# Perioperative Hypertension: What's New and What's Useful?

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It is estimated that approximately 2–3 million patients with hypertension undergo surgical procedures every year in the United States (1). Hypertensive patients at particular risk for perioperative cardiovascular events include those with overt or covert ischemic heart disease (IHD), valvular heart disease, or congestive heart failure (CHF). A primary goal is to decrease blood pressure below 180/110 mm Hg without compromising organ perfusion. Antihypertensive medication, especially β-blockers, should be continued until the time of surgery and then restarted as soon as possible. Risks presented by hypertension include direct sympathoadrenal injury to heart, brain, and kidney, as well as platelet activation and increased risk for plaque rupture, coronary vasospasm, and myocardial injury (1).

Two broad clinical patterns of hypertension are usually encountered (Table 1). "Vasoconstricted" hypertension is encountered in the medical patient with chronic renovascular hypertension. It is characterized by diastolic hypertension, increased systemic vascular resistance (SVR) with normal or even decreased cardiac output (CO) and heart rate (HR). "Hyperdynamic" hypertension is encountered in the postoperative surgical patient, with acute systolic hypertension, widened pulse pressure, and increased CO, HR, and SVR. It is important to match treatment to the patient's hemodynamic state. In hyperdynamic hypertension a pure vasodilator may exacerbate reflex tachycardia and myocardial oxygen imbalance ($MVO_2$). In renovascular hypertension, a β-blocker may impair cardiac output and oxygen delivery. In many patients, a combination of a vasodilator and a negative inotropic agent works best.

## Vasodilator Agents

Direct vasodilator drugs may be classified on the basis of their predominant effect on the circulation (Table 2). Arterial dilators (e.g., hydralazine, ACE inhibitors, nicardipine) predominantly dilate the arterial resistance circulation, decrease afterload, and enhance CO when myocardial contractility is impaired. Venodilators (e.g., nitroglycerine) predominantly dilate the venous capacitance circulation and decrease preload, pulmonary congestion, and edema. Balanced vasodilators (e.g., sodium nitroprusside [SNP]) dilate both the arterial and venous systems and simultaneously decrease afterload and preload. Vasodilator agents benefit myocardial wall stress and oxygen balance when they are used in the presence of elevated preload and/or afterload. Cardiac output is increased as long as preload is not excessively decreased. Both nitroglycerine and SNP have a long history of reliability in the control of postoperative hypertension, especially after cardiac surgery (2).

SNP and nitroglycerine act as prodrugs or therapeutic substitutes in that they are carriers, or donors, of nitric oxide, which mediates their vasodilator action (3). Nitric oxide is released spontaneously from SNP, but nitroglycerine requires a cofactor such as cysteine (a thiol). This may account for the predominant venodilator effect of nitroglycerine.

### *Limitations and Adverse Effects of Vasodilator Agents*

1. Acute hypotension in hypovolemic patients.
2. Increased "sensitivity" to vasodilation with advancing age, resulting from an attenuated baroreceptor response and impaired reflex tachycardia.
3. Reflex release of catecholamines and activation of the renin-angiotensin system, resulting in reflex tachycardia, tachyphylaxis, and rebound hypertension if the drug is suddenly discontinued.
4. Hypoxemia, resulting from reversal of hypoxic pulmonary vasoconstriction in the presence of localized impairment of ventilation, e.g., postoperative atelectasis.
5. Increased cerebral blood flow (CBF), increased intracranial pressure (ICP), and decreased cerebral perfusion pressure (CPP) in patients with closed head injury or intracranial hypertension.
6. Salt and water retention with longer-term administration, triggered by secondary hyperaldosteronism, which requires concurrent diuretic administration for effective antihypertensive therapy.
7. Adverse effects on ($MVO_2$) (see below).

**Table 1.** Patterns of Hypertension

| | Type of Hypertension | |
|---|---|---|
| | Vasoconstricted | Hyperdynamic |
| Milieu | Chronic, Renovascular Hypertension | Acute, Postoperative Hypertension |
| SVR | Increased | Increased |
| CO | Normal or Decreased | Increased |
| HR | Normal or Decreased | Increased |
| HTN | Diastolic | Systolic |
| Treatment | Vasodilators, ACE Inhibitors | Beta or Calcium Blockers |

SVR = systemic arterial resistance; CO = cardiac output; HR = heart rate; HTN = hypertension.

