Anesthetic Agents and Cardiac Electromechanical Activity

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In recent years electrocardiographic monitoring has been used during virtually every anesthetic procedure. The incidence of cardiac dysrhythmias has been shown to be much greater than was previously supposed. For this reason a knowledge of basic cardiac electrophysiology and the effects of anesthetic agents on cardiac electromechanical activity is important to the anesthesiologist.

In this article we review data obtained from studies: a) in a single cardiac cell, with the use of microelectrodes, b) in the isolated heart, and c) in the intact organism. The first provides fundamental information about basic electrophysiology and responses to anesthetic agents. The second provides information about impulse formation and conduction. The third provides information obtained during experimental conditions that are as near as is possible to clinical situations. Many of these experimental findings have yet to be confirmed in man, but they do give an indication of what may be expected during the course of anesthesia.

Electrophysiology of the Conducting System

The normal cardiac impulse arises by spontaneous activity in the sinoatrial (SA) node. This leads to excitation of atrial fibers and rapid conduction to the atrioventricular (AV) node. AV nodal excitation of the ventricular muscle is via the bundle of His. This rather tenuous pathway is the only link between the SA node, with its multitude of neural and hormonal influences, and the ventricular myocardium.

Some 20 years ago it became possible, with the introduction of microelectrodes, to measure the transmembrane potential difference of a cardiac cell. In the following discussion we will see that cardiac cells are basically of two types. The cardiac impulse arises in

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† Histologically the cells of the SA node are arranged in an interlacing network of supporting collagen to which the basement membranes of these cells are attached. These intertwining bundles of fibers form clusters of nodal cells, an arrangement that contrasts with the more regular pattern of the atrial fibers. Both the pacemaker cells of the SA node and the nodal or N cells of the AV node are characterized by a paucity of myofibrils compared with atrial and ventricular muscle cells.1

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Fig. 1. Schematic representation of the transmembrane action potential in a pacemaker cell. These cells are constantly undergoing slow progressive and spontaneous diastolic depolarization (phase 4) and will form an action potential as soon as threshold potential (TP), usually between −60 to −40 mV, is reached. They therefore do not have a resting potential but a maximal diastolic potential in the −60 to −70 mV range.

and the major current carriers. Although this model provides an ideal way of discussing and explaining the passage of ions, it has yet to be proven as a physiologic entity.

Inside the cell there is a high concentration of potassium with a low concentration of sodium. Although the cell membrane is permeable to both ions, in the resting state, it is far more so to potassium. It is this differential permeability that makes the inside negative and produces the resting transmembrane potential. Energy is necessary for the maintenance of these ionic gradients, which produce and maintain the transmembrane potential. This energy is produced by hydrolysis of adenosine triphosphate (ATP) involving a specific Na⁺−K⁺-activated magnesium (Mg⁴⁺)-dependent ATPase. This enzyme is confined to the cell membrane and is activated by K⁺ on the outer surface and Na⁺ at the inner surface.

If the membrane were only permeable to potassium, potassium ions would leave the cell because their concentration is low outside. Sodium ions would try to enter since sodium concentration is low inside, but would be unable to because the membrane blocks their entry. This would result in a relative deficit of potassium ions inside the cell. Thus, the inside would become negative, and this negativity would increase until its pull was sufficient to balance the concentration gradient driving the potassium out of the cell. At equilibrium the inside would normally be 100 mV negative to the outside, i.e., we would reach Eᵦ. Eᵦ is the equilibrium potential corresponding to the concentration gradient [Kᵦ]/[Kᵢ] (where Kᵦ = K⁺ outside cell and Kᵢ = K⁺ inside cell). If the membrane were permeable only to sodium, the converse would be true, and the inside would become positive, i.e., we would reach Eᵦ (the equilibrium potential for Na⁺). In fact, the membrane reaches a level at which the inside is negative but not so negative as it would be if there were zero membrane permeability to sodium (potassium permeability Pᵦ being much greater than sodium permeability Pᵦ).

Resting membrane potential can be calculated from the Goldman constant-field equation.

\[
\text{Membrane potential mV} = \frac{RT}{F} \log \frac{Pᵦ[Kᵦ] + Pᵦ[Na⁺]}{Pᵦ[Kᵦ] + Pᵦ[Na⁺]}
\]

R = gas constant; F = Faraday's constant; T = temperature (absolute at 37°C, \( \frac{RT}{F} = 61.5 \)).

Since Pᵦ is much greater than Pᵦ in the resting fiber, membrane potential approaches Eᵦ. During de-

Fig. 2. Schematic representation of the transmembrane action potential in a Purkinje fiber. Depolarization (phase 0) and the phases of repolarization (phases 1, 2, 3) are labelled, as is phase 4, the resting diastolic phase. When the fiber is in the resting state, the inside of the cell is −90 mV negative in relationship to the outside (resting potential). At the peak of the action potential the interior of the cell becomes approximately 30 mV positive (i.e., there is a reversal or overshoot). The movements of the three major ions Na⁺, K⁺, and Ca⁺⁺ are shown at the bottom of the figure. ↑ = inwards into the cell ↓ = outwards from the cell. See text for details.
polarization (Phase 0) $P_K$ does not change but there is an enormous increase in $P_{Na}$ and as a result membrane potential moves toward $E_{Na}$. The resting membrane potential, in a Purkinje fiber, is approximately $-90$ mV (fig. 2). The cell membrane is slightly permeable to sodium ions and maintains an intracellular sodium ratio of 1:7. Although potassium can cross the cell membrane more easily than sodium, it is retained within the cell by the negative intracellular potential. When a stimulus reaches the cell membrane, there is a shift from the resting level of $-90$ mV to the threshold potential of about $-70$ mV due to inward movement of sodium ions. This voltage change causes, at threshold, a further increase in permeability to sodium ($P_{Na}$). At this level sodium ions rush into the cell and reverse the transmembrane potential to $+30$ mV (Phase 0), i.e., there is an increase in sodium permeability ($P_{Na}$) and membrane potential moves to $E_{Na}$.

The resting potential varies with $K_p$. It is virtually independent of changes in $Na_p$. The membrane potential at the peak of the action potential varies with $Na_p$. The maximum velocity, $dV/dt_{max}$, of the upstroke of the action potential is reduced when $Na_p$ is reduced. Shifts in the membrane potential away from the resting level towards the active level reduce the amount by which $P_{Na}$ can increase and thus diminish the amplitude of the action potential.

The resistance to current flow along the length of the fiber is less than the resistance to current flow across the membrane. Thus, when depolarization occurs in the area receiving a stimulus, depolarization of adjacent segments brings them to threshold potential, causing an increase in $P_{Na}$. In this way activity is conducted along the length of the fiber. Phase 0 depolarization is complete within a few milliseconds. Repolarization is a slower process and lasts several hundred milliseconds.

Following depolarization there is a phase of early rapid repolarization (Phase 1), which is followed by sustained depolarization (actually extremely slow repolarization) near the level of zero membrane potential (the plateau or Phase 2). Phase 1 probably depends to a large extent on inactivation of the inward rapid Na current, but may also depend on a transient repolarizing current carried by chloride ions.

Phase 2, or the plateau, is believed to depend on a slow inward current and a decrease in $P_K$. The slow inward current does not appear until depolarization is significant. The threshold potential for this current is approximately $-50$ mV. Unlike the rapid inward current responsible for the upstroke of the action potential, the slow inward current either is not subject to voltage-dependent inactivation or undergoes inactivation far more slowly.

It is likely the slow inward current can be carried by sodium or calcium ions. Since $Na_p$ is far greater than $Ca_p$, it seems probable that sodium ions are responsible for the inward current during the plateau of the action potential of normal Purkinje fibers. It is because of the presence of sodium or persistent action potential that the cardiac action potential persists for several hundred milliseconds instead of the few milliseconds of neural tissue. This causes an increased duration of the absolute refractory period. This is necessary for the orderly progression of excitation–contraction in the heart. Membrane potential is not stable during the plateau but moves slowly in the direction of repolarization. This slow repolarization may be the result of a slow increase in a repolarizing current carried by potassium or other ions or a slow decrease in the slow inward current carried by sodium or calcium ions. Noble and co-workers have shown that both an increase in outward current and a simultaneous decay in the slow inward current are involved.

Phase 3 is the phase of late relatively rapid repolarization. It is initiated partly by inactivation of the second inward current, but activation of an outward current is also necessary. There is more than one outward current mechanism. Noble and Tsien have described a potassium current ($i_K$) that controls the time course of the pacemaker potential ($i_K$ is the background or leakage $K^+$ current). This $i_K$ current is not responsible for repolarization, as it is active in the wrong voltage range and the reaction rate is too rapid. They have described another current, the plateau current mechanism, which differs from $i_K$ not only in its activation threshold but also in its composition. Since the ionic components other than potassium are unknown it is called $i_X$. This itself has been shown to be formed by more than one current component, and so these are labelled $i_X^1$ and $i_X^2$. The former activates within a second and the latter takes ten seconds or more. The $i_X^1$ current is obviously more important in the mechanism controlling repolarization.

