT, Geselowitz DB, Barr RC, Kootsey JM, Johnson EA: The discontinuous nature of propagation in normal canine cardiac muscle. Evidence for recurrent discontinuities of intracellular resistance that affect membrane currents. Circ Res 489:39–54, 1981
20. Gadsby DC, Wit AL: Electrophysiologic characteristic of cardiac cells and genesis of cardiac arrhythmias. Cardiac Pharmacology. Edited by Wilkersen RB. New York, Academic Press, 1981, pp 229–241
21. Zipes DP: Genesis of cardiac arrhythmias: Electrophysiologic considerations. Heart Disease. 3rd Edition. Edited by Braunwald E. Philadelphia, W. B. Saunders Co., 1988, pp 581–620
22. Gilmour RF Jr, Heger JJ, Prystowsky EN, Zipes DP: Cellular electrophysiologic abnormalities of diseased human ventricular myocardium. Am J Cardiol 51:137–144, 1983
23. Cranefield PF: The Conduction of the Cardiac Impulse. Mount Kisco, NY, Futura Publishing Co, 1975, pp 199–265
24. Elharrar V, Zipes DP: Voltage modulation of automaticity in cardiac Purkinje fibers. The Slow Inward Current and Cardiac Arrhythmias. Edited by Zipes DP, Bailey JC, Elharrar V. The Hague, Martinus Nijhoff, 1980, pp 357–373
25. Imoto Y, Ehara T, Matsuura H: Voltage- and time-dependent block of i_{K1} underlying Ba^{2+}-induced ventricular automaticity. Am J Physiol 252:H325–H333, 1987
26. Delmar M, Jalife J: Low Ba-induced pacemaker current in well-polarized cat papillary muscle. Am J Physiol 252:H258–H268, 1987
27. Horowitz LN, Spear JF, Moore EN: Subendocardial origin of ventricular arrhythmias in 24-hour-old experimental myocardial infarction. Circulation 53:56–63, 1975
28. Han J, Cameron JS: Effects of epinephrine on automaticity of Purkinje fibers from infarcted ventricles. Cardiac Electrophysiology and Arrhythmias. Edited by Zipes DP, Jalife J. Orlando, Grune and Stratton, 1985, pp 331–335
29. Cranefield PF: Action potentials, afterpotentials, and arrhythmias. Circ Res 41:415–423, 1977
30. Marban E, Smith TW. Digitalis. The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 1573–1596
31. Ferrier GR, Saunders JH, Mendez C: A cellular mechanism for the generation of ventricular arrhythmias by acetylstrophanthidin. Circ Res 32:600–609, 1983
32. Rosen MR, Gelband H, Merker C, Hoffman BF: Mechanisms of digitalis toxicity. Effects of ouabain on phase 4 of canine Purkinje fiber transmembrane potential. Circulation 47:681–689, 1973
33. Wit AL, Cranefield PF: Triggered and automatic activity in the canine coronary sinus. Circ Res 41:435–445, 1977
34. Wit AL, Fenoglio JJ Jr, Hordof AJ, Reemtsma K: Ultrastructure and transmembrane potentials of cardiac muscle in the human anterior mitral valve leaflet. Circulation 59:1284–1292, 1979
35. Dangman KH, Danilo P, Hordof AJ, Mary-Rabine L, Reder RF, Rosen MR: Electrophysiologic characteristics of human ventricular and Purkinje fibers. Circulation 65:362–368, 1982
36. Lazzara R, Hope RR, Yeh BK: Implication of cAMP and calcium as mediators of automaticity induced in working myocardium (abstract). Am J Cardiol 41:417, 1978
37. Kano T, Nishi K: External *p*H dependency of delayed afterdepolarization in rabbit myocardium. Am J Physiol 251:H324–H330, 1986
38. Le Marec H, Dangman KH, Danilo P, Rosen MR: An evaluation

of automaticity and triggered activity in the canine heart one to four days after myocardial infarction. Circulation 71:1244–1236, 1985
39. Dangman KH, Hoffman BF: The effects of single premature stimuli on automatic and triggered rhythms in isolated canine Purkinje fibers. Circulation 71:813–822, 1985
40. Pogwizd SM, Onufer JR, Kramer JB, Sobel BE, Corr PB: Induction of delayed afterdepolarizations and triggered activity in canine Purkinje fibers by lysophosphoglycerides. Circ Res 59:416–426, 1986
41. Gintant GA, Cohen IS: Advances in cardiac cellular electrophysiology: Implications for automaticity and therapeutics. Annu Rev Pharmacol Toxicol 28:61–81, 1988
42. Damiano BP, Rosen MR: Effects of pacing on triggered activity induced by early afterdepolarizations. Circulation 69:1013–1025, 1984
43. Attwell D, Cohen I, Eisner D, Ohba M, Ojeda C: The steady state TTX-sensitive ("window") sodium current in cardiac Purkinje fibres. Pflugers Arch 379:137–142, 1979
44. Gadsby DC, Cranefield PF: Two levels of resting potential in cardiac Purkinje fibers. J Gen Physiol 70:725–746, 1977
45. Gintant GA, Datyner NB, Cohen IS: Slow inactivation of a tetrodotoxin-sensitive current in canine cardiac Purkinje fibers. Biophys J 45:509–512, 1984
46. Carmeliet E, Saikawa T: Shortening of the action potential and reduction of pacemaker activity by lidocaine, quinidine, and procainamide in sheep cardiac Purkinje fibers: An effect on Na or K currents? Circ Res 50:257–272, 1982
47. Carmeliet EE: Slow inactivation of the sodium current in rabbit cardiac Purkinje fibres. Pflugers Arch 408:18–26, 1987
48. Rosen MR: The links between basic and clinical cardiac electrophysiology. Circulation 77:251–263, 1988
49. Mines GR: On dynamic equilibrium in the heart. J Physiol (Lond) 46:349–382, 1913
50. Mines GR: On circulating excitations in heart muscles and their possible relation to tachycardia and fibrillation. Trans R Soc Can [Section IV]:43–52, 1914
