AUTONOMIC CONTROL OF CARDIAC RHYTHM*

BRIAN F. HOFFMAN

Department of Pharmacology
Columbia University College of Physicians and Surgeons
New York, N. Y.

THE objective of this paper is to describe the manner in which the mediators liberated by the postganglionic nerve terminals of the sympathetic and parasympathetic divisions of the autonomic nervous system influence the generation and conduction of impulses in the heart.

In essence this is a description of the effects of norepinephrine and acetylcholine on cells of the mammalian sinoatrial node, atrium, and atrioventricular node and the effects of norepinephrine on cells of the His-Purkinje system and ventricle.

For the most part the description will be made in terms of the transmembrane potentials recorded through an intracellular microelectrode from a single cardiac cell or fiber.[1] The main reason for using this technique in a study of the control of cardiac rate and rhythm is that it provides graphic evidence of two sorts which cannot be obtained readily from the electrocardiogram. First, it permits records to be obtained from a single cell or small group of cells in the cardiac syncytium. Thus instead of having to read the output of a presumptive pacemaker from the P wave or QRS complex, one is able to record directly from the automatic cell or cell group acting as pacemaker. This permits more precise identification of both actual and latent pacemakers in terms of location and mechanism. Second, records of transmembrane potentials show the mechanism, to the extent that the electrical signal can be thought of as a mechanism, by which agents alter rate or rhythm. This has permitted a better understanding of the action of autonomic mediators on cardiac automaticity and conduction.

Before considering the manner in which autonomic mediators influence cardiac cells it is necessary to describe a typical recording of cardiac transmembrane potential, the changes in transmembrane

*Presented at the *Conference on Mechanisms and Management of Arrhythmias,* held by the New York Heart Association at the Hotel Waldorf-Astoria, New York, N. Y., January 24, 1967.

Original studies were supported in part by grants from the U.S. Public Health Service (HE-08508 from the National Heart Institute); the American Heart Association, Inc.; the New York Heart Association, Inc.; and from Eli Lilly and Company.

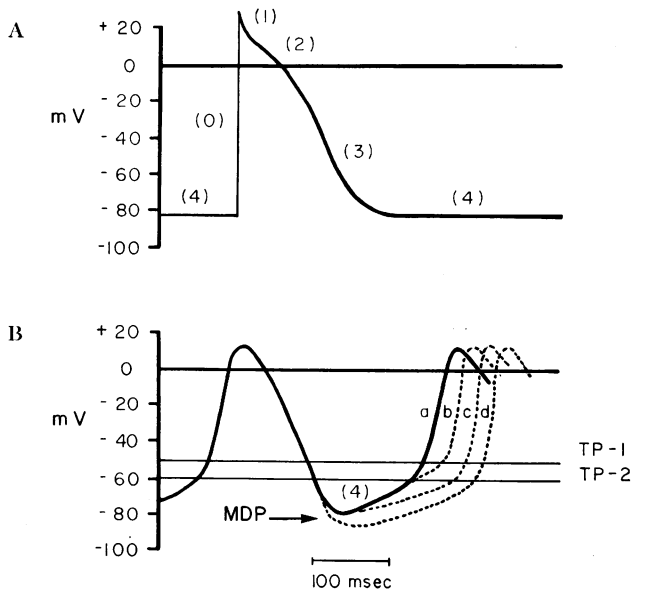

Fig. 1. Diagrammatic records of transmembrane potentials recorded from a single atrial muscle fiber (*A*) and a single fiber in the sinoatrial node (*B*). The record in A shows a steady resting potential (phase 4) and an action potential with a rapid phase of depolarization (phase 0) and slower repolarization (phases 1, 2, and 3). The record in B, from the nodal fiber, shows a slower depolarization during the action potential upstroke, repolarization which reaches a maximum value (MDP) and then a slow, spontaneous depolarization during phase 4. The slow phase 4 depolarization lowers membrane potential to the threshold potential (TP-1) and initiates an automatic beat (*a*). A change in the level of threshold potential to TP-2 delays the response to (*b*); an increase in cycle length also might result either from a decrease in the slope of phase 4 depolarization (*c*) or from an increase in maximum diastolic potential (*d*).

