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# Calcium Channel Blockers

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## Abstract

Vasospasm refers to a condition in which an arterial spasm leads to vasoconstriction. This can lead to tissue ischemia and necrosis. Coronary vasospasm can lead to significant cardiac ischemia associated with symptomatic ischemia or cardiac arrhythmia. Cerebral vasospasm is an essential source of morbidity and mortality in subarachnoid hemorrhage patients. It can happen within 3–15 days with a peak incidence at 7 days after aneurysmal subarachnoid hemorrhage (SAH). Calcium channel blockers are widely used in the treatment of hypertension, angina pectoris, cardiac arrhythmias, and other disorders like SAH vasospasm related and Migraine. The specific treatment of cerebral vasospasm helps improving cerebral blood flow to avoid delayed ischemic neurologic deficit by reducing ICP, optimizing the rate of cerebral oxygen demand, and enhancing cerebral blood flow with one of the following approaches: indirect pharmacological protection of brain tissue or direct mechanical dilation of the vasospastic vessel. Nimodipine is the standard of care in aneurysmal SAH patients. Nimodipine 60 mg every 4 hours can be used for all patients with aneurysmal SAH once the diagnosis is made for 21 days.

**Keywords:** coronary vasospasm, cerebral vasospasm, calcium channel blockers, cerebral blood flow, nimodipine

## 1. Introduction

Vasospasm is a condition which is associated with an arterial spasm and vasoconstriction, which may lead to tissue ischemia and necrosis. Coronary vasospasm can lead to significant cardiac ischemia associated with symptomatic ischemia or cardiac arrhythmia. Cerebral vasospasm may arise as a complication of subarachnoid hemorrhage (SAH). The most common cause of delayed cerebral ischemia after SAH is assumed to be vasospasm; delayed cerebral ischemia contributes substantially to morbidity and mortality after SAH especially aneurysmal SAH. Calcium channel blockers are widely used in the treatment of hypertension, angina pectoris, cardiac arrhythmias, and other disorders like SAH vasospasm related and migraine. Data is suggesting that their use reduces the risk of subsequent cardiovascular events [1, 2]. Besides, some meta-analyses have suggested that calcium channel blockers may be more effective than other drugs in reducing stroke risk [3, 4]. Fleckenstein's work in the 1960s led to the concept that drugs alter cardiac and smooth muscle contraction by blocking the entry of  $\text{Ca}^{2+}$  into myocytes. Godfraind and associates showed that the effect of the diphenylpiperazine analogs in the prevention of agonist-induced vascular smooth muscle contraction could be overcome by raising the concentration

of  $\text{Ca}^{2+}$  in the extracellular medium. Hass and Hartfelder reported in 1962 that verapamil, a coronary vasodilator, possessed negative inotropic and chronotropic effects that were not seen with other vasodilatory agents, such as GTN. In 1967, Fleckenstein suggested that the negative inotropic effect resulted from an inhibition of excitation-contraction coupling and that the mechanism involved reduced movement of  $\text{Ca}^{2+}$  into cardiac myocytes. Verapamil was the first clinically available  $\text{Ca}^{2+}$  channel blocker; it is a congener of papaverine. Many other  $\text{Ca}^{2+}$  entry blockers with a wide range of structures are now available [5].

## 2. Mechanism of action and effects

Calcium is an essential element for excitation-contraction coupling in muscle cells. The increase in the cytosolic  $\text{Ca}^{2+}$  concentration leads to an increased contraction in both cardiac and vascular smooth muscle cells [6]:

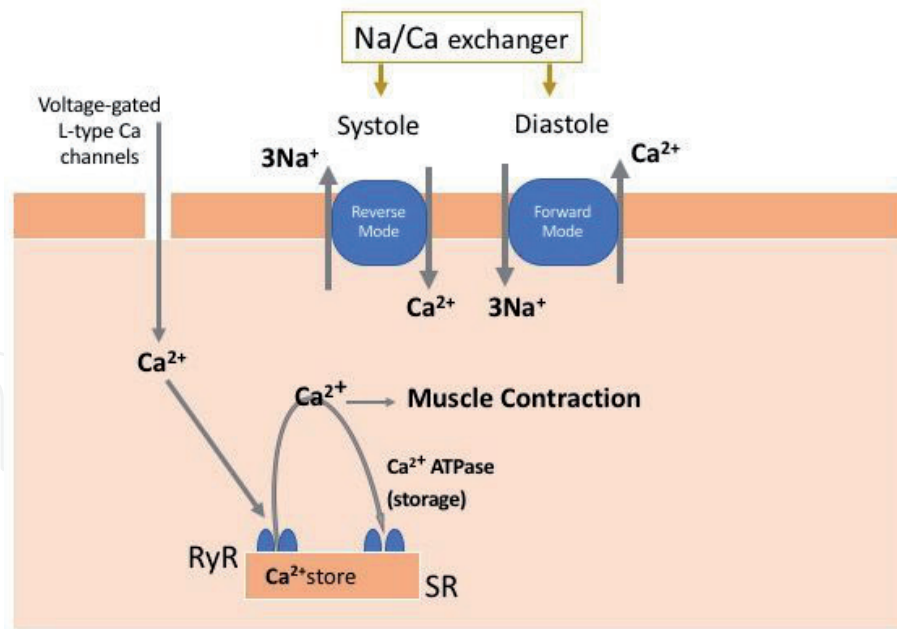
1. In smooth muscle and cardiac muscle cells,  $\text{Ca}^{2+}$  can enter cells through transmembrane voltage-gated and ligand-gated channels (**Figures 1 and 2**).
2. In striated and cardiac muscle cells, a rise in intracellular free  $\text{Ca}^{2+}$  promotes the release of further  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum (SR) through actions at ryanodine receptors (**Figures 1 and 2**).
3. Ligand-gated channels linked to G-protein-coupled receptors promote the release of  $\text{Ca}^{2+}$  from intracellular stores in the sarcoplasmic reticulum.
4.  $\text{Ca}^{2+}$  leaves striated and cardiac muscle cells in exchange for  $\text{Na}^+$  via the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger (**Figure 1**).