51. Garrey WE: Auricular fibrillation. Physiol Rev 4:215–250, 1924
52. Schmitt FO, Erlanger J: Directional differences in the conduction of the impulse through heart muscle and their possible relation to extrasystolic and fibrillary contractions. Am J Physiol 87: 326–347, 1929
53. Antzelevitch C, Moe GK: Electrotonically mediated delayed conduction and reentry in relation to "slow responses" in mammalian ventricular conduction tissue. Circ Res 49:1129–1139, 1981
54. Rozanski GJ, Jalife J, Moe GK: Reflected reentry in nonhomogeneous ventricular muscle as a mechanism of cardiac arrhythmias. Circulation 69:163–173, 1984
55. Allessie MA, Bonke FIM, Schopman FJG: Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: A new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 41:9–18, 1977
56. Mendez C, Gruhzit CC, Moe GK: Influence of cycle length upon refractory period of auricles, ventricles, and AV node in the dog. Am J Physiol 184:287–295, 1956
57. Mendez C, Mueller WJ, Merideth J, Moe GK: Interaction of transmembrane potentials in canine Purkinje fibers and at Purkinje fiber-muscle junctions. Circ Res 24:361–372, 1969
58. Sasyniuk BI, Mendez C: A mechanism for reentry in canine ventricular tissue. Circ Res 28:3–15, 1971
59. Allessie MA, Bonke FIM, Schopman FJG: Circus movement in rabbit atrial muscle as a mechanism of tachycardia. II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. Circ Res 39:168–177, 1976
60. Mendez C, Mueller WJ, Urguiaga X: Propagation of impulses across the Purkinje ventricular-fiber junctions in the dog heart. Circ Res 26:135–159, 1970
61. Veenstra RD, Joyner RW, Rawling DA: Purkinje and ventricular activation sequences of canine papillary muscle: Effects of quinidine and calcium on Purkinje-ventricular conduction delay. Circ Res 54:500–515, 1984
62. Veenstra RD, Joyner RW, Wiedmann RT, Young ML, Tan RC: Effects of hypoxia, hyperkalemia, and metabolic acidosis on canine subendocardial action potential conduction. Circ Res 60: 93–101, 1987
63. Joyner RW, Overholt ED, Ramza B, Veenstra RD: Propagation through electrically coupled cells: Two in homogeneously coupled cardiac tissue layers. Am J Physiol 247:H596–H609, 1984
64. Spach MS, Dolber PC: Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ Res 58: 356–371, 1986
65. Downer E, Waxman MB: Depressed conduction and unidirectional block in Purkinje fibers. The Conduction System of the Heart. Edited by Wellens HJJ, Lie KI, Janse MJ. Philadelphia, Lea & Febiger, 1976, pp 393–409
66. Gettes LS, Reuter H: Slow recovery from inactivation of inward currents in mammalian myocardial fibres. J Physiol (Lond) 240: 703–724, 1974
67. Rosen MR: Mechanisms for arrhythmias. Am J Cardiol (Suppl) 61:2A–8A, 1988
68. Bosnjak ZJ, Kampine JP: Effects of halothane, enflurane, and isoflurane on the SA node. ANESTHESIOLOGY 58:314–321, 1983
69. Atlee JL, Brownlee SW, Burstrom RE: Conscious-state comparisons of the effects of inhalation anesthetics on specialized atrioventricular conduction times in dogs. ANESTHESIOLOGY 64: 703–710, 1986
70. Seagard JL, Bosnjak ZJ, Hopp FA Jr, Kotrly KJ, Ebert TJ, Kampine JP: Cardiovascular effects of general anesthesia. Effects of Anesthesia. Edited by Covino BJ, Fozzard HA, Rehder K, Strichartz G. Bethesda, American Physiological Society, 1985, pp 149–177
71. Reynolds AK, Chiz JF, Pasquet AF: Halothane and methoxyflurane: A comparison of their effects on cardiac pacemaker fibers. ANESTHESIOLOGY 33:602–610, 1970
72. Logic JR, Morrow DH: An effect of halothane on ventricular automaticity. ANESTHESIOLOGY 36:107–111, 1972
73. Hauswirth O: Effects of halothane on single atrial ventricular and Purkinje fibers. Circ Res 24:745–750, 1969
74. Turner LA, Bosnjak ZJ, Kampine JP: Electrophysiological effects of halothane on Purkinje fibers from normal and infarcted canine hearts. ANESTHESIOLOGY 67:619–629, 1987
75. Atlee JL, Rusy BF: Halothane depression of A-V conduction studied by electrograms of the bundle of His in dogs. ANESTHESIOLOGY 36:112–118, 1972
76. Turner LA, Zuperku EJ, Purtock RV, Kampine JP: *In vivo* changes in canine ventricular cardiac conduction during halothane anesthesia. Anesth Analg 59:327–334, 1980
77. Atlee JL, Rusy BF: Atrioventricular conduction times and atrioventricular nodal conductivity during enflurane anesthesia in dogs. ANESTHESIOLOGY 47:498–503, 1977
78. Blitt CD, Raessler KL, Wightman MA, Groves BM, Wall CL, Geha DG: Atrioventricular conductions in dogs during anesthesia with isoflurane. ANESTHESIOLOGY 50:210–212, 1979
79. Atlee JL, Rusy BF, Kreul JF, Eby T: Supraventricular excitability

in dogs during anesthesia with halothane and enflurane. ANESTHESIOLOGY 49:407–413, 1978
80. Atlee JL, Dayer AM, Houge JC: Chronic recording from the His bundle of the awake dog. Basic Res Cardiol 79:627–638, 1984
81. Atlee JL, Yeager TS: Electrophysiologic assessment of the effects of enflurane, halothane, and isoflurane on properties affecting supraventricular reentry in chronically instrumented dogs. ANESTHESIOLOGY 71:941–952, 1989
82. Morrow DH, Townley NT: Anesthesia and digitalis toxicity: An experimental study. Anesth Analg 43:510–519, 1964