potential which are responsible for normal automaticity, and the changes commonly responsible for alterations in rate.[1, 2] Figure 1 shows records of transmembrane potentials from an atrial fiber (*A*) and a fiber in the sinoatrial node (*B*). For the atrial fiber it is possible to describe a resting potential (phase 4) and a transmembrane action potential. The latter usually is subdivided into phases of depolarization (phase 0) and repolarization (phases 1, 2, and 3). It should be noted that the resting, or diastolic, potential (phase 4) is constant until the onset of phase 0. The transmembrane potential recorded from the automatic fiber in the sinoatrial node differs in several respects from that of the atrium; the rate of depolarization during phase o is less and the voltage-time course of repolarization is different. More important, however,

is the voltage-time course of membrane potential during phase 4. At the end of repolarization the fiber attains its maximum diastolic potential (MDP); immediately thereafter a slow depolarization lowers transmembrane potential toward zero. If this slow diastolic depolarization reduces transmembrane potential to a critical value called the threshold potential (TP), excitation of the cell occurs and an action potential results. This spontaneous depolarization during phase 4 is the normal automatic mechanism for cardiac cells and is present in the sinus node, ectopic supraventricular pacemakers, and cells of the His-Purkinje system. Since slow diastolic depolarization is present normally in all these cells,[3] they may all be designated as latent pacemakers; that cell which first attains threshold and generates an action potential usually serves as pacemaker. Exceptions to this rule occur if conduction from the cell which fires first is slow enough to permit another automatic cell to activate the heart or if two or more automatic cells which are appropriately separated in the heart fire more or less synchronously.

The record in Figure 1*B* also demonstrates the usual changes in membrane behavior which are responsible for changes in the rate of a normal automatic fiber. Briefly stated, anything which changes the time required for phase 4 depolarization to lower membrane potential to the threshold potential will change the rate of an automatic fiber. The most obvious variable is the slope of membrane potential during phase 4. Other variables which have been shown to alter rate are the level of maximum diastolic potential and threshold potential. An increase in the slope of phase 4, a decrease in maximum diastolic potential, or an increase in the level of threshhold potential (i.e., a larger negative value) will increase the rate of the automatic fiber. A change in any one variable in the opposite direction will decrease the rate; simultaneous changes in two or more will act synergistically or antagonistically depending on the direction of change for each.

In theory, then, the autonomic nervous system might change the rate by acting on any one or all three of these variables. In addition, effects on rate and rhythm might result from simultaneous effects on different automatic foci and from effects on conduction that will be described subsequently. Also, it is important to realize that equal concentrations of mediator may have effects on different cells and cell types which differ either quantitatively or qualitatively, and that during activation of the efferent autonomic cardiac fibers the concentration of