Therefore, in striated muscle, free  $\text{Ca}^{2+}$  in the cytosol comes only from the sarcoplasmic reticulum, while in smooth muscle, it must enter the cell through transmembrane  $\text{Ca}^{2+}$  channels. Cardiac muscle uses both mechanisms.

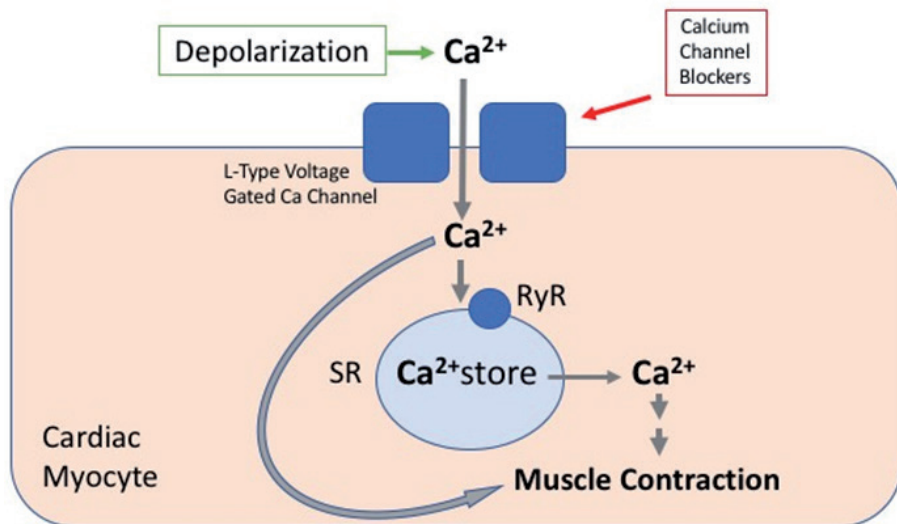
Four types of transmembrane calcium channels, differing in location and function, have been identified:

- A. L type, located in skeletal, cardiac, and smooth muscles, causing contraction of muscle cells.
- B. T type, found in pacemaker cells, causing  $\text{Ca}^{2+}$  entry, inactivated at more negative potentials and more rapid than the L type.
- C. N type is available in neurons and acting in transmitter release.
- D. P type is in Purkinje cells whose function is unknown currently.

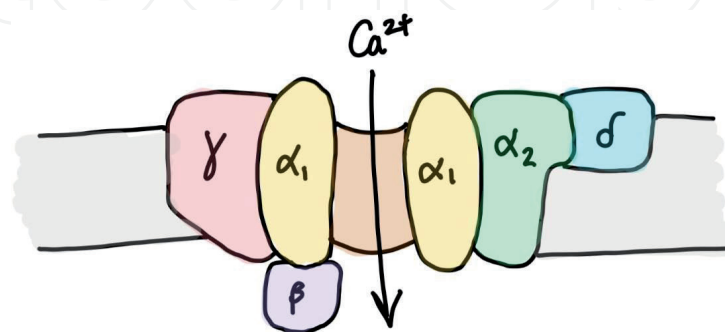
5- Voltage-gated L-type  $\text{Ca}^{2+}$  channels (long-acting, high threshold-activated, slowly inactivated) are found in the cell membranes of a large number of excitable cells, including cardiac and vascular smooth muscle.  $\text{Ca}^{2+}$  enters the cell through these channels when the cell membrane is depolarized. The cardiac and vascular smooth muscle L-type  $\text{Ca}^{2+}$  channels have different subunit structures. L-type channels are essential therapeutically. The L-type calcium channel, acted on by calcium channel blockers, consists of five different subunits ( $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ ,  $\delta$ ,  $\gamma$ ). **Figure 3** represents the L type of  $\text{Ca}^{2+}$  channel [7].



**Figure 1.**  
 Regulation of calcium in cardiac myocytes and blood vessels.



**Figure 2.**  
 Mechanism of contraction of the cardiac myocyte by L-type voltage-gated Ca channel.



**Figure 3.**  
 Subunits of the L-type calcium channel.

6- Voltage-gated T-type  $\text{Ca}^{2+}$  channels (transient, low threshold-activated, fast inactivated) are found in pacemaker cells of the sinoatrial and atrioventricular nodes and are also present in vascular smooth muscle. Calcium channel blockers

have different chemical structures, but their standard action is to reduce  $\text{Ca}^{2+}$  influx through voltage-gated L-type  $\text{Ca}^{2+}$  channels in smooth cardiac muscle (**Figure 2**).

There are clinically significant differences among the different types of calcium channel blockers, which bind to discrete receptors on the L-type  $\text{Ca}^{2+}$  channel. The receptor for verapamil is intracellular, while diltiazem and the dihydropyridines (e.g., nifedipine, amlodipine) have extracellular binding sites; however, the receptor domains for verapamil and diltiazem overlap. Verapamil and diltiazem exhibit frequency-dependent receptor binding and gain access to the  $\text{Ca}^{2+}$  channel when it is in the open state; in contrast, the dihydropyridines preferentially bind to the channel in its inactivated state. As more  $\text{Ca}^{2+}$  channels are in the inactive state, dihydropyridines selectively bind to  $\text{Ca}^{2+}$  channels in vascular smooth muscle. These receptor binding characteristics account for the relative vascular selectivity of the dihydropyridines and the antiarrhythmic properties of verapamil and diltiazem [6].