83. MacLeod BA, Augereau P, Walker MJA: Effects of halothane anesthesia compared with fentanyl anesthesia and no anesthesia during coronary ligation in rats. ANESTHESIOLOGY 59:44–52, 1983
84. Jang JL, MacLeod BA, Walker MJA: Effects of halogenated hydrocarbon anesthetics on responses to ligation of a coronary artery in chronically prepared rats. ANESTHESIOLOGY 59:309–315, 1983
85. Kroll DA, Knight PR: Antifibrillatory effects of volatile anesthetics in acute occlusion/reperfusion arrhythmias. ANESTHESIOLOGY 61:657–661, 1984
86. Wit AL, Bigger JT: Possible electrophysiologic mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. Circ Res 51–52(Suppl III):96–115, 1975
87. Ikemoto Y, Yatani A, Arimura H, Yoshitake J: Reduction of the slow inward current in isolated rat ventricular cells by thiamylal and halothane. Acta Anaesthesiol Scand 29:583–586, 1985
88. Ikemoto Y, Yatani A, Imoto Y, Arimura H: Reduction in the myocardial sodium current by halothane and thiamylal. Jpn J Physiol 36:107–121, 1986
89. Lynch C, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981
90. Lynch C, Vogel S, Pratila M, Sperelakis N: Enflurane depression of myocardial slow action potentials. J Pharmacol Exp Ther 222:405–409, 1982
91. Lynch C: Differential depression of myocardial contractility by halothane and isoflurane *in vitro*. ANESTHESIOLOGY 64:620–631, 1986
92. Bosnjak ZJ, Rusch NJ: Calcium currents are decreased by halothane, enflurane, and isoflurane in isolated canine ventricular and Purkinje cells (abstract). ANESTHESIOLOGY 69:A452, 1988
93. Niluns B, Hess P, Lansman JB, Tsien RW: A novel type of cardiac calcium channel in ventricular cells. Nature 316:443–446, 1985
94. Orchard CH, Eisner DA, Allen DG: Oscillation of intracellular Ca^{++} in mammalian cardiac muscle. Nature 304:735–738, 1983
95. Bosnjak ZJ, Kampine JP: Effects of halothane on transmembrane potentials, Ca^{2+} transients and papillary muscle tension in the cat. Am J Physiol 251:H374–H381, 1986
96. Bosnjak ZJ, Aggarwal A, Turner LA, Kampine JP: Differential effects of halothane, enflurane, and isoflurane on Ca^{++} transients and papillary muscle tension in the guinea pig (abstract). ANESTHESIOLOGY 69:A88, 1988
97. Komai H, Rusy BF: Negative inotropic effects of isoflurane and halothane in rabbit papillary muscles. Anesth Analg 66:29–33, 1987
98. Allen JD, Brennan FJ, Wit AL: Action of lidocaine on transmembrane potentials of subendocardial Purkinje fibers surviving in infarcted canine hearts. Circ Res 43:470–481, 1978
99. Roizen MF, Plummer GO, Lichtor JL: Nitrous oxide and dysrhythmias. ANESTHESIOLOGY 66:427–431, 1987
100. Hanich RF, Levine JH, Spear JF: Autonomic modulation of ventricular arrhythmias in cesium chloride-induced long QT syndrome. Circulation 77:1149–1161, 1988
101. Riley DC, Schmeling WT, Al-Wathiqui MH, Kampine JP, Warltier DC: Prolongation of the QT interval by volatile anesthetics in chronically instrumented dogs. Anesth Analg 67:741–749, 1988
102. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. ANESTHESIOLOGY 51:285–287, 1979
103. Davis NL, de Jong RH: Successful resuscitation following massive bupivacaine overdose. Anesth Analg 61:62–64, 1982
104. Edde RR, Deutsch S: Cardiac arrest after interscalene brachial-plexus block. Anesth Analg 56:446–447, 1977
105. Prentiss JE: Cardiac arrest following caudal anesthesia. ANESTHESIOLOGY 50:51–53, 1979
106. Gould DB, Aldrete JA: Bupivacaine cardiotoxicity in a patient with renal failure. Acta Anaesthesiol Scand 27:18–21, 1983
107. Conklin KA, Ziadlou-Rad F: Bupivacaine cardiotoxicity in a pregnant patient with mitral valve prolapse (letter). ANESTHESIOLOGY 58:596, 1983
108. Rosenberg PH, Kalso EA, Tuominen MK, Linden HB: Acute bupivacaine toxicity as a result of venous leakage under the tourniquet cuff during a Bier block. ANESTHESIOLOGY 58:95–98, 1983
109. Morishima HO, Pedersen H, Finster M, Hiraoka H, Tsuji A, Feldman HS, Arthur R, Covino BG: Bupivacaine toxicity in pregnant and nonpregnant ewes. ANESTHESIOLOGY 63:134–139, 1985
110. de Jong RH, Ronfeld RA, DeRosa RA: Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 61:3–9, 1982
111. Hotvedt R, Refsum H, Helgesen KG: Cardiac electrophysiologic and hemodynamic effects related to plasma levels of bupivacaine in the dog. Anesth Analg 64:388–394, 1985
112. Komai H, Rusy BF: Effects of bupivacaine and lidocaine on AV conduction in the isolated rat heart. Modification by hyperkalemia. ANESTHESIOLOGY 55:281–285, 1981
113. Tanz RD, Heskett T, Loehning RW, Fairfax CA: Comparative cardiotoxicity of bupivacaine and lidocaine in the isolated perfused mammalian heart. Anesth Analg 63:549–556, 1984
114. Bosnjak ZJ, Stowe DF, Kampine JP: Comparison of lidocaine and bupivacaine depression of sinoatrial nodal activity during hypoxia and acidosis in adult and neonatal guinea pigs. Anesth Analg 65:911–917, 1986
115. Sage DJ, Feldman HS, Arthur R, Datta S, Ferretti AM, Norway SB, Covino BG: Influence of lidocaine and bupivacaine on isolated guinea pig atria in the presence of acidosis and hypoxia. Anesth Analg 63:1–7, 1984
116. Stowe DF, Bosnjak ZJ, Kampine JP: Effect of hypoxia on adult and neonatal pacemaker rates. Obstet Gynecol 66:649–656, 1985