**Table 2.** Classification of Vasodilator Drugs

| Arterial dilators | Balanced dilators | Venodilators |
|---|---|---|
| Hydralazine | Nitroprusside | Nitroglycerine |
| ACE inhibitors | | |
| Nicardipine | | |

## *Vasodilator Therapy and Myocardial Oxygen Balance*

In the left ventricle (LV), 70%-90% of coronary artery perfusion occurs during diastole and is governed by aortic diastolic pressure (ADP). In the presence of ischemic heart disease, the coronary arteries are usually maximally dilated and coronary perfusion is largely pressure dependent. The pressure gradient that determines coronary artery perfusion pressure (CPP), the transmyocardial gradient (TMG), is the difference between the ADP and the LV diastolic pressure (LVDP) or pulmonary artery occlusion pressure (PAOP): TMG = ADP − LVDP or TMG = ADP − PAOP. The impact of different types of vasodilators on the TMG is illustrated in Table 3.

A pure arterial dilator (e.g., hydralazine) can decrease ADP without affecting LVDP, and worsen TMG, especially if reflex tachycardia occurs. A balanced dilator (e.g., SNP) can decrease both ADP and LVDP, advantageous in hypertension with CHF, but dangerous if ADP is markedly decreased in a patient with acute myocardial ischemia. A predominant venodilator (e.g., nitroglycerine) can selectively decrease LVDP without decreasing ADP, thereby improving myocardial oxygen balance. When nitroglycerine induces a decline in arterial blood pressure, it signals an excessive dose. To regain its benefit, decrease the infusion rate or give a fluid challenge to restore arterial blood pressure. In the myocardium, SNP dilates both epicardial conductance and intramyocardial resistance vessels and, in the presence of coronary artery obstruction, shunts blood away from ischemic zones (coronary steal). Nitroglycerine preferentially dilates conductance vessels and directs more blood toward ischemic zones (4). It the most appropriate vasodilator drug to use with myocardial ischemia.

## *Limitations of Sodium Nitroprusside (SNP)*

SNP is an inexpensive, potent, and rapid acting vasodilator. Its balanced vascular effect results in both afterload and preload reduction. However, there are number of limitations and caveats to its use:

1. Excessive preload reduction; fluid challenges may be required to maintain adequate preload, maximize cardiac output, and prevent hypotension.
2. Hyperdynamic response to SNP, mediated by reflex catecholamine release with angiotensin activation. It is likely to occur in the postanesthesia care unit (PACU) or intensive care unit (ICU) when patients are emerging from the modulating effects of anesthesia (Table 4). There is progressive widening of the arterial pulse pressure, implying worsened TMG, myocardial oxygen imbalance, and a very real danger of acute myocardial ischemia (5). The most effective management is to add a $\beta$-blocker such as esmolol, metoprolol, or labetalol, which will suppress reflex tachycardia, narrow the pulse pressure, and treat the hypertension at a substantially decreased dose of SNP. Note that abrupt discontinuation may result in rebound hypertension.
3. Acute cyanide toxicity. SNP contains a nitroso group (the nitric oxide moiety, NO-) bound to a ferrous ($Fe^{2+}$) ion, with loose bonding to five cyanide ($CN^-$) ions. On exposure to blood, SNP literally falls apart, releasing the nitric oxide group and resulting in the rapid onset (and offset) of vasodilation (6). Released $CN^-$ binds much more tightly to ferric ion ($Fe^{3+}$) than ferrous ion ($Fe^{2+}$). Cyanide enters the cell where it binds and inactivates $Fe^{3+}$-cytochrome oxidase and blocks cellular uptake of oxygen (cytotoxic anoxia). Cyanide intoxication occurs when detoxification pathways are overwhelmed by rapid administration of SNP ($>8\ \mu g \cdot kg^{-1} \cdot min^{-1}$) (7). There is progressive elevation of mixed venous saturation ($Svo_2$) and profound lactic acidosis, and death occurs rapidly with little clinical prodrome. Treatment is based on an understanding of the normal pathways of detoxification of cyanide.