Calcium concentrations in cardiac cells and vascular smooth muscles are under the influence of different mechanisms. Calcium entry through voltage-gated L-type  $\text{Ca}^{2+}$  channels stimulates ryanodine receptors (RyR) in the sarcoplasmic reticulum, releasing stored  $\text{Ca}^{2+}$  (a process known as  $\text{Ca}^{2+}$ -induced calcium release, CICR). Intracellular  $\text{Ca}^{2+}$  is also regulated by exchange with  $\text{Na}^+$  via the  $\text{Na}^+/\text{Ca}^{2+}$  exchangers (NCX) in the cell membrane.

The depolarization phase during the action potential activates the voltage-gated channels, and the influx of  $\text{Ca}^{2+}$  into the cell results in myosin phosphorylation and muscle contraction. It also promotes further  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum by stimulation of ryanodine receptors. L-type  $\text{Ca}^{2+}$  channels can, therefore, be reduced directly by calcium channel blockers.

### **3. Pharmacokinetics**

Most calcium channel blockers are lipophilic compounds with similar pharmacokinetic properties. Calcium channel blockers are typically administered in oral dosage forms, but orally administered calcium channel blockers undergo significant first-pass metabolism in the gut and liver, which can significantly reduce bioavailability to 10–30%. Most oral calcium channel blockers have a rapid onset of action between 20 minutes and 2 hours like nifedipine resulting in reflex tachycardia, which can worsen myocardial ischemia due to shortening diastolic phase of the cardiac cycle. Most of the agents typically have short elimination half-lives (2–10 hours), necessitating short dosing intervals or extended-release formulations. Amlodipine was developed in an attempt to overcome the pharmacokinetic limitations of nifedipine. This drug has an increased oral bioavailability of 60%. The time of onset is 6 hours, and prolonged elimination half-life is 40 hours. These kinetic properties are likely due, in part, to its lipophilic character and its positive charge at physiologic pH, which leads to increased association with negatively charged plasma membranes. Some of the calcium channel blockers also have intravenous formulations like diltiazem and verapamil, while clevidipine is a dihydropyridine agent that is available only as an intravenous formulation. All calcium channel blockers are metabolized by the liver. Diltiazem is primarily excreted by the liver, while dihydropyridines and verapamil are mainly excreted in the urine [6–8].

### **4. Pharmacological actions**

The main targets of calcium channel blockers are vascular tissue and cardiac cells.  $\text{Ca}^{2+}$  channel blockers inhibit the voltage-dependent  $\text{Ca}^{2+}$  channels in vascular

smooth muscle and decrease  $\text{Ca}^{2+}$  entry. All  $\text{Ca}^{2+}$  channel antagonists relax arterial smooth muscle and thereby reduce arterial resistance, blood pressure, and cardiac afterload.  $\text{Ca}^{2+}$  channel blockers do not influence cardiac preload significantly when given at regular doses, suggesting that capacitance veins that determine venous return to the heart are resistant to the relaxing effect of  $\text{Ca}^{2+}$  channel antagonists. Depolarization in the SA and AV nodes depends mainly on the movement of  $\text{Ca}^{2+}$  through the slow channel. The impact of a  $\text{Ca}^{2+}$  channel blocker on AV conduction and the rate of the sinus node pacemaker depend on whether the agent delays the recovery of the slow channel.

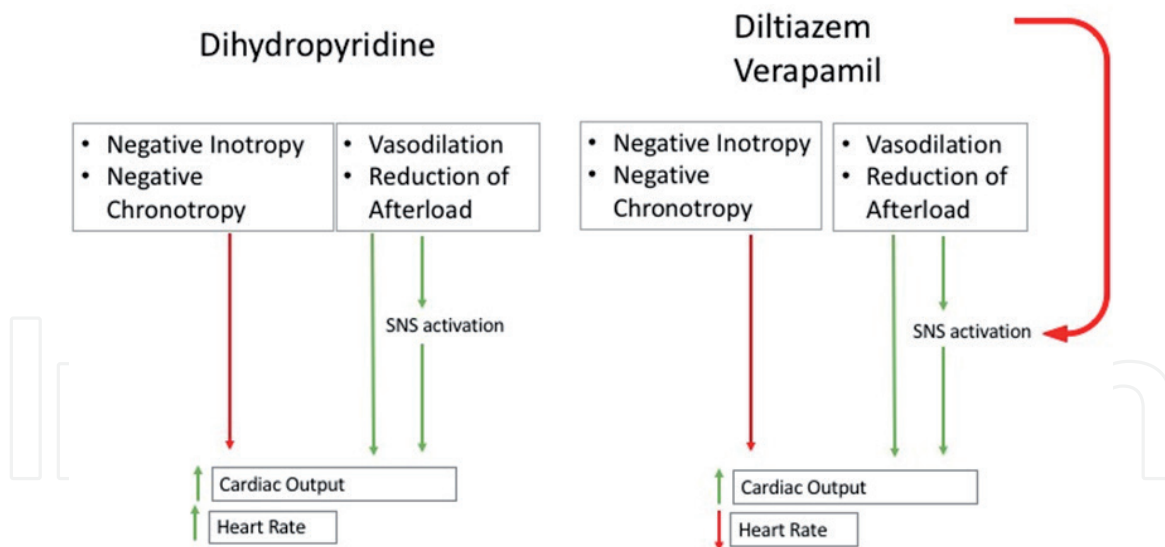
Diltiazem and verapamil decrease the rate of the SA node pacemaker and slow AV conduction at clinically used doses; the latter effect is the basis for their use in the treatment of supraventricular tachyarrhythmias [6–8].