To restore conditions to the resting state, extrusion of sodium ions and uptake of potassium ions must take place against the concentration gradient. This requires even more energy than is used to maintain the resting state.

We have discussed above the function of the slow inward current in its contribution to the plateau (phase of persistent depolarization) in the Purkinje fiber. It is now believed that in the SA and AV nodes the upstrokes of the propagated action potentials are due only to this slow inward current, producing slow
response action potentials (fig 1). Fibers with slow response action potentials have a slow upstroke velocity, delayed recovery of excitability, slow propagation with unidirectional block, summation, inhibition and reentry. It is almost certain that propagated activity in such fibers depends on an inward current carried by Ca$$^{++}$. This is suggested by the slow upstroke, less than 10 V/sec (SA node 2–3 V/sec and N cell of AV node 6–7 V/sec) and low conduction velocity (0.02–0.1 m/sec) and by the low density of inward current (fig. 1). However, it is better to avoid the term "calcium channel" as the slow channel is believed to be permeable to both calcium and sodium as described above. The threshold potential for the slow inward current is −50 to −40 mV. Injury or disease can depolarize a fast cardiac fiber, thereby inactivating the fast sodium conductance and converting it into a slow-channel calcium inflow-dependent cardiac fiber. In cardiac muscle, the slow inward current is essential for coupling excitation of the cell membrane to activation of the contractile proteins.

Pacemaker fibers have the ability to be spontaneously and rhythmically to produce excitation, which spreads throughout the heart. Dudel and Trautwein showed that the pacemaker potential was an afterpotential of the action potential, due, they felt, to a relatively high potassium conductance at the end of the repolarization phase of the action potential. Later work by Noble and Tsien and Vassalle showed that the pacemaker potential is due to a potassium current, which flows at the end of repolarization and slowly decreases during diastole (IKp).

The sinoatrial node normally serves as the cardiac pacemaker, since it has the most rapid rate of spontaneous Phase 4 depolarization, 15–60 mV/sec, compared with 5–40 mV/sec for the Purkinje system. Any cell capable of spontaneous Phase 4 depolarization shows automaticity. The ionic mechanism for automaticity in slow cardiac fibers, e.g., SA nodal fibers, appears to be an inward calcium current and the decreasing K+ current described above. The underlying mechanism of pacemaker action has remained a mystery until very recently. Pollack has presented evidence that may support a previously unrecognized role for catecholamines. His hypothesis is that intracellular vesicles (in pacemaker cells) discharge catecholamines into the extracellular space. The discharge rate is slow initially, as the cell is well polarized (−50 to −60 mV) and intracellular Ca$$^{++}$ concentration is low. These discharged catecholamines bind to the outside of the cell membrane and activate adenylyl cyclase, thereby increasing cyclic adenosine monophosphate (AMP) and bringing about the phosphorylation of membrane proteins, with transient opening of Ca$$^{++}$ channels, allowing Ca$$^{++}$$ to enter and further depolarize the cell. This causes an increased rate of catecholamine discharge and so the feedback system continues until all catecholamines are discharged. Adenylyl cyclase activity ceases, AMP returns to baseline levels, calcium channels close, and the cell ceases depolarizing. Repolarization occurs by Ca$$^{++}$$ extrusion, catecholamine vesicles are replenished, and when this reaches a certain level, spontaneous discharge occurs and the cycle begins again. While much of this hypothesis requires experimental confirmation, it is an attractive possibility. The relationships between membrane permeabilities and automaticity, excitability and conduction velocity have been well reviewed by Olson and Waud.

**The Refractory Period**

Excitability of the cell is recovered in the period during which the cell is refractory to stimulation following Phase 0 depolarization. This period is divided into phases according to the "degree of refractoriness." The cell is unable to respond to any stimulus, of whatever magnitude, until repolarization has restored the transmembrane potential to −55 mV. This is the **absolute refractory period**. As membrane potential continues to become more negative, a response to high-intensity stimulation occurs. This response is weak and non-propagated. The earliest propagated response marks the end of the **effective refractory period**. From the end of the effective refractory period to the start of Phase 4 is the **relative refractory period**. The absolute refractory period is shortened by an increase in heart rate, while the relative refractory period is not altered significantly. From the onset of Phase 0 depolarization to the end of the relative refractory period is the total refractory period. The following period is the **supernormal period**. Threshold is somewhat lower than it will be in Phase 4. A response obtained in this period has a reduced amplitude and rate of upstroke and may propagate at a slower velocity than would a response obtained in a fully recovered fiber. **Full recovery time** extends from depolarization to the end of the supernormal period.

**Excitation-Contraction Coupling**

In order to complete this basic review of the electrophysiology of the conducting system we must mention briefly the second part of the process that will result in myocardial contraction, i.e., excitation-contraction (E-C) coupling. Following excitation and
membrane depolarization with influx of Na\(^+\) and Ca\(^{2+}\) and efflux of K\(^+\), the end result is an increased myoplasmic concentration of Ca\(^{2+}\), which produces the ultimate trigger for the onset of mechanical response. There is some controversy as to whether the major part of the Ca\(^{2+}\) necessary is obtained from extra- or intracellular sources in cardiac muscle. Voltage-clamp studies of ventricular muscle\(^{38-39}\) show the magnitude of the slow inward current is proportional to the extracellular Ca\(^{2+}\) concentration, and the threshold of this current (approximately -40 mV) must be reached before contractile activation can occur. The amount of this Ca\(^{2+}\) influx, however, is barely enough to achieve 10 per cent activation of contractile force.\(^{40}\) It has therefore been suggested that the major portion of the Ca\(^{2+}\) required is derived from intracellular sites.\(^{41,42}\) However, ionic exchange studies using E-C uncouplers\(^{43,44,45}\) show that the source of this Ca\(^{2+}\) is external to the sarclemma, and its movement must be via an electroneutral current.

The cardiac myofibril consists of interdigitating, partly overlapping actin and myosin filaments.\(^{46}\) When the muscle contracts these thin actin filaments slide along the myosin filaments, without change in their length.\(^{47}\) Cross-bridges, formed by side chains from the myosin filaments, link actin and myosin filaments.\(^{46}\) They facilitate the displacement of the actin on the myosin filament\(^{48}\) and are sites for the Mg\(^{2+}\) dependent ATPase enzymes that produce energy for this displacement—by hydrolysis ATP.

The actin in the cardiac myofibril, unlike that of skeletal muscle, lacks Ca\(^{2+}\) sensitivity. Sensitivity to Ca\(^{2+}\) is supplied by the troponin–tropomyosin (T–T) protein complex.\(^{49}\) Troponin is either bound to, or is a part of, the actin filament. Troponin binds only with the actin–tropomyosin complex, not with actin or tropomyosin alone. This T–T complex acts as a regulator of the actin-induced activation of the myosin ATPase enzyme. It inhibits it when Ca\(^{2+}\) is lacking and facilitates it when Ca\(^{2+}\) is present. Formation and activation of the cross-bridges occur on activation of the myosin ATPase, and contraction occurs.

**Automaticity**

The rate of firing of an automatic cell depends on three factors: 1) The slope of Phase 4 diastolic depolarization. 2) The level of threshold potential. 3) The level of maximum diastolic potential. Decreases in 1 and 2 and/or an increase in 3 gives a slower rate (fig. 3). Increases in 1 and 2 and/or a decrease in 3 gives an increased rate (fig. 4).

Anesthetic agents affect the SA node by their effect on the rate of Phase 4 depolarization, or the threshold potential of the cells. Decreasing the rate favors emergence of pacemaker function in lower automatic cells unless they are similarly affected. Similarly, factors that tend selectively to increase the rate of spontaneous Phase 4 depolarization, with the upper cells maintaining a normal rate, also favor the appearance of extrasystoles generated by lower pacemaker activity.

The main mechanism slowing the discharge rate of higher pacemaker cells is efferent vagal activity with the release of acetylcholine. This is virtually limited to myocardial cells above the bundle of His due to the anatomic distribution of the vagi. Examples of this are the vagotonic effects of halothane or cyclopropane. The factors that increase the discharge rates of automatic cells above and below the A–V node are: increased rate of sympathetic efferent activity with release of n-epinephrine, exogenous or endogenous epinephrine, hypoxia, hypercarbia, and metabolic acidosis. The hypoxic or acidotic cell has an unstable membrane, which is more readily depolarized.\(^{50}\)

**Conduction Abnormalities**

In addition to increased automaticity described above, disturbances in rhythm can result from abnormalities in conduction. These can occur by conduction through abnormal anatomic pathways that bypass a part of the atroventricular junction. This is less common, however, than a localized delay in impulse conduction due to an abnormality in the electrophysiologic properties of the cardiac fiber.\(^{51}\) In normal conditions, the impulse passing through the conducting system of the heart ends when the atria and ventricles have been activated because the cardiac tissue has been recently excited and is therefore in a refractory phase. The concept of re-entry requires that the propagating impulse not die out but persist to re-excite the heart after completion of the refractory period. The effective refractory period in man is long (approximately 150 msec in atria and 500 msec in ventricular conducting tissue). Since the impulse must continue to conduct during this time, it has been estimated that the pathway would have to be as much as 1 m long.\(^{52}\) The authors considered this unlikely to occur in the heart, however circuitous the path.\(^{52}\)

Slowing the conduction rate would however, remove the necessity for such a long pathway. Cardiac fibers that have slow response action potentials may allow re-entry to occur. These fibers are normally present in the SA and AV nodes, but slow response action potentials may develop in fibers whose normal
Fig. 3. Schematic representation of transmembrane potentials from a single fiber in the S-A node, illustrating the mechanisms that decrease the rate of firing. In A there is a decrease in the slope of phase 4 depolarization, i.e., a longer time is necessary to reach threshold, when threshold potential (TP) and maximal diastolic potential (MDP) remain constant. In B an increase in maximal diastolic potential (MDP), threshold potential (TP) and the slope of phase 4 depolarization being constant, would increase the time needed for phase 4 depolarization to reach threshold, with a resultant slowing in rate. In C a decrease in the level of threshold potential to TPc, the slope of phase 4 depolarization and MDP being constant, delays the achievement of threshold and again slows the rate.

