Calcium slow channel blockers:  
Physiology and anesthetic interactions  

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The author reviews the role of calcium in the cardiovascular system and explains the pharmacologic and physiologic effects of the three major calcium channel blocking agents available today. The proposed interactions between calcium blockers and inhalational anesthetics are also elucidated.

The anesthetist is well aware of the fatal consequences of a calcium abnormality when confronted with the metabolic syndrome malignant hyperthermia. The clinical emergence of a new class of drugs, the calcium slow channel blocking agents, emphasizes the need to review the role of calcium in the cardiovascular system in general.

With the recent Federal Drug Administration (FDA) approval of intravenous verapamil and oral nifedipine, it will not be long before many surgical candidates present for anesthetic evaluation on calcium channel blocking therapy. These agents will have a major impact on the therapy of numerous cardiovascular disorders including cardiac arrhythmias, myocardial ischemic states, hypertension and hypertrophic cardiomyopathy.1

Consequently, the role of calcium in myocardial specialized conducting cells and smooth muscle contraction is elucidated in this article. A review of the three major calcium blocking agents and indications for their use, in turn, provides a preview of the type of patient the anesthetist could encounter on calcium channel blocking therapy. Lastly, although still in the dawn of discovery, some proposed interactions between calcium channel blocking agents and inhalational anesthetics are explored.

The membrane action potential

The calcium ion is the functional link between the electrical excitation initiated by pacemaker cells in the heart and the actual mechanical contraction of contractile cardiac tissue. The electrical activity of myocardial cells is dependent upon ionic movement across cell membranes. In the heart, that membrane is called the sarcolemma. Electrical stimulation of the cardiac cell results in a membrane action potential that is a five phase process (Table I).

Phase 4—Membrane resting potential: The voltage difference between the inside and outside of a non-stimulated cardiac cell is the membrane resting potential, –90 millivolts. It is due primarily to the movement of the potassium ion. The con-

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The concentration of potassium is greater inside the cell, therefore, potassium tends to diffuse outward. However, the opposing strong ionic negative force within the cell counterbalances the simple diffusion out of the cell and an equilibrium of forces is reached at −90 millivolts.

**Phase 0—Depolarization:** Although the sarcolemma is impermeable to sodium, when a stimulus of sufficient intensity is applied to the cell membrane, sodium specific channels open and sodium rapidly enters the cell. The fast channel is selectively enhanced by tetrodotoxin (produced by the Japanese puffer fish), local anesthetics, or a low sodium environment. Sympathomimetic amines cause hyperpolarization and augment the fast channel response. With the exception of nodal tissue, most myocardial fibers are dependent on fast channel activity for conduction.

**Phase 1—Overshoot:** The fast sodium channels close immediately after they open. The overshoot occurs because enough sodium has rapidly entered the cell to render the inside of the cell positive.

**Phase 2—Plateau Phase:** The membrane potential remains at zero and the slow channel now opens. Due to concentration differences, calcium diffuses into the cell and muscle contraction is now initiated as calcium flows intracellularly. The amount of calcium ion entering the cell is actually too small to activate the contractile proteins and enzymes necessary for contraction. Large amounts of calcium are bound intracellularly to the sarcoplasmic reticulum. The sarcoplasmic reticulum is a membranous system in the muscle cell that controls the amount and duration of calcium availability. (It may also be an important site at which inhalational anesthetics inhibit contractility.)

There is a direct relationship between the amount of calcium entering the cell via the slow channel and the amount of calcium released from the intracellular storage sites. The more extracellular calcium entering the cell, the more stored intracellular calcium is released.

**Phase 3—Repolarization:** After the slow channels have closed, the return to resting membrane potential occurs when the membrane permeability to potassium, which initially falls during the phase of rapid depolarization, returns at the end of the plateau to the high levels characteristic of the resting cell. The opening of potassium channels, along with the closure of the slow channels, allows the return to a state of high potassium conductance. Potassium ions are thereby permitted to flow out of the cell, generating an outward (repolarizing) current. The resting membrane potential of −90 millivolts is now re-established (Figure 1).

To explain the effects of the calcium channel blocking agents, it is beneficial to further explore the biochemical properties of the calcium slow channel, phase 2 of the cardiac cycle.

The threshold voltage for activation is much lower in the slow channel and the conduction velocity is approximately one-tenth that of the fast channel. The lower threshold voltage, between −30 and −40 millivolts, along with the slower conduction velocity, renders the slow response more prone to arise in partially depolarized fibers of the heart, such as ischemic zones. Here, slow channel activity may give rise to re-entrant excitation caused by excessively depressed conduction and ectopic tachyarrhythmias. Re-entrant excitation is also augmented by low sodium, high calcium media and catecholamines.

