Calcium Entry Blockers: Uses and Implications for Anesthesiologists

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A STRUCTURALLY DIVERSE GROUP of compounds which specifically block the entry of calcium ions across cell membranes have important applications in cardiovascular therapy. There are several excellent general reviews on this subject1-11; the most complete is the two part review by Antman, Stone, and co-authors.5,6 The list of Ca ++ entry blockers (referred to also as Ca ++ antagonists, Ca ++ channel blockers, and Ca ++ influx blockers) includes verapamil, nifedipine, diltiazem, perhexiline, prynylamine, and lidoflazine. Verapamil and nifedipine have been studied the most extensively and are already available in this country and, therefore, will be emphasized in this review of the pharmacologic action of Ca ++ channel blockers, their uses, and clinical implications for anesthesiologists.

Calcium and Calcium Blockers

It is well-known that calcium plays a fundamental role in excitation, contraction, and excitation-contraction coupling of all muscles. In excitation, Ca ++ is necessary for the changes in membrane potential during cardiac or smooth muscle activity. The role of Ca ++ is distinct from that of Na ++ and K ++ during excitation; movement of Na ++ through “fast” channels into the cell, as well as movement of Ca ++ through “slow” channels, contribute to the formation of the action potential. “Slow” channels are 100 times more selective for Ca ++ than for Na ++ or K ++.12 The respective roles of Na ++ and Ca ++ in the formation of the action potential depend on the phase of the action potential and type of cardiac cells (fig. 1). In ventricular contractile cells, Ca ++ movement contributes mostly to the plateau of the action potential (phase 2). However, in the sinus node and A-V node, Ca ++ (instead of Na ++) plays a vital role in the formation of phase 0.13,14 Under abnormal conditions (ischemia, hypoxia, exposure to catecholamines), depolarization of atrial and ventricular cells also may depend primarily on Ca ++ movement.15,16 Thus, the role of Ca ++ in the process of membrane excitation is especially significant in the sinus node, A-V node, and in myocardial cells under abnormal conditions.

Calcium ions, derived mainly from the extracellular space and sarcoplasmic reticulum, cause contraction by interacting with contraction regulating proteins: troponin in myocardial cells and calmodulin in vascular smooth muscle cells.17,18 Cardiac muscle, and especially vascular smooth muscle, contain relatively small amounts of endoplasmic Ca ++, and are therefore more dependent on Ca ++ influx than skeletal muscle.1,19 This accounts for the sensitivity that cardiac and smooth muscle have to the Ca ++ channel blockers. According to current concepts, an action potential causes depolarization of the sarcotema and extracellular Ca ++ moves inside the cell through the “slow” channels within the cell membrane (the channels have not yet been identified as distinct anatomic structures21). This Ca ++ influx probably triggers the release of some internal Ca ++ store to account for the rapid rise in sarcoplasmic Ca ++ concentration.22 The source of calcium ion for excitation-contraction coupling in cardiac muscle is controversial.
According to the hypothesis of Fabiato and Fabiato, the small amount of Ca$^{2+}$ that crosses the cell membrane during the action potential, triggers the release of Ca$^{2+}$ from the sarcoplasmic reticulum which in turn facilitates contraction. Thus, the so-called "Ca$^{2+}$-induced release of Ca$^{2+}$" appears to be the link between the action potential of the sarcolemma and the release of Ca$^{2+}$ from the sarcoplasmic reticulum in the muscle cells of the heart. However, there is considerable evidence that the sarcolemma participates as much, or perhaps, more than the sarcoplasmic reticulum in cardiac muscle Ca$^{2+}$ kinetics. Another mechanism for calcium passage into the cell is calcium-sodium ion exchange at the sarcolemma.

Calcium channel blockers inhibit the normal Ca$^{2+}$ influx into cells. As mentioned previously, for the influx of Na$^+$ and Ca$^{2+}$ across the cell membrane, there are two separate transport systems: "fast" channels for Na$^+$ and "slow" channels for Ca$^{2+}$. Certain pharmacologic compounds inhibit ionic movement across these two channels. Lidocaine, or other local anesthetics act predominantly on the "fast" channels and inhibit the Na$^+$ influx (Fig. 2). The Ca$^{2+}$ channel blockers selectively block "slow" channels. In contrast, adrenergic beta-receptor stimulating agents (isoproterenol, epinephrine, and others) selectively increase Ca$^{2+}$ influx during the process of excitation. They do so by initiating a cascade of complex cyclic-AMP-mediated membrane regulatory reactions that ultimately determine the magnitude of calcium entry. Beta blocking agents also act on the transmembrane Ca$^{2+}$ influx, but they do so indirectly by neutralizing the promoter effects of catecholamines on the "slow" channels (Fig. 2). Although Ca$^{2+}$ entry blockers are regarded as specific calcium channel blocking agents, one has to keep in mind that all drugs have a spectrum of activity. For example, verapamil also has a high local anesthetic potency (1.6 times that of procaine), which means that it can affect not only "slow", but also "fast" channels. Because the effect on "slow" channels predominates, verapamil is primarily considered a calcium channel blocker.