Fig. 4. Schematic representation of transmembrane potentials from a single fiber in the S-A node, illustrating the mechanisms that increase the rate of firing. In A there is an increase in the slope of phase 4 depolarization, resulting in a diminution in time necessary to reach threshold, when threshold potential (TP) and maximal diastolic potential (MDP) remain constant. In B a decrease in maximal diastolic potential to MDPB, (TP and slope of phase 4 depolarization being constant) would increase the rate, since less time is needed to reach threshold. In C an increase in the level of threshold potential to TPc again shortens the time to reach threshold (when MDP and the slope of phase 4 depolarization are constant).

Fast response has been slowed by disease or drug actions.

A schematic representation of Purkinje fibers and the ventricular muscle is shown in figure 5A. Purkinje fibers usually generate fast response action potentials (they conduct at a velocity of 1-4 m/sec). A normal impulse is initiated at the sinus node and ends by passage through the Purkinje system to the ventricular muscle, where the impulses die out because they are surrounded by refractory tissue. For re-entry to occur, conduction must be slowed and a region where conduction is unidirectional must be present. Figure 5B shows such a situation. Impulses can pass down both limbs but are blocked at the depressed area (shaded in diagram). Impulses that pass down the unblocked limb are, however, able to pass through the blocked area in a retrograde manner. When the re-entrant impulse returns to the main bundle, it may also re-invade the unblocked limb of Purkinje fibers and again conduct back through the re-entrant pathway (the circus movement).

The slow conduction and unidirectional block that produce re-entry are, as described above, usually the result of a disease process. The normally fast fibers may be converted to fibers with a slow response action potential by reducing the transmembrane potential of the fibers, thus inactivating the strong inward sodium current, and replacing it with a slow response action potential dependent on calcium or sodium ions. A local release of potassium in ischemic areas may contribute to the decrease in membrane potential (as a result of partial depolarization) and thus decrease conduction velocity. Conduction must be slow enough to allow the fibers in the main branch to recover excitability. When the fiber is still in the refractory phase no re-entry dysrhythmia can occur.
Equally, a unidirectional retrograde block must be present. When antegrade conduction is re-established, or a bidirectional block occurs, there can be no re-entry.

Re-entry in the sinus and AV nodes results from the same mechanisms described above, slow conduction and unidirectional block. Both the sinus and AV nodes develop slow response action potentials normally, and therefore a disease process to produce partial depolarization is not necessary for re-entry to occur. Groups of upper AV nodal cells have different refractory periods. Early premature atrial impulses, as they conduct into the node, may find refractory nodal tissue in the region that has the longest effective refractory periods. Early premature atrial impulses, as other nodal tissue that has a shorter effective refractory period and has, therefore, partly recovered excitability. The former tissue then provides an area of unidirectional block and re-entrant arrhythmias can occur. Similar conditions can exist in the sinus node.

Re-entry due to inequalities in lengths of refractory periods can also occur in cardiac fibers with fast response activity. Slowing of conduction and unidirectional conduction are still prerequisites, but the changes are not the result of partial depolarization but are due to regional alterations in refractory periods.

**Effects of Anesthetic Drugs**

**Halogenated Agents**

Reynolds et al. have investigated the effects of halothane on cardiac pacemaker fibers (in vitro). At 1 per cent concentration, halothane had a moderate, negative chronotropic action on the SA nodal fibers. This was the result of a slightly reduced rate of slow diastolic depolarization (Phase 4) and an increase in threshold potential. At 2 per cent halothane there was further reduction in the slope of Phase 4 depolarization. Maximum diastolic potential, overshoot and amplitude also decreased at this concentration. The duration of the action potential increased. However, changes in rate alone are known to modify the action potential. The decrease in rate was not prevented by atropine. This confirms the work of Morrow and co-workers. At 4 per cent halothane, there was progressive reduc-
tion in maximum diastolic potential, overshoot and amplitude. Arrest of the fiber occurred. This did not follow progressive slowing of the heart rate, but was associated with a marked loss of maximum diastolic potential, increase in the threshold potential, and ultimate loss of excitability. These fibers could not be driven electrically. This effect was completely reversed by washing out the halothane. When the rate was increased by epinephrine, exposure to halothane caused a reduction in rate.

Hauswirth showed,\(^7\) in his in-vitro studies, that rabbit atrial fibers are not very sensitive to even 2 per cent halothane. Although the overshoot is significantly decreased and repolarization is slightly prolonged, there is no marked change in resting potential or amplitude of the action potential such as is seen in the SA node.

Atlee and Rusy,\(^8\) in vivo, in dogs, found a concentration-dependent depression of AV conduction by halothane, using catheter electrocardiography. Depression of conduction was most marked proximal to the bundle of His (intra-atrial and AV node). Vagal blockade with atropine did not significantly alter the effect of halothane; therefore depression of conduction by halothane is not due to increased vagal activity. Beta-blockade with propranolol further slowed conduction, suggesting there is sympathetic enhancement of AV conduction even at 2 per cent halothane. Fast rates of atrial pacing slow AV conduction. This is probably due to the arrival of a premature impulse during the absolute refractory period (no impulse transmitted) or during the relative refractory period (decremental or slowed conduction). The mechanism of halothane depression of AV conduction is probably prolongation of the refractory period. Atlee and co-workers\(^9\) also studied the modifying effects of lidocaine and diphenylhydantoin in the presence of halothane. They used the same technique of His-bundle electrocardiography. Increasing the concentration of halothane prolonged AV conduction with further depression with lidocaine and diphenylhydantoin. Atioventricular conduction was more sensitive to drug affects than His–Purkinje or total intraventricular conduction. They believed this might represent potentiation of the normal slowing of conduction through the AV node in response to increases in heart rate (fatigue response). They concluded that lidocaine and diphenylhydantoin failed to reverse the depressant effect of halothane on AV conduction, and that this may explain their ineffectiveness in the treatment of certain dysrhythmias during halothane anesthesia.

When quiescent canine Purkinje fibers were exposed in vitro to 1 per cent halothane,\(^4\) the resting membrane potential remained unchanged and there was virtually no effect on the rate of slow diastolic depolarization. Hauswirth,\(^7\) however, found that in sheep Purkinje fibers the resting potential was increased and the overshoot and duration of the action potential were decreased at 1 per cent halothane. This disparity is probably due to species difference. In spontaneously active fibers, exposure to 2 per cent halothane or more caused a slowing of the spontaneous rate due to an increase in the threshold potential and a decrease in the slope of Phase 4 depolarization. There was also a steep increase in the slope of Phase 2, which resulted in almost complete disappearance of the plateau. Duration of the action potential was reduced. In electrically driven fibers the same increase in the slope of Phase 2 was seen. In many fibers the duration of the action potential remained the same due to a decrease in the rate of Phase 3. Phase 0 was unaffected. Halothane depresses intraventricular conduction, but to a lesser extent than conduction through the AV node.\(^4,45\) Ventricular automaticity is slightly depressed by halothane. This has been shown in single cells\(^44,45\) and in the intact animal.\(^46-48\) Hauswirth,\(^57\) using sheep ventricular cells, found at 2 per cent halothane the resting potential was virtually unchanged, overshoot decreased significantly, duration of action potential was reduced, and the effective refractory period was shortened. The rate of rise of Phase 0 (dV/dt) decreased.