## 5. Cardiovascular effects of different $\text{Ca}^{2+}$ channel blockers

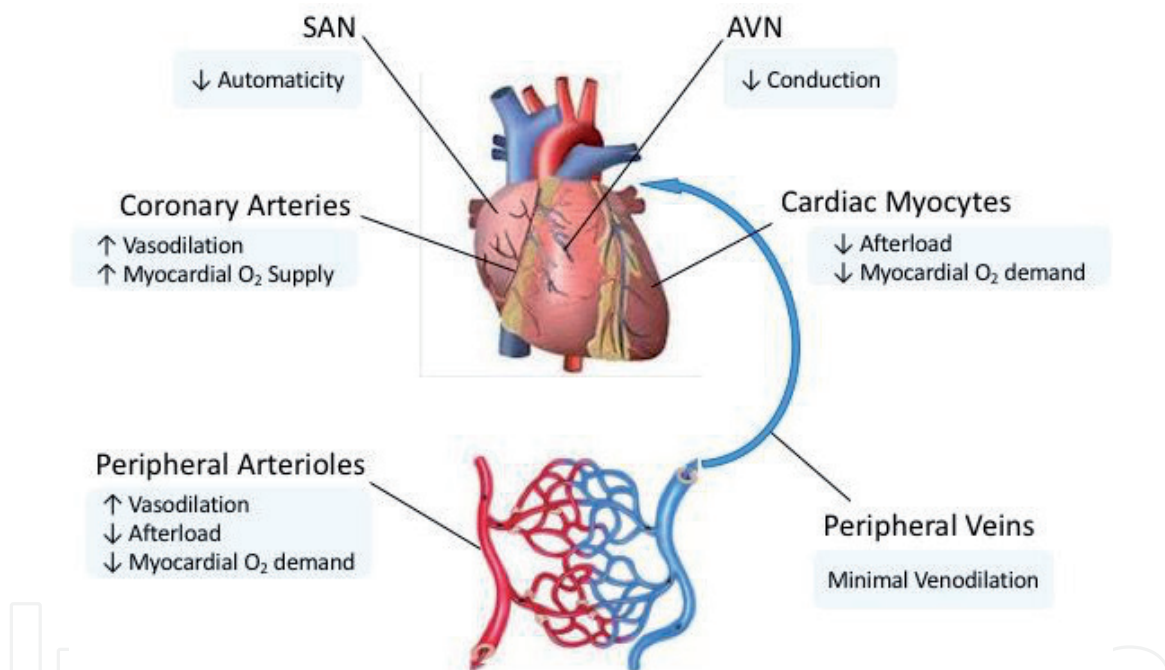
The hemodynamic profiles of the  $\text{Ca}^{2+}$  channel blockers approved for clinical use differ and depend mainly on the ratio of vasodilating and negative inotropic and chronotropic effects on the heart (Table 1, Figures 4 and 5). Although all calcium channel blockers are vasodilators, dihydropyridine derivatives such as nifedipine and amlodipine are the most potent and have the most significant vascular selectivity. Arterial dilation reduces peripheral resistance and lowers blood pressure, which reduces the work of the left ventricle and therefore reduces myocardial oxygen demand. Most dihydropyridines have a rapid onset of action. A rapid reduction in blood pressure can lead to reflex sympathetic nervous system activation and tachycardia. Amlodipine or modified-release formulations of short-acting dihydropyridines are more slowly absorbed and gradually reduce blood pressure with little reflex tachycardia. But generally, the differences between the relatively vaso-selective dihydropyridines and the much less-selective diltiazem and verapamil have essential consequences because the decrease in arterial blood pressure elicits reflex sympathetic activation, resulting in the stimulation of heart rate, AV conduction velocity, and myocardial force, just the opposite of the direct effect of  $\text{Ca}^{2+}$  channel blockers. While direct and indirect impacts usually balance each other in the case of verapamil and diltiazem, sympathetic stimulation often prevails in dihydropyridines, causing an increase in heart rate and contractility. Cardiac depressant effects

Comparative Cardiovascular Effects of Calcium Channel Blockers				
Example (Drug class)	Vasodilation	Decreased cardiac contractility	Decreased automaticity (SA node)	Decreased conduction (AV node)
Verapamil (phenylalkylamine)	4	4	5	5
Diltiazem (benzothiazepine)	3	2	5	4
Amlodipine (dihydropyridine)	5	1	1	0
Nifedipine (dihydropyridine)	5	1	1	0

**Table 1.** Comparative cardiovascular effects of calcium channel blockers graded from 0 (no effect) to 5 (prominent effect).



**Figure 4.**  
Effects of calcium channel blocker agents.



**Figure 5.**  
Calcium channel blocker sites of action.

of dihydropyridines may be unmasked, though, in the presence of  $\beta$  blockers and patients with heart failure.

Also, they can have a significant impact on coronary artery dilation; for this reason, CCB can prevent or relieve coronary vasospasm and improve myocardial blood flow. On the other hand, CCBs have negative chronotropic effect. Verapamil and diltiazem (but not the dihydropyridines) slow the rate of firing of the sinoatrial node and slow the conduction of the electrical impulse through the atrioventricular node. Reflex tachycardia does not occur with these drugs, and they also slow the rate of rising in heart rate during exercise. CCBs play an essential role in reducing cardiac contractility as most calcium channel blockers (particularly verapamil) have some negative inotropic effects. Amlodipine does not impair myocardial contractility.

## 6. Calcium channel blocker agents

There are two types of CCBs:

**A. Dihydropyridines:** amlodipine, clevidipine, felodipine, isradipine, lercanidipine, nicardipine, nifedipine, nimodipine, and nisoldipine

Dihydropyridines exhibit much higher arterial vasodilation than non-dihydropyridines while having relatively little impact on cardiac tissue (i.e., there is less depression on myocardial contractility, less impairment on SA node automaticity, and less slowing on AV node conduction velocity) (**Table 1, Figure 4**).

**B. Non-dihydropyridines:**

- Benzothiazepines (diltiazem)
- Phenylalkylamines (verapamil)

Non-dihydropyridines are more effective in tissue with frequent channel openings (i.e., SA node, AV node, and cardiac myocytes), and channel inhibition increases in proportion to heart rate. The negative chronotropic and inotropic effects on non-dihydropyridine agents appear greater for verapamil than diltiazem. The phenylalkylamine verapamil and the benzothiazepine diltiazem have both cardiac and vascular actions (**Table 1, Figure 4**). These drugs have antiarrhythmic, antianginal, and antihypertensive activity.