**Table 3.** Impact of Vasodilators on Coronary Perfusion Pressure (CPP)

| Agent | Action | ADP | LVDP | CPP |
|---|---|---|---|---|
| Hydralazine | Arterial dilation | – | 0 | Worsened |
| Nitroprusside | Balanced dilation | – | – | Unchanged/worsened |
| Nitroglycerine | Venodilation | 0 | – | Improved |

ADP = aortic diastolic pressure; LVDP = left ventricular diastolic pressure; – = decreased; 0 = no change.

**Table 4.** Hyperdynamic Response to Nitroprusside

| Nitroprusside dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$) | MAP (mm Hg) | BP (mm Hg) | HR (bpm) | CO (L/min) | SVR ($dyne \cdot s \cdot cm^{-5}$) |
|---|---|---|---|---|---|
| 0 | 115 | 165/90 | 92 | 3.1 | 2000 |
| 3.0 | 113 | 220/60 | 105 | 5.9 | 1000 |

In the above situation, the order to the nursing staff is to administer nitroprusside to decrease mean arterial pressure (MAP) from 115 mm Hg to 90 mm Hg. Nitroprusside is titrated to 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ but there is little decrease in MAP and the patient appears to have developed tachyphylaxis. In reality, as systemic arterial resistance (SVR) has halved, cardiac output (CO) has doubled, with reflex tachycardia and dramatic widening of the pulse pressure.

Cyanide ion oxidizes the $Fe^{2+}$ in hemoglobin to $Fe^{3+}$, and tightly binds to it, forming cyanmethemoglobin. Thus, plasma cyanide levels correlate poorly with toxicity. Cyanide ion also binds to an endogenous red cell substrate, thiosulfate, which is converted to thiocyanate (SCN), which is excreted in the urine and may accumulate and cause neurotoxicity in renal failure. Resuscitative measures include oxidization of hemoglobin to methemoglobin (amyl nitrite, sodium nitrite), and administration of sodium thiosulfate, or huge doses of hydroxycobalamin, which binds cyanide to form cyanocobalamin (Vitamin $B_{12}$).

## Beta-Blockers

### *Advantages and Limitations of Beta-Blockers*

Beta-adrenergic receptor blocking agents have several inherent advantages over vasodilators in the treatment of hypertension. Blood pressure is decreased without reflex tachycardia or widening of the pulse pressure; in fact, $MVO_2$ is improved by decreasing heart rate and myocardial contractility. Beta-blockers also have intrinsic antiarrhythmic activity and suppress both ventricular and supraventricular ectopic rhythms. Unlike vasodilators, they have no effect on hypoxic pulmonary vasoconstriction (8).

Adverse effects of $\beta$-blockade include the following:

1. Nonselective blockade of $\beta_2$ receptors. This promotes reflex vasoconstriction through unopposed $\alpha$ receptor activity and may induce Raynaud's phenomenon or worsening of peripheral vascular ischemia. It may further diminish CO through increases in afterload, and impair overall tissue perfusion. Bronchospasm may be induced in susceptible individuals. Choosing a selective $\beta_1$ blocker may minimize these adverse effects.
2. Cardiac depression. $Beta_1$ blockade induces myocardial depression and increased wall tension and pulmonary congestion or edema may result (9). Patients with compromised cardiac function may decompensate.
3. Hyperkalemia in renal failure. Potassium flux, i.e., the maintenance of a high (40:1) intracellular to extracellular potassium ion concentration, is governed by a sodium-ATPase pump at the cell membrane. The pump is under the influence of $\beta$-adrenergic stimulation, which enhances the inward movement of potassium. Beta-blockers inhibit the pump, and may result in acute extracellular hyperkalemia when administered to patients in renal failure.