Structure, Biotransformation, and Pharmacokinetics

The list of calcium entry blockers constantly increases by the synthesis of new compounds and by the discovery of calcium antagonistic properties among old drugs from different pharmacologic groups (phenytoin, hexestrol, diazoxide, and others). The diversity of their structure is remarkable; for example, nifedipine and verapamil are structurally unrelated (Fig. 3). Verapamil is a synthetic papaverine derivative. Stereospecificity is demonstrated since the L isomer is very specific for slow channel blocking effect. The commercial preparation

Fig. 1. Schematic representation of the role of Ca$^{2+}$ in the formation of the action potential in a ventricular contractile cell and a sinoatrial node cell. The numbers, 0, 1, 2, 3, 4 represent phases of the action potential. Cross-hatched regions of the curve of the action potential are mostly due to the entry of Ca$^{2+}$ via the slow channels. In ventricular contractile cells, Ca$^{2+}$ movement contributes mostly to the plateau of the action potential (phase 2); whereas in the sinus node cells, it also plays a key role in the formation of phase 0 of the action potential.

Fig. 2. Schematic representation of pharmacologic interventions which alter calcium and sodium influx across the cell membrane. Lidocaine (and other local anesthetic drugs) acts predominately on the "fast" channels and inhibits the Na$^+$ influx, verapamil (and other Ca$^{2+}$ antagonists) selectively blocks "slow" channels and, therefore, interferes with Ca$^{2+}$ influx. Propranolol (and other beta blocking agents) also inhibits the transmembrane Ca$^{2+}$ influx, but does it indirectly by neutralizing the promoter effect of catecholamines on the "slow" channels. Isoproterenol (and other beta agonists) produce Ca$^{2+}$ entry by initiating a cascade of complex cyclic-AMP-mediated membrane regulatory reactions that may be inhibited by competitive blockade with beta adrenergic blockers.
is the racemic mixture of 1. and D isomers, with predicted effect. In 1962, verapamil first was introduced as a coronary vasodilator, and five years later, was found to selectively inhibit transmembrane fluxes of calcium. It is of interest to note that it was reported later that the parent drug, piperine, also has the property of blocking the inward slow Ca\(^{2+}\) current. In 1968, nifedipine also was synthesized in a program which started with an obsolete coronary vasodilator.

![Structural formula of Verapamil and Nifedipine](image)

**TABLE 1. Pharmacologic Characteristics of Nifedipine and Verapamil**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nifedipine</th>
<th>Verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oral</td>
<td>10–20 mg, tid</td>
<td>80–160 mg, tid</td>
</tr>
<tr>
<td>iv</td>
<td>5–15 μg/kg</td>
<td>150 μg/kg</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
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<td></td>
</tr>
<tr>
<td>oral (%)</td>
<td>&gt;90</td>
<td>&gt;90</td>
</tr>
<tr>
<td>bioavail (%)</td>
<td>60–70*</td>
<td>10–20</td>
</tr>
<tr>
<td><strong>Onset action (min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oral</td>
<td>&lt;20</td>
<td>&lt;30</td>
</tr>
<tr>
<td>subl</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>iv</td>
<td>1–3</td>
<td>1–3</td>
</tr>
<tr>
<td><strong>Protein binding (%)</strong></td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td><strong>Elimination t(_1/2) (h)</strong></td>
<td>5</td>
<td>2–7†</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (%)</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Fecal (%)</td>
<td>&lt;15</td>
<td>15</td>
</tr>
</tbody>
</table>

Bioavail = bioavailability, subl = sublingual.

* Nifedipine is light sensitive and should be protected from light (see text).
† Normal patients (see text for discussion of patients with liver disease).

Data from references 5 and 36–38.

however, its calcium blocking property was established without delay.

The biotransformation of Ca\(^{2+}\) channel blockers is still being investigated. Nifedipine is oxidized by light and therefore must be protected from light during preparation, storage, and administration. In vivo biotransformation occurs in the liver where nifedipine is oxidized to a free acid or lactate. Metabolites are reported to be "inactive." Nifedipine plasma disappearance curves fit a two-compartment model with a distribution (α) half-time of 150–180 minutes, and an elimination half-time (β) of 4–5 hours. Other characteristics of nifedipine pharmacokinetics and bioavailability are listed in table 1. Verapamil biotransformation occurs in the liver where approximately 80–90% of the drug is cleared during the initial circulation through the liver. Verapamil biotransformation consists primarily of N-alkylation, and cleavage products have 5 to 10 per cent activity of the parent compound. Verapamil kinetics have fitted two-compartment and three-compartment models. The α half-time ranged from 2 to 10 minutes (mean 3.5 min) in young healthy patients to 18 to 35 minutes in three older volunteers. The β half-time varied from 1.82 to 5.3 hours in healthy patients, and up to 13.6 hours in patients with liver disease. Elderly patients with atrial fibrillation have an elimination half-time of 6.3 hours, and chronic oral dosing leads to "significant cumulation" of the active metabolite norverapamil. Like nifedipine, verapamil is highly protein-bound (table 1), and the presence of other highly protein-bound drugs such as diazepam, lidocaine, and propranolol, significantly increase the free (active) fraction of verapamil.

In summary, verapamil and nifedipine have relatively short plasma half-lives, but verapamil has an active metabolite of longer half-life which accumulates with chronic administration. Variables such as liver disease and old age may decrease the clearance of these compounds. Concurrent administration of drugs with a high affinity for plasma proteins may displace verapamil and nifedipine.

