Review Article

Vasodilator therapy in the perioperative period

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The present trend in the treatment of cardiac dysfunction has been to optimize cardiac function by manipulating the peripheral circulation. Previously, attention was directed towards decreasing preload by diuresis or tourniquets or increasing contractility with positive inotropes (Figure 1). Unfortunately, these earlier approaches did not achieve optimal results in moderate or severe congestive heart failure and were potentially harmful. This is because under these circumstances increased impedance to outflow usually predominates as opposed to mainly fluid overload, which occurs in mild congestive heart failure. Investigators studying the effects of preload reduction by diuresis, in the failing heart demonstrated that cardiac index (CI) was decreased.[1,2] There are also data demonstrating that positive inotropes can increase infarct size, as measured by creatine phosphokinase (CPK) levels and elevation of ST segments.[3] Therefore positive inotropes are usually reserved for situations when afterload reduction yields less than optimal results. The rationale for afterload reduction is clear (Figure 2), when one considers the determinants of myocardial oxygen balance (Table I).

We will review various agents with vasodilatory properties used to improve cardiac performance, with an emphasis on perioperative management. Other major effects of the pharmacologic agents will be briefly discussed, where indicated. These agents act on the peripheral vasculature, and do not have positive inotropic effect.[4] The disease states which may require vasodilator therapy are many and include hypertension, congestive heart failure, valvular dysfunction with impairment of cardiac output, dissecting aortic aneurysm, and control of blood pressure during and after repair of coarctation of the aorta. This review will focus on these conditions.

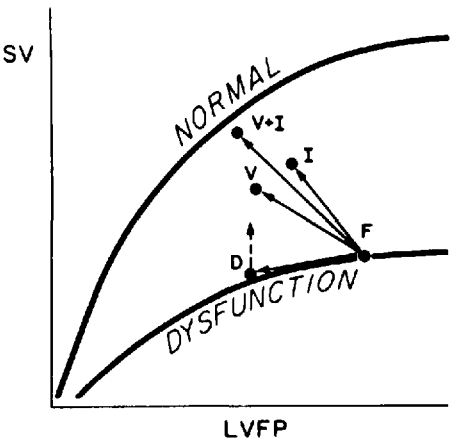

FIGURE 1 Frank-Starling left-ventricular-function curve relating left ventricular filling pressure (LVFP) to stroke volume (SV). Depressed curve of heart failure can be shifted toward normal by inotropic drugs (I) or vasodilator drugs (V), and these effects are complementary when the drugs are infused together (V + I). Note that diuretics (D) usually reduce filling pressure (F) without augmenting output. The dashed line suggests that stroke volume may later rise, perhaps by virtue of a gradual improvement in ventricular function. From: *Cohn JN, Franciosa JA.* N Engl J Med 1977; 297: 27–31. (With permission.)

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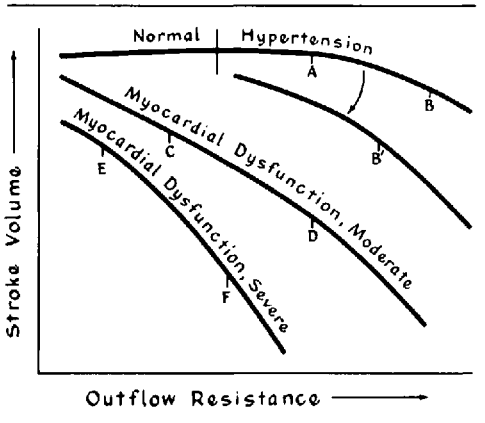

FIGURE 2 Relation of left ventricular stroke volume to systemic outflow resistance in normal and diseased hearts. A family of curves may be described, depending on the severity of the myocardial disease. If cardiac function is normal a rise in resistance results in hypertension, since cardiac output remains fairly constant. Heart failure in a hypertensive patient could be shown either by a move to point B, a high resistance with normal function, or point B', which represents a shift to a slightly depressed ventricular-function curve. When myocardial dysfunction is more severe, as shown by the lower two curves, blood pressure is no longer directly determined by resistance since stroke volume and resistance are inversely related. Consequently arterial pressure may be similar at points E and F despite marked differences in cardiac output and resistance. From: *Cohn JN, Franciosa JA*. N Engl J Med 1977; 297: 27–31. (With permission.)