### 6.1 Nifedipine

It is a dihydropyridine that does not resemble the other calcium antagonists in chemical structure. Although it is not a nitrate, its nitro group is essential for its antianginal effect. Also, it has peripheral vasodilatory effects. It works by inhibiting the voltage-dependent calcium channel in the vascular smooth muscles and has little or no direct suppressant effect on the SA or AV nodes. Nifedipine is thought to be more effective in patients with coronary vasospasm, and it is usually used for vasospastic angina along with angina pectoris.

Additionally, it is used in selected patients to treat hypertension because of its vasodilatory properties. Nifedipine has efficient absorption with buccal or oral administration. Around 90% of nifedipine is protein-bound. The bioavailability of an oral dose reaches 65%. Nifedipine gets metabolized into two inactive metabolites which are found in equilibrium with each other. Only a limited amount of unchanged nifedipine is found in the urine [7].

### 6.2 Amlodipine

Similar to second-generation dihydropyridines, it has a higher selectivity for the vascular smooth muscles than the myocardial tissue. It has a longer half-life (34 hours) but less negative inotropic effect than nifedipine. It is used in the treatment of chronic stable angina and essential hypertension [7]. Amlodipine increases exercise duration, decreases anginal attacks, and reduces the consumption of **nitroglycerin**. It is given once daily (at a dose of 5 or 10 mg). Common side effects of the dihydropyridines are less likely with amlodipine.



### **6.3 Nicardipine**

It is a short-acting dihydropyridine with a side effect profile similar to nifedipine; it has also been shown to be useful in angina. It is remarkably effective in vasospastic angina.

### **6.4 Felodipine**

It is a second-generation dihydropyridine channel blocker of the nifedipine type. It is more selective for vascular smooth muscles than myocardial tissue. And it serves as an effective vasodilator. It is usually used in the treatment of angina and essential hypertension. Additionally, it exhibits a high degree of protein binding and has a half-life ranging from 10 to 18 hours.

### **6.5 Nimodipine**

It is a dihydropyridine calcium channel blocker that differs from other dihydropyridines as it dilates the cerebral blood vessels more than other dihydropyridines do. It is indicated in the treatment of subarachnoid hemorrhage-associated neurological deficits.

### **6.6 Verapamil**

It is a phenylalkylamine. It was introduced in 1962 as a coronary vasodilator. It is used for the treatment of angina pectoris, arrhythmias due to ischemic cardiac syndromes, and supraventricular arrhythmias as well. Verapamil's primary effect is on the slow  $\text{Ca}^{2+}$  channel, which results in a slowing of AV conduction and the sinus rate. It has a rapid absorption following oral administration. However, it is metabolized quickly and, therefore, has low bioavailability. Its main site of first-pass metabolism is the liver, forming several products. Yet, its metabolites have no significant biological effects. Verapamil has an elimination half-life of around 5 hours. Verapamil, like the dihydropyridines, causes little impact on venous return and preload but has more direct negative inotropic and chronotropic effects than the dihydropyridines at doses that produce arteriolar dilation and afterload reduction (**Figure 4**). Thus, the consequences of a reflex increase in adrenergic tone are generally offset by the direct cardio depressant effects of the drug. In patients without heart failure, oral administration of verapamil reduces peripheral vascular resistance and blood pressure with minimal changes in heart rate. Ventricular performance is not impaired and may improve, especially if ischemia limits performance. In contrast, in patients with heart failure, intravenous verapamil can cause a marked decrease in contractility and left ventricular function. The antianginal effect of verapamil, like that of all  $\text{Ca}^{2+}$  channel blockers, is due primarily to a reduction in myocardial  $\text{O}_2$  demand [7].

### **6.7 Diltiazem**

It was introduced in Japan as a cardiovascular agent for the treatment of angina pectoris. It was detected to dilate peripheral arteries and arterioles. By relieving coronary artery spasm, diltiazem increases myocardial oxygen supply, and by decreasing heart rate, it reduces myocardial oxygen demand. It is used in patients with variant angina as well. Additionally, it has electrophysiological properties similar to those of verapamil and, therefore, is used as an antiarrhythmic agent, but it is less potent than verapamil. It has a rapid oral absorption through the digestive tract, and it reaches peak plasma

levels within 1 hour of administration. Nevertheless, the sustained-release preparations provide peak plasma levels within 3–4 hours of oral administration.

Diltiazem is metabolized extensively by the first-pass metabolism after oral administration. Hence, its bioavailability is about 40%. It undergoes several biotransformations, including deacetylation, oxidative O- and N-demethylations, and conjugation of the phenolic metabolites. Although it has various metabolites, only deacetyldiltiazem is pharmacologically active, which has about 40–50% of the potency of the parent drug [7].

## 6.8 Side effects

- Headache, flushing, and dizziness due to arterial dilation, although tolerance often occurs with continued use.
- Ankle edema probably arises from increased transcapillary hydrostatic pressure. It happens mostly with dihydropyridines, and it is frequently resistant to diuretics.
- Decompensated heart failure is due to reduced cardiac contractility, especially in patients with preexisting poor left ventricular function, particularly with verapamil, but amlodipine does not depress cardiac contractility.
- Tachycardia and palpitations can arise with dihydropyridines, especially with rapid-release formulations.
- Bradycardia and heart block can occur with verapamil and diltiazem.
- Constipation is most common with verapamil and less with diltiazem.
- Heartburn associated with Amlodipine and other dihydropyridines use is due to lower esophageal sphincter relaxation.
- Gum hyperplasia.