### *Classification of Beta-Blockers*

It is convenient to group $\beta$-blockers according to their pharmacologic elimination half-life ($t_{1/2}$) as long-acting, intermediate-acting, or short-acting (Table 5). Within each group, one can identify an example of a $\beta_1$ selective or nonselective antagonist:

1. Long-acting agents undergo hepatic biotransformation into inactive, water-soluble glucuronide conjugates, which are excreted unchanged by the kidney.
2. Intermediate-acting agents are rapidly hydroxylated by the liver into inactive metabolites. Approximately 80% of the ingested drug is metabolized during a single circulation through the liver ("first pass effect"). Thus, the IV dose is only one-tenth the oral dose, a property shared by drugs with similar handling, such as labetalol. For example, the IV dose of metoprolol is 2.5–5 mg, compared with 25–50 mg when it is given orally.
3. Short-acting agents are inactivated by red cell esterases within the blood itself, have a half-life

**Table 5.** Classification of Beta-Blockers

| Drug | Beta$_1$ selectivity | $t_{1/2}$ | Elimination route |
|---|---|---|---|
| Long-acting | | | |
| Nadolol | Nonselective | 12–18 h | Kidney |
| Atenolol | Selective | 6–10 h | |
| Intermediate-acting | | | |
| Propranolol | Nonselective | 4–6 h | Liver |
| Metoprolol | Selective | 4–6 h | |
| Ultra short-acting | | | |
| Flestolol | Nonselective | 5–6 min | Red cell esterase |
| Esmolol | Selective | 8–9 min | |

of approximately 8 min, and clearance that is independent of hepatic or renal function. Compare other drugs cleared in the blood; e.g., succinylcholine (pseudocholinesterase), cisatracurium (Hoffman elimination), and remifentanil (non-specific esterases).

### *Perioperative Indications for Beta-Blockade*

1. Control of intra- and postoperative hypertension and tachycardia as monotherapy or combined with a pure vasodilator (SNP), especially during induction, aortic manipulation, and during emergence (10–12). It is useful in outpatient anesthesia to prevent "breakthrough" in anxious, unpremedicated patients. Although some studies have suggested that esmolol is more effective at slowing heart rate than decreasing blood pressure (13), its effectiveness in limiting hypertension during anesthetic induction and emergence is well established (14).
2. Rate control and/or pharmacologic conversion of supraventricular tachycardia, atrial fibrillation, and atrial flutter.
3. Myocardial protection (negative inotropy, chronotropy) in ischemic heart disease, aortic stenosis, or idiopathic hypertrophic subaortic stenosis (IHSS).
4. Control sympathetic response to electroconvulsive therapy.
5. Control peripheral manifestations of hyperthyroidism.

### *Esmolol*

Esmolol is a potent $\beta_1$ selective agent and is extremely useful because of its rapid onset and offset of activity (12). If untoward effects arise (e.g., bronchospasm, excessive bradycardia, cardiac depression), drug administration can quickly be discontinued. Esmolol was first formulated for IV infusion only, as 2.5 g/250 mL (10 mg/mL), to be given as a loading dose (0.5 mg/kg over 2 min) followed by a maintenance infusion (50–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Subsequently, dosing by intermittent bolus (10–50 mg IV) was FDA-approved and a 100 mg/10 mL ampoule became available (15).

### *Metoprolol*

Metoprolol is a $\beta_1$ selective agent with a longer duration of action suitable for "steady state" $\beta$-blockade (24 hr) by intermittent bolus dosing at 1–5 mg IV prn q4h, titrated to effect. Patients with renovascular or accelerated hypertension may require doses as high as 10 mg IV q4h.

## Labetalol

Labetalol is a unique agent that combines weak $\alpha$-blockade (1/10 as potent as phentolamine) and nonselective $\beta$-blockade (1/7 as potent as propranolol), but the combination of negative inotropy and chronotropy with vasodilation provides an effective antihypertensive action (16). In patients with renovascular (vasoconstricted) hypertension, labetalol appears to act predominantly as a vasodilator but without reflex tachycardia. In patients with postoperative (hyperdynamic) hypertension, labetalol acts predominantly as a $\beta$-blocker (negative chronotropy and inotropy), but without reflex vasoconstriction (17). In a study on geriatric patients undergoing ambulatory surgery, it was found that labetalol was as effective as esmolol in controlling hypertension, but with significantly less bradycardia (18).

