

## Slow Channel Inhibitors, Anesthetics, and Cardiovascular Function

VERAPAMIL was one of the two original compounds known as "calcium antagonists." In fact, the group is more properly classified as "calcium channel or slow channel inhibitors."<sup>1</sup> Although none of the drugs are presently available for clinical use in the United States, it is likely that one or more will be approved by the FDA within the next six months.<sup>2</sup> Consequently, the article in this issue of ANESTHESIOLOGY by Kapur and Flacke is most timely.<sup>3</sup>

The mechanism of action of the slow channel inhibitors is generally considered to be interference with calcium ion flux across excitable membranes. This flux is responsible for the plateau phase (phase 2) of the action potential in excitable membranes and, indeed, almost the total depolarization action potential in sinoatrial and atrio-ventricular nodal tissue (fig. 1).<sup>4</sup> This ion movement channel is referred to as "slow" in contrast to the "fast" sodium channel which is responsible for the rapid phase 0 and 1 depolarization in muscle and other excitable membranes. For both channels, there appears to be at least two different loci of action. On the extracellular membrane surface is a voltage dependent gate which is either open or closed (fig. 2).<sup>5</sup> Electrical depolarization of the membrane opens the gate and repolarization closes it. A second gate on the intracellular surface modulates ion influx. The major factor controlling the inner calcium ion gate is thought to be the cyclic nucleotides. Cyclic AMP facilitates widening of this gate and increases calcium ion flux and cyclic GMP

has the opposite effect. The effects of adrenergic and cholinergic stimulation on the membranes are thought to be modulated through these mechanisms. For the fast channel, the local anesthetics are postulated to act at the inner-modulating gate in similar fashion. It would appear that verapamil also acts via the inner locus. However, the other major slow channel inhibitor, nifedipine, probably blocks via the voltage dependent, "all-or-nothing," outer gate.<sup>1,4</sup>

Any drug which alters slow channel kinetics could be expected to have four different pharmacologic effects. All drugs tested thus far possess negative chronotropic, dromotropic (conduction velocity), inotropic, and vasodilating actions. However, the relative potency of the effects are variable for different drugs. Verapamil depresses heart rate and conduction much more (10 times) than contractile and vascular smooth muscle function. Nifedipine is equally potent for all four actions. The other widely tested drug, diltiazem, closely resembles verapamil.<sup>1,4,6</sup> The direct vasodilatory and negative inotropic effects appear to be equal with all three drugs, however. In contrast to the statement by Kapur and Flacke,<sup>3</sup> both verapamil and diltiazem are also fast channel blockers. In fact, the dextro isomer of verapamil is practically devoid of slow channel inhibition (the commercial preparation is the racemic mixture). Nifedipine is more potent (intravenous dose 5-15  $\mu\text{g}/\text{kg}$ ) than the other two (75-150  $\mu\text{g}/\text{kg}$ ). All are well absorbed from the gastrointestinal tract, but verapamil is subject to hepatic extraction and hence the bioavailability is lower. Elimination half-lives are similar (3-6 h) and all are

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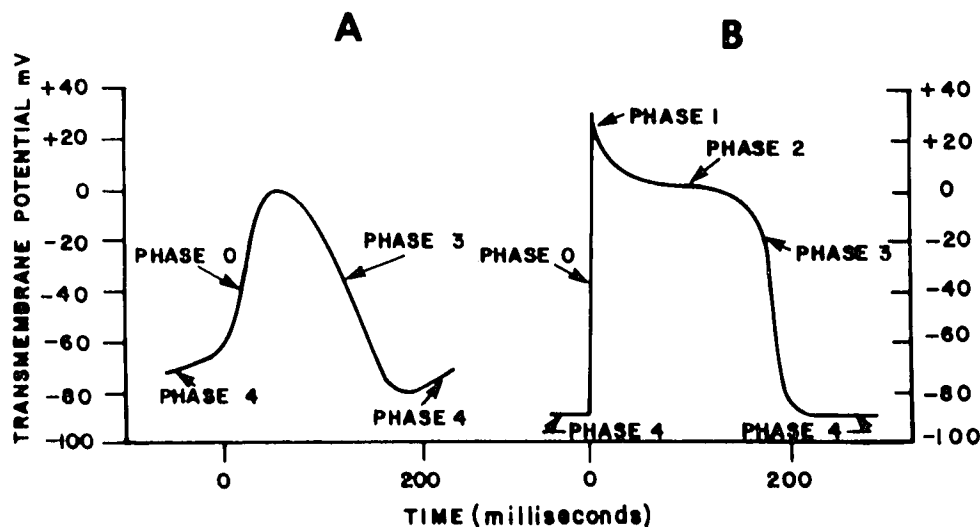