Determinants of myocardial oxygen balance

In order to appreciate the beneficial effects of vasodilator therapy on the cardiovascular system, one must first understand the determinants of myocardial oxygen balance. It will then be clear how these agents produce favourable results even though they do not act directly on the myocardium.

Myocardial oxygen balance is determined by oxygen supply and demand (Table I). Factors which contribute to supply include those which regulate coronary blood flow and oxygen delivery. The major portion of myocardial perfusion occurs during diastolic filling time, thus coronary blood flow is inversely proportional to heart rate. Perfusion pressure, another determinant of oxygen supply, is necessary to provide adequate blood flow to the tissues. The last factor controlling coronary blood flow is coronary vascular tone which is autoregulated at the tissue level and depends on oxygen demand. As the need for oxygen increases vasodilatation occurs. Variables which determine oxygen delivery include haemoglobin concentration, oxygen-haemoglobin saturation and red blood cell 2,3-DPG levels. These factors which contribute to the supply side of the equation are frequently normal or, with the exception of heart rate and perfusion pressure not as amenable to therapy as the variables which control oxygen demand.

Determinants which affect myocardial oxygen consumption are more responsive to vasodilator therapy than those which regulate oxygen supply. Heart rate, is directly proportional to oxygen consumption. Ventricular wall tension is another major determinant of myocardial oxygen balance. It is also one of the variables most responsive to vasodilator therapy. There are two components which determine ventricular wall tension, preload and afterload. Preload is ventricular volume at end diastole. Pulmonary capillary wedge pressure correlates closely with left ventricular preload under most circumstances. When preload is elevated, ventricular diameter is increased, leading to an increase in wall tension and oxygen consumption. Afterload is myocardial wall stress during peak systole. In the absence of an anatomic obstruction to ventricular outflow, such as aortic stenosis, asymmetric septal hypertrophy, etc., there is a good correlation between afterload and systemic vascular resistance (SVR). Since SVR represents the major component impeding left ventricular outflow, it is frequently used interchangeably with afterload. However, under the circumstances mentioned above this correlation may not exist. Contractility, the last determinant of myocardial oxygen con-

TABLE I Determinants of myocardial oxygen balance

Myocardial oxygen supply	*Myocardial oxygen demand*
Determinants of coronary blood flow	Heart rate
– Heart rate	Ventricular wall tension
– Perfusion pressure	– preload
– Vascular tone	– afterload
Determinants of oxygen delivery	Myocardial contractility
– Haemoglobin concentration	
– Oxygen-haemoglobin saturation	
– 2–3 DPG levels	

Modified from J.A. Kaplan: Cardiovascular Physiology. *In*: Anesthesia. Second Edition. Miller RD (Ed)., vol. 2. pg. 1192, 1986, Churchill Livingstone (with permission of the publisher).

sumption, is the intrinsic ability of the myocardium to perform work.

When one considers the effects vasodilator therapy have on the above parameters, it can be predicted how ventricular function will be altered. If the arterioles are dilated by one of these agents, reducing SVR, the ventricle will have to work less hard to eject volume, myocardial oxygen balance will improve, leading to an improvement in cardiac output. The extent cardiac output increases depends on a number of factors, such as preexisting myocardial function and volume status.[4–6] A severely impaired myocardium will benefit the most by the reduction in SVR and the normal myocardium will benefit the least, if at all. Volume status of the patient is another important determinant of response. If hypovolemia exists, vasodilatation will further increase capacitance, compromising venous return to the extent that stroke volume and cardiac output are diminished. Alternatively, if fluid overload is present, vasodilator therapy will decrease ventricular diameter, reducing wall tension and permitting the ventricle to function more efficiently. Under these circumstances cardiac output frequently increases.