## 7. Calcium channel blocker indications

### 7.1 Calcium channel blockers for hypertension

CCBs are prevalent antihypertensive drugs. CCBs lower BP by causing peripheral arterial dilation, with the rank order of potency being dihydropyridines > diltiazem > verapamil. They are generally well-tolerated, do not require monitoring with blood tests, and have proven safe and effective in many large RCTs. CCBs also have antianginal and some antiarrhythmic effects and seem to provide more protection against stroke than other antihypertensive agents do.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and subsequent RCTs showed that CCBs (represented by amlodipine) prevent coronary events as effectively as diuretics and RAS blockers do.

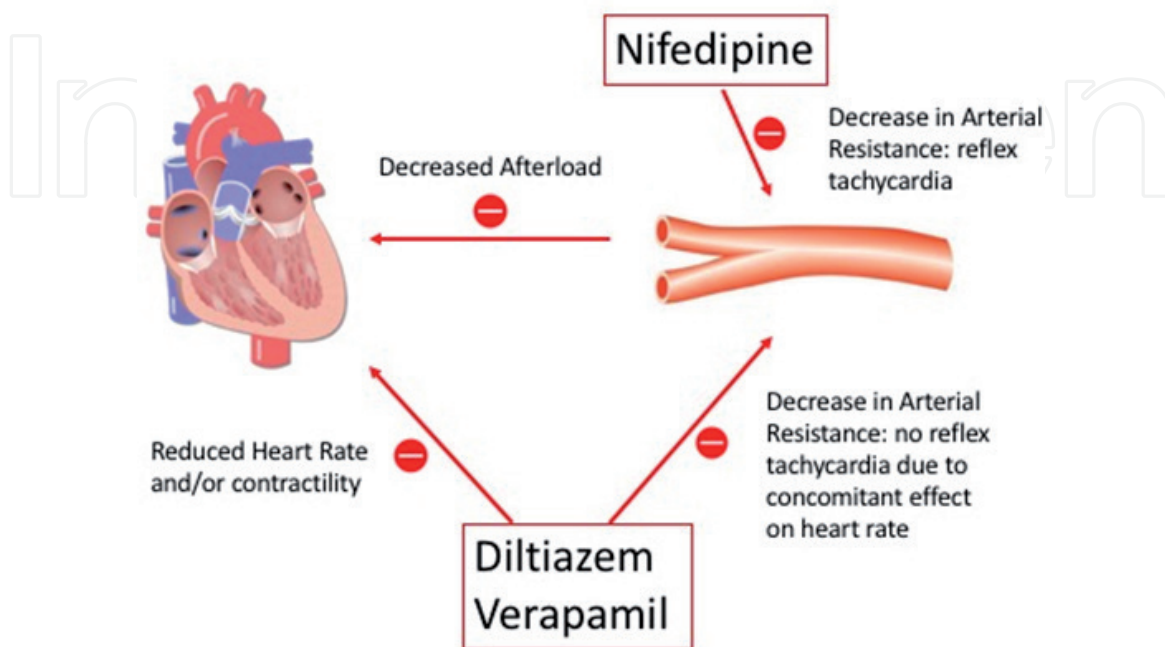
### 7.2 Calcium channel blockers for coronary vasospasm

Coronary spasm results in transient functional occlusion of a coronary artery that is reversible with nitrate vasodilation. It occurs in the setting of coronary

stenosis. Variant angina results from reduced blood flow (a consequence of transient localized vasoconstriction) rather than increased O<sub>2</sub> demand. Drug-induced causes (e.g., cocaine, amphetamines, sumatriptan, and related antimigraine drugs) should be excluded. CCBs are effective in about 90% of patients. These agents are considered first-line treatment and may be combined with nitrate. The effects of pharmacologic vasodilators on coronary flow reflect direct actions on vascular smooth muscle as well as secondary adjustments in resistance artery tone. All calcium channel blockers induce vascular smooth muscle relaxation and are to various degrees pharmacologic coronary vasodilators (**Figure 6**). In epicardial arteries, the vasodilator response is like nitroglycerin and is effective in preventing coronary vasospasm superimposed on coronary stenosis as well as in normal arteries of patients with variant angina. They also submaximally vasodilate coronary resistance vessels. In this regard, dihydropyridine derivatives such as nifedipine are particularly potent and can sometimes precipitate subendocardial ischemia in the presence of critical stenosis. This arises from a transmural redistribution of blood flow (coronary steal) as well as the tachycardia and hypotension that transiently occur with short half-life formulations of nifedipine. One study demonstrated that the use of calcium channel blocker therapy was an independent predictor of myocardial infarct-free survival in vasospastic angina patients.

### 7.3 Calcium channel blockers for stable angina

All calcium channel blockers can be used in the treatment of stable angina pectoris. They vasodilate coronary arteries, reduce coronary resistance, increase coronary blood flow, and may enhance the development of coronary collaterals. The vasodilatation and increase in coronary artery blood flow result from the blockade of calcium influx as well as an increase in the levels of nitric oxide and bradykinin; therefore, the increase in coronary artery blood flow is a result of bradykinin/nitric oxide-dependent and bradykinin/nitric oxide-independent mechanisms. They elicit a strong reflex beta-adrenergic response, making any potential negative inotropic or chronotropic effect clinically insignificant. This adrenergic response often includes



**Figure 6.**  
*Sites of effects of calcium channel blockers in angina.*

a reflex tachycardia. Verapamil and diltiazem are useful in angina because they decrease myocardial oxygen demand by acting as a negative inotropic and chronotropic effect, by lowering the systemic blood pressure, and by lowering heart rate by blocking AV node (**Figure 6**). The use of short-acting dihydropyridines, such as nifedipine, can exacerbate ischemia due to reflex tachycardia, and therefore, it can be used as a monotherapy in this setting. Calcium channel blockers are used with combination therapy with beta-blockers, which can be more effective than either therapy alone. Amlodipine or felodipine could be considered before other calcium channel blockers, given their better side effect profiles when used in combination with beta-blockers. In stable angina patients with suspension of a vasoactive component, a trial of a calcium channel blocker can be added to beta blocker agents. Calcium channel blockers, particularly verapamil and diltiazem, should be used with caution in patients with left ventricular systolic dysfunction, such as those with an ejection fraction less than 40 percent or heart failure due to their negative inotropic effect.