**Calcium Blockers: Cardiovascular Actions**

All cardiovascular effects of verapamil and nifedipine can be explained on the basis of selective inhibition of transmembrane influx of Ca\(^{2+}\) (table 2). Inhibition of Ca\(^{2+}\)-dependent membrane excitation accounts for the depressive effect of calcium entry blockers on sinus automaticity and atrioventricular conductivity. Interference with the excitation-contraction coupling process is the reason for their negative inotropic effect. The effects of calcium entry blockers on the vascular smooth muscle may result from either inhibition of excitation-
constriction coupling or from suppression of Ca

**CHRONOTROPIC AND DROMOTROPIC EFFECTS**

The cells that depend in large part on Ca
influx for phase 0 depolarization are: sinus node cells, A-V nodal cells, and abnormally depolarized atrial, ventricular, or Purkinje fibers. Calcium channel blockers have a profound effect on the electrical activity of cardiac pacemaker and conducting tissue cells. The most important effects of calcium entry blockers, principally verapamil, on electrophysiologic properties of the heart are: 1) the depression in rate of SA node discharge, 2) prolongation of A-V node refractoriness, and 3) slowing of A-V nodal conduction. Negative chronotropic and dromotropic actions of calcium antagonists (verapamil and nifedipine) which constitute the basis for their electrophysiologic effects are seen in isolated SA and A-V node preparations. However, in humans, nifedipine, in contrast to verapamil, is devoid of any effect on the A-V nodal conduction. The reason for this is the relative strength of nifedipine's action on various parts of the cardiovascular system (fig. 4). Vascular smooth muscles seem to be much more susceptible to nifedipine than the A-V node or myocardial cells. Thus, vaso- dilation and reduced blood pressure evoke a sympathetic reflex which counteracts its negative chronotropic and dromotropic actions. With verapamil, sympathetic reflexes to its hypotensive effect also occur, but they are less pronounced than with nifedipine. Differences between the oral and intravenous hemodynamic effects of verapamil are partially dependent on these sympathetic reflexes. Intravenous verapamil usually results in a decrease in blood pressure with a reflex increase in heart rate. These effects rarely occur with oral administration.

Nifedipine and verapamil are likely to produce different effects on heart rate; increases follow nifedipine, and little change is seen with verapamil. The administration of verapamil in patients with coronary artery disease and good ventricular function significantly lengthens the P-R interval, and may cause junctional rhythm. There are many reports of verapamil-induced second-degree block. The concurrent administration of verapamil (and possibly other Ca++ channel blockers with A-V blocking properties such as diltiazem) with beta-adrenergic blocking agents can produce second- and third-degree A-V block. Of interest, is the fact that verapamil's effects on heart rate and conduction occur at lower blood levels than hemodynamic effects probably reflecting verapamil's greater potency for electrophysiologic effects (fig. 4). In a canine laboratory investigation, Mangiardi and co-workers found a good association between the drug levels of verapamil and A-H interval, but the effects on A-V conduction occurred at a lower level than those of vasodilation and contractility. If the same is true in humans, then lower dosages of verapamil will produce electrophysiologic effects while hemodynamics are less affected. Electrophysiologic effects of verapamil are more difficult to reverse with CaCl_2 than the hemodynamic effects.

**INOTROPIC EFFECTS**

Many investigations have shown that Ca++ channel blockers decrease myocardial contractility. These decreases can be reversed by the administration of CaCl_2. In humans, investigators documented decreases in dp/dt MAX with both nifedipine and verapamil. In an investigation of the direct effects of nifedipine on

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**TABLE 2. Mechanism of Action of Calcium Channel Blockers on Various Cardiovascular Functions**

<table>
<thead>
<tr>
<th>Cardiovascular function</th>
<th>Direction of action</th>
<th>Inhibition of Ca++-dependent Membrane Excitation</th>
<th>Inhibition of Excitation-Contraction Coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus automaticity</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Arrivoventricular conducivity</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vascular tone</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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**Fig. 4.** Relative strength of action of nifedipine and verapamil on the various components of the intact (in vivo) cardiovascular system. Two arrows denote more pronounced action than a single arrow. Arteriolar (vasodilation) are more susceptible to nifedipine than A-V node (negative dromotropic effects) or myocardium (negative inotropic effects). Verapamil's preferential effect is depression of A-V node conduction.
normal and coronary artery diseased patients, Rousseau and co-workers injected 0.1 mg directly into the left main coronary artery, and measured hemodynamic changes over the ensuing 5 minutes. Thirty seconds after injection, nifedipine produced a significant decrease in dP/dt MAX (16%) and systolic blood pressure (4%). There were simultaneously significant increases in heart rate (HR, 16%) and left ventricular end-diastolic pressure (LVEDP, 13%). These findings have been confirmed with injections of 2 mg/kg of nifedipine into patent coronary grafts of 10 patients. Thus, the direct myocardial effects of nifedipine are decreases in contractility with a resultant increase in LVEDP. The decrease in blood pressure occurs before systemic vasodilation and this reflects a decrease in cardiac output. The direct myocardial changes are very transient and are no longer significantly different from control one minute after injection. The early negative inotropic effects of Ca++ blockers are counterbalanced by vasodilation and a reflex sympathetic response (vide supra), so that patients with normal ventricular function actually may manifest increased cardiac output. In patients with impaired ventricular function, nifedipine (10 mg po) significantly reduced pulmonary artery wedge pressure and apparently improved left heart function secondary to afterload reduction. Sublingual nifedipine (20 mg) is also effective in augmenting cardiac output by afterload reduction in patients with left ventricular dysfunction. Likewise, verapamil (iv infusion) significantly improved cardiac output and stroke work index in patients with moderately reduced ejection fraction, but in three patients with ejection fraction of <0.35, stroke work index was reduced and pulmonary artery wedge pressure was increased. Oral nifedipine can produce pulmonary edema in patients with preexisting impaired ventricular function. Thus, in patients with normal ventricular function, direct negative inotropic actions of Ca++ antagonists are counterbalanced by their reflex effects. In patients with poor ventricular function, Ca++ blockers may improve ventricular function by afterload reduction, but in patients with severely impaired function, their negative inotropic effects can precipitate congestive heart failure.