Indications for nitroprusside during cardiovascular dysfunction

Systemic hypertension

During and immediately following coronary artery surgery, hypertension is a frequent occurrence. In one series 36 per cent of the patients became hypertensive.[7] Hypertension can result in myocardial oxygen balance being adversely affected, because of an increase in myocardial oxygen consumption (MVO_2). Frequently the systemic vascular resistance (SVR) is increased as a result of surgical stimulation. The efficacy of sodium nitroprusside (SNP) and nitroglycerin (NTG) in controlling hypertension associated with coronary artery bypass graft (CABG) has previously been demonstrated.[8,9] This is predictable, when one considers the vasodilatation produced by SNP and high dose NTG on resistance vessels. Sodium nitroprusside and NTG were equally effective in controlling hypertension and improvements in pulmonary capillary wedge pressure (PCWP), CI, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and left ventricular stroke work index (LVSWI) were similar. Eight of ten patients receiving NTG infusion for treatment of systemic hypertension during elective coronary artery bypass surgery had improvement of ST segment depression. In the group receiving SNP, only six of eight patients improved and three had worsening of the ST segment, possibly resulting from intracoronary steal.[10] This suggests that NTG may be preferable in control of hypertension, in patients with or who have the potential for ischaemic myocardium (see NTG section for further discussion).

Left ventricular failure

Previously, treatment of LV failure has concentrated on diuresis and inotropy of the heart. Afterload received little, if any, attention. Not only was this treatment ineffective at times, there was potential for untoward effects on the heart.[1–3]

Sodium nitroprusside's efficacy for improving left ventricular (LV) function and various low output syndromes associated with high SVR has previously been described.[4,9–11] When afterload is increased in a normal left ventricle, the Starling mechanism allows for increased contractility, thereby maintaining stroke volume (SV) and cardiac output (CO). Patients with poor LV function may be unable to increase contractility in response to high afterload, resulting in a decrease in SV, leading to a low cardiac output state. In 1972, the salutory effects of SNP infusion were demonstrated when it was used for afterload reduction in the treatment of LV failure.[11] The therapeutic rationale is that a reduction in SVR will lead to lower wall tension, resulting in less LV work and a more favourable myocardial O_2 balance. The same end result occurs through decreasing preload. Under these improved conditions the heart will function more efficiently. Over the last few years, the use of vasodilators to decrease afterload, in order to treat cardiac dysfunction from various aetiologies, has gained wide acceptance.[4,11–15]

Patients with the poorest haemodynamic profile experienced the most improvement, while those with normal or low filling pressures did not benefit from SNP.[4] This lack of effect is presumably due to decreasing preload to a level, where an adequate SV can not be maintained. This emphasizes the importance of maintaining adequate filling pressures in order to achieve optimal effect.

Patients who have undergone open heart surgical

procedures frequently have low–normal or low cardiac outputs, in the immediate postoperative period. Systemic vascular resistance is frequently elevated in these low output states as a result of increased sympathetic activity.[12,16] The effects of afterload reduction have been looked at in the immediate postoperative period in a group of patients who underwent CABG.[13] After infusing SNP in a dose range of 45 to 180 $\mu g \cdot min^{-1}$, the CI increased from 2.7 ± 1 to $3.3 \pm 0.2\ L \cdot min^{-1} \cdot m^{-2}$, and there was a significant decrease in MAP from 108 to 92 mmHg and in SVR from 36.7 to 25.7 units. However, it was clearly shown that if adequate filling pressures are not maintained, maximal benefit of afterload reduction will not be obtained.

Although SNP has achieved a prominent status with our appreciation of afterload reduction in treating LV dysfunction, inotropes continue to be used in combination with vasodilators to obtain optimal results in the failing heart.[17,18] The combination may yield more favourable results than either agent alone.