117. Kotelko DM, Schnider SM, Dailey PA, Brizgys RV, Levinson G, Shapiro WA, Koike M, Rosen MA: Bupivacaine-induced cardiac arrhythmias in sheep. ANESTHESIOLOGY 60:10–18, 1984
118. Rosen MA, Thigpen JW, Schnider SM, Foutz SE, Levinson G, Koike M: Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 64:1089–1096, 1985
119. Clarkson CW, Hondeghem LM: Mechanisms for bupivacaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. ANESTHESIOLOGY 62:396–405, 1985
120. Clarkson CW, Hondeghem LM: Evidence for a specific receptor site for lidocaine, quinidine, and bupivacaine associated with cardiac sodium channels in guinea pig ventricular myocardium. Circ Res 56:496–506, 1985
121. Hondeghem LM, Datzung BG: Time and voltage dependent interactions of antiarrhythmic drugs with cardiac sodium channels. Biochim Biophys Acta 472:373–398, 1977

122. Lynch C III: Depression of myocardial contractility *in vitro* by bupivacaine, etidocaine, and lidocaine. Anesth Analg 65:551–559, 1986
123. Coyle DE, Sperelakis N: Bupivacaine and lidocaine blockade of calcium-mediated slow action potentials in guinea pig ventricular muscle. J Pharmacol Exp Ther 242:1001–1005, 1987
124. Wheeler DM, Bradley EL, Woods WT Jr: The electrophysiologic actions of lidocaine and bupivacaine in the isolated, perfused canine heart. ANESTHESIOLOGY 68:201–212, 1988
125. Moller RA, Covino BG: Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesth Analg 67:107–114, 1988
126. Heavner JE: Cardiac dysrhythmias induced by infusion of local anesthetics into the lateral cerebral ventricule of cats. Anesth Analg 65:133–138, 1986
127. Thomas RD, Behbehani MM, Coyle DE, Denson DD: Cardiovascular toxicity of local anesthetics: An alternative hypothesis. Anesth Analg 65:444–450, 1986
128. de Jong RH, Bonin JD: Benzodiazepines protect mice from local anesthetic convulsions and deaths. Anesth Analg 60:385–389, 1981
129. de Jong RH, Heavner JE: Diazepam and lidocaine-induced cardiovascular changes. ANESTHESIOLOGY 39:633–638, 1973
130. Gregg RV, Turner PA, Denson DD, Stuebing RC, Sehlhorst CS, Forsberg T: Does diazepam really reduce the cardiotoxic effects of intravenous bupivacaine? Anesth Analg 67:9–14, 1988
131. Kasten GW, Martin ST: Bupivacaine cardiovascular toxicity, comparison of treatment with bretylium and lidocaine. Anesth Analg 64:911–916, 1985
132. Kasten GW, Martin ST: Successful cardiovascular resuscitation after massive intravenous bupivacaine overdosage in anesthetized dogs. Anesth Analg 64:491–497, 1985
133. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 255:2905–2989, 1986
134. Koscove EM, Paradis NA: Successful resuscitation from cardiac arrest using high-dose epinephrine therapy. JAMA 259:3031–3034, 1988
135. Frankl WS, Poole-Wilson PA: Effects of thiopental on tension development, action potential, and exchange of calcium and potassium in rabbit ventricular myocardium. J Cardiovasc Pharmacol 3:554–565, 1981
136. Ikemoto Y: Reduction by thiopental of the slow-channel-mediated action potential of canine papillary muscle. Pflugers Arch 372: 285–286, 1977
137. Kiba T: Effects of thiopental and pentobarbital sodium on the transmembrane potentials of the rabbit's atria in special reference to interaction with catecholamine. Jpn J Pharmacol 16: 168–179, 1966
138. Komai H, Rusy BF: Calcium and thiopental-induced spontaneous activity in rabbit papillary muscle. J Mol Cell Cardiol 18:73–79, 1986
139. Komai H, Rusy BF: Differences in the myocardial depressant action of thiopental and halothane. Anesth Analg 63:313–318, 1984
140. Mantelli L, Manzini S, Mugelli A, Ledda F: The influence of some cardiodepressant drugs on the histamine-induced restoration of contractility in potassium-depolarized heart preparations. Arch Int Pharmacodyn Ther 254:99–108, 1981
141. Bednarski RM, Majors LJ, Atlee JL: Potentiation by thiamylal and thiopental of halothane-epinephrine induced ventricular arrhythmias in dogs. Am J Vet Res 46:1829–1831, 1985
142. MacCannell KL, Dresel PE: Potentiation by thiopental of cyclopropane-adrenaline cardiac arrhythmias. Can J Physiol Pharmacol 42:627–639, 1964
143. Atlee JL, Malkinson CE: Potentiation by thiopental of halothane-epinephrine-induced arrhythmias in dogs. ANESTHESIOLOGY 57:285–288, 1982
144. Atlee JL, Roberts FL: Thiopental and epinephrine-induced dysrhythmias in dogs anesthetized with enflurane or isoflurane. Anesth Analg 65:437–443, 1986
145. Daskalopoulos N, Laubie M, Schmitt H: Localization of the central sympatho-inhibitory effects of a narcotic analgesic agent, fentanyl in cats. Eur J Pharmacol 33:91–97, 1975
146. Reitan JA, Stengert KB, Wymore ML, Martucci RW: Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. Anesth Analg 57:31–36, 1978
147. Foldes FF, Shiffman HP, Kronfeld PP: The use of fentanyl, meperidine, or alphaprodine for neuroleptanesthesia. ANESTHESIOLOGY 33:35–42, 1970
148. Arndt JO, Mikat M, Parasher C: Fentanyl's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. ANESTHESIOLOGY 61:355–361, 1984
149. Loeb JM, Lichtenthal PR, de Tarnowsky JM: Parasympathomimetic effects of fentanyl on the canine sinus node. J Auton Nerv Syst 11:91–94, 1984