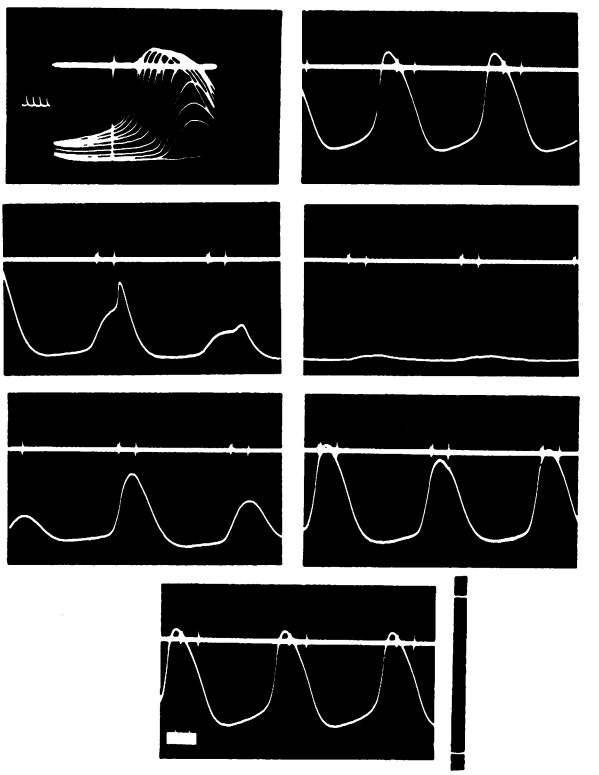

Fig. 2. Transmembrane potentials recorded from a fiber in the sinoatrial node of the isolated rabbit atrium showing the effects of acetylcholine. In each figure the upper trace serves as the zero reference line and also shows an electrogram recorded directly from atrial muscle. Time marks in the first frame are at intervals of 10 and in the last frame at intervals of 100 msec; voltage calibration after the final frame = 100 mV. The first frame shows the effects of acetylcholine as a series of superimposed traces; the other frames show the same changes in separate records. Note that after local application of acetylcholine from an extracellular micropipette there is a decrease in the slope of phase 4, an increase in maximum diastolic potential, and then a decrease in the response recorded through the microelectrode until only small graded electrotonic potentials remain. At this time atrial activity continues, as shown by the electrogram. The last two frames show recovery from the effects of acetylcholine.

mediator achieved in the vicinity of different cells may be quite variable.

The effects of acetylcholine or vagal stimulation on automaticity of the sinoatrial node have been demonstrated by several investigators[4, 5] and are similar to those shown for the sinus venosus[6, 7] of the frog. The action of acetylcholine on a pacemaker cell results in three changes: there is a decrease in the slope of diastolic depolarization, an increase in maximum diastolic potential, and usually a shift of the pace-

maker to another site in the node. If vagal action is weak, the first two effects predominate; if vagal action is stronger, a shift in the site of the pacemaker seems to be an inevitable consequence. This shift in site may result either from differences in local sensitivity to acetylcholine or from differences in the local concentration of transmitter. In the case of vagal stimulation, the density of nerve terminals may not be uniform; in the case of administered acetylcholine, access of drug to sensitive membrane may not be uniform. Thus it is difficult to evaluate the two possibilities separately or to rule out one or the other.

With high concentrations of acetylcholine two other effects may occur. Phase 4 depolarization may be abolished completely, resulting in sinus arrest, or conduction within the node may be markedly impaired. The latter effect is shown in Figure 2. Although we are familiar with the concept that acetylcholine increases decrement of conduction to the point of block in the atrioventricular node,[8] the fact that it also causes decrement and block in sinus fibers is less familiar.[9] This observation is of some importance in that it shows one possible mechanism by which an impulse initiated in the sinus node might be prevented from exciting the atria; also, it shows that an impulse conducted in the atria may be blocked during its passage into the node and thus fail to discharge a sinus pacemaker. Both these possibilities are of some importance in a consideration of supraventricular arrhythmias.

The effects of acetylcholine on automatic atrial cells located outside the sinoatrial node are similar to those just described but often are less intense. Thus automatic cells of the crista terminalis, whether they are true or latent pacemakers, will be slowed as a result of a decrease in the slope of phase 4 depolarization and an increase in maximum diastolic potential. It is of interest in this regard to comment on certain of the specialized atrial fiber tracts described most recently by James.[10, 11] We have attempted to record from the anterior and posterior internodal tracts in the rabbit heart, structures identified as the sinoatrial ring bundle by Paes de Carvalho,[12] and from the anterior internodal tract and Bachmann's bundle in the canine atria.[13] Although the fibers of the anterior internodal tract and Bachmann's bundle show many electrophysiological characteristics which reinforce the concept that they are different from ordinary atrial muscle, we have not recorded phase 4 depolarization from either structure. It thus is not permissible to assume that all specialized fibers will be automatic.