FIG. 1. Typical action potentials recorded from cells with sinoatrial mode (A) and ventricular myocardium (B). Note the slower rate of rise and smaller amplitude of the sinoatrial node action potential. (Reprinted with permission of the author and publisher, *Ann Intern Med* 93: 876, 1980.)

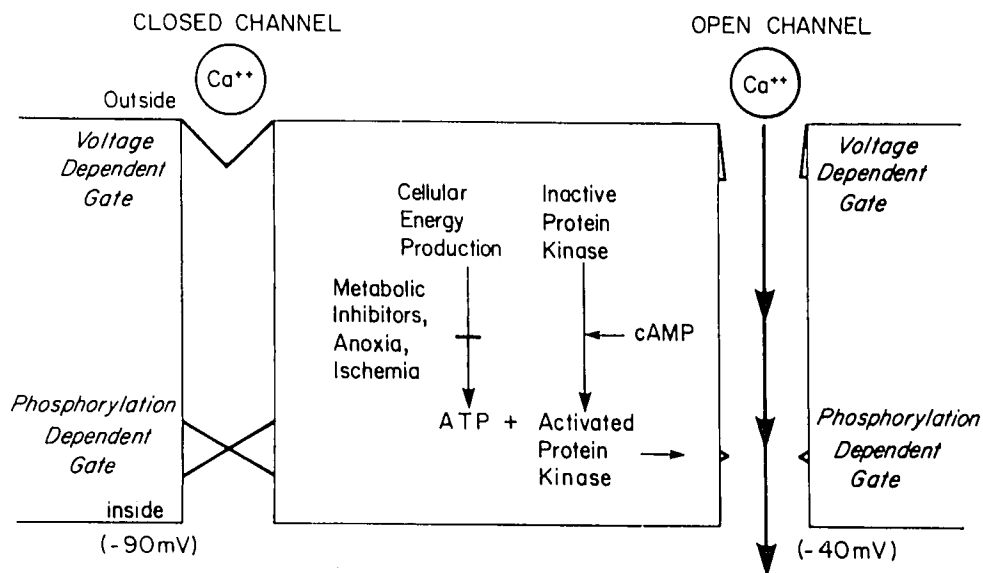


FIG. 2. Schematic model of a slow calcium channel. (Reprinted with permission of the author and publisher, *Ann Intern Med* 93:877, 1980.)

extensively protein bound (90 per cent) and metabolized. At present, the two well-established clinical indications for the drugs are the treatment of arrhythmias and ischemic heart disease.<sup>1,6</sup> As might be predicted from the basic pharmacology, verapamil and diltiazem are more effective antiarrhythmic drugs. In contrast to the use proposed by Kapur and Flacke, the major antiarrhythmic usefulness of these drugs is in the treatment of supraventricular arrhythmias. They also have been used to slow the ventricular response to atrial fibrillation and flutter.<sup>1,6</sup> The more widespread use will undoubtedly be for the treatment of patients with ischemic heart disease, particularly where coronary vasospasm is a component.<sup>1,6</sup> The combination of a negative chronotropic, negative inotropic, coronary vasodilatory, and peripheral vasodilatory effects all are positive features in the treatment of ischemic heart disease. Less well-established uses include treatment of obstructive cardiomyopathy (asymmetric septal hypertrophy) and for unloading the failing heart. A major disadvantage of verapamil and diltiazem compared to nifedipine is the high incidence of heart block produced. A combination of these former drugs and beta-adrenergic blocking drugs is contraindicated primarily for this reason. Although there are a number of other clinical situations where smooth muscle relaxation is desired, such as bronchospasm, pulmonary hypertension, biliary spasm, renal colic, etc., there is minimal information concerning the use of slow channel inhibitors in these states. However, they certainly are possible sites of pharmacologic action. Consequently, an increasing number of surgical patients will be treated with these drugs.