Beta adrenergic agonists such as isoproterenol, epinephrine and cyclic AMP all increase the magnitude of the slow inward current. These agents augment the slow response by (1) increasing the quantity of calcium influx through the slow channels of the surface membrane and (2) enhancing the release of calcium from the sarcoplasmic reticulum.

The gate model

When contemplating the summary response of any slow channel activity, the situation is clarified by the gate model of calcium slow channel activity (Figure 2). There are two separate "gates" in the slow calcium channel. One gate is voltage dependent and may be completely open or completely closed. The second gate is less dependent on voltage and may open in varying degrees depending on anatomic modifications. The second gate may be modified by an increase in cyclic AMP levels which could occur by stimulation of catecholamines or by inhibition of the phosphodiesterases.
that degrade cyclic AMP. For example, caffeine inhibits phosphodiesterases.

The ultimate magnitude of the slow inward current is determined by the number of slow channels open and the extent of their opening. The slow response is the normal conduction pathway for the pacemaker cells of the SA node and cells in the proximal region of the AV node. These slow responses are observed in other cardiac cells under abnormal conditions such as ischemia, hypoxia and exposure to catecholamines.\(^1\)

Slow channel inhibition not only affects the plateau phase of the cardiac action potential, it also blocks excitation contraction coupling in smooth muscle, thereby producing various degrees of peripheral and coronary vasodilation. In the normal contraction sequence, calcium binds with the troponin-tropomyosin protein complex (which activates ATPase), thus releasing the energy necessary for contraction. Therefore, the two factors promoting contraction (deblocking of binding sites and sufficient energy) are produced by the increased calcium ion concentration within the cell.\(^1\) The calcium channel blocking agents are 3-10 times more effective at inhibiting contraction in coronary artery smooth muscle than in myocardial contractile cells. This differential effect permits calcium blockers to dilate the coronary arteries at dosages that do not decrease myocardial contractility.\(^5\)

**Anesthetic implications for calcium blockers**

The variability of effects of the three calcium blockers (nifedipine, verapamil, diltiazem) is due to: (1) different loci of action and (2) variable tissue sensitivities. For example, nifedipine prevents the activation of the slow channel; its location of action is theoretically the voltage dependent gate. Verapamil, however, works at the phosphorylation gate which alters the kinetics of activation and recovery from inactivation of the slow channels.\(^5\) Also, the sensitivity of calcium channels to pharmacologic response may vary in different tissues, just as the response to alpha or beta stimulation varies in different tissues. The different loci of action and variable tissue sensitivity allow the calcium slow channel blocking agents to evoke a variety of responses such as coronary artery vasodilation as well as suppression of AV nodal conduction.\(^5\)

Nifedipine specifically inhibits calcium at the voltage dependent gate so that calcium does not enter the cell. Nifedipine is a potent coronary artery vasodilator, and of the three blocking agents, appears to have the least untoward effect on AV conduction.\(^6\) In fact, the weak suppression of AV conduction caused by nifedipine is overcome by a reflex increase in sympathetic tone. The strong reflex beta-adrenergic response counterbalances the negative chronotropic and inotropic effect of nifedipine so the net result is pure vasodilation with little electrophysiologic effect.\(^6\)

Clinically, nifedipine may be used to: (1) treat acute hypertension; (2) prevent coronary artery spasm, especially post-cardiopulmonary bypass reperfusion spasm; (3) treat classic Prinzmetal's variant angina; (4) treat classic exertional angina (by decreasing afterload); and (5) provide possible protection of ischemic myocardium during open heart operations.

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**Figure 2**

Gate Model of calcium slow channel activity

In the treatment of hypertension, nifedipine causes arterial vasodilation similar to the effects of hydralazine. Unlike hydralazine, however, nifedipine reduces coronary vascular resistance, thus increasing coronary blood flow and decreasing myocardial oxygen consumption. Nifedipine is therefore very suitable for the treatment of hypertension in the patient with pre-existing coronary artery disease.

The mechanisms by which nifedipine protects the myocardium are as follows: (1) in the presence of fixed coronary occlusion, nifedipine dilates coronary collateral vessels, thereby increasing perfusion to ischemic areas; (2) the negative inotropic and reduced afterload may improve the relationship between oxygen supply and demand; and (3) the ability to block calcium influx may improve the chances of survival of a cell exposed to a given level of ischemia.  