150. DeSilva RA, Verrier RL, Lown B: Protective effect of vagotonic action of morphine sulfate on ventricular vulnerability. Cardiovasc Res 12:167–172, 1978
151. Lechner RB, Gurll NJ, Reynolds DG: Intracoronary naloxone in hemorrhagic shock: Dose-dependent stereospecific effects. Am J Physiol 249:H272–H277, 1985
152. Lindgren L, Saarnivaara L, Klemola U-M: Protection of fentanyl against cardiac dysrhythmias during induction of anesthesia. Eur J Anaesthesiol 4:229–233, 1987
153. Hauswirth O: Effects of droperidol on sheep Purkinje fibers. Naunyn-Schmiedebergs Arch Pharmacol 261:133–142, 1968
154. Bertolo L, Novakovic L, Penna M: Antiarrhythmic effects of droperidol. ANESTHESIOLOGY 37:529–535, 1972
155. Gomez-Arnau J, Marquez-Montes J, Avello F: Fentanyl and droperidol effects on refractoriness of the accessory pathway in the Wolff-Parkinson-White syndrome. ANESTHESIOLOGY 58:307–313, 1983
156. Abdul-Rasool IH, Sears DH, Katz RL: The effect of a second dose of succinylcholine on cardiac rate and rhythm following induction of anesthesia with etomidate or midazolam. ANESTHESIOLOGY 67:795–797, 1987
157. Hannallah RS, Oh TH, McGill WA, Epstein BS: Changes in heart rate and rhythm after intramuscular succinylcholine with or without atropine in anesthetized children. Anesth Analg 65: 1329–1332, 1986
158. Nigrovic V: Succinylcholine, cholinoceptors, and catecholamines: Proposed mechanism of early adverse haemodynamic reactions. Can Anaesth Soc J 31:382–394, 1984
159. Inoue K, Reichelt W: Asystole and bradycardia in adult patients after a single dose of suxamethonium. Acta Anaesthesiol Scand 30:571–573, 1986
160. Inoue K, Arndt JO: Efferent vagal discharge and heart rate in response to methohexitone, althesin, ketamine, and etomidate in cats. Br J Anaesth 54:1105–1115, 1982
161. Brandt MR, Viby-Mogensen J: Halothane anesthesia and suxamethonium III. Acta Anaesthiol Scand (Suppl) 67:76–83, 1978
162. Cozanitis DA, Dundee JW, Khan MM: Comparative study of atropine and glycopyrrolate and suxamethonium-induced changes in cardiac rate and rhythm. Br J Anaesth 52:291–293, 1980
163. Schoenstadt DA, Whitcher CE: Observations on the mechanism of succinylcholine-induced cardiac arrhythmias. ANESTHESIOLOGY 24:358–362, 1963
164. Yasuda I, Hirano T, Amaha K, Fudeta H, Obara S: Chronotropic

effects of succinylcholine and succinylmonocholine on the sinoatrial node. ANESTHESIOLOGY 57:289–292, 1982
165. Williams CH, Deutsch S, Linde HW, Bullough JW, Dripps RD: Effects of intravenously administered succinyldicholine on cardiac rate, rhythm, and arterial blood pressure in anesthetized man. ANESTHESIOLOGY 22:947–954, 1961
166. Stoelting RK, Peterson C: Heart-rate slowing and junctional rhythm following intravenous succinylcholine with and without intramuscular atropine preanesthetic medication. Anesth Analg 54:705–709, 1975
167. Miller RD, Savarese JJ: Pharmacology of muscle relaxants and their antagonists. Anesthesia. 2nd Edition. Edited by Miller RD. New York, Churchill Livingstone. 1986, pp 889–943
168. Iwatsuki N, Kuroda N, Amaha K, Iwatsuke K: Succinylcholine-induced hyperkalemia in patients with ruptured cerebral aneurysms. ANESTHESIOLOGY 53:64–67, 1980
169. Powell DR, Miller R: The effect of repeated doses of succinylcholine on serum potassium in patients with renal failure. Anesth Analg 54:746–748, 1975
170. Stoelting RK: Pharmacology and Physiology in Anesthetic Practice. Philadelphia, J. B. Lippincott, 1987, pp 169–216
171. Carter JG, Sokoll MD, Gergis DS: Effect of spinal cord transection on neuromuscular function in the rat. ANESTHESIOLOGY 55: 542–546, 1981
172. Dierdorf SF, McNiece WL, Rao CC, Wolfe TM, Krishna G, Means LJ, Haselby KA: Effect of succinylcholine on plasma potassium in children with cerebral palsy. ANESTHESIOLOGY 62: 88–90, 1985
173. McCammon RL, Stoelting RK: Exaggerated increase in serum potassium following succinylcholine in dogs with beta blockade. ANESTHESIOLOGY 61:723–725, 1984
174. Inaba H, Ohwada T, Sato J, Mizuguchi T, Hirasawa H: Effects of salbutamol and hyperventilation on the rise in serum potassium after succinylcholine administration. Acta Anaesthesiol Scand 31:524–528, 1987
175. Magee DA, Gallagher EG: "Self-taming" of suxamethonium and serum potassium concentration. Br J Anaesth 56:977–980, 1984
176. Aldrete JA, Zahler A, Aikawa JK: Prevention of succinylcholine-induced hyperkalaemia by magnesium sulfate. Can Anaesth Soc J 17:477–484, 1970
177. Miller RD, Way WL: The interaction between succinylcholine and subparalyzing doses of d-tubocurarine and gallamine in man. ANESTHESIOLOGY 35:567–571, 1971
178. Stoelting RK, Peterson C: Adverse effects of increased succinylcholine dose following d-tubocurarine pretreatment. Anesth Analg 54:282–288, 1975
179. Evers W, Racz GB, Levy AA: Changes in plasma potassium and calcium levels and in the electrocardiogram after a single dose of succinylcholine preceded by d-tubocurarine. Can Anaesth Soc J 23:383–394, 1976
180. Collier CB: Dantrolene and suxamethonium: The effect of preoperative dantrolene on the action of suxamethonium. Anaesthesia 34:152–158, 1979