Mitral regurgitation

In mitral regurgitation (MR) LV stroke volume is ejected in two directions. The forward or effective ejection fraction goes into the aorta and the regurgitant ejection fraction passes backward across the incompetent mitral valve, into the left atrium. The severity of regurgitation is dependent on the size of the orifice, compliance of the left atrium and impedance to forward ejection, which in the absence of aortic stenosis or IHSS is largely determined by SVR. Symptoms of MR result from low CO and/or pulmonary venous congestion. In many patients with severe regurgitation, SVR is elevated. The efficacy of afterload reduction has been demonstrated in patients with MR.[19,20] Baseline values were abnormally high for mean pulmonary artery pressure (MPAP), PCWP, large "V" waves, SVR, and pulmonary vascular resistance and forward or effective CO was reduced. Nitroprusside was administered intravenously (IV) in a dose range of 16–100 $\mu g \cdot min^{-1}$ and forward SV increased secondary to a large decrease in regurgitant fraction. Associated with the increased forward flow, there was a decrease in PAP of 30 per cent, PCWP 40 per cent, "V" wave 46 per cent and SVR of 35 per cent. However, the improvement which occurred may have at least partially been due to a decreased preload and subsequent decreased LV diameter, permitting the mitral valve apparatus to function more efficiently.

Through the use of afterload reduction, patients may be stabilized until they are at better surgical risk or until oral vasodilators can produce a beneficial effect.[14]

Aortic regurgitation

During aortic regurgitation (AR) part of the total SV of the LV regurgitates from the aorta back into the ventricle resulting in a volume overload. This regurgitant fraction causes a decrease in effective SV. A number of factors determine the regurgitant volume and include: valve area; pressure gradient from aorta to LV which is determined by a number of variables: compliance of the systemic circulation, compliance of LV, LVESV, and diastolic arterial blood volume; heart rate which is inversely related to diastolic filling, during which regurgitation occurs.

Factors that increase the pressure gradient across the aortic valve will accentuate regurgitation: elevated SVR, distensible LV and bradycardia. Aortic regurgitation will be decreased by opposite changes.

The haemodynamic changes in acute AR are more marked and the symptoms usually more dramatic than in chronic AR because the LV has not had time to compensate and is poorly compliant, resulting in relatively large increases in LVEDP, even with only a small regurgitant volume. In order to maintain aortic diastolic pressure, a baroreceptor reflex increases SVR.[21] When AR is severe, there may be equalization of LV and aortic pressures at the end of diastole. This is termed diastasis and the LV pressure may be enough to cause closure of the mitral valve, before atrial emptying is complete, further decreasing forward blood flow.

Afterload reduction is used in severe AR to increase effective CO.[22,23] However, the response of patients with AR to SNP is not as consistent as it is with MR, and not always beneficial. Nitroprusside infusion will benefit those patients with AR when the effective SV is decreased and the SVR and LVEDP are increased.[23–25] This haemodynamic profile usually fits those with chronic AR with decompensated LV failure or those with severe acute AR. Patients with normal filling pressures may not benefit from infusion of SNP.[23]

Coarctation of the aorta

Hypertension during and after correction of coarctation of the aorta occurrs in as many as 10–20 per cent of patients.[26] Intraoperatively it can result from surgical stimulation of the aortic baroreceptors by the aortic cross clamp and surgical manipulation, eliciting a reflex sympathetic discharge. This can lead to a marked increase in SVR and blood pressure. Intraoperative hypertension can be effectively treated with SNP. In the immediate postoperative period hypertension can persist, while the aortic and carotid baroreceptors are adjusting to lower pressure after the surgical correction. Before the repair, the obstruction to flow causes a higher blood pressure, and "stretching" of the baroreceptors proximal to it. With the alleviation of this obstruction, and before the baroreceptors have a chance to adjust, they perceive this lesser "stretch" as inadequate blood pressure, and produce a sympathetic reflex to "correct it." Untreated hypertension can result in, among other things, abdominal pain caused by a mesenteric arteritis. This is probably a result of sudden high pressure perfusion of the mesenteric system. Treatment, usually, with SNP or hydralazine, alleviates the symptoms.

Dissecting aortic aneurysms

Treatment of dissecting aortic aneurysms should decrease the systolic blood pressure to a level that is consistent with adequate tissue perfusion. The pulsatile force, which impacts against the aortic wall, facilitates dissection. Sodium nitroprusside decreases afterload, thereby decreasing systolic pulsation against the aorta. Control of BP at the desired level is easily obtainable. This agent should be administered in combination with a beta antagonist in doses sufficient to produce adequate beta-blockade. If SNP is infused alone, myocardial contractility (dp/dt) and heart rate may increase reflexly, increasing the shear force, resulting in extension of the dissection.