### *Indications for Labetalol*

1. Hyperdynamic hypertension: patients with heart rate > 90 bpm and cardiac index (CI) >2.5 L/min/M$^2$.
2. Tachyphylaxis with SNP–addition of labetalol is an alternative.
3. Intracranial hypertension (labetalol does not increase CBF or ICP).
4. Toxemia of pregnancy (labetalol does not appear to be toxic to the fetus).

### *Dosing*

The response to labetalol is quite different under general anesthesia, where a little goes a long way, and in the emerging patient in the PACU or ICU, where tachyphylaxis is not uncommon. The initial "test dose" should be no more than 2.5 - 5 mg IV. A positive response is usually heralded by a noticeable decrease in heart rate within 2 min, followed by a decrease in blood pressure that may be sustained for 5–20 min or longer. An absence of change in heart rate usually implies that a larger dose will be required. If there is no effect within 5–10 min, the dose can be progressively doubled (i.e., 5 mg, 10 mg, 20 mg, 40 mg q

5–10 min to a maximum of 100 mg). Once a clinically satisfactory response is achieved the dose can be repeated q2–4h. Larger doses are sometimes administered by intermittent infusion over 20 min, q4h.

### *Adverse Effects*

1. Unwanted negative inotropy (see above).
2. Prolonged duration of action with high doses. Caution should be used when treating postoperative hypertension in hypothermic patients. When patients subsequently rewarm, persistent $\beta$-blockade may blunt reflex increases in cardiac output and exacerbate rewarming hypotension.
3. Bronchospasm can occur with high doses in susceptible patients (labetalol is not $\beta_1$ selective).
4. Acute hyperkalemia in renal failure. Use of large doses of labetalol to treat refractory hypertension in patients undergoing renal transplantation with poor graft function has been associated with acute hyperkalemia (19).

## Angiotensin Converting Enzyme Inhibitors

Angiotensin converting enzyme (ACE) inhibitors are used sparingly in the immediate perioperative period because of relatively slow onset and offset of action, and limited titratability. Only enalapril is currently available for parenteral injection. The pharmacology of three commonly used ACE inhibitors is summarized in Table 6.

The ACE inhibitors provide predominantly arterial vasodilation, and have become primary therapy for the treatment of CHF by afterload reduction. Cardiac output is increased without excessive decrease in preload, with a favorable effect on survival. If postoperative hypertension persists after initial stabilization with other short-acting agents, enalapril may be useful for longer-term control, especially in the setting of impaired myocardial contractility. It is initially dosed at 0.625 mg IV q8h, and can be gradually advanced over the subsequent few days to as high as 5 mg IV q6h. More recently, specific angiotensin II receptor antagonists (e.g., losartan) have been introduced. Their primary advantage over ACE inhibitors is a reduction in side effects such as dry cough. They are available only in oral formulation and used for long-term afterload reduction or blood pressure control.

### *Effect of ACE inhibitors on Renal Function*

ACE inhibitors appear to have a biphasic effect on renal function, depending on baseline blood pressure (20). If a high blood pressure is normalized in patients with hypertension, diabetes and/or CHF, renal function usually improves. Elevated renal vascular resistance is normalized, and renal blood flow (RBF) and glomerular filtration rate (GFR) increase. Pretreatment with captopril in patients with normal renal function undergoing CPB appeared not to compromise intraoperative renal function (21). However, if normal blood pressure is decreased, renal function may rapidly deteriorate, especially in the presence of hypovolemia, hypotension, renal insufficiency, and renoocclusive disease. In these situations, GFR is preserved by compensatory efferent arteriolar constriction, mediated by angiotensin II. Blockade decreases glomerular filtration pressure and GFR, and may result in acute hyperkalemia.