181. James MFM, Cork RC, Dennett JE: Succinylcholine pretreatment with magnesium sulfate. Anesth Analg 65:373–376, 1986
182. Weiner N, Taylor P: Drugs acting at synaptic and neuroeffector junctional sites. The Pharmacological Basis of Therapeutics. 7th Edition. Edited by Gilman AG, Goodman LS, Rall TW, Murad F. New York, Macmillan Publishing Co. 1985, pp 66–99
183. Son SL, Waud BE: Potencies of neuromuscular blocking agents at the receptors of the atrial pacemaker and the motor endplate of the guinea pig. ANESTHESIOLOGY 47:34–36, 1977
184. Hughes R, Chapple DJ: Effects of non-depolarizing neuromuscular blocking agents on peripheral autonomic mechanisms in cats. Br J Anaesth 48:59–68, 1976
185. Son SL, Waud DR: A vagolytic action of neuromuscular blocking agents at the pacemaker of the isolated guinea pig atrium. ANESTHESIOLOGY 48:191–194, 1978
186. Geha DG, Rozelle BC, Raessler KL, Graves BM, Wightman MA, Blitt CD: Pancuronium bromide enhances atrioventricular conduction in halothane-anesthetized dogs. ANESTHESIOLOGY 46: 342–345, 1977
187. Jacobs HK, Lim S, Salem MR, Rao TLK, Mathru M, Smith BD: Cardiac electrophysiologic effects of pancuronium. Anesth Analg 64:693–699, 1985
188. Schick LM, Chapin JC, Munson ES, Kushins LG: Pancuronium, d-tubocurarine, and epinephrine-induced arrhythmias during halothane anesthesia in dogs. ANESTHESIOLOGY 52:207–209, 1980
189. Kirkwood I, Duckworth RA: An unusual case of sinus arrest. Br J Anaesth 55:1273, 1983
190. Milligan KR, Beers HT: Vecuronium-associated cardiac arrest (letter). Anaesthesia 40:385, 1985
191. Pollok AJP: Cardiac arrest immediately after vecuronium. Br J Anaesth 58:936–937, 1986
192. Clayton D: Asystole associated with vecuronium. Br J Anaesth 58:937–938, 1986
193. Starr NJ, Sethna DH, Estafanous FG: Bradycardia and asystole following the rapid administration of sufentanil with vecuronium. ANESTHESIOLOGY 64:521–523, 1986
194. Yeaton P, Teba L: Sinus node exit block following administration of vecuronium. ANESTHESIOLOGY 68:177–178, 1988
195. Inoue K, El-Banayosy A, Stolarski L, Reichelt W: Vecuronium-induced bradycardia following induction of anaesthesia with etomidate or thiopentone, with or without fentanyl. Br J Anaesth 60:10–17, 1988
196. Katz RL, Katz GJ: Surgical infiltration of pressor drugs and their interactions with volatile anaesthetics. Br J Anaesth 38:712–718, 1966
197. Katz RL, Epstein RA: The interaction of anesthetic agents and adrenergic drugs to produce arrhythmias. ANESTHESIOLOGY 29:763–784, 1968
198. Oliver G, Schafer EA: On the physiological action of extract of the suprarenal capsules. J Physiol 18:230–279, 1895
199. Johnston RR, Eger EI II, Wilson C: A comparative interaction of epinephrine with enflurane, isoflurane, and halothane in man. Anesth Analg 55:709–712, 1976
200. Horrigan RW, Eger EI II, Wilson C: Epinephrine-induced arrhythmias during enflurane anesthesia in man: A nonlinear dose-response relationship and dose-dependent protection from lidocaine. Anesth Analg 57:547–550, 1978
201. Katz RL, Matteo RS, Papper EM: The injection of epinephrine during general anesthesia: 2, Halothane. ANESTHESIOLOGY 23: 597–600, 1962
202. Karl HW, Swedlow DB, Lee KW, and Downes JJ: Epinephrine-halothane interactions in children. ANESTHESIOLOGY 58:142–144, 1983
203. Koehntop DE, Liao JC, Van Bergen FH: Effects of pharmacologic alterations of adrenergic mechanisms by cocaine, tropoline, aminophylline, and ketamine on epinephrine-induced arrhythmias during halothane-nitrous oxide anesthesia. ANESTHESIOLOGY 46:83–93, 1977
204. Wong KC, Puerto AX, Puerto BA, Blatnick RA: Influence of imipramine and pargyline on the arrhythmogenicity of epinephrine during halothane, enflurane, or methoxyflurane anesthesia in dogs. Life Sci 27:2675–2678, 1980
205. Spiss CK, Smith CM, Maze M: Halothane-epinephrine arrhythmias and adrenergic responsiveness following chronic imipramine administration in dogs. Anesth Analg 63:297–300, 1984
206. Liu WS, Wong KC, Port JD, Andriano KP: Epinephrine-induced arrhythmias during halothane anesthesia with the addition of

nitrous oxide, nitrogen, or helium in dogs. Anesth Analg 61: 414–417, 1982
207. Pace NL, Ohmura A, Wong KC: Epinephrine-induced arrhythmias: Effect of exogenous prostaglandins and prostaglandin synthesis inhibition during halothane-O_2 anesthesia in the dog. Anesth Analg 58:401–404, 1979
208. Prokocimer PG, Nicholls E, Gaba DM, Maze M: Epinephrine arrhythmogenicity is enhanced by acute, but not chronic, aminophylline administration during halothane anesthesia in dogs. ANESTHESIOLOGY 65:13–18, 1986
209. Zink J, Sasyniuk BI, Dresel PE: Halothane-epinephrine-induced cardiac arrhythmias and the role of the heart rate. ANESTHESIOLOGY 43:548–555, 1975
210. Tucker WK, Rackstein AD, Munson ES: Comparison of arrhythmic doses of adrenaline, metaraminol, ephedrine, and phenylephrine during isoflurane and halothane anaesthesia in dogs. Br J Anaesth 46:392–396, 1974
211. Miletich DJ, Albrecht RF, Seals C: Responses to fasting and lipid infusion of epinephrine-induced arrhythmias during halothane anesthesia. ANESTHESIOLOGY 48:245–249, 1978