Nitroprusside and rewarming during cardiopulmonary bypass and maintaining body temperature

Induced hypothermia during open heart surgery is common in order to maximize myocardial protection. Unequal heart distribution and inadequate rewarming may lead to shivering and systemic vasoconstriction, which further increases oxygen consumption. In addition oesophageal temperatures frequently drift down to the low 30's °C after weaning from cardiopulmonary bypass (CPB). Nitroprusside infusion facilitates warming and minimizes temperature decreases in the ICU.[27,28] This is probably a result of better heart distribution resulting from vasodilatation, and not from a larger heat transfer.

Nitroprusside related toxicity

Although SNP has been shown to be safe and efficacious, the potential for toxicity exists. It results when cyanide becomes bound with cytochrome, impairing aerobic respiration. Anaerobic respiration occurs, yielding lactic acid and a metabolic acidosis. Early signs of cyanide toxicity include an unexplained metabolic acidosis, tachyphylaxis (which may be a normal reponse) and arrythmias. Thiocyanate, which is produced from SNP metabolism can also lead to toxicity which results in confusion, hyperreflexia or convulsions. The toxic dose for SNP has not been firmly established and maximum dosage recommendations have varied from 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[29,30] Before prescribing SNP, one should be familiar with the signs and symptoms of cyanide toxicity and its treatment (Table II).

Nitroglycerin

Although venodilatation is the predominant effect of NTG, arteriolar dilatation also can occur, especially with higher doses of intravenous NTG.[31,32] This is in contrast to the effect of SNP which affects the venous and arteriolar beds about equally.[33]

Nitroglycerin relieves the pain of angina by improving myocardial oxygen balance in the ischaemic area. Myocardial oxygen consumption is reduced by favourably altering one or more determinants of oxygen consumption,[5,6,34–37] (Table I).

Recent studies using computer assisted measure-

TABLE II Treatment of cyanide toxicity

Stop SNP infusion!!
Inhalation of amyl nitrate every two minutes
Intravenous infusion of sodium nitrate in a dose of 5 $mg \cdot kg^{-1}$ in 20 ml of water over 3–4 minutes
Intravenous infusion of sodium thiosulfate 150 $mg \cdot kg^{-1}$ in 50 ml of water over 15 minutes
Intravenous infusion of hydroxycobalamin 12.5 mg per 30 minutes

ments have also shown that in patients with symptomatic ischaemic heart disease there is dilatation of diseased vessel segments as well as normal areas.[38]

In view of the above, it is likely that the beneficial effects of NTG result from a combination of actions; increased flow through the dilated lesion and collateral vessels[39,40] and decreased MVO_2. Because of this it is used in the management of various disease states (Table III).

TABLE III Indications for nitroglycerin

Ischaemic heart disease
– unstable angina
– acute myocardial infarction–possible reduction in infarct size
Congestive heart failure
Surgical applications
– hypertension during and after CABG
– deliberate hypotension

(Modified from: Hill N *et al.*[45])

Treatment of myocardial ischaemia/myocardial infarction

The benefits of NTG in the treatment of angina, have been recognized for over a century. Until recently, however, this agent was avoided in patients during an acute MI. There was concern that NTG would induce hypotension and reflex tachycardia and extend the infarct. Because of more recent data demonstrating NTG's beneficial effects during an acute MI it has become a first-line drug for treatment of persistent pain in this setting.

During acute coronary occlusion in dogs, ischaemic damage was assessed by measuring ST segment elevation recorded from intramyocardial electrocardiographic (ECG) leads and myocardial content of CPK.[41] After NTG was given as a bolus of 400 μg IV, followed by a continuous infusion of 300 $\mu g \cdot min^{-1}$, less evidence of myocardial ischaemia was found. The beneficial effects were potentiated if methoxamine was used to maintain BP and heart rate at control values. In another study using the same dog model the benefits of NTG were confirmed, especially when BP was maintained with methoxamine. Survival rate was greater in the NTG–methoxamine group compared to the group which received only NTG; 12/15 vs 10/16 and there was less evidence of ischaemic injury on gross pathologic examination of heart.[42] These studies demonstrate the complexity of interactions that can result from NTG and coronary artery disease.