**Vasodilation**

The most prominent hemodynamic action of Ca++ channel blockers is a decrease in systemic blood pressure and systemic vascular resistance (SVR). All vascular beds are dilated by Ca++ blockers. Observations with in vitro arterial strips from coronary, pulmonary, mesenteric, hind limb, hepatic, femoral, uterine, renal, and cerebral circulations show profound relaxant characteristics of these drugs. With regard to potency, nifedipine and verapamil produce 1,000- and 100-fold, respectively, greater relaxation of K+-induced contraction of isolated coronary strips than papaverine, the well-known coronary vasodilator. Nifedipine is a more potent vasodilator of arterial resistance vessels than verapamil. Fleschsteinein, with numerous in vitro investigations, has shown that the coronary dilation produced in K+ depolarized coronary strips by Ca++ blockers significantly differs from the commonly used coronary vasodilators, the nitrates, in three potentially therapeutically important ways: 1) onset of action is more rapid with nitrates; 2) relaxation is less complete with nitrates; and 3) nitrate relaxation is transient even in the continued presence of drug. Additionally, although incontrovertible evidence does not exist, most investigators agree that Ca++ channel blocking agents have little effect on venous capacitance vessels, whereas nitrates cause marked dilatation of this system. There is conflicting evidence which may be species-dependent concerning the dilation of small and large arteries. In humans, there is abundant evidence that the Ca++ channel blockers are potent dilators of large coronary arteries as well as the smaller resistance vessels in the systemic circulation. In laboratory studies, it appears that Ca++ channel blockers relax small resistive arteries and arterioles, whereas nitroglycerin acts on the larger coronary arteries of isolated muscle and intact dogs.

In summary, the primary hemodynamic effect of Ca++ channel blockers is a decrease in SVR and blood pressure with variable responses in heart rate, cardiac output, and contractility. Neither acute nor chronic administration of Ca++ channel blockers produces any changes in heart rate and contractility. Neither acute nor chronic administration block sympathetic responses; indeed, a reflex tachycardia and increase in contractility are observed. The most important electrophysiologic effect of verapamil is prolongation of A-V node conduction and refactoriness.

**Perioperative Uses of Verapamil and Nifedipine**

The Ca++ channel blockers are important new drugs with many potential uses (table 3). Braunwald bails them as “a substantial advance in cardiovascular therapeutics”. They are important for two reasons: 1) they have a uniquely specific mode of action, and 2) they appear to be the pharmacologic treatment of choice and widely used for at least two maladies, supraventricular arrhythmias and coronary vasospasm. They are also useful adjuncts in the medical management of classical angina pectoris. Their use is controversial in medical management of hypertrophic cardiomyopathy, systemic hypertension, and pulmonary hypertension. The Ca++ blockers are of theoretical use in myocardial protection during heart surgery, cerebral...
arterial spasm, and for uterine relaxation. Anesthesiologists may administer Ca\(^{++}\) blockers in the perioperative period for any of the above indications. Of the potential perioperative uses for Ca\(^{++}\) blockers, only the use of verapamil has been demonstrated in anesthetized patients. In poorly designed (uncontrolled) investigations, verapamil has been used for treatment of arrhythmias and for induced hypotension during anesthesia.

**ARRHYTHMIAS**

Verapamil is a very effective antiarrhythmic drug for supraventricular arrhythmias, whereas nifedipine is not. Verapamil may prevent or terminate episodes of paroxysmal supraventricular tachycardia (PSVT) by prolonging A-V nodal conduction and/or refractoriness (table 2). All forms of PSVT which depend on the establishment of a circus rhythm by way of a reentrant circuit may be blocked by verapamil. Verapamil is the drug of choice for the treatment of acute episodes of PSVT in adults and children because of its superative efficacy. In a combined series of 291 patients with PSVT, verapamil converted 96.7% to normal sinus rhythm within 1 to 3 minutes. The dosage for treatment of PSVT in adults is 0.075 to 0.15 mg/kg infused over 1–3 minutes, and to sustain the effect, an infusion of 0.005 mg·kg\(^{-1}\)·min\(^{-1}\) has been recommended. An infusion model based on the kinetics of a three-compartment model also has been devised by Kates and co-workers. The success of verapamil in slowing ventricular rate in atrial flutter and fibrillation has been demonstrated. The success of verapamil in slowing the ventricular rate in atrial fibrillation and atrial flutter results from decreased A-V conduction and increasing A-V block. It appears that verapamil is no better than cardiac glycosides in converting atrial fibrillation to sinus; however, verapamil is faster (3 min) in slowing ventricular rate. Also, the administration of verapamil appears to be safer than digitalis for use before electrical countershock conversion therapy. Ventricular arrhythmias are not particularly responsive to verapamil or nifedipine; certainly, other antiarrhythmics are more effective. A possible exception is ventricular fibrillation caused by coronary artery spasm. In anecdotal cases, nifedipine was effective in treatment and prevention of this life-threatening arrhythmia in patients with coronary artery spasm.

