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Halothane: Cause or Cure for Arrhythmias?

CARDIAC ARRHYTHMIAS result from abnormalities of impulse initiation, impulse conduction, or both.[1] In the more than 25 yr since this simple classification was first proposed by Hoffman and Cranefield, there have been frequent modifications, so that there are presently a number of mechanisms which can lead to abnormal impulse initiation or propagation (table 1).[2,3]

Automaticity is spontaneous diastolic depolarization whereby cardiac pacemaker fibers do not remain quiescent during diastole (phase 4), but, rather, gradually depolarize (*i.e.*, resting membrane potential becomes less negative) until threshold potential is reached. Alternatively, the pacemaker fiber is depolarized by a propagated action potential before reaching threshold. When diastolic depolarization begins from a normal level of membrane potential, *normal automaticity* exists. Normal automaticity occurs in the sinus node, subsidiary atrial pacemakers located along the sulcus terminalis, AV junctional region, and His-Purkinje system (in order of decreasing automaticity). Spontaneous diastolic depolarization leading to initiation of action potentials may also occur in fibers that normally have a high level of resting membrane potential (−80 to −90 mV: atrial and ventricular muscle, Purkinje fibers) when their resting membrane potential is reduced to around −50 to −60 mV.[2,3] This is termed abnormal automaticity.[2,3] Somewhat different from normal or abnormal automaticity is *triggered activity*, which also involves repetitive diastolic depolarization. With triggering, however, diastolic depolarization is not spontaneous. Rather, it is critically dependent on prior impulses for is initiation.[4] Triggering may occur in fibers with normal or abnormal resting membrane potentials, and in almost all cardiac fiber types.[3,5] Triggering is initiated from small changes in membrane potential referred to as early or late afterdepolarizations.[6]

Abnormal impulse propagation may lead to *slowed conduction* (1° AV block, aberrant conduction) or *conduction block* (bundle branch or fascicular block, 2° or 3° AV block). Unidirectional conduction block, along with critical alterations in refractoriness, are required for arrhythmias due to reentrant excitation.[2] Finally, conduction block is required for *reflection*, whereby the propagating impulse travels in one direction and meets an area of impaired conduction (depressed zone) where active transmission pauses.[7] The impulse, however, does not die out. Instead, it electrotonically spans the depressed zone to reexcite the proximal segment.[7]

Simultaneous abnormalities of impulse initiation and propagation are required for *parasystole* and *slowed conduction due to phase 4 depolarization.* With the former, an abnormally automatic focus is "protected" by an area of entrance conduction block. With the latter, normally automatic Purkinje fibers are made abnormally automatic by a reduction in membrane potential. The reduction in membrane potential may be caused by ischemia and infarction, high extracellular potassium, or other interventions.[2,3] Purkinje fibers with a reduced level of diastolic membrane potential, in addition to exhibiting abnormal automaticity, also conduct more slowly. Thus, there can be coexisting abnormalities of automaticity and conduction in depressed Purkinje fibers.

Anesthesiologists have long regarded anesthetics as a potential cause for cardiac arrhythmias in terms of anesthetic or interactive drug effects on essentially normal electrical properties of the heart.[8] Consequently, halothane is often considered arrythmic because it suppresses normal automaticity in pacemaker fibers,[9] slows conduction,[10] or promotes ("sensitizes") epinephrine-anesthetic arrhythmias.[11] This no longer appears to be the complete story. In this issue of ANESTHESIOLOGY, Turner *et al.* report the effects of halothane on electrical properties of Purkinje fibers derived from infarcted hearts.[12] It is apparent that *halothane has both arrhythmic and antiarrhythmic properties in this model.* In Purkinje

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TABLE 1. Mechanisms for Cardiac Arrhythmias

Altered Impulse Initiation
1. Automaticity
a. Normal—arising from normal level of membrane potential
b. Abnormal—arising from abnormal level of membrane potential
2. Triggered activity
a. From early afterdepolarizations
b. From late afterdepolarizations
Altered Impulse Propagation
1. Slowing of conduction and conduction block
2. Unidirectional conduction block and reentrant excitation
3. Conduction block, electrotonic transmission, and reflection
Simultaneous Alterations in Both
1. Parasystole
2. Slowed conduction due to phase 4 depolarization

fibers from infarcted hearts, halothane (reversibly) increased the range of premature stimulus coupling intervals which induced probable reentrant responses. That is, halothane acted to promote reentry of excitation. In contrast, in infarcted hearts, halothane decreased the rate of spontaneous activity originating from the ischemic region. Spontaneous activity could have been due either to abnormal automaticity or, as suggested by the author's figure 7, triggered activity. Thus, halothane appeared to be both arrhythmic (facilitated reentry) and antiarrhythmic (opposed abnormal automaticity and triggering).

Why are these findings important to anesthesiologists? Effective arrhythmia prevention and management, be it by pharmacologic or electrical means, is designed to alter normal or abnormal mechanisms for cardiac arrhythmias.[13] But, first, we must know how the anesthetic, or anesthetic interacting with other factors, affects those mechanisms. Consequently, anesthetics or drugs used to treat arrhythmias may act in strange or unpredictable ways to promote or oppose arrhythmias, depending on the circumstances. For example, halothane and verapamil *were*, but lidocaine *was not*, effective in preventing malignant ventricular tachyarrhythmias following acute coronary occlusion and reperfusion in dogs.[14] A possible explanation for this finding, one somewhat at odds with the commonly held notion that lidocaine is universally effective against ventricular tachyarrhythmias, is that verapamil was effective in suppressing abnormal automaticity.[15] Alternatively, verapamil abolished reentry in depressed fibers by converting areas of unidirectional conduction block to complete block. Regardless, far worse than ineffective drug or electrical therapy for arrhythmias, would be the exacerbation of existing arrhythmias or the production of new ones with inappropriate therapy. A good example for the latter is the initiation of dangerous ventricular tachyarrhythmias by DC cardioversion in patients with overt or covert (secondary to hypokalemia) digitalis toxicity. Arrhythmias in the setting of digitalis toxicity are likely to involve abnormal mechanisms, including triggering.[16] From the above, it is extremely important to select the proper therapy, not only to correct the rhythm disturbance, but also for the prevention of new and possibly more dangerous arrhythmias.

I welcome the contribution by Turner *et al.* in this issue of ANESTHESIOLOGY which suggests that halothane can be both a cause and a cure for arrhythmias—instead of just a cause, the earlier held notion.[8–10] I look forward to additional studies of anesthetic and interactive drug effects on abnormal cardiac electrophysiologic mechanisms.

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