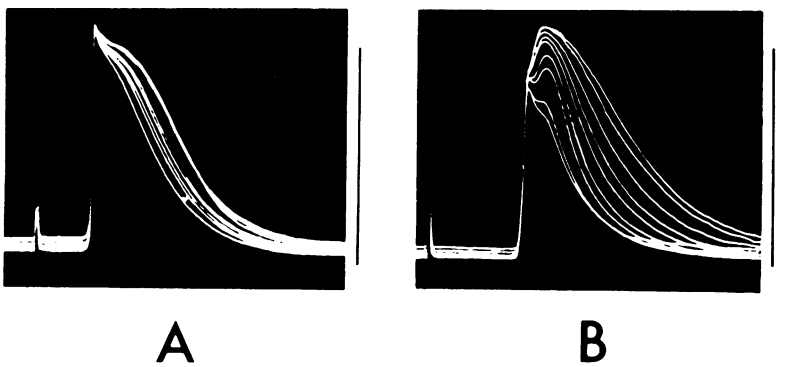

Fig. 3. The effects of acetylcholine on transmembrane action potentials recorded from two different types of fibers in the isolated rabbit atrium. The preparation was driven by regularly applied stimuli and acetylcholine was applied locally, in the vicinity of the recording electrode, from a small extracellular micropipette. In *A* it can be seen that acetylcholine increases the rate of repolarization and slightly increases the resting potential but does not change the amplitude of the action potential upstroke (phase 0). In *B*, application of the same concentration of acetylcholine to a different type of fiber causes, in addition to an increase in the rate of repolarization and the magnitude of the resting potential, a significant decrease in the amplitude of the upstroke of the action potential. (Modified from Paes de Carvalho, ref. 19).

One other action of acetylcholine deserves brief mention; this is its well-known effect on the duration of action potential. Changes in the duration of action potentials recorded from fibers in the sinus node are not marked; acceleration of repolarization becomes more prominent for automatic cells of the crista terminalis and is most marked in the case of ordinary atrial muscle fibers. Recently[14] it has been shown that the action potential of atrial fibers consists of two components and that the latter part of the upstroke may be inscribed at a lower rate than the initial segment of phase o (Figure 3). If fibers showing this type of upstroke are exposed to acetylcholine, not only is repolarization enhanced but also the amplitude of the action potential is decreased. This change in amplitude of the action potential may have effects on conduction; for example, it has been implicated as one cause of the changes in A-V transmission induced by acetylcholine.[1]

The effects of stimulation of the sympathetic nerves or of administration of catecholamines on automaticity of sinus node fibers have been studied by a number of investigators.[15, 16] In general, the changes in rate caused by the action of sympathetic transmitters such as norepinephrine result largely from an increase in the slope of diastolic de-

polarization. Again, as in the case of vagal action, shifts in the site of the pacemaker are frequent; this has made it difficult to evaluate the possibility that threshold potential also may be changed. One other effect of catecholamines is important if we consider its action on fibers which are not normal. When the resting potential has been decreased by a variety of experimental interventions or pathological conditions, exposure of the fibers to catecholamines usually causes an increase in the magnitude of the resting potential. In some instances this increase in resting potential may improve excitability and responsiveness to the extent that conduction will return to areas of block. In this sense one might assume that effects of sympathetic activity on atrial rhythm also may result from abolition of partial, or complete, block between the pacemaker and the remainder of the atrium. In general, the actions of the parasympathetic and sympathetic transmitters are opposite with respect to the initiation and conduction of impulses.

The effects of autonomic transmitters on the electrophysiological properties of the atrioventricular node are well known[1, 17, 18] and will not be reviewed at this time. Instead, we shall consider the actions of acetylcholine and catecholamines on the fibers of the His-Purkinje system. We have consistently found that locally applied acetylcholine, even in high concentrations, does not change the transmembrane potentials recorded from fibers in the His bundle, the bundle branches, or the peripheral Purkinje system; these studies have employed tissue from canine[1] and leporine[19] hearts. It can be assumed, therefore, that activation of the vagus will not by any direct action influence the automaticity of the cells which make up these tissues. On the other hand, catecholamines have a pronounced effect on the slope of diastolic depolarization of the Purkinje fibers. The rate of diastolic depolarization is increased and under appropriate conditions a latent pacemaker will become an actual pacemaker, or multiple pacemakers may appear. There are no important direct effects on the level of maximum diastolic potential of normal fibers. In relation to the effects of the autonomic nervous system on cardiac rate and rhythm one thus would expect that activation of the vagus would slow supraventricular pacemakers by a direct action and permit escape of subsidiary automatic foci in the His-Purkinje system. This seems to be a fortunate arrangement since, under most conditions of reflex activation of the vagus, there is a simultaneous decrease in sympathetic activity. Were acetylcholine to