Verapamil has been used to treat operative and postoperative arrhythmias. In an uncontrolled study of 383 patients anesthetized with “light halothane,” verapamil was used successfully to treat the majority of supraventricular and ventricular arrhythmias. Verapamil is efficacious in postoperative cardiac surgical patients. Atrial fibrillation is a common postoperative arrhyth-

### TABLE 3. Uses of Calcium Channel Blockers

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Widely Used</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraventricular arrhythmias</td>
<td>3, 4, 43, 54, 72–74, 80–84, 86, 87</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>55, 101–107</td>
<td></td>
</tr>
<tr>
<td>Coronary spasm</td>
<td>53, 109–113, 156–158</td>
<td></td>
</tr>
<tr>
<td>Classic angina pectoris</td>
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<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>159–163</td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>125–127</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>129–132</td>
<td></td>
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<tr>
<td>Myocardial protection</td>
<td>115–120, 164</td>
<td></td>
</tr>
<tr>
<td>Cerebral arterial spasm</td>
<td>63, 134–139</td>
<td></td>
</tr>
<tr>
<td>Uterine relaxation</td>
<td>163–169</td>
<td></td>
</tr>
</tbody>
</table>

* FDA approved uses as of April 1982: verapamil = treatment of paroxysmal supraventricular tachycardias, control of rapid ventricular rate in atrial flutter and fibrillation, treatment of angina (vasospastic unstable and stable); nifedipine = treatment of angina (vasospastic and stable).

Verapamil at 0.075 mg/kg iv significantly and significant ventricular slowing may be achieved with verapamil 0.075 mg/kg iv (fig. 5). Treatment with verapamil is almost always associated with transient hypotension, but there are many cases in which hemodynamics improve with the return of sinus rhythm in PSVT or slowing of ventricular rate in atrial fibrillation or flutter.

The efficacy of verapamil is clear, but a warning regarding drug interactions must be mentioned. Verapamil given to patients on beta-adrenergic blocking drugs may depress cardiac function. Verapamil (unlike nifedipine) when given to patients on beta-adrenergic blocking drugs can produce third-degree A-V block and asystole. In a study of patients with ischemic heart disease, combined therapy of propranolol with verapamil (40, 80, and 120 mg, po) did cause significant increase in P-R interval in the high-dose verapamil group, but no second- or third-degree block occurred. Combination with digoxin appears safe, however, chronic administration of verapamil significantly reduces digoxin clearance and prolongs digoxin’s elimination half-life. Another potential adverse drug interaction is verapamil and K⁺ cardioplegia, both of which cause A-V block.

**MYOCARDIAL ISCHEMIA**

Prinzmetal described a variant form of angina in 1959 which now bears his name, or may be called...
variant angina, atypical angina, coronary-artery spasm angina, and coronary spasm. Spasm of relatively large and small coronary arteries can occur. Variant angina is characterized by chest pain at rest with transient ST-segment changes, and is caused by coronary artery spasm.31,95 There may be many more episodes of ST changes than symptomatic anergic pain in patients with variant angina. There are two recent excellent reviews of this topic.96,97 Coronary artery spasm occurs in the perioperative period,98–100 and should be considered any time there are ST changes suggestive of myocardial ischemia when there are no indications of increased oxygen consumption (tachycardia and hypertension) and/or decreased myocardial oxygen supply (hypoxia and hypotension).

Many recent reports demonstrate the usefulness of Ca++ channel blockers for variant angina,53,101–107 but unfortunately, the large studies are uncontrolled for the most part, and the controlled studies have extremely small numbers of patients. In a small (10 patients) but well-designed study, Johnson and associates101 examined the efficacy of both verapamil and nifedipine in patients with variant angina. Patients initially were randomized to receive either placebo or verapamil (400 mg, qd) at intervals of 2 months, and during the final 2 months of the 8-month study, they were given nifedipine (82 mg, qd). Both verapamil and nifedipine significantly reduced anginal frequency. Likewise, there were significant decreases in nitroglycerin tablets required per week, and Holter monitored ST segment deviations from control per week. We have found that calcium channel blockers improve the myocardial energy imbalance of experimental vasospasm in rabbits more than that of a fixed coronary obstruction, suggesting that the antagonistic effect of Ca++ blockers is important in the treatment of vasospastic myocardial ischemia.108 The coronary spasm which occurs intraoperatively or postoperatively may be treated effectively with either verapamil or nifedipine. Verapamil may be administered intravenously, but nifedipine must be given by the oral, sublingual, or nasal route. The choice of a particular Ca++ blocker for the anesthetized patient will depend on potential drug interactions, and perhaps on ease of administration.

Typical angina pectoris generally is considered simply a result of imbalance in oxygen supply and demand. The underlying cause is atheromatous obstructive lesions of the coronary arteries. Exercise and other sympathetic nervous system stimulation exacerbate angina of this type because regions of the heart utilize more oxygen than can be supplied. Calcium channel blockers are effective antianginal compounds in the treatment of stable,109 unstable,53 exercise-induced,106,110,111 and cold pressor test provoked110 ischemic heart disease. The mechanism of action of Ca++ channel blockers in ischemic heart disease probably is a combination of vasodilatation (coronary and systemic) as well as direct myocardial depression. Most investigators believe the predominant antianginal effect is related to a decrease in myocardial oxygen consumption, and to a lesser extent, to an increase in oxygen supply. For example, Ferlinz and Turlow,111 found that the salutary actions of verapamil appeared to be related primarily to a decrease in measured myocardial oxygen demand rather than increase in supply.111 In studies with humans, Hugenholtz and co-workers112 demonstrated that nifedipine (2 mg/kg) injected into the left heart circulation does indeed decrease regional myocardial contractility pro-
duc ing an "oxygen sparing" effect. The Ca\(^{2+}\) entry blockers appear to decrease \(\text{MV}_{\text{o2}}\) by decreasing wall tension and contractility (and heart rate in the case of verapamil); oxygen supply may be increased if concurrent spasm is relieved. The place of verapamil and nifedipine in the treatment of intraoperative myocardial ischemia is yet to be established, and whether they will replace propranolol and nitroglycerin or merely become useful adjuncts to their use remains to be seen.