The effects of halothane on Phase 4 depolarization are more characteristic of an antidisrhythmic agent. Many investigators have shown that halothane significantly reduces the cardiotoxicity of the digitalis compounds.\(^42,43\) It has been shown to have therapeutic effectiveness in ouabain-induced ventricular tachycardia in intact dogs.\(^44\) Damato et al.,\(^45\) using electrode catheter techniques in dogs, have shown the site of the ectopic pacemaker in digitalis-induced ventricular tachycardia was either the left bundle branch or the more distal Purkinje fibers with retrograde activation of the bundle of His. The study of Logic and Morrow\(^48\) shows halothane is capable of suppressing glycoside enhancement of such ectopic pacemakers. They consistently observed that halothane suppressed both physiologic escape and ectopic pacemaker activity far more in the presence of ouabain. If spontaneous depolarization in pacemaking fibers represents a time-dependent decrease in the conductance of the membrane for K\(^+\) ions,\(^46\) then halothane must have altered the time-dependent conductance change in the electrically excitable membranes of pacemaker fibers. It is also possible the effect is a decrease in the level of threshold potential. Such an effect would slow the inherent rate of pacemaking fibers. The marked changes in pacemaker activity seen whenever ouabain was administered in toxic amounts suggest that ouabain may
influence pacemaker fiber tissue conductance in ways necessitating an even greater membrane-stabilizing effect of halothane and other antidyssrhythmic membrane-active drugs before the time-dependent decrease in $K^+$ conductance can bring the pacemaker fiber to its critical threshold potential and initiate a propagated response.

Having discussed the role of halothane as an antidysrhythmic agent, we should also review the mechanism for halothane–catecholamine-induced dysrhythmias. Hashimoto, in intact dogs and in isolated papillary muscle, and Zink, in intact dogs, and their co-workers have investigated the possible role of increased automaticity or re-entry. Evidence is in favor of the latter. Myerberg et al. have shown marked disparity between times of recovery of adjacent fibers in the distal conducting system. Prolonged duration of action potentials and refractory periods in some Purkinje fibers could prevent propagation of premature impulses across these fibers. They postulate if sufficient fibers were refractory and conduction velocities such that the premature impulse re-entered the conduction pathway before the next normal impulse arrived, conditions for re-entry of excitation would be present. If this occurred when an area of the myocardium had achieved sufficient repolarization, ventricular fibrillation could occur. In Zink's work a critical level of blood pressure and a critical atrial rate were necessary for induction of dysrhythmias. Stretch of Purkinje fibers as a result of increases in intraventricular systolic pressure has been suggested as a cause of bigemini. Stretch of Purkinje fibers slows conduction velocity and increases the rate of diastolic depolarization, both of which favor re-entry. Zink and co-workers believe the bigeminal beat is a fusion beat of a re-entrant impulse that originates in the upper part of the interventricular septum with the next normal beat conducted through the AV node. This is supported by the work of Reynolds and Chiz, which showed that epinephrine, in concentrations that had no significant effect on the velocity of impulse conduction in Purkinje fibers, markedly potentiated a modest slowing of conduction produced by halothane. This effect was antagonized by an alpha-adrenergic block with phentolamine but not by beta-adrenergic blockade with propranolol.

Methoxyflurane has been shown by Reynolds et al. in *vitro* to have a biphasic effect on the SA node. The major effect is a decrease in rate, which is preceded by a brief initial acceleration. The acceleration is due chiefly to a slight loss in maximum diastolic potential. It is not prevented by propranolol. The decrease in rate is associated with a further loss in maximum diastolic potential and a marked increase in threshold potential. Overshoot is reduced. At 1 per cent methoxyflurane the authors found almost invariably, an arrest of activity. This frequently occurred at 0.5 per cent. It was associated with a loss of maximum diastolic potential, increase in threshold potential, and finally, loss of excitability. This effect was reversible. When the rate was increased by epinephrine, exposure to methoxyflurane had little effect.

In intact unpremedicated dogs methoxyflurane produced a dose-dependent increase in the functional refractory period of the AV conduction system. This was unaffected by vagotomy, which suggests the effect is independent of parasympathetic control. When quiescent Purkinje fibers were exposed to methoxyflurane, 1 per cent, resting potential became slightly less negative but automaticity did not develop. In spontaneously active fibers, concentrations of 0.5 per cent and 1 per cent caused marked increases in rate, mainly due to an increased rate of Phase 4 depolarization. This was also true of electrically driven preparations. There was a sharp increase in the slope of Phase 2, while duration of the action potential remained about the same, due to a decrease in the terminal part of Phase 3 repolarization. A slight decrease in the rate of Phase 0 depolarization was also noted.

The combination of primary pacemaker depression and secondary pacemaker stimulation favors shift of pacemaker activity to the ventricular conducting system. The marked increase that methoxyflurane combined with epinephrine produces on Phase 4 depolarization results almost invariably in dysrhythmias, which probably originate in an ectopic pacemaker. A decrease in the level of threshold potential also results, which contributes to decremental conduction and local block, both of which favor re-entry of impulses. These conclusions are drawn from studies carried out at the cell membrane level and in *in vitro* preparations, and may not be entirely applicable to intact man. There is very little information available to elucidate the effects of other halogenated anesthetic agents on the conducting system of the heart. Krishna and Paradise recently reported the effect of enflurane on isolated rat atria. Enflurane elicited a dose-dependent positive chronotropic effect, which was, however, of lesser magnitude when compared with the effects of methoxyflurane and diethyl ether. Atlee has investigated the effects of enflurane on the AV node using His-bundle electrocardiography. He concluded that increasing depth of anesthesia impaired AV nodal conduction while having minimal effects on His–Purkinje conduction. This was true in both spontaneously beating hearts and in—
incrementally (atrial) paced dog hearts. He also found that spontaneous rate varied little with increasing depth of anesthesia. This is in agreement with the work of others.78–80

Iwatssuki81 and co-workers have shown, in isolated heart muscle, that enflurane decreased both duration and intensity of the active state at a given time interval of stimulation. It appears that enflurane causes alterations in the ionic movements of Na⁺, Ca²⁺, and K⁺ across the membrane during excitation–contraction coupling.

**Non-halogenated Agents**

Davis *et al.*84,85 investigated the effects of cyclopropane. *In vitro*, cyclopropane appears to have no effect on the sinus node. It enhances the slope of Phase 4 depolarization of Purkinje fibers and potentiates the increased slope and magnitude of Phase 4 depolarization produced by epinephrine. Cyclopropane also accelerated repolarization during the plateau or Phase 2 of the Purkinje fiber action potential. Dysrhythmias are common. Propranolol antagonizes this potentiation. The effects of cyclopropane are markedly influenced by the concentration of calcium in the medium.86 Lowering calcium concentration minimized or prevented the faster rate of repolarization initiated by cyclopropane. Increasing the calcium concentration enhanced the effect of cyclopropane on repolarization and also increased the rate and magnitude of diastolic depolarization.

Cullen *et al.*87 found heart rate to be unaltered during anesthesia with cyclopropane in healthy male volunteers who had normal temperatures and PaCO₂ levels. Nor was it altered with a change in concentration or duration of anesthesia. This is possibly due to a balance of opposing stimuli. In man, cyclopropane stimulates norepinephrine release by increased sympathetic activity.88 Tachycardia might result unless the associated hypertension caused a reflex bradycardia. Parasympathetic stimulation by cyclopropane is a possible reason also, since a marked increase in heart rate is obtained with atropine, 0.4 mg, iv, during clinical cyclopropane anesthesia.89 The same authors found that tachycardia that occurred in conscious subjects in response to an increasing PaCO₂ was almost abolished by 25–30 per cent cyclopropane. This may

1 The active state has been defined by Soenneblick90 as the chemical process that takes place within the contractile machinery of the activated muscle. Lange91 has suggested that more Ca²⁺ moves toward the myofilament/unit of time when the intensity of the active state is increased. The duration of the active state is closely related to the duration of depolarization of the membrane, which depends on the movement of Na⁺, Ca²⁺, and K⁺ across the membrane.

have been due to several effects of cyclopropane. Both Price92 and Garfield,89 in vivo in dogs, have shown that cyclopropane has ganglionic blocking properties. Thus, increased preganglionic sympathetic activity might not induce a heart rate response. Cyclopropane is also a sympathetic stimulant, and the effect on the heart rate of additional stimulation resulting from an increase in PaCO₂ may not be apparent. Any increase in parasympathetic tone with cyclopropane would tend to block chronotropic stimuli.82 Finally, the central stimulatory response to CO₂ would be nonspecifically depressed by any general anesthetic.