212. Chapin JC, Kushins LG, Munson ES, and Schick LM: Lidocaine, bupivacaine, etidocaine, and epinephrine-induced arrhythmias during halothane anesthesia in dogs. ANESTHESIOLOGY 52:23–26, 1980
213. Maze M, Smith CM: Identification of receptor mechanism mediating epinephrine-induced arrhythmias during halothane anesthesia in the dog. ANESTHESIOLOGY 59:322–326, 1983
214. Sharma PL: Effect of propranolol on catecholamine-induced arrhythmias during nitrous oxide-halothane anaesthesia in the dog. Br J Anaesth 38:871–877, 1966
215. Kapur PA, Flacke WE: Epinephrine-induced arrhythmias and cardiovascular function after verapamil during halothane anesthesia in the dog. ANESTHESIOLOGY 55:218–225, 1981
216. Iwatsuki N, Katoh M, Ono K, Amaha K: Antiarrhythmic effect of diltiazem during halothane anesthesia in dogs and in humans. Anesth Analg 64:964–970, 1985
217. Melgrave AP: The use of epinephrine in the presence of halothane in children. Can Anaesth Soc J 17:256–260, 1970
218. Wallbank WA: Cardiac effects of halothane and adrenaline in hare-lip and cleft-palate surgery. Br J Anaesth 42:548–552, 1970
219. Metz S, Maze M: Halothane concentration does not alter the threshold for epinephrine-induced arrhythmias in dogs. ANESTHESIOLOGY 62:470–474, 1985
220. Sharma PL: Selective adrenergic beta-receptor blockade in the prevention of adrenaline-evoked ventricular arrhythmias in dogs anaesthetized with halothane in oxygen. Br J Anaesth 41:481–488, 1979
221. Pontinen PJ: Cardiovascular effects of local adrenaline infiltration during halothane anaesthesia and adrenergic beta-receptor blockade in man. Acta Anaesthesiol Scand 22:130–144, 1978
222. Pontinen PJ: Cardiovascular effects of local adrenaline infiltration during neuroleptic analgesia and adrenergic beta-receptor blockade in man. Acta Anaesthesiol Scand 22:145–153, 1978
223. Adler-Graschinsky E, Langer SZ: Possible role of a beta-adrenoceptor in the regulation of noradrenaline release by nerve stimulation through a positive feed-back mechanism. Br J Pharmacol 53:43–50, 1975
224. Hoffman BB, Lefkowitz RJ: Alpha-adrenergic receptor subtypes. N Engl J Med 302:1390–1396, 1980
225. Spiss CK, Maze M, Smith CM: Alpha-adrenergic responsiveness correlates with epinephrine dose for arrhythmias during halothane anesthesia in dogs. Anesth Analg 63:297–300, 1984
226. Maze M, Hayward E Jr, Gaba DM: Alpha$_1$-adrenergic blockade raises epinephrine-arrhythmia threshold in halothane-anesthetized dogs in a dose-dependent fashion. ANESTHESIOLOGY 63: 611–615, 1985
227. Dresel PE: Cardiac alpha receptors and arrhythmias. ANESTHESIOLOGY 63:582–583, 1985
228. Hayashi Y, Sumikawa K, Tashiro C, Yoshiya I: Synergistic interaction of alpha$_1$- and beta-adrenoceptor agonists on induction arrhythmias during halothane anesthesia in dogs. ANESTHESIOLOGY 68:902–907, 1988
229. Hodgkin AL, Huxley AF: A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol (Lond) 117:500–544, 1952
230. Hamill OP, Marty A, Neher E, Sakmann B, Sigworth FJ: Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. Pflugers Arch 391:85–100, 1981
231. Soto-Aquilar MC, DeShazo RD, Waring NP: Anaphylaxis. Why it happens and what to do about it. Postgrad Med 82(5):154–170, 1987
232. Bristow MR, Ginsberg R, Harrison DC: Histamine and the human heart: The other receptor system. Am J Cardiol 49:249–251, 1982
233. Wolff AA, Levi R: Histamine and cardiac arrhythmias. Circ Res 58:1–16, 1986
234. Stowe DF, Bosnjak ZJ, Marijic J, Kampine JP: Effects of halothane with and without histamine and/or epinephrine on automaticity, intercardiac conduction times, and the development of dysrhythmias in the isolated guinea pig heart. ANESTHESIOLOGY 68:695–706, 1988
235. Needleman P, Corr PB, Johnson EM Jr: Drugs used for the treatment of angina: Organic nitrates, calcium channel blockers, and β-adrenergic antagonists. The Pharmacological Basis of Therapeutics. 7th Edition. Edited by Gilman AG, Goodman LS, Rall TW, Murad F. New York, Macmillan Publishing Co, 1985, pp 806–826
236. Henry PD: Mechanisms of action of calcium antagonists in cardiac and smooth muscle. Calcium Channel Blocking Agents in the Treatment of Cardiovascular Disorders. Edited by Stone PH, Antman EM. Mt. Kisco, New York, Futura Publishing Co., 1983, pp 107–154
237. Kohlhardt M, Fleckenstein A: Inhibition of the slow inward current by nifedipine in mammalian ventricular myocardium. Naunyn-Schmiedebergs Arch Pharmacol 298:267–272, 1977
238. Triggle DJ, Janis RA: Calcium channel ligands. Annu Rev Pharmacol Toxicol 27:347–369, 1977
239. Schwartz A, McKenna E, Vaghy PL: Receptors for calcium antagonists. Am J Cardiol 62:3G–6G, 1988
240. Nowycky MC, Fox AP, Tsien RW: Three types of neuronal calcium channel with different calcium agonist sensitivity. Nature 316:440–443, 1985
241. McCleskey EW, Fox AP, Feldman D, Tsien RW: Different types of calcium channels. J Exp Biol 124:177–190, 1986
242. Miller RJ: Multiple calcium channels and neuronal function. Science 235:46–52, 1987
243. Ehara T, Kaufmann R: The voltage- and time-dependent effects of (−)− verapamil on the slow inward current in isolated cat ventricular myocardium. J Pharmacol Exp Ther 207:49–55, 1978