Administered orally, 90% of nifedipine is absorbed with a peak onset of 1 to 2 hours and a half-life of 4 to 5 hours. It is 90% protein bound, completely metabolized to inert products with 75% renal excretion and 15% GI tract elimination. Nifedipine does not interact with other drugs and may safely be administered with nitrates, beta blockers, digoxin, anticoagulants, antihypertensives and antidiabetic drugs. Side effects are mild and are related to its vasodilatory effects.  

Verapamil is currently available for intravenous use and is now the drug of choice for treating paroxysmal supraventricular tachycardia (PSVT). Verapamil has been shown to cause conversion of PSVT in 90% of cases, whereas the beta-adrenergic agonists have been shown to be 50-60% effective. Verapamil acts primarily to suppress AV nodal conduction. At higher doses coronary vasodilation is seen; however, AV conduction block also becomes more pronounced. Lower antiarrhythmic doses of verapamil have little hemodynamic consequences.  

Verapamil affords protection against ventricular tachycardia and ventricular fibrillation during myocardial reperfusion after 25 minutes of ischemia. The mechanism of ventricular fibrillation is the activation of the sympathetic nervous system, an effect which verapamil specifically antagonizes.  

The negative inotropic effect of verapamil is potentiated by beta-blockers. Therefore, verapamil should not be given in concurrence with beta-blockers. Additionally, the AV conduction delay seen with verapamil may be additive when given with the digitalis preparation. This combination should be avoided.  

When administered intravenously, verapamil acts within 1-2 minutes, peaks in 5 minutes, and has a half-life of 3.7 hours. The initial hypotension seen with verapamil is transient and is gone within 10 minutes, but the antiarrhythmic effect on the AV node lasts up to six hours. Verapamil is completely absorbed by the GI tract with 70% renal excretion. The use of verapamil is contraindicated in the presence of AV block, sinus node dysfunction and pre-existing hypotension.  

Diltiazem is not yet available for clinical use. Studies indicate that it has no negative inotropic effect, even when administered after complete beta-blockade with propranolol. Of the major calcium slow channel blockers, diltiazem has the least effect on the SA or AV node. Diltiazem is expected to be used in the treatment of variant angina—its major advantage is that it could conceivably be administered in conjunction with the beta-blockers.  

The interaction between inhalational anesthetics and calcium channel blockers has recently been investigated by Kapur and Flacke. They studied the effect of verapamil on epinephrine-induced arrhythmias and the cardiovascular response to verapamil under halothane anesthesia. Recent evidence suggests that halothane itself depresses slow channel conductance, and halothane and catecholamines are a known arrhythmogenic combination. Kapur and Flacke demonstrated that verapamil produced a sustained rise in the arrhythmogenic threshold and abolished ongoing epinephrine-induced arrhythmias in the intact dog under halothane anesthesia. They also concluded that concentrations of verapamil too low to slow AV conduction at normal rates will slow the conduction of premature impulses and interfere with the transmission of high atrial rates.  

Kapur and Flacke also stated that the time course of the pharmacodynamic effects of verapamil administration showed significant differences. Following rapid administration (30 seconds), the first effect was vasodilation; cardiac effects developed more slowly. Maximum effects on contractility as well as PR interval occurred at five minutes. Hemodynamic effects had returned to baseline at a time when antiarrhythmic effects were still very much in evidence. This suggests that the antiarrhythmic dose of verapamil under halothane anesthesia may be effective at doses that cause only minor changes in hemodynamic parameters. The hemodynamic effects overall are reduced with a slower rate of intravenous administration.  

**Summary**  
Although the interaction between calcium
channel blocking agents and all anesthetics has not been formally studied, it is known that autonomic effects may be important in predicting the activity of calcium channel blockers and anesthetics. Beta-agonists such as epinephrine increase the amplitude of the slow channel current. Beta-blockers decrease calcium ion influx into cells.²

It will become increasingly imperative for the anesthetist to be aware of the mechanism of action of the calcium channel blockers in the non-anesthetized state so that when called upon to administer an anesthetic to an individual on calcium channel blocking therapy, an informed assessment can be made regarding potential consequences and interactions. Although the absolute mechanism of interaction between calcium channel blocking agents and general inhalational anesthetics may not be fully elucidated for many years, by understanding the electrophysiologic and hemodynamic effects of the drugs, the anesthetist can advance sound recommendations for the correction of any adverse cardiovascular effects.

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