**Myocardial Protection**

The effectiveness of calcium channel blocking agents as an adjunct to protecting jeopardized myocardium during global ischemia is the subject of recent laboratory and clinical research. Several investigators, using isolated heart \(^{114,117}\) and intact animal preparations, \(^{118-120}\) have demonstrated preservation of myocardial structure and function when calcium channel blocking agents are administered prior to, or immediately following the onset of global ischemia. Adding these agents late in the ischemic period or during reperfusion does not reverse the deleterious effects of ischemic damage, although they may prevent extension of injury during reperfusion. \(^{117,121}\) The calcium channel blocking agents appear to exert their beneficial effect primarily by suppressing energy-dependent, calcium-mediated, myocardial activity at a time when high-energy phosphates and substrates are needed to maintain structural integrity of cellular membranes and organelles. The prevention of structural damage during ischemia permits resumption of normal metabolism and function following reperfusion. \(^{117}\)

Several studies have compared myocardial protective effects of calcium channel blocking agents with potassium-induced cardioplegia. In an isolated, isovolemic, feline heart model, nifedipine preservation of myocardial structure and function was similar to that obtained with cold potassium cardioplegia during 90 minutes of hypothermic ischemic arrest and 45 minutes of normothermic reperfusion. \(^{116}\) Nifedipine protection was dose-dependent, and return of ventricular function was delayed in nifedipine-treated cats. Studies using intact dogs undergoing 60 minutes of normothermic global ischemia during cardiopulmonary bypass, suggest that optimal preservation is achieved when the calcium blocking agent (verapamil) is used in combination with potassium. \(^{120}\) Presumably, the combined inactivation of calcium-mediated slow channels with verapamil and sodium-mediated fast channels with potassium result in a greater reduction of myocardial oxygen consumption and, therefore, better preservation of structure and function than can be achieved with either agent alone.

Whether or not different calcium channel blocking agents in varying doses, alone, or in combination with potassium, will be effective in protecting human myocardium during periods of aortic cross-clamping remains to be established. Preliminary studies by Clark et al. suggest a beneficial effect. \(^{122}\) In humans, the presence of ventricular hypertrophy, previous myocardial damage, obstructive coronary artery lesions, and non-coronary collateral flow impose unique problems in the homogeneous distribution and maintenance of cardioplegia not commonly observed in animal studies. Thus, documentation of effectiveness in human myocardial preservation depends on the optimal use of supplemental methods designed to insure uniform distribution, rapid initiation, and maintenance of effect. Furthermore, in view of low levels of myocardial damage currently achieved with cold potassium cardioplegia, large patient populations will be required to statistically demonstrate the efficacy of calcium channel blockade in preservation of mycardiums of humans. The high doses of Ca\(^{2+}\) entry blockers used for myocardial protection could depress cardiac function.

**Systemic Hypertension**

The efficacy of Ca\(^{2+}\) channel blockers for the treatment of systemic arterial hypertension is established \(^{123-127}\); however, the superiority over currently available compounds has not been demonstrated to date. The potent vasodilation of nifedipine makes it useful to significantly reduce SVR and elevated blood pressure in a dose-related fashion in patients with essential hypertension. \(^{124,126}\) Decreases in SVR are presumably a reflection of relaxation of the relatively small resistive vessels. Oral nifedipine (doses 10–30 mg) has peak hemodynamic effects in 30–60 minutes that lasts 6–10 hours. \(^{124,125}\) Oral nifedipine (10 mg) has been used to control severe hypertension and the associated symptoms of hypertensive encephalopathy. \(^{125}\) The decreases in blood pressure are associated with increases in heart rate and cardiac output. \(^{123,125}\) This sympathetic response can be blunted by concurrent administration of propranolol. Increased heart rate is not associated with verapamil (120 mg, tid, po) in the treatment of essential hypertension. \(^{127}\) The theoretical advantages of Ca\(^{2+}\) channel blockers to control hypertension are that they may decrease blood pressure by decreasing SVR as well as decreasing cardiac output. Also, these drugs, like the beta-adrenergic blocking drugs, are not accompanied by significantly increased renin release. \(^{126,127}\) The primary use of Ca\(^{2+}\) antagonists as antihypertensive agents in the perioperative period may be in hypertensive patients with ischemic heart disease because of associated coronary artery vasodilation. Choice of the particular drug will depend on desired heart rate and potential drug interactions.
It is unlikely that the Ca\(^{++}\) blockers will replace the commonly used vasodilators for treatment of hypertension.

**Hypotensive Anesthesia**

A use for Ca\(^{++}\) blockers is selectively induced hypotensive anesthesia. Oates compared verapamil infusion with nitroprusside in the rat, and found the dose-related effects of verapamil slower in onset and offset, but acceptable.\(^{128}\) With continued (30 minutes) infusion, tachyphylaxis occurred with nitroprusside but not with verapamil. Of potential importance, is the fact that with verapamil, there was no rebound increase (overshoot) in pressure after discontinuation of drug. In humans, Zimpfer and co-workers gave a single injection of verapamil (0.07 mg/kg) to electively decrease systemic blood pressure during neuroleptanesthesia. The mean blood pressure decreased from 108 to 84 mmHg (\(P < 0.001\)), but heart rate and pulmonary artery pressures were unchanged. Significant prolongation of the P-R interval occurred. The hemodynamic effects of verapamil were abolished by 15 mg/kg calcium gluconate, iv.\(^{75}\) There are several attractive features of Ca\(^{++}\) channel blockers for use in hypotensive anesthesia: 1) perhaps some of the reflex increases in contractility may be blocked; 2) coronary and cerebral arteries would be dilated to maximize flow despite lowered perfusion pressure; and 3) with verapamil, reflex tachycardia would be blocked to some degree. Though never compared as adjunctive agents in hypotensive anesthesia, theoretically nifedipine is a more potent vasodilator than verapamil. Verapamil would have less associated tachycardia and a shorter duration of action. For a sustained hypotensive effect, an infusion of verapamil will be necessary. The Ca\(^{++}\) blockers have not been administered to hypovolemic patients, and should not be until normal volume is established.