Kendig and Bunker,93 using Sprague-Dawley rats in vivo, have compared muscle resting potentials and electrolyte levels during halothane and cyclopropane anesthesia. The level of resting membrane potential has a number of determinants. These include the ratio of potassium concentration across the cell membrane, the permeability of the membrane to sodium and potassium, and the rate of active sodium transport out of the cell. They selected a tissue with a large ouabain-sensitive component and therefore presumably dependent on continuous sodium-pump activity. They found that cyclopropane, which in relatively low concentrations stimulates active sodium transport in the toad bladder,84 leads to hyperpolarization, and halothane, which at all concentrations depresses sodium transport,95 causes depolarization. Prior depletion of catecholamines, which reverses the cyclopropane-induced stimulation of sodium transport,96 similarly reverses the effect of cyclopropane on resting membrane potential. The difference between intracellular sodium concentrations during halothane and during cyclopropane anesthesia supports the concept of contrasting effects on sodium transport. Changes in resting potential are secondary to changes in catecholamine output and/or in catecholamine effects at the target organ. Therefore, halothane, which depresses catecholamine release, depolarizes the membrane. Cyclopropane hyperpolarizes the membrane in normal animals but fails to produce significant hyperpolarization in reserpined animals. The effects of cyclopropane on resting potential are predictable since it has a catecholamine-dependent effect on sodium extrusion.96

Krishna *et al.*97 have investigated the action of diethyl ether on the atrium. They found it had a direct positive chronotropic action on the isolated rat atrium independent of central innervation. Their results indicated this positive chronotropic effect was not mediated via catecholamine release, since it remained unimpaired in rat atrial preparations catecholamine-depleted by pretreatment with reserpine. The possibility of direct beta-adrenergic receptor stimulation was
also excluded by the use of dl-propranolol and d-propranolol (the latter being nine times less powerful as a beta-blocker than the former). Responses were the same in the presence of either, and therefore it can be concluded that ether has no direct effect on beta-adrenergic receptors. This is supported by the work of Brown and Crout in isolated cat papillary muscles.88 Cholinergic block is also not a factor, since concentrations of atropine that completely block the negative chronotropic actions of a test dose of acetycholine did not increase atrial rate. Jones et al. have shown that of all the measured cardiovascular indices only heart rate showed a good correlation with ether concentrations in the blood.90 This would seem to support the direct action of ether on atrial pacemakers.

Ether is known to increase sympathetic activity100 and depress vagal activity,101 although the contribution of these effects on the atrial rate in man appear to be minimal. A direct stimulant effect of ether on atrial pacemakers might be effective in some arrhythmias, by an action similar to that of atrial pacing.102 and this could possibly explain the protective action of ether against cyclopropane induced ventricular dysrhythmias.

INTRAVENOUS AGENTS

Chiba et al. have recently studied the effects of agents injected directly into the sinus node artery. Sodium pentobarbital103 produces a negative chronotropic response with sinoatrial block and AV nodal rhythm at higher doses. This bradycardia was not blocked by atropine or propranolol but could be partially antagonized by norepinephrine.

The effect of haloperidol104 on sinus acceleration induced by dopamine and norepinephrine has also been studied by this method. Generally a negative response was obtained, with sinus dysrhythmia at higher doses.

Barbiturates prolong AV junctional conduction time.105 Studies with cardiac muscle fibers have shown the initial repolarization following an action potential (ascribed to inactivation of sodium conductance) is more rapid and the later repolarization (ascribed to an increase in potassium conductance) is slowed after exposure to pentobarbital. Decreases in both the gain of sodium and the loss of potassium by isolated ventricular strips of rabbit heart have been observed after pentobarbital treatment.106 Morrow studied the effects of pentobarbital and thiopental on digoxin toxicity in intact dogs. The dose of digoxin necessary to produce ventricular automaticity was unaltered by either barbiturate, unlike the effect of halothane.107 Anesthetic agents have been shown to influence the central control of the circulation.108 Barbiturate anesthesia resets the heart rate at a higher value for a given blood pressure.109 The decrease in pulse interval is caused at least partially by the decrease in baroreflex sensitivity (the “vagal brake”).110

Many investigators have shown that ketamine in dosage ranges of as much as 10 mg/kg body weight causes a marked increase in heart rate. Traber et al.111 found that heart rate was not increased by ketamine in heart–lung preparations, and suggested that the positive chronotropic effects were not due to direct cardiac action. The same investigators, working with mongrel dogs in vivo, showed that ketamine-induced tachycardia can be completely blocked by hexamethonium or a combined vagal and alpha-adrenergic block with atropine and phentolamine.112,113 However, beta-adrenergic blocking agents were ineffective in obviating the cardiovascular response to ketamine. Traber and associates114 therefore believe that cardiovascular stimulation by ketamine is mainly due to central sympathetic stimulation and parasympathetic inhibition. They also observed a vagolytic action of ketamine. Chodoff’s patient with an acute spinal-cord transection at C8 and a functional vagotomy with 2 mg atropine iv had no change in pulse rate with ketamine.115 This would support Traber’s conclusions.

Takki et al.116 have reported an increase in plasma catecholamine levels following ketamine administration in man. Ivankovich and co-workers,117 using an animal model in which it was possible to separate central and peripheral effects of drugs, have been able to demonstrate very convincingly that the cardiovascular effects of ketamine are the result of a stimulatory action on CNS structures, and also that they are not secondary to the action of ketamine on baroreceptors, as postulated by Dowdy and Kaya.118 The work of Slogoff in neurologically intact dogs would seem to support this.119

Ketamine increases tolerance to digitalis, whether administered before or after the appearance of digitalis toxicity.120 This is surprising, since increased sympathetic activity can produce digitalis toxicity in digitalized subjects.121 Dowdy and Kaya119 showed that in an isolated heart preparation ketamine produced a negative inotropic effect and a prolonged functional refractory period, which is an effect characteristic of quinidine-like drugs. They also showed that ketamine produced a reversal of epinephrine-induced ventricular tachycardia in halothane-anesthetized dogs. This antidysrhythmic property of ketamine is probably the main factor in reversing digitalis-induced dysrhythmias and increasing tolerance to digitalis. Ivankovich et al.122 showed that ketamine caused a transient decrease in arterial blood pressure dur-
ing ouabain-induced ventricular tachycardia. Such decreases have been reported previously \(^{118–122}\) and are believed due to a direct myocardial depressant effect of ketamine. This lowering of blood pressure decreases the threshold for dysrhythmias, \(^{123}\) and this may contribute to the antidysrhythmic effect of ketamine.

When morphine was injected directly into the sinus node artery, \(^{124}\) concentrations of morphine equivalent to those producing peripheral vasodilation when given intravenously did not affect the SA pacemaker activity \textit{in situ}, and in isolated SA node preparations larger doses of morphine produced a negative chronotropic response that was not prevented by atropine. This was occasionally followed by an increased rate, which decreased with repeated administration and was blocked by propranolol. This indicates that a large dose of morphine causes norepinephrine release. Morphine did not prevent the effects of vagal stimulation or acetylcholine injected into the sinus node artery.

In isolated spontaneously beating hearts, morphine increased the bradycardic effect produced by a reduction of Ca\(^{2+}\) in the perfusate. This was not antagonized by ouabain. \(^{125}\) In hearts perfused with normal concentrations of Ca\(^{2+}\) and without previous exposure to morphine, ouabain caused tachydyssrhythmias. This antidysrhythmic effect of morphine on ouabain-induced tachydyssrhythmias may be related to the prevention of accumulation of tissue Ca\(^{2+}\). \(^{126,127}\) Mule has shown that calcium ion is transported across a methylamino-water–chloroform interface in the presence of phosphatidylcholine or phosphatidic acid, and this is inhibited by morphine, which suggests morphine may compete for sites that bind calcium ions. \(^{128}\)

Intravenous administration of morphine (1 mg/kg) has minimal effects on the cardiovascular system of man. \(^{129}\) In the conscious dog, morphine results in tachycardia and a sharp but transient increase in blood pressure. \(^{130}\) In pentobarbital-anesthetized dogs, morphine resulted in hypotension and bradycardia, due to a cardiac-depressant effect. \(^{131}\) Intravenous administration of morphine in anesthetized rats has been shown by Evans \textit{et al.} \(^{132}\) and Fennessy and Rathrnan \(^{133}\) to slow the heart rate. This response was thought to be mediated via the vagus, since section of the vagi abolished the slowing in heart rate after the first injection of morphine. Other \(^{134,135}\) believe morphine exerts a depressant effect on the sympathetic nervous system. Chiang \textit{et al.} \(^{136}\) have investigated the effects of large doses of morphine on the autonomic system of the cat. They showed that morphine has an alpha-adrenergic blocking effect, which appears to be due to competitive inhibition. They found no apparent effect on either beta-adrenergic or postganglionic myocardial parasymathetic receptors. This supports the work previously reported by Ward and co-workers, \(^{137}\) who found in chloralose-anesthetized dogs that morphine appeared effectively to block sympathetically mediated constriction of peripheral veins. They felt this action might explain, in part, the efficacy of morphine in the management of acute pulmonary edema. Marta \textit{et al.} \(^{138}\) observed that prior administration of morphine attenuated the heart rate increase after atropine 0.2 mg. iv.

The failure of atropine to prevent the bradycardia occurring when halothane is added to morphine is important. This does not occur with nitrous oxide or fluroxene. Studies \textit{in vitro} have shown a depressant effect of halothane and a cholinergic effect of morphine \(^{139,140}\) on the SA node and the automaticity (rate of Phase 4 depolarization to achieve threshold of excitation) of rabbit hearts. These bradycardic effects of morphine and halothane on the SA node may result in poor vagolytic response of the SA node to intravenous administration of atropine.