In patients with an acute MI, the effects of 1.5–2.5 mg sublingual NTG were studied within 17 hours of onset of symptoms.[43] In the group of patients without left ventricular failure, mean systemic blood pressure decreased from 99 to 82 mmHg and PCWP went from 11 to 5 mmHg but ECG ST segment changes were inconsistent. However, when the BP and heart rate were returned to control values with phenylephrine, the ST segment elevations fell to below control values in all patients. These results are similar to those in the dog model. When NTG induced hypotension and tachycardia are prevented with a vasopressor, ischaemic injury improves. However, the patients who had LV failure benefited from sublingual NTG alone and uniform reduction of ST segment elevation was seen. Although there was a fall in mean systemic pressure of 26 mmHg, the use of phenylephrine to abolish this was associated with ST segment elevation.

The beneficial effects of NTG on perfusion of ischaemic myocardium has been confirmed in animal models and human studies.[10] After acute occlusion of the left anterior descending artery and control values were obtained, IV NTG was begun as a bolus of 300 μg, and continued as an infusion, 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This resulted in significant improvement of ST elevation in dogs and a marked increase in blood flow to ischaemic areas as measured by radioactive microspheres, when compared to controls. Furthermore, the endocardial/epicardial flow ratio in ischaemic areas increased in the treated group, compared to no increase in the controls.

The effects of sublingual NTG on ischaemic myocardium in humans was evaluated using ST segment changes as a marker for ischaemia. Patients were studied within eight hours of the onset of an acute MI and after sublingual NTG; ST segments were significantly reduced.

Both SNP and NTG have been shown to produce similar beneficial haemodynamic effects on LV function in patients with an acute MI or CHF.[10,39] However, a controversy has existed as to which vasodilator improves myocardial perfusion. The effects of SNP and NTG on ischaemic myocardium during an acute MI have been compared.[10] The haemodynamic alterations caused by the two agents were similar. However, infusion of SNP resulted in

worsening of ischaemia in a dog model, as judged by increase in ST segment elevation and decrease of blood flow to ischaemic myocardium, which was assessed by intravenous injection of radioactive microspheres. This is in marked contrast to the beneficial effect NTG had on the ischaemic area. Both markers of tissue ischaemia, ST segment changes, and myocardial perfusion, improved significantly. When the effects of SNP and NTG were observed in ten patients with acute transmural MIs, the findings in the dog model were confirmed. Nitroglycerin improved ECG evidence of ischaemia, and SNP resulted in increased ECG evidence of ischaemia.

The effects of SNP on coronary blood flow was investigated in patients undergoing coronary catheterization for evaluation of chest pain.[39] ^{133}Xenon washout technique was used to measure regional myocardial perfusion. Patients with angiographically proven coronary artery disease had a significant decrease in regional myocardial perfusion following SNP administration compared to patients with normal coronary arteries who had no change in blood flow with SNP infusion. In a previous study, NTG was shown to increase regional myocardial perfusion in coronary patients with well developed collaterals.[36,44] The haemodynamic alterations resulting from NTG and SNP were similar, so it is unlikely that this accounted for the difference in perfusion.

The advantage of NTG when compared to SNP in improving ischaemic ECG alterations has also been noted in patients undergoing CABG.[9] Eight out of ten patients who received NTG to control BP had improvement of ST segment depression, while SNP improved electrocardiographic evidence of ischaemia in six patients and worsened it in three.

The opposite effects nitroglycerin and SNP may have on blood flow to ischaemic areas is probably related to their different sites of action.[6,31,39,43,45–47] Nitroglycerin dilates large conduction vessels[36,37] increasing collateral flow and improving the ratio of endocardial/epicardial perfusion.[48] Sodium nitroprusside dilates resistance vessels[6,40,46] causing a redistribution of blood away from the ischaemic area, resulting in an intracoronary "steal" phenomenon.[10] Steal occurs because the vessels in the ischaemic area are already "maximally" dilated, and the resistance vessels in non-ischaemic area can still be dilated, resulting in a redistribution of blood flow away from ischaemic myocardium.