#### **7.4 Calcium channel blockers for acute coronary syndrome**

Calcium channel blockers have been effective in reducing ischemia in patients with NSTEMI-ACS and persistent ischemia despite treatment with full-dose nitrates and beta-blockers as well as in patients with contraindications to beta-blockers and among those with hypertension. Such patients should receive non-dihydropyridine calcium channel-blocking agents that lower the heart rate [9, 10].

#### **7.5 Calcium channel blockers for hypertrophic cardiomyopathy (HCM)**

Verapamil improves left ventricular outflow obstruction and symptoms in patients with HCM.

#### **7.6 Calcium channel blockers in the treatment of cardiac arrhythmias**

Calcium channel blockers (CCBs) are useful antiarrhythmic agents in the management of certain arrhythmias, primarily supraventricular tachyarrhythmias. Verapamil is the drug of choice to terminate idiopathic fascicular ventricular tachycardia.

#### **7.7 Calcium channel blockers for migraine**

Verapamil can be used in the prevention of migraine headaches but is considered a second-choice drug.

#### **7.8 Calcium channel blockers for aneurysmal subarachnoid hemorrhage**

It is essential to review the cause behind intracranial arterial spasm, mechanisms, diagnostic tools, and management to understand the role of CCBs in vasospasm among patients with aneurysmal subarachnoid hemorrhage.

Vascular calcification is specific for arteries, which can involve all arteries, including the carotid artery and cerebral arteries. Intracranial arterial calcification (IAC) was first detected in the early 1960s. It is associated with atherosclerosis, especially in older people. Vascular calcification is an integral part of the active process of atherosclerosis, occurring in up to 90% of atherosclerotic lesions. Recent clinical studies have consistently found the intracranial internal carotid artery (IICA) to be the most common site of IAC. The incidence of IICA calcification has been reported

to range from 60 to 90% according to ethnicity, age, and stroke or other risk factors. The vertebral artery is the second most common artery affected by calcification, while other arteries have been affected only by less than 5%. An unenhanced CT scan is the most accessible and direct method to evaluate IAC in patients.

The prevalence of intracranial artery calcification is:

- Internal carotid artery: 60%
- Vertebral artery: 20%
- Middle cerebral artery: 5%
- Basilar artery: 5%

Risk factors of intracranial artery calcification:

Advanced age.  
Diabetes mellitus.  
Hypercholesterolemia.  
Hypertension.  
History of cardiovascular disease.  
Excessive alcohol intake.  
End-stage renal disease with long duration of hemodialysis [11–13].

#### *7.8.1 Hemodynamic and clinical effects of IAC*

IAC can lead to three significant hemodynamic effects: Firstly, it can lead to increase the arterial stiffness. This phenomenon is associated with aging and accelerated by other vascular risk factors. It can be measured by the pulse wave velocity (PWV) and may indicate early atherosclerotic changes. Several studies have verified the correlation between IAC and arterial stiffness, and this may increase the risk of stroke. Secondly, arterial stenosis can be linked to arterial calcification, which may lead to ischemic stroke due to direct luminal stenosis. Thirdly, IAC may lead to plaque stability. Intravascular ultrasound studies found heavily calcified plaques to be more resistant to plaque progression. Therefore, the findings for CAC suggest that substantial calcification may help stabilize atherosclerotic plaques. Also, a heavy plaque burden hidden in heavily calcified arteries may partially account for the association between severe arterial calcification and ischemic events regardless of plaque vulnerability.

#### *7.8.2 Vasospasm and delayed cerebral ischemia*

Cerebral vasospasm is an essential source of morbidity and mortality in subarachnoid hemorrhage patients. Vasospasm is one of the most common acute complications. It can happen within 3–15 days with a peak incidence at 7 days after aneurysmal SAH. Symptomatic vasospasm occurs in 20–40% of subarachnoid hemorrhage cases and is considered as the least understood component in their care. The symptom severity depends upon the artery affected and the degree of collateral circulation. Strokes from vasospasm account for nearly 50% of the early deaths in patients who survive the initial subarachnoid hemorrhage treatment. It is characterized by a pathological; diffuse, affecting all layers of the involved arterial wall; and long-lasting narrowing of the lumen of the vessel of large-capacity cerebral arteries

at the base of the brain either close or distal to the bleeding site. And it is associated with reduced perfusion of the territories distal to the affected vessel.

Risk factors for vasospasm include:

1. The severity of bleeding
2. The proximity to the significant intracerebral blood vessels
3. The location and extent of blood on CT scan and radiologic grading scales
4. Age less than 50 years
5. Hyperglycemia
6. Glasgow Coma Scale score < 14

### 7.8.3 Mechanism

While the underlying mechanisms causing vasospasm are not fully understood, a proliferative inflammatory arteriopathy is the pathological feature of cerebral vasospasm. The intima shows disruption of the internal elastic lamina, and the media is thickened and fibrotic, with an increased smooth muscle cell proliferation. The adventitia is infiltrated with inflammatory cells, and the neuronal endings are impaired [14]. A significant predictor of vasospasm after SAH is the volume of blood present around the cerebral arteries of the circle of Willis which can be measured by transcranial Doppler (TCD), although it has been clearly demonstrated that prolonged exposure of cerebral arteries to perivascular blood is essential for the development of vasospasm. It is not possible to identify a single causative molecule as the culprit of vasospasm. However, vasospasm is believed to be produced by spasmogenic substances generated during the lysis of subarachnoid blood such as oxyhemoglobin (a product of auto-oxidation of hemoglobin), nitric oxide, and endothelin-1. Those agents may be contributors to the pathological event of vasospasm.