Grundy \(^{141}\) has shown, in the Langendorff preparation of the guinea-pig heart, that a single administration of meperidine, in doses from 10 mg to 2 \(\mu\)g produces a dose-dependent decrease in the amplitude of mechanical contraction, which at higher doses is accompanied by bradycardia and dysrhythmias, including AV block and cardiac arrest. Grundy and Trithart \(^{142}\) studied the effects of meperidine in papillary muscles of the cat, guinea-pig and rhesus monkey and also in the trabecula carnea of the cat. In the presence of lower concentrations of meperidine (0.22–6.5 \(\mu\)g/ml), the most consistent electrical effect was a dose-dependent diminution in the upstroke velocity, usually with a corresponding impairment of the rate of conduction and of excitability but without a significant decrease in the resting potential or the height of the action potential. This fall in upstroke velocity could be detected even when mechanical tracings showed a positive inotropic effect. Meperidine caused time-related depression of isometric peak tension and upstroke velocity without alteration in resting potential. This is similar to the effects of lidocaine in perfusion concentrations of 43.2 \(\mu\)g/ml. The authors therefore assumed that meperidine acts as a membrane stabilizer. With higher concentrations of meperidine (11.8–109 \(\mu\)g/ml) the predominant effects were decreases in resting potential and in the height of the action potential, with a marked reduction in upstroke velocity. This was thought to be due to the depression of the myocardial Na\(^{+}\)–K\(^{+}\)–Mg\(^{++}\)-dependent ATPase. Tammisto \textit{et al.} \(^{143}\) studied the cardiovascular responses to five sequential intravenous in-
jections of meperidine (1 mg/kg body weight) at 15-minute intervals. In conscious volunteers, meperidine increased the heart rate by 15 per cent. These increases were not sustained. In patients anesthetized with \(N_2O-O_2-d\)-tubocurarine there was a 20–25 per cent diminution in heart rate following meperidine administration. Stephen et al.\(^{144}\) gave meperidine to patients during \(N_2O-O_2\)-halothane anesthesia. Heart rate was not significantly changed after the injection of 30 mg meperidine, iv. This was confirmed by Davie using similar methods.\(^{146}\)

Commonly, during fentanyl administration, bradycardia occurs with a slowing of 5 to 20 beats/min.\(^{146}\) As with other opium alkaloids, it is probably due to a central stimulation of the vagal cardioinhibitory center, leading to an increased release of acetylcholine at cholinergic fiber endings in the heart.\(^{166,147}\) A direct negative chronotropic effect cannot be excluded, however. Tammisto and co-workers,\(^{143}\) in their investigations of the cardiovascular responses to five sequential intravenous injections of fentanyl (0.001 mg/kg body weight) at 15-minute intervals, showed that in conscious volunteers the heart rate tended to decrease slightly. In anesthetized (\(N_2O-O_2-d\)-tubocurarine) patients there was a 20–25 per cent reduction in heart rate.

Diazepam has been shown to produce an anti-dysrhythmic effect when given iv in a dose of 0.5–1 mg/kg body weight. It is said to elevate the diastolic ventricular stimulus threshold and augment the antidyshyrhythmics efficacy of lidocaine.\(^{148}\) Van Loon\(^{148}\) has reported the conversion of multifocal ventricular extrasystoles to sinus rhythm by diazepam 20 mg, iv, in a patient in whom lidocaine and other standard antidysrhythmic drugs were ineffective. We had one patient with multiple atrial premature contractions who reverted to sinus rhythm following administration of diazepam, 10 mg, iv. Nevins and associates\(^{158}\) have, however, reported that diazepam failed to convert digitalis-induced ventricular tachycardia to a supraventricular mechanism. Ventricular fibrillation was reported to occur when diazepam was administered to digitalized animals and digitalized man.\(^{151}\)

Hauswirth,\(^{152}\) working on isolated sheep Purkinje fibers, showed that droperidol in high dosage increased the effective refractory period, and like other antidysrhythmic agents it decreased the speed of Phase 0 depolarization. Resting potential and amplitude of the action potential were unchanged. Bertolo et al.\(^{153}\) reported that droperidol was effective in preventing not only epinephrine–halothane-induced ventricular tachycardia in cats but also ventricular fibrillation induced by coronary occlusion. They also found that droperidol increases the effective refractory period in the isolated cat papillary muscle. Kern et al.\(^{154}\) reported that droperidol prolongs the functional refractory period by inhibiting the sodium-carrying system. Since quinidine and procainamide affect the functional refractory period and sodium conductance in the same manner, droperidol can be added to this group of drugs. Ivankovich et al.\(^{155,149}\) working with dogs, showed the effectiveness of droperidol in increasing tolerance to digitalis and converting ouabain-induced ventricular tachycardia, thereby demonstrating its antidysrhythmic properties.

**The Muscle Relaxants**

It is well known that a single dose of succinylcholine causes a decrease in heart rate in children,\(^{166}\) and that the second and subsequent doses do so in adults.\(^{157}\) Cardiac arrest can occur as a result of depression of conduction at all cholinergic receptor sites. There are two possible explanations of this bradycardia and dysrhythmia with succinylcholine. First, that succinylcholine, like acetylcholine, stimulates the pressor receptors in great vessel walls with intense vagal stimulation and suppression of myocardial activity. Second, that succinylcholine has a direct action on the cholinergic receptors in the myocardium. This is supported by the work of Galindo et al.,\(^{158}\) who showed that a very small dose of succinylcholine (20 mg) can convert nodal to sinus rhythm. It is possible that small doses of succinylcholine stimulate the activity of the SA node while larger doses depress it. In addition to slowing of the heart rate, junctional rhythm may follow intravenous administration of succinylcholine.\(^{159}\) The vagal origin of these cardiac alterations is suggested by their reversal by intravenous administration of atropine.\(^{157}\) Galindo and Davis\(^{160}\) showed in rhesus monkeys (Macaca mulatta) that succinylcholine lowered the cardiac excitability threshold. The authors explained this on the basis of a sympathetic postganglionic stimulation by succinylcholine combined with a direct myocardial effect. Also, Foldes\(^{161}\) has shown that its action as a depolarizing drug is related to an alteration of the repolarizing process at the myoneural junction. That is, there is a change in permeability in the cell membrane to potassium with a loss of intracellular potassium content and a decrease in the resting membrane potential. This occurring at the cardiac cell membrane could produce dysrhythmias. Williams et al.\(^{162}\) studied the effects of trimethaphan in normal human subjects. They felt that the ability of trimethaphan to suppress circulatory responses to succinylcholine indicates these responses are mediated via sympathetic and parasympathetic efferent nerves, and are not the result of the direct action of succinylcholine on vascular smooth muscle or the heart.
Studies of isolated heart preparations have suggested the existence of multiple cholinergic receptors, which may be either excitatory (nicotinic) or inhibitory (muscarnic).\textsuperscript{157,163} Ohmura and co-workers\textsuperscript{164} investigated the effects of succinylcholine and succinylmonocholine in rabbits \textit{in vivo} and \textit{in vitro}. Succinylcholine has a predominant nicotinic (excitatory) effect \textit{in vivo} but a muscarinic (inhibitory) effect \textit{in vitro}. Succinylmonocholine produces nicotinic and muscarinic effects \textit{in vitro}, but less nicotinic effect \textit{in vivo}. They found that succinylmonocholine and succinylcholine, administered separately or together, produced bradycardia in experiments performed both \textit{in vivo} and \textit{in vitro}. A combination of the two drugs has a direct dysrhythmia effect in addition to an indirect reflexly mediated cardiac effect. Since there are structural similarities between acetylcholine and these two drugs, and acetylcholine is known to have potent muscarinic and nicotinic effects, they could alter the balance between sympathetic and parasympathetic control. If muscarinic activity predominates, the SA node would be suppressed as the principal pacemaker. Since ventricular muscle is devoid of cholinergic fibers, simultaneous nicotinic stimulation could enhance other potential pacemakers and cause cardiac dysrhythmias. The cardiac dysrhythmicity of the mixture \textit{in vivo} requires an intact central nervous system.

Dowdy and associates\textsuperscript{165} studied the effects of neuromuscular blocking agents in isolated digitalized mammalian hearts. They concluded that succinylcholine in the digitalized heart increased the effect of digitalis on the conduction system and made the ventricles more irritable. They found the heart always stopped in fibrillation. Ventricular dysrhythmias caused by digitalis overdose or by the action of succinylcholine on a digitalized heart are reversible with \textit{d}-tubocurarine. They postulated the adverse action of succinylcholine in the digitalized patient was due to a direct action on the heart.

Mathias and Evans-Prosser\textsuperscript{166} presented evidence that quite small amounts of \textit{d}-tubocurarine (5–6 mg) are effective in blocking succinylcholine-induced dysrhythmias. This evidence was obtained from patients during thiopental-induced, nitrous oxide–oxygen anesthesia. Dysrhythmias obtained were sinus bradycardia with periods of asystole. Similar results were obtained by Golosky and Umanov.\textsuperscript{167} They also obtained their results during clinical anesthesia. The dysrhythmias in their series were bradycardia, sinus bradydysrhythmia that changed into AV nodal rhythm with variable periods of asystole. Very rarely, tachycardia occurred. In this series, \textit{d}-tubocurarine, 2.5- and 5 mg, was used. In one patient who received \textit{d}-tubocurarine before succinylcholine, asystole occurred, lasting 13 seconds. With \textit{d}-tubocurarine alone a slow pulse is often present. This is assumed to be a result of increased vagal activity during light anesthesia. It is easily corrected with atropine.