It is our practice to defer or avoid the use of ACE inhibitors in the postoperative period if there is hemodynamic instability or any evidence of renal insufficiency. In situations (e.g., cardiomyopathy) where it is considered that renal function might benefit from increased cardiac output induced by afterload reduction, a careful trial of enalapril is started, but discontinued at the first sign of renal deterioration.

**Table 6.** Pharmacology of ACE Inhibitors

| | Captopril | Enalapril | Lisinopril |
|---|---|---|---|
| Protein binding % | 30 | 50 | ACE |
| Onset (h) | 0.5–1 | 1–2 | 2–4 |
| Duration (h) | 3–4 | 12–24 | 24 |
| Elimination | Hepatic | Hepatic | Hepatic |
| Dose (po) | 25–50 mg | 5–40 mg | 10–40 mg |
| Frequency | tid | qd | qd |
| Dose (IV) | | 0.625–5 mg | |
| Frequency | | q 6–8 h | |

Lisinopril binds to angiotensin-converting enzyme (ACE) itself. The onset and offset of action refer to oral dosage. All three agents undergo hepatic biotransformation to inactive metabolites that are excreted in the urine. Only enalapril is available as a parenteral preparation.

## Calcium Channel Blockers

The calcium channel blockers consist of three chemically dissimilar classes of compounds whose indications (Table 7) reflect their differences in action (Table 8).

The three primary actions of calcium channel blockers are negative inotropic effect, atrioventricular (AV) conduction block (negative dromotropic effect), and vasodilation of multiple vessel beds (systemic, splanchnic, coronary, pulmonary).

Verapamil has potent negative inotropic, dromotropic, and vasodilator effects, which makes it useful for the medical management of aortic stenosis and IHSS, conversion of atrial re-entry tachyarrhythmias and treatment of coronary artery spasm (Prinzmetal angina). In contrast, the dihydropyridines (e.g., nifedipine, nicardipine) are virtually pure arterial vasodilators and lack a clinically significant negative inotropic and dromotropic effect (although reflex tachycardia is negligible). They

**Table 7.** Classes of Calcium Channel Blockers and Indications for Use

| Class | Drugs | Indications |
|---|---|---|
| Phenylalkylamines | Verapamil | Conversion of supraventricular (atrial) tachycardia<br>Coronary artery spasm |
| Benzothiazines | Diltiazem | Rate control of tachycardia, tachyarrhythmias<br>Renal protection |
| Dihydropyridines | Nifedipine | Hypertension |
| | Nicardipine | Afterload reduction |
| | Nimodipine | Cerebral vasospasm, ischemia |
| | Nitrendipine | Renal protection |
| | Isradipine | |

**Table 8.** Actions of Calcium Channel Blockers

| Drug | Negative inotropy | AV block | Vasodilation |
|---|---|---|---|
| Verapamil | +++ | +++ | + |
| Diltiazem | ++ | ++ | + |
| Nifedipine | 0 | 0 | +++ |
| Nicardipine | 0 | 0 | +++ |

AV = atrio-ventricular.

have the most potent and reliable antihypertensive action. Diltiazem fits between these two groups (i.e., less negative inotropic and dromotropic effect than verapamil, but substantially more than the dihydropyridines). Its lesser dromotropic effect is reflected in its use as a rate-control agent in atrial fibrillation and atrial tachycardia, rather than a converting agent like verapamil.

Infusion dosing is summarized in Table 9.

## *Effect of Calcium Blockade on Myocardial Oxygen Balance*

Verapamil and diltiazem may enhance myocardial oxygen balance by decreasing myocardial oxygen consumption through afterload reduction and/or their negative inotropic effect and by increasing myocardial oxygen delivery ($DO_2$) through coronary vasodilation (22). They also decrease reperfusion injury after ischemia. In contrast, the dihydropyridine vasodilators may worsen $MVO_2$ by causing diastolic hypotension and reflex tachycardia and should be used with caution or not at all in patients with acute myocardial ischemia.