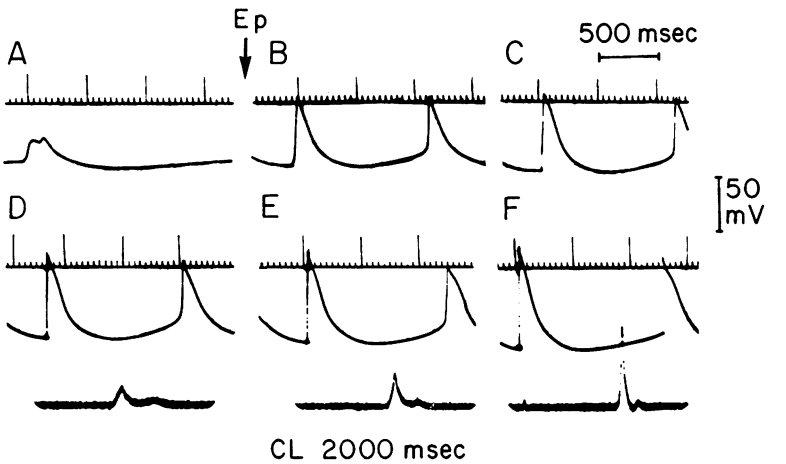

Fig. 4. Effects of epinephrine on transmembrane potentials from a deteriorated, partially depolarized canine Purkinje fiber stimulated at a cycle length of 2000 msec. Deterioration resulted from anoxia in conjunction with the sustained low rate. *A*. Partially depolarized fiber. *B-F*. Addition of l-epinephrine (Ep), 10^{-6} γ/cc, resulted in restoration of maximum diastolic potential toward normal and improvement in amplitude and dV/dt of the action potentials. Also note increased spontaneous phase 4 depolarization and resultant spontaneous beats. Combination of driven and spontaneous beats caused bigeminy. The first action potential in each pair was driven; the second occurred spontaneously. Maximum upstroke velocity (dV/dt) of driven action potentials in *D-F* indicated by amplitude of differentiated spike in bottom trace. (Modified after Singer et al.[22])

decrease the automaticity of all cardiac cells, cardiac arrest would be frequent.

As in the case of acetylcholine, the effects of catecholamines depend in part on the condition of the fiber and of the heart. Under some conditions the action of norepinephrine or epinephrine may impair conduction in the His-Purkinje system. This occurs if there is a marked generalized increase in the slope of diastolic depolarization and if threshold potential is low, i.e., closer to zero than usual. As a result of these two changes the action potential of the Purkinje fibers may be initiated at such a low level of membrane potential that upstroke velocity and amplitude are reduced.[20] Such changes in the amplitude and configuration of the action potential would decrease the velocity of conduction and increase the likelihood of block. In extrapolating from these findings, made on *in vitro* preparations of canine Purkinje fibers, to the diseased heart in situ, one might assume that under certain conditions enhanced sympathetic activity might impair conduction

from automatic foci. Conversely, if the transmembrane potential of Purkinje fibers is low because of the action of drugs or pathological processes, it has been clearly demonstrated that catecholamines in proper concentration increase resting potential and improve conduction.[21, 22] Moreover, they may do this without causing much if any increase in automaticity (Figure 4). Again, we are forced to accept the fact that the action of autonomic mediators depends in large part on their concentration, on the condition of the tissue, and on the sensitivity of the tissue to the mediator.

In summary, although the primary direct actions of acetylcholine and norepinephrine on the formation and conduction of impulses can be demonstrated with ease on normal preparations of isolated cardiac tissue, it is not always possible to predict the net effect of variations in autonomic tone on the rhythm of the normal heart. Also, it is even more difficult to predict the effect of such changes in the presence of cardiac disease or after administration of drugs which act on the heart. Because of the possibility that variations in vagal and sympathetic tone may cause arrhythmias due either to altered automaticity or to altered conduction, it seems likely that at least some of the disturbances of rhythm encountered in the clinic are a result of action of the autonomic nervous system.