Interactions between neuromuscular blocking agents and drugs used in the therapy of cardiac dysrhythmias have been described.\textsuperscript{168–174} Neuromuscular blocking agents may be potentiated by lidocaine,\textsuperscript{176,172,174} propranolol,\textsuperscript{171,174} diphenylhydantoin,\textsuperscript{173,174} quinidine\textsuperscript{175,176} and procainamide,\textsuperscript{166,174} all of which protect against atrial and/or ventricular dysrythmias. This suggests a common site of action. Wong and co-workers\textsuperscript{178} have evaluated the antidysrhythmic effects of \textit{d}-tubocurarine, gallamine and succinylcholine on dysrhythmias induced by intravenous administration of epinephrine. They studied the actions of these drugs in mongrel dogs mechanically ventilated with nitrous oxide and oxygen, and also compared the effects of the muscle relaxants with those of thiopental. The severity and incidence of ventricular dysrhythmias were significantly reduced by the muscle relaxants in comparison with thiopental. The atropinelike effect of gallamine and the ganglionic blocking action of \textit{d}-tubocurarine are possible antidysrhythmic factors. It has been suggested that succinylcholine produces both parasympathetic and sympathetic nervous system stimulation.\textsuperscript{157,160,162} It should therefore have a lesser protective effect on epinephrine-induced dysrhythmias than either \textit{d}-tubocurarine or gallamine. This has been shown to be so in the work of Wong \textit{et al.},\textsuperscript{175} described above, where it was intermediate between thiopental and the nondepolarizing relaxants in its effects on ventricular dysrhythmias produced by epinephrine.

Katz and Bigger\textsuperscript{169} studied the effects of succinylcholine in decerebrate cats anesthetized with halothane. They found dysrhythmias in nine cats and hypertension in 17 cats. These dysrhythmias could be prevented either by beta-adrenergic blockade alone or by ganglionic blockade. They concluded that the cardiovascular effects of succinylcholine were due to ganglionic stimulation. The protective effect of \textit{d}-tubocurarine thus would be in its ganglionic-blocking property. Tucker and Munson\textsuperscript{177} investigated the effects of succinylcholine and \textit{d}-tubocurarine on epinephrine-induced cardiac dysrhythmias during halothane anesthesia in mechanically ventilated dogs. They found succinylcholine markedly increased the dysrhythmogenicity of epinephrine and \textit{d}-tubocurarine slightly decreased its dysrhythmic effect. Prior administration of atropine resulted in a partial but significant reversal of this action of succinylcholine.

Dowdy\textsuperscript{178} and others\textsuperscript{178} have shown that the various antibacterial preservatives added to commercial preparations of \textit{d}-tubocurarine have a significant
The depressant effect on the contractile amplitude of stimulated rabbit atrial strips. This should be considered in evaluating the effects of d-tubocurarine. Dowdy et al. studied the effects of d-tubocurarine in isolated perfused rabbit heart, and observed a quinidine-like action.\textsuperscript{163}

The increase in pulse rate associated with gallamine has been reported as an atropine-like action, but Brown and Crout\textsuperscript{186} have claimed it has, in addition, a direct beta-adrenergic stimulant effect on the receptors of the heart. Walts and Prescott\textsuperscript{184} believed the incidence of dysrhythmias when gallamine was injected during cyclopropane anesthesia was due to a sympathomimetic effect. Lee Son and Waud\textsuperscript{185} have recently determined drug receptor dissociation constants (K\textsubscript{D}) for d-tubocurarine, metocurine (dimethyltubocurarine), pancuronium, and gallamine at the cardiac pacemaker and at the motor end-plate. Isolated guinea pig right atria and lumbarish muscles were used for the study. The ratios K\textsubscript{A} atrium:K\textsubscript{B} lumbarish were high for the curare drugs; therefore, interaction at muscarinic sites would require large doses of these drugs. For pancuronium and gallamine the ratios were low. Thus, doses producing clinical relaxation would occupy a substantial number of cardiac muscarinic receptors. The authors postulate that this might produce vagal blockade and produce the increased heart rate seen with both pancuronium and gallamine.

Pancuronium significantly increases heart rate by 20 to 50 per cent. That this does not occur when pancuronium is preceded by intravenous administration of atropine suggests the effect is largely the result of vagolytic activity.\textsuperscript{183} Pancuronium has been shown to block cardiac muscarinic receptors selectively.\textsuperscript{184,185} It not only suppresses the inhibiting effects of vagal stimulation but also antagonizes the negative inotropic and chronotropic actions of parasympathomimetic compounds without appreciably modifying their peripheral vascular effects. Geha and colleagues\textsuperscript{186} investigated the effect of pancuronium on atrioventricular conduction by His-bundle electrocardiography, and showed that atrioventricular conduction is increased. Atrial-to-His bundle (A-H) conduction is significantly decreased, while His-bundle-to-ventricle time is unchanged. This is of more than academic interest. A recent report describes a patient with atrial fibrillation controlled with digitoxin and propranolol in whom a rapid ventricular response developed following the injection of pancuronium. This enhanced AV conduction was unaffected by additional propranolol but was terminated by neostigmine.\textsuperscript{187}

### The Local Anesthetic Agents

Lidocaine is the most commonly used local anesthetic agent of the amide group. It is used therapeutically for treatment of cardiac dysrhythmias. The frequency of pacemaker discharge is said to be little reduced following rapid intravenous injection of a normal dose of lidocaine (1-4 mg/kg body weight).\textsuperscript{188} Animal experiments have shown it is difficult to produce sinoatrial block with lidocaine.\textsuperscript{189} Cheng and Wadhwa,\textsuperscript{190} however, recently reported a case in which sinus arrest followed intravenous lidocaine administration with the onset of a slow junctional rhythm. They theorize the mechanism is possibly a depression of the depolarization of impulse-creating fibers in the sino-atrial nodal pacemaker or a conduction block between the SA node and the specialized atrial fibers. Parameswaran and Goldberg\textsuperscript{191} investigated the effects of lidocaine on impulse formation and conduction in the sinus node using isolated rabbit heart preparations and standard glass microelectrode techniques. Lidocaine in concentrations of as much as 20 mg/l in the perfusate had no significant effect on the spontaneous rate of the sinus node. Sinoatrial block with occasional failure of conduction from the sinus node to the atrium occurred at concentrations of 8-10 mg/l lidocaine. Advanced sinoatrial block occurred at concentrations of 10-15 mg/l lidocaine. These concentrations of lidocaine did not produce block when the potassium in the perfusate was decreased from 4.5 to 2.5 mmol/l. These findings suggest that bradycardia during lidocaine therapy may be due to sinoatrial block and this may be modified by the level of extracellular potassium.

Lidocaine decreases automaticity (i.e., the rate of Phase 4 depolarization).\textsuperscript{192} It has little or no effect on conduction velocity or on the amplitude of the action potential. Membrane responsiveness, which is the dV/dt\textsubscript{max} of Phase 0 depolarization related to the level of membrane potential at which the action potential is initiated, is also little affected by lidocaine until concentrations of 11-50 \(\mu\text{g/ml}\) are obtained. Thus, the dV/dt\textsubscript{max} of Phase 0 depolarization may be decreased (at higher concentrations) or unchanged (at lower concentrations). It decreases the duration of the action potential and also the effective refractory period, although not to the same extent as the action potential duration.\textsuperscript{51} Lidocaine acts primarily by increasing membrane conductance for potassium. This has been demonstrated in Purkinje fibers and ventricular muscle.\textsuperscript{190-196} Lidocaine increases the i\(\text{K}_a\) current, thus leading to a decrease in the slope of Phase 4 depolarization.
At therapeutic concentrations (usually about 5 μg/ml plasma levels) lidocaine lacks effect on sodium conductance in the normal cardiac Purkinje fiber and therefore there is no change in conduction velocity. An injured Purkinje fiber would be in a partially depolarized state, with resulting inactivation of sodium conductance and a decreased conduction velocity. Lidocaine would, by its effect on membrane potassium conductance, cause the transmembrane voltage to return towards the normal level. This repolarization of the membrane would restore sodium conductance and therefore enhance conductivity. That is, the injured fibers would be restored to their rapid action potential state from the slow response state. Dysrhythmias produced as a result of re-entry phenomena would be effectively eliminated, since improved conduction would eliminate unidirectional block. This effect of lidocaine may also abolish the source of potential difference that gives rise to boundary currents.