## *Effect of Calcium Blockade on Renal Function*

In the treatment of hypertension, calcium channels blockers increase RBF and GFR, and induce a natriuresis. They are also protective in renal transplantation (23) (Table 10), against a variety of nephrotoxic insults, including cyclosporine A, cisplatinum, aminoglycosides and radiocontrast media, and may protect renal function in high risk surgery (24). Mechanisms include reversal of renal vasoconstriction (e.g., induced by cyclosporine A), prevention of intracellular calcium overload and a reduction in interleukin-1 receptor density. Diltiazem allows higher levels of cyclosporine A to be achieved with more immunosuppression and less renal injury (25). It also suppresses the metabolism of cyclosporine A, allowing the maintenance dose to be decreased by approximately a third, with considerable cost savings. The benefits of calcium blockers may be reversed if they induce hypotension, which can result in reflex catecholamine release and angiotensin activation, and decreases in RBF and GFR.

**Table 9.** Infusion Dosing of Calcium Channel Blockers

| | Load | Infusion |
|---|---|---|
| Verapamil | 2.5–10 mg | 2.5 mg/h |
| Diltiazem | 5–20 mg | 10–20 mg/h |
| Nicardipine | 10–15 mg/h | 3–5 mg/h |

Verapamil and diltiazem are usually loaded to a maximum of 10 and 20 mg respectively, by divided boluses of 2.5 to 5 mg IV. Nicardipine is initiated by a loading infusion (10–15 mg/h) for 10–15 min, and the dose is then decreased to maintenance levels.

**Table 10.** Calcium Channel Blockade in Renal Transplantation

| Parameter | Control | Diltiazem |
|---|---|---|
| Incidence of transplant ATN | 41% | 10% |
| Hemodialyses per patient | 3.5 ± 0.4 | 0.6 ± 0.2 |
| GFR (day 7) mL/min | 24 | 39 |
| Serum creatinine ($\mu$M/L) | 378 ± 21 | 226 ± 9 |
| Rejections per patient | 0.5 ± 0.3 | 0.15 ± 0.02 |

In Wagner S et al. (Am J Nephrol 1987; 7:287), diltiazem was administered to donors intra- and postoperatively, and used in the renal preservation solution. Compared with control patients, there was a significant decrease in the incidence of acute tubular necrosis (ATN) in the transplanted kidney and the requirement for postoperative hemodialysis. Transplant kidney function was generally improved, reflected in a higher GFR and lower serum creatinine. There was also a significantly lower incidence of rejection.

## *Nicardipine*

Nicardipine is a dihydropyridine derivative of nifedipine, with an added phenol ring that renders it water

**Table 11.** Dopaminergic Receptors

| Receptor | Site | Actions |
|---|---|---|
| $DA_1$ | Renal, splanchnic beds | Vasodilation, increased RBF |
| | Proximal renal tubule | Natriuresis |
| $DA_2$ | Postganglionic sympathetic nerves (presynaptic membrane) | Inhibit presynaptic norepinephrine release (vasodilation) |
| | | Decreased RBF |

soluble and light insensitive and facilitates IV injection and infusion (26). It is a potent vasodilator of the systemic, coronary and cerebral circulations, without a clinically important negative inotropic or dromotropic effect (27). It is metabolized in liver, with a redistribution half-life of 2.7 min, and elimination half-life of 45 min. Its antihypertensive effect usually decreases by 50% every 2 h after discontinuation, but the duration of offset depends on the duration of administration and may be slow after prolonged infusion.

Infusion dosing is summarized in Table 9. Nicardipine has been used by intermittent bolus to attenuate blood pressure responses to tracheal intubation, in a dosage of 0.5–1.0 mg (28), but was found in one study to be less effective than diltiazem in controlling the hypertensive response to extubation (29). Onset of action is rapid (20–30 s) with a variable duration of action, usually 15–20 min.

Nicardipine is very useful for the parenteral control of hypertension in the PACU and ICU (30). It has slower onset and offset of action than SNP, but is much easier to use, with fewer blood pressure perturbations and no risk of rebound hypertension on withdrawal (31). Reflex tachycardia usually amounts to a rate increase of $<10$ bpm. It use has been studied in various other situations, including induced intraoperative hypotension, myocardial protection during cardiac surgery, afterload reduction for CHF, and prevention of cerebral vasospasm after subarachnoid hemorrhage.