REFERENCES

1. Hoffman, B. F. and Cranefield, P. F. *Electrophysiology of the Heart.* New York, McGraw-Hill, 1960.
2. Weidmann, S. *Elektrophysiologie der Herzmuskelfaser.* Bern, Huber, 1956.
3. Hoffman, B. F. and Cranefield, P. F. The physiological basis of cardiac arrhythmias. *Amer. J. Med. 37*:670-84, 1964.
4. West, T. C. Ultramicroelectrode recording from the cardiac pacemaker. *J. Pharmacol. Exp. Therap. 115*:283-90, 1955.
5. Dudel, J. und Trautwein, W. Der Mechanismus der automatischen rhythmischen Impulsbildung der Herzmuskelfaser. *Pflügers Arch. Ges. Physiol. 267*: 553-65, 1958.
6. Castillo, J. del and Katz, B. Production of membrane potential changes in the frog's heart by inhibitory nerve impulses. *Nature 175*:1035, 1955.
7. Hutter, O. F. and Trautwein, W. Effect of vagal stimulation on the sinus venosus of the frog's heart. *Nature 176*:512-13, 1955.
8. Cranefield, P. F., Hoffman, B. F. and Paes de Carvalho, A. Effects of acetylcholine on single fibers of the atrioventricular node. *Circ. Res. 7*:19, 1959.
9. Paes de Carvalho, A. and Almeida, D. F. Spread of activity through the atrioventricular node. *Circ. Res. 8*:801, 1960.
10. James, T. N. The connecting pathways between the sinus node and A-V node and between the right and left atrium in the human heart. *Amer. Heart J. 66*:498, 1963.
11. James, T. N. Cardiac innervation: Anatomic and pharmacologic relations, *Bull. N.Y. Acad. Med. 43*:1041-46, 1967.
12. Paes de Carvalho, A., de Mello, W. C. and Hoffman, B. F. Electrophysiological

evidence for specialized fiber types in rabbit atrium. *Amer. J. Physiol. 196:* 483, 1959.

13. Wagner, M. L., Lazzara, R., Weiss, R. M. and Hoffman, B. F. Specialized conducting fibers in the interatrial band. *Circ. Res. 18:*502-18, 1966.
14. Paes de Carvalho, A., Hoffman, B. F. and Langan, W. B. Two components of the cardiac action potential. *Nature 211:*938-40, 1966.
15. West, T. C., Falk, G. and Cervoni, P. Drug alteration of transmembrane potentials in atrial pacemaker cells. *J. Pharmacol. Exp. Therap. 117:*245-52, 1956.
16. Trautwein, W. Generation and conduction of impulses in the heart as affected by drugs. *Pharmacol. Rev. 15:*277-332, 1963.
17. Hoffman, B. F., Paes de Carvalho, A., de Mello, W. C. and Cranefield, P. F. Electrical activity of single fibers of the atrioventricular node. *Circ. Res. 7:*11-18, 1959.
18. Paes de Carvalho, A. and Langan, W. B. Influence of extracellular potassium levels on atrioventricular transmission. *Amer. J. Physiol. 205:*375, 1963.
19. Paes de Carvalho, A. Excitation of the atrioventricular node during normal rhythm. Effects of acetylcholine. In: *Mechanisms and Therapy of Cardiac Arrhythmias,* Dreifus, L. S. and Likoff, W., eds., New York, Grune, Stratton, 1966, pp. 341-352.
20. Hoffman, B. F. Impulse transmission in the mammalian heart. *Circ. Res. 14 & 15,* Suppl. II: 202-209, 1964.
21. Hutter, O. F. and Trautwein, W. Vagal and sympathetic effects on the pacemaker fibers in the sinus venosus of the heart. *J. Gen. Physiol. 39:*715-33, 1956.
22. Singer, D. H. In preparation.