Singh and Vaughan Williams have produced evidence seemingly contradictory to the results of the above-mentioned work. They have shown that lidocaine has a depressant effect on the cardiac action potential in rabbit atrial and ventricular tissue, decreasing the amplitude and the maximum rate of Phase 0 depolarization and slowing conduction. This depression became more marked as K0 was increased. They felt that lidocaine acted like other local anesthetics by decreasing the inward sodium current during Phase 0 depolarization. These contradictory findings may be due to both species and tissue differences. Weld and Bigger have shown that at higher plasma levels (but still within therapeutic ranges) of lidocaine there is a decrease in the voltage-dependent inward sodium current and a marked prolongation of the time necessary for reactivation of this current following repolarization. This has also been demonstrated by Rosen and colleagues in their studies of membrane responsiveness. Lidocaine produced a concentration-dependent depression of the membrane responsiveness curve. Rosen et al. suggested that lidocaine can slow conduction through its effects on Phase 0 depolarization and membrane responsiveness. This depression could convert areas of unidirectional conduction block into bidirectional conduction block, abolishing re-entry. Lidocaine is effective against automatic and re-entry dysrhythmias but not against supraventricular dysrhythmias. Mandel and Bigger found that concentrations of lidocaine in excess of 23 μg/ml were needed to alter sinus rate, the slope of Phase 4 depolarization in the sinus node, and to induce significant decreases in the amplitude of the action potential and dV/dtmax of the specialized atrial conducting fibers. Kabelka pretreated canine atrial and ventricular muscle and Purkinje fibers with K. Lidocaine produced a greater efflux of the isotope from ventricular muscle and Purkinje fibers than from atrial tissue. He suggested that lidocaine has a greater effect on potassium conductance in Purkinje and ventricular tissue than in atrial muscle. This may explain the lack of effect of lidocaine in supraventricular dysrhythmias.

Lidocaine shortens the effective and relative refractory periods of the His–Purkinje system without altering His–Purkinje conduction time. Although it slows the idioventricular rate, it has little effect on intraventricular conduction. It impairs responses of both Purkinje and ventricular muscle fibers to rapid stimulation.

Procaine, an example of the ester-type local anesthetic agent, has effects that are virtually the same as those of procainamide. The latter was introduced in order to provide a greater duration of action in cardiac therapy and a decreased incidence of central nervous system effects. Its actions resemble those of quinidine. These drugs are thought to act primarily by interfering with depolarization of the cardiac cell membrane so that there is reduction in the maximum rate of rise of Phase 0 depolarization. There is neither change in resting potential nor marked prolongation of the action potential. This decrease in dV/dtmax is believed to be due to a decrease in transmembrane sodium conductance. Evidence for this has been obtained in atrial, Purkinje and ventricular tissues. Since the entry of depolarizing current is restricted, repolarization must be of greater magnitude before a depolarization current with an adequate rate of rise for propagation is obtained. This causes prolongation of the effective refractory period. Conduction velocity is decreased. This converts uni- to bi-directional block and interrupts re-entrant pathways. Giardina has shown that the coupling interval of re-entrant premature ventricular depolarization increases in direct relationship to procainamide levels in the plasma, which would be expected if increasing concentrations of the drug increase conduction delay through the depressed segment prior to the conversion of uni- to bidirectional block. Procaine also slows the rate of spontaneous Phase 4 depolarization and is therefore effective in abolishing dysrhythmias produced by increased automaticity. The actions of these drugs are at times complex. Procainamide (and also quinidine) decreases membrane responsiveness and in high concentration markedly slows conduction. However, when Phase 4 depolarization is present over
most of the conducting system these agents in low concentrations may increase conduction velocity because they decrease the slope of Phase 4 depolarization, thus permitting an impulse to be initiated at a higher level of membrane potential. Procaine, since it increases the duration of the transmembrane action potential, may block a premature impulse either initially or when it is propagated. Although this is true, also possible is that procaine could delay the propagation of a premature impulse by its effect on the refractory period and produce a re-entry dysrhythmia. In addition, when the impulse is delayed in an area because of a local increase in the duration of the action potential, procaine, by accelerating repolarization, may exert an antidysrhythmic effect. Atioventricular conduction is delayed (P–R interval is increased), as is intraventricular conduction (QRS widened). Complete heart block, or even asystole, can occur, since the lower pacemakers which normally assume control of the ventricles may also be suppressed.

**Miscellaneous Drugs**

Atropine has long been known to block the parasympathetic or vagal inhibiting system of the heart, resulting in an unopposed acceleration effect from its sympathetic innervation. After tachycardia, simple AV dissociation has been reported as the commonest cardiac effect, but nodal (junctional) premature contractions and ventricular premature contractions have also been described. Massumi and colleagues have also reported ventricular fibrillation and tachycardia after intravenous administration of atropine for the treatment of bradycardias.

A dual action has been proposed for atropine, in which it initially stimulates vagal activity centrally and eventually blocks it peripherally. Averill and Lamb suggested that atropine has three distinct effects on the heart. First, a vagotonic effect, followed by a transient period of vagal imbalance at different levels of the conduction system and finally, prolonged parasympathetic blockade. Carrow et al. reported AV dissociation occurred rapidly, indicating its occurrence during the brief initial vagotonic phase. Bigemini appeared after 2 minutes, when vagal blockade was established.

Previous investigators showed a greater incidence of dysrhythmias. Jones et al. found AV dissociation in six of seven healthy unanesthetized subjects following injection of atropine, 0.4 mg, iv. Cardiac rate decreased in all but one, in whom, however, AV dissociation developed. No patient anesthetized with thiopental–N₂O had dysrhythmia. One patient of 11 anesthetized with diethyl ether had AV dissociation following atropine, 0.4 mg, iv. Of 12 patients receiving halothane, 40 per cent had dysrhythmias following atropine, 0.4 mg, iv. Three had AV dissociation and two had ventricular premature contractions. Of 13 patients anesthetized with cyclopropane, ten had dysrhythmias, which were ventricular in nine. The severity was dose-related for both cyclopropane and atropine. Cardiac rates increased in all anesthetized patients. Another study showed a 76 per cent incidence of dysrhythmias (12 per cent of which were ventricular) in patients anesthetized with cyclopropane-succinylcholine following 0.2 atropine, 0.2 mg, iv. The decreased incidence of dysrhythmias in the study of Carrow and co-workers, approximately 3 per cent, was thought by the authors to be due to the larger dose (3 mg, iv) and the rapidity of the injection, obviating the early vagotonic phase. All but 14 of the 123 patients studied had increases in heart rate. Also involved could be the ventilatory state of the patients, since hypercarbia and hypoxia predispose to dysrhythmias. Heart rate increases were greater with regional, diethyl ether, fluroxene, ketamine or cyclopropane anesthesia than with halothane, enfurane or neuroleptanaesthesia. These increases were significantly different only when cyclopropane was compared with halothane or enfurane.

Atropine has been reported to cause a decrease in heart rate with small doses (less than 0.2 mg) and an increase with larger doses. This slowing was related to central vagal stimulation. However, only Gravenstein has adequately reported this effect in man. Marta et al. believes Gravenstein's work may have been invalid since his results were obtained by random sampling of R-R intervals for heart rate. Marta found a high incidence (as much as 87 per cent) of sinus dysrhythmia in these patients and, therefore, R-R interval is not a true measure of heart rate. Their study suggested the need for higher doses of atropine in those medicated with Innovar or morphine. They felt this to be particularly relevant in patients with heart disease, who may have impaired cardiovascular regulation due to abnormal parasympathetic control.

Neostigmine has been reported to produce dysrhythmias in anesthetized patients and also in digitalized animals. Since neostigmine is a cholinesterase inhibitor, one would expect its effects to be due to acetylcholine accumulation. Acetylcholine releases intracellular potassium, which may initiate the release of norepinephrine. This was investigated by Ivanovich et al. Their findings indicate that since neostigmine did not increase norepinephrine release and reduced K⁺ efflux, its anticholinesterase property would not appear to be involved in its action of in-
creasing cardiac excitability. The inhibition of norepinephrine uptake by neostigmine with resulting intensification of catecholamine action could provide a rationale for episodes of neostigmine-induced cardiac dysrhythmias.

Neostigmine prolongs AV conduction. The prolonged conduction varies from bradycardia to complete AV block. In digitalized and nondigitalized dogs, neostigmine after atropine does not cause AV block. Injection of high concentrations of naloxone alone produced no side effect on the cardiovascular system. When administered in the presence of an opium alkaloid, competition for the identical receptor sites in the central nervous system takes place. As naloxone displaces fentanyl at these narcotic receptor sites, the usual low-dose effect of fentanyl became apparent, with subsequent hyperactivity of the autonomic nervous system. This includes tachycardia. This persists until all narcotic receptor sites are occupied by naloxone. Only then does the fentanyl-excited autonomic nervous system return to normal.

Summary

We have reviewed the literature on the basic electrophysiology of the heart. While there remains controversy in many areas, for example of the roles of Na⁺ and Ca²⁺ in producing the slow inward current, a somewhat dogmatic approach has been used in the interest of clarity. The information is also that accepted by the majority of workers in the field of electrophysiology.

In the second part of this paper we have reviewed the effects of agents used during anesthesia on cardiac electromechanical activity. As stated during the introduction, much of the experimental work has yet to be confirmed in man. The majority of the work has also been done on normal tissue. Future studies concerned with responses to these agents in diseased tissue will be needed for us to be able fully to apply the information to clinical situations.

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