Potential adverse effects include excessive hypotension through drug interactions ($\beta$ blockade, volatile anesthetic agents) that may be treated with fluid, calcium, or phenylephrine. Coronary steal syndrome can occur in acute myocardial ischemia. Like other vasodilators, it may worsen ventilation-perfusion mismatch by overcoming hypoxic pulmonary vasoconstriction (32). Its prolonged duration of action may limit its titratability in controlled intraoperative hypotension (33), but this may actually be of benefit postoperatively.

## Dopaminergic Agonists

Dopamine receptors are classified into $DA_1$ and $DA_2$ subtypes (Table 11) (34). Stimulation of $DA_1$ receptors causes renal vasodilation as well as inhibition of active sodium transport in the proximal tubule, leading to natriuresis (sodium diuresis) (35). Stimulation of presynaptic $DA_2$ receptors inhibits norepinephrine release and promotes peripheral vasodilation but appears to attenuate the beneficial effects of $DA_1$ effectors on renal blood flow. Dopamine is a nonselective $DA_1$ and $DA_2$ agonist. Its unpredictable $\beta$- and $\alpha$-adrenergic actions (36) preclude its use as an antihypertensive agent.

### *Fenoldopam*

Fenoldopam is a selective $DA_1$ agonist that induces renal and splanchnic vasodilation and natriuresis. It is 10–100 times as potent as dopamine at the $DA_1$ receptor, and causes a dose-related increase in RBF in the dose range of 0.03 to 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Unlike dopamine, it has no $\beta$- or $\alpha$-adrenergic activity and increasing doses result in increasing vasodilation without tachycardia or tachyarrhythmias. However, reflex tachycardia may occur with rapid onset of vasodilation (37). Fenoldopam relaxes norepinephrine-induced vasoconstriction in isolated vascular rings in vitro. In hypertensive states, systolic blood pressure is decreased while RBF is maintained. Parenteral fenoldopam has a rapid onset and offset of effect (although slower than SNP), with an elimination half-life of approximately 10 min. Unlike dopamine, plasma levels of fenoldopam are dose-related, stable, and rapidly decline when the infusion is discontinued.

FDA approval of fenoldopam was based on studies in patients admitted to emergency rooms with accelerated hypertension (38). In this setting, fenoldopam proved as effective as SNP in controlling blood pressure, but with the added benefit of doubling of creatinine clearance, urine flow, sodium, and potassium excretion. It was released in early 1998 for use as an in-hospital parenteral antihypertensive agent for 24 h (39). Prepared in a concentration of 10 mg in 250 mL (40 $\mu g/mL$), the recommended starting dose is 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This should be titrated to effect by 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 10–15 min, to a maximum dose of 0.5–0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The drug should not be bolused; the incidence of reflex tachycardia is related to rapidity of upward titration. In contrast to SNP, an indwelling arterial catheter is not mandatory. There are few data on drug interactions, but it should be assumed that the combination of fenoldopam with negative chronotropic agents (e.g.,

β-blockers, calcium blockers) would enhance its antihypertensive effect and possibly lead to unwanted hypotension.

Data from preliminary studies suggested that fenoldopam is as effective as SNP for the control of postoperative hypertension (40,41). However, fenoldopam is an expensive drug that, except in patients with renal insufficiency, has not replaced SNP as a first-line parenteral antihypertensive agent. However, there is increasing interest in its use as a primary renal protective and diuretic agent at much lower doses: 0.03 to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At this low dose range there is still an appreciable increase in RBF but little systemic hemodynamic effect. In this situation it has distinct advantages over low-dose dopamine: predictable plasma levels, lack of inadvertent tachycardia, tachyarrhythmias and hypertension, and ability to infuse by peripheral catheter without concern for extravasation-induced cutaneous necrosis. Fenoldopam may have an additional diuretic effect even in presence of low-dose dopamine or furosemide infusion. In addition, preliminary data suggest a possible protective effect against the nephrotoxic effects of radiocontrast dyes and cyclosporine A, and studies are in progress examining its renal protective effect in cardiac surgery and renal transplantation.

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