**Pulmonary Hypertension**

Pulmonary arterial hypertension is very difficult to treat. In fact, it is thought that whatever the etiologic factors of primary pulmonary hypertension, therapy must be instituted early, before development of medial hypertrophy and other fixed anatomic changes which make drug therapy almost useless.\(^{129}\) In nine patients with primary pulmonary artery hypertension, and in three with a secondary cause (mean age entire group 49 years), verapamil (0.15 mg/kg, iv) significantly reduced mean pulmonary artery pressure (12%), however, cardiac index also decreased and calculated pulmonary artery resistance, therefore, was unchanged.\(^{130}\) Verapamil then appears to be ineffective in decreasing the increased pulmonary vascular resistance (PVR) seen in patients with primary pulmonary artery hypertension. When hypoxia is the cause of pulmonary artery hypertension, the Ca\(^{++}\) channel blockers are effective in reducing the pulmonary vasoconstriction. In patients with chronic airflow obstruction and acute respiratory failure, nifedipine (20 mg sublingual) significantly reduced pulmonary artery pressure (17%), PVR (37%), and increased cardiac output (19%).\(^{131}\) Because the underlying mechanism of reflex pulmonary artery vasoconstriction during hypoxia appears to be mediated by Ca\(^{++}\) influx,\(^{132}\) it may be that Ca\(^{++}\) channel blockers will be particularly useful in reducing the elevated PVR and associated right heart failure seen with hypoxic pulmonary artery hypertension. The fact that Ca\(^{++}\) channel blockers do not uniformly decrease PVR in primary pulmonary artery hypertension could mean that inappropriate drug and/or doses have been tried (e.g., verapamil is not as potent a vasodilator as nifedipine) or the disease may have progressed so that anatomic changes make the resistance vessels resistant to pharmacologic therapy. Also, it is important to remember that the Ca\(^{++}\) channel blockers do not reduce normal pulmonary artery pressures as they do systemic arterial pressure\(^{127,61}\); therefore, efficacy of the drugs as pulmonary vasodilators may be only in cases of secondary pulmonary artery hypertension. In summary, the Ca\(^{++}\) blockers are not the long sought answer to the very difficult perioperative clinical problem of right heart failure secondary to increased pulmonary vascular resistance.

**Cerebral Artery Vasospasm**

Cerebral vasospasm is commonly associated with such intracerebral pathologic features as subarachnoid hemorrhage and trauma.\(^{133}\) Ca\(^{++}\) channel blockers are potent cerebral arterial dilators.\(^{63,134,135}\) Cerebral arterial spasm of multiple etiologic characteristics produced in laboratory animals is blocked by nifedipine and verapamil.\(^{136-138}\) This suggests that whatever the cause of cerebral arterial spasm, Ca\(^{++}\) channel blockers relieve it as they do coronary artery spasm. There are no large, well-designed investigations in humans showing the efficacy of Ca\(^{++}\) channel blockers in intracerebral arterial spasm, but the laboratory data is promising. A potential use of Ca\(^{++}\) blockers in neurosurgical patients is control of hypertension. In a retrospective survey of 136 patients in our neurosurgical intensive care unit, hypertension was associated with a significantly greater mortality than normotension.\(^{139}\) It is possible that calcium channel blockers with their dual effects of preventing cerebral artery spasm and antihypertensive effects may prove particularly useful in the treatment of hypertension in the neurosurgical intensive care unit. The im-
important question of whether Ca\textsuperscript{2+} channel vasodilation impairs intracranial compliance has not been investigated in humans. If studies show little change in intracranial pressure with the Ca\textsuperscript{2+} channel blockers, they may indeed be very important vasodilators in the neurosurgical patient.

**Implications of Ca\textsuperscript{2+} Blockers in Surgical Patients**

An increasing number of patients requiring anesthesia will be taking Ca\textsuperscript{2+} channel blockers. Therefore, it is imperative that we consider implications of their use in surgical patients.\textsuperscript{140}

**Interactions with General Anesthetics**

General anesthetics as a group are cardiovascular depressants, and it is now fairly well-established that the myocardial depression\textsuperscript{22,141,142} and vascular dilation\textsuperscript{143} are at least in part related to interference with movement and/or translocation of Ca\textsuperscript{2+} across membranes and intracellularly. The negative inotropic effects of halothane are not fully understood, but appear to be related to changes in intracellular Ca\textsuperscript{2+} kinetics.\textsuperscript{141,144} Halothane and enflurane prolong A-V conduction,\textsuperscript{145-147} halothane in part by Ca\textsuperscript{2+} channel blockade.\textsuperscript{148} There is considerable potential then for drug interactions related to the cardiovascular system between general anesthetic drugs and Ca\textsuperscript{2+} channel blockers.