The favourable effects of sublingual or IV NTG on ischaemic myocardium have also been demonstrated in the operating room[8,9,37] and in the intensive care unit.[10,37,41,42,45]

Intravenous NTG was used to control intraoperative hypertension in patients undergoing CABG.[37] Some patients had acute ST segment depression associated with the hypertension which was alleviated, with administration of NTG.

Based on the above data, it is clear that NTG has an important role in the therapy of coronary ischaemia, whether or not it is associated with acute infarction.

Treatment of congestive heart failure

Use of vasodilators in the treatment of LV failure has gained wide acceptance over the last decade.[4–6,11–13,49–53] Nitroglycerin predominantly affects preload, and SNP affects preload and afterload in a balanced manner.[6,46] Haemodynamic response may vary, depending on the haemodynamic profile of the patient.[6,50] Both agents decrease LV filling pressures.[6,8–10,46,49] However, the ultimate goal in the treatment of LV failure with vasodilators is to reduce ventricular wall tension, leading to an increase in CO. This will be determined by the complex interrelationship between LVEDP, impedance to left ventricular ejection and the effect they have on SV.

Changes in CO in response to NTG are not uniform. If the LVEDP is decreased to too low a level, SV will be compromised and CO will not increase.[5,6,50,53]

In order to achieve optimal results from vasodilator therapy, it is critical to have a full haemodynamic profile for the patient. Therefore, most patients will require invasive monitoring.

Treatment of systemic hypertension

Nitroglycerin is an effective agent in the control of intraoperative systemic hypertension during CABG (see SNP for further discussion).[8,9] However, it has been our experience that on occasion NTG is inadequate for blood pressure control when the SVR is markedly elevated. In these situations SNP proves effective.

Nitroglycerin has certain advantages when compared to SNP. The incidence of hypotension is

TABLE IV Indications for calcium entry blockers

Angina pectoris
– rest and effort associated
Hypertension
– chronic treatment and induced hypotension
Superventricular arrhythmias
Possible indications
Myocardial preservation during cardiopulmonary bypass
Hypertrophic cardiomyopathy

lower and the wide fluctuations in blood pressure are less with NTG. Perfusion of ischaemic myocardium appears to be better and there are no known serious toxicities associated with NTG use.

Nitroglycerin-related toxicity

Adverse effects related to nitroglycerin are usually dose related and cause haemodynamic alterations. However, NTG administration can lead to significant levels of methemoglobinemia. Up to two per cent of haemoglobin can exist in this form normally, which results from auto-oxidation. Nitrite, a degradation product of NTG, can lead to much higher levels of methemoglobin. Although NTG Infusions rarely cause this, it has been reported.[54,55] Under these circumstances, blood appears dark with a normal PO_2 and PCO_2. The World Health Organization has recommended limiting the dose of nitrates to $5\ mg \cdot kg^{-1} \cdot 24^{-1} \cdot h^{-1}$ to minimize the risk of toxicity.[56] Treatment consists of the administration of 100 per cent oxygen, methylene blue $2\ mg \cdot kg^{-1}$ intravenously and exchange transfusions if necessary.

Calcium entry blockers

Calcium entry blockers have been used in the treatment of Printzmetal's angina,[57–59] classic angina,[60,61] hypertension,[62] and arrhythmias[63,64] (Table IV). Verapamil, nifedipine, and diltiazem have received FDA approval.

In view of the key role that calcium (Ca^{+2}) plays in the electromechanical activity in many cardiovascular functions, it is not surprising that alteration of calcium fluxes by calcium entry blockers (CEB)s can modify many of these activities. Although these agents are grouped under one broad category and result in decreased levels of intracellular Ca^{+2}, their mechanisms of action may be different.[65] It is postulated that diltiazem acts by stimulating calcium extrusion, while verapamil works by inhibiting calcium influx. Possibly because of different mechanisms of action, the various CEBs have different potencies in affecting coronary vascular tone