Oxyhemoglobin may directly or indirectly trigger arterial vasoconstriction.

Oxyhemoglobin can also exert a scavenging effect on nitric oxide. It has been demonstrated that nitric oxide (a potent vasodilator) depleted during vasospasm and can stimulate endothelial cells to produce endothelin-1.

Endothelin-1 is the most potent and long-lasting vasoconstrictor effect, which is also associated with morphological changes, mimicking the delayed cerebral vasospasm. It has been shown that endothelin-1 levels are increased, not only in the cerebrospinal fluid during SAH and severe neuronal injury due to vasospasm or bleeding event. Moreover, endothelin levels change in neurological symptoms, but they do not predict vasospasm as assessed by transcranial Doppler. These observations suggest that endothelin-1 acts as a marker of cerebral ischemic injury [15, 16].

### 7.8.4 Diagnosis

#### 7.8.4.1 Transcranial Doppler

It is a noninvasive tool and is useful for the detection and evaluation of vasospasm. It can be performed at the bedside.

It used as a screening tool in high-grade World Federation of Neurological Surgeons (WFNS) scale patients in whom a neurological examination cannot be readily followed to identify those at higher risk [17].

It is a highly specific noninvasive exam but has a low level of sensitivity, and it is operator-patient dependent, and its value is debated.

In 2004, the American Academy of Neurology conducted a systematic review of the literature and concluded that TCDs could be used reliably to screen for the presence of vasospasm in the only MCA. Their criteria for the diagnosis or exclusion of vasospasm include flow velocity > 200 or 120 cm/s, respectively, significant increase in the flow velocities from day to day (>50 cm/s), and a Lindegaard ratio (MCAvelocity/ICAvelocity) > 6 [18].

#### 7.8.4.2 CT scan

Noninvasive angiography with CT angiography (CTA) to confirm vasospasm for patients with elevated velocities on transcranial Doppler ultrasound. The plane CT scan is useful for ruling out other causes in the event of the occurrence of a deficit or worsening of the clinical state like rebleeding or ischemia. Several prospective cohorts showed a correlation between CTA and DSA in predicting vasospasm and that many unnecessary angiograms could be avoided by using CTA as a screening test [19, 20]. A recent meta-analysis found a sensitivity and specificity for CTA of 80 and 93%, respectively [21].

#### 7.8.4.3 MRI

MRI can help to identify and diagnose cerebral ischemia at the early stage.

#### 7.8.4.4 Cerebral angiography

Cerebral angiography is the gold standard radiographic tool for the diagnosis of cerebral vasospasm. Angiography is used to identify patients with symptomatic vasospasm who might benefit from treatment.

In 30–70% of patients with SAH, angiographic vasospasm occurs, but it leads to clinically evident signs and symptoms in 20–30% of patients who experience delayed ischemic neurological deficits. About half of the symptomatic group of patients suffer severe permanent neurological dysfunction or death.

#### 7.8.5 Treatment

The specific treatment of cerebral vasospasm helps improving cerebral blood flow to avoid delayed ischemic neurologic deficit by reducing ICP, optimizing the rate of cerebral oxygen demand, and enhancing cerebral blood flow with one of the following approaches: indirect pharmacological protection of brain tissue or direct mechanical dilation of the vasospastic vessel.

Nimodipine is the standard of care in aneurysmal SAH patients. Nimodipine 60 mg every 4 hours can be used for all patients with aneurysmal SAH once the diagnosis is made for 21 days. Nimodipine is to be given orally or by nasogastric tube because intravenous administration causes serious adverse events, including death. The mechanism of benefit of nimodipine in SAH is unknown. Oral nimodipine is the only Class I evidence regarding cerebral vasospasm used in the publication of the AHA subarachnoid hemorrhage guidelines [22]. Early aneurysm treatment, HHH-therapy (hypertension, hypervolemia, and hemodilution), cerebral angioplasty, and selective intra-arterial vasodilator therapy were recommended based on Class II evidence.

In summary, nimodipine was initially studied in SAH to prevent vasospasm. However, despite its vasodilatory effects on cerebral vessels, the evidence of nimodipine effects on the incidence of either angiographic or symptomatic vasospasm is not convincing [23]. Nevertheless, nimodipine has been demonstrated to improve outcomes in SAH and is the agent of choice in these patients [23].

### **7.9 Calcium channel blockers for reversible cerebral vasoconstriction syndrome**

Reversible cerebral vasoconstriction syndrome (RCVS) represents a group of conditions that show a reversible narrowing of the cerebral arteries with clinical manifestations that typically include thunderclap headache and less commonly neurologic deficits related to brain edema, seizure, or stroke. The clinical outcome is usually benign, although major strokes can result in severe disability and death in a minority. The pathophysiology of the abrupt-onset headache and the prolonged but reversible vasoconstriction is not known. Reversible angiographic narrowing suggests an abnormality in the control of cerebrovascular tone [24].

RCVS has been associated with a variety of conditions including pregnancy, migraine, use of vasoconstrictive drugs, neurosurgical procedures, hypercalcemia, unruptured saccular aneurysms, cervical artery dissection, and cerebral venous thrombosis. The diagnosis of RCVS is based upon the characteristic clinical, brain imaging, and angiographic features. Nimodipine and verapamil and brief courses of magnesium sulfate, serotonin antagonists, and dantrolene have been administered to relieve the vasoconstriction. Data from two prospective case series suggest that nimodipine does not affect the time course of cerebral vasoconstriction [25, 26]. However, nimodipine might relieve the number and intensity of headaches and has documented effects on the smaller vasculature not easily imaged by angiography. Calcium channel blockers can be discontinued after resolution of symptoms or angiographic abnormalities if they are used.

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