The large clinical series of verapamil treatment of arrhythmias in patients lightly anesthetized with halothane demonstrates that these two drugs can be used together safely,\textsuperscript{72} but decreases in blood pressure of 5-minute duration and a 4% incidence of increased P-R interval occurred. These clinical findings would be predicted by the laboratory work of Kapur and colleagues\textsuperscript{149} who demonstrated transient but significant decreases in SVR, blood pressure, LV dP/dt, and increases in LVEDP, cardiac output, and P-R interval in dogs anesthetized with 1.1 MAC halothane and given verapamil (0.2 mg/kg iv over 30 seconds). Except for the P-R interval, these changes were brief, generally returning toward control in 10–20 minutes. The cardiovascular changes could be minimized by giving the same dose over a longer time period.\textsuperscript{149} The administration of verapamil during isoflurane and enflurane produces hemodynamic consequences qualitatively similar to those during halothane, but infusion of verapamil produces less hemodynamic depression during 1 MAC isoflurane than 1 MAC enflurane.\textsuperscript{150} When afterload is kept constant, dose-related decreases in left ventricular function have been demonstrated with the combination of verapamil and isoflurane.\textsuperscript{151} A serious drug interaction of inhalation anesthetics with verapamil is the potential development of A-V block, since both drugs significantly prolong A-V conduction\textsuperscript{72,147,149} and reversal of block is difficult. If verapamil plus enflurane, isoflurane, or halothane combinations are used, the P-R interval should be monitored carefully. Another potential drug interaction is with verapamil and neuromuscular-blocking agents. There is evidence that relatively high doses of verapamil diminish the muscle twitch amplitude of the pentobarbital-anesthetized cat.\textsuperscript{152} The mechanism for this action is unclear, but probably involves some non-Ca\textsuperscript{2+} entry blocking properties of verapamil. The clinical significance of verapamil’s action on skeletal muscle and interaction with neuromuscular blockers need further study.

We have investigated the interaction of nifedipine (10–15 µg/kg, iv, over 2 minutes) and halothane in normal dogs and found that there is an initial decrease in SVR, blood pressure, cardiac output, left ventricular dP/dt, and contractile force after nifedipine administration, which by 30 minutes is not significantly different from baseline 1% or 2% halothane.\textsuperscript{153} Using isolated perfused rat hearts to examine the interaction of nifedipine and halothane on myocardial contractility (dP/dt) and peak systolic tension within clinical dose ranges, we found that the direct negative inotropic effects of nifedipine and halothane are mostly additive. The clinical implications of these investigations are that in normal humans, the cardiovascular depression of inhalation anesthetics and nifedipine are probably close to being additive; therefore, lower doses of each should be given initially, but the combination is probably safe. In fact, in our limited experience in 10 patients taking nifedipine and requiring anesthesia for coronary bypass grafting, both halothane and enflurane have been given in our usual dose range\textsuperscript{154} with remarkably stable hemodynamics (fig. 6). However, patients with congestive heart failure or poor ventricular function should be given inhalation agents and calcium channel blockers with caution because of the potential additive negative inotropic and vasodilation actions.

**Response to Stress**

The “stresses” of awake exercise may not be completely applicable to those of anesthesia and surgery, but hemodynamic changes of exercise are qualitatively similar to those frequently encountered during surgery. The chronic administration of Ca\textsuperscript{2+} channel blockers does not impair hemodynamic function nor block the heart rate and blood pressure responses to exercise. Exercise to the same workload in patients with Prinzmetal angina produced an increase in ejection fraction, blood pressure, and heart rate, but the increase in heart rate was significantly less during verapamil than nifedipine treatment.\textsuperscript{191} In nine patients with angina from
coronary artery disease. nifedipine (5–7 µg/kg, iv) significantly decreased the exercise-induced increase in LVEDP and V max, but not in heart rate, blood pressure, dP/dt, and cardiac index. There was, however, no angina in four patients with the same exercise that produced angina in all nine patients before drug therapy. These results in patients with ischemic heart disease indicate that exercise stresses and perhaps others (like intubation, incision, and surgical manipulation) may evoke expected hemodynamic responses in patients chronically taking Ca++ channel blockers, but the hemodynamic responses may be blunted somewhat. Because angina did not occur in awake patients with ischemic heart disease, the coronary blood flow probably was increased to compensate for the increases in oxygen demand during these stresses. Whether calcium channel blockers provide similar protection in anesthetized patients with or without ischemic heart disease needs to be determined.

Conclusions

The Ca++ entry blockers are valuable new drugs in the treatment of many cardiovascular diseases. Because of the prevalence of these diseases, anesthesiologists will anesthetize many patients maintained on Ca++ antagonists and will wish to administer them to some patients under their care. Verapamil and nifedipine are available for use in the United States. Verapamil is useful for the treatment of supraventricular arrhythmias, whereas nifedipine and verapamil are indicated in the treatment of coronary vasospasm. There is no good information regarding whether or not the drugs need to be discontinued for a specified interval before anesthesia. Our clinical experience with both compounds is that they may be continued safely right up to the morning of surgery. Both nifedipine and verapamil are potent vasodilators and must be administered with caution during anesthesia and in the perioperative period, especially in patients with impaired ventricular function and/or hypovolemia. Additionally, verapamil may produce varying degrees of A-V block and must be given very carefully in patients anesthetized with enflurane, isoflurane, and halothane, in patients with A-V nodal block, or in patients maintained on beta-adrenergic blocking drugs. There is little experience to guide the anesthesiologists in the perioperative use of these drugs, but their potential uses are great. The calcium channel blockers are an important addition to our formulary, with many of their uses in anesthesiology yet to be confirmed or discovered.

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