244. Kapur PA, Bloor BC, Flacke WE, Olewine SK: Comparison of cardiovascular responses to verapamil during enflurane, isoflurane, or halothane anesthesia in the dog. ANESTHESIOLOGY 61: 156–160, 1984
245. Chelly JE, Rogers K, Hysing ES, Taylor A, Hartley C, Merin RG: Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. I. Verapamil and halothane. ANESTHESIOLOGY 64:560–567, 1986
246. Rogers K, Hysing ES, Merin RG, Taylor A, Harley C, Chelly JE: Cardiovascular effects of an interaction between calcium

blocking drugs and anesthetics in chronically instrumented dogs. II. Verapamil, enflurane, isoflurane. ANESTHESIOLOGY 64:568–575, 1986

247. Chelly JE, Hysing ES, Abernethy DR, Doursout M-F, Merin RG: Effects of inhalational anesthetics on verapamil pharmacokinetics in dogs. ANESTHESIOLOGY 65:266–271, 1986
248. Priebe HJ, Skarvan K: Cardiovascular and electrophysiologic interactions between diltiazem and isoflurane in the dog. ANESTHESIOLOGY 66:114–121, 1987
249. Atlee JL, Hamann SR, Brownlee SW, Kreigh C: Conscious state comparisons of the effects of the inhalation anesthetics and diltiazem, nifedipine, or verapamil on specialized atrioventricular conduction times in spontaneously beating dog hearts. ANESTHESIOLOGY 68:519–528, 1988
250. Hung J, Lamb IH, Connolly SJ, Jutzy KR, Goris ML, Schroeder JS: The effect of diltiazem and propranolol, alone and in combination, on exercise performance and left ventricular function in patients with stable effort angina: A double-blind, randomized, and placebo-controlled study. Circulation 68:560–567, 1983
251. Kieval J, Kirsten EB, Kessler KM, Mallon SM, Myerburg RJ: The effects of intravenous verapamil on hemodynamic status of patients with coronary artery disease receiving propranolol. Circulation 65:653–659, 1982
252. Packer M, Meller J, Medina N, Yushak M, Smith H, Holt J, Guererro J, Todd GD, McAllister RG Jr, Gorlin R: Hemodynamic consequences of combined beta-adrenergic and slow calcium channel blockade in man. Circulation 65:660–668, 1982
253. Winniford MD, Markham RV Jr, Firth BG, Nicod P, Hillis LD: Hemodynamic and electrophysiologic effects of verapamil and nifedipine in patients on propranolol. Am J Cardiol 50:704–710, 1982
254. Hartwell BL, Mark JB: Combinations of beta-blockers and calcium channel blockers: A cause of malignant perioperative conduction disturbances? Anesth Analg 65:905–907, 1986
255. Hantler CB, Wilton N, Learned DM, Hill AEG, Knight PR: Impaired myocardial conduction in patients receiving diltiazem therapy during enflurane anesthesia. ANESTHESIOLOGY 67:94–96, 1987
256. Kapur PA, Matarazzo DA, Fung DM, Sullivan KB: The cardiovascular and adrenergic actions of verapamil or diltiazem in combination with propranolol during halothane anesthesia in the dog. ANESTHESIOLOGY 66:122–129, 1987
257. Hill DC, Chelly JE, Dlewati A, Abernethy DR, Doursout MF, Merin RG: Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. VI. Verapamil and fentanyl-pancuronium. ANESTHESIOLOGY 68:874–879, 1988
258. Marijic J, Bosnjak ZJ, Stowe DF, Kampine JP: Effects and interaction of verapamil and volatile anesthetics on the isolated perfused guinea pig heart. ANESTHESIOLOGY 69:914–922, 1988
259. Foex P: Alpha- and beta-adrenoceptor antagonists. Br J Anaesth 56:751–765, 1984
260. Kopriva CJ, Brown ACD, Pappas G: Hemodynamics during general anesthesia in patients receiving propranolol. ANESTHESIOLOGY 48:28–33, 1978
261. Bernstein KJ, Gangat Y, Verosky M, Vulliemoz Y, Triner L: Halothane effect on beta-adrenergic receptors in canine myocardium. Anesth Analg 60:401–405, 1981
262. Stowe DF, Dujic Z, Bosnjak ZJ, Kalbfleisch JH, Kampine JP: Volatile anesthetics attenuate sympathomimetic actions on the guinea pig SA node. ANESTHESIOLOGY 68:887–894, 1988
263. Mason JW: Amiodarone. N Engl J Med 316:455–466, 1987
264. Navalgund AA, Alifimoff JK, Jakymec AJ, Bleyaert AL: Amiodarone-induced sinus arrest successfully treated with ephedrine and isoproterenol. Anesth Analg 65:414–416, 1986
265. McKinnon G, Landymore R, Marble A: Should oral amiodarone be used for sustained ventricular tachycardia in patients requiring open-heart surgery? Can J Surg 26:355–357, 1983
266. Gallagher JD, Lieberman RW, Meranze J, Spielman SR, Ellison N: Amiodarone-induced complications during coronary artery surgery. ANESTHESIOLOGY 55:186–188, 1981
267. Cote P, Bourassa M, Delay J, Janin A, Froment R, David P: Effects of amiodarone on cardiac and coronary hemodynamics and on myocardial metabolism in patients with coronary artery disease. Circulation 59:1165–1172, 1979
268. Woosley RL, Funck-Brentano C: Overview of the clinical pharmacology of antiarrhythmic drugs. Am J Cardiol (Suppl) 61: 61A–69A, 1988
269. Fenster PE, White NW, Hanson CD: Pharmacokinetic evaluation of the digoxin-amiodarone interaction. J Am Coll Cardiol 5: 108–112, 1985
270. Klein HO, Beker B, DiSegni E, Kaplinsky E: Asystole produced by the combination of amiodarone and digoxin. Am Heart J 113:399–400, 1987
271. Nademanee K, Kannan R, Hendrickson J, Ookhtens M, Kay I, Singh BN: Amiodarone-digoxin-interaction: Clinical significance, time course of development, potential pharmacokinetic mechanisms, and therapeutic implications. J Am Coll Cardiol 4:111–116, 1984