In Kapur and Flacke's study there appeared to be

almost a qualitative difference in the effect of verapamil on the pumping function of the heart in one of the animals anesthetized with halothane.<sup>3</sup> Such variability in response to both verapamil and nifedipine in awake animals and humans has been noted previously.<sup>1,6</sup> Although the *in vitro* negative inotropic and vasodilatory effects are equal, the two postulated mechanisms for this discrepancy are the reflex sympathetic response to the initial cardiovascular depression and the positive effect of decreased afterload on cardiac output. Usually nifedipine produced less depression of cardiac output than verapamil, possibly because the lack of fast channel blocking activity preserved the reflex response. The direct effect of a decrease in afterload on cardiac output depends in large measure on the basal function of the ventricle. Decreased afterload has little effect on cardiac output in normally functioning hearts, whereas it may be extremely beneficial in depressed hearts.<sup>7</sup> In fact, *increased* afterload in halothane depressed hearts has been shown to produce further failure.<sup>8</sup> If the depressed ventricle is more susceptible to the negative inotropic effects of the drug as suggested by Kapur and Flacke,<sup>3</sup> then another mechanism might be the interference in synchronous atrial contraction. The atrial "kick" provides a little extra pump function during anesthesia.<sup>9</sup> If this is a mechanism, then nifedipine would be expected to show less depression of cardiac output in the halothane anesthetized heart. In view of the importance of this interaction for the clinical use of these drugs, clearly further studies are necessary with both verapamil and nifedipine to elucidate the nature of the interaction between slow channel inhibitors and anesthetics on ventricular function.

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## Another Point of View on Intermittent Hypoxia

IN 1946, Von Euler and Liljestrand<sup>1</sup> observed that ventilation with hypoxic gas mixtures induced pulmonary vasoconstriction. It was soon widely appreciated that hypoxic pulmonary vasoconstriction (HPV) could be a control mechanism for adjusting regional blood flow, serving to divert blood away from regions of alveolar hypoxia and thereby reducing the scatter of ventilation-perfusion ratios. In other words, HPV might be one of the very few active (as opposed to passive) intrapulmonary physiologic responses that reduce arterial hypoxemia.

Despite a considerable body of research that has accumulated in the subsequent thirty years, the importance of HPV in clinical practice remains a controversial topic. Some believe that HPV in the adult is just a physiologic curiosity or a vestigial remnant of a fetal property. Others, including this writer, believe that HPV may underly the signs and symptoms of a wide variety of pathophysiologic states from high-altitude pulmonary edema to hypoxemia during general anesthesia.<sup>2,3</sup>

A series of studies from the laboratory of Drs. E. Wahrenbrock and J. L. Benumof in San Diego have confirmed and extended the observations of earlier workers and provided overwhelming evidence of the

reproducibility and functional possibilities of HPV. Their studies together with those of Dr. M. K. Sykes in England and Dr. L. J. Bjertnaes in Norway have particularly warranted the serious attention of anesthesiologists,<sup>4-6</sup> for all are agreed that HPV is inhibited by many volatile anesthetic agents and by other drugs (*e.g.*, nitroprusside) employed by anesthesiologists. The work carries the clear implications that arterial hypoxemia during anesthesia may often follow abolition of HPV. The same mechanism, namely HPV, is responsible for reducing blood flow through atelectatic regions of the lung.<sup>7</sup> Thus, patients or animals with substantial atelectasis or regional hypoxia show a deterioration of arterial oxygen tension when HPV is abolished pharmacologically.<sup>8</sup>

A rational therapeutic aim would be to improve arterial oxygenation by enhancing HPV. This is the subject of a paper by A. F. Pirlo, J. L. Benumof, and F. R. Trousdale in this issue of *ANESTHESIOLOGY*.<sup>9</sup> These authors have observed that diversion of blood flow from the hypoxic left lower lobe of the dog is enhanced following three or four preliminary brief exposures to hypoxia. Hypoxia was induced either by alternating oxygen with nitrogen or by inducing atelectasis repeatedly; and the results were essentially the same with either method. The authors conclude from these experiments that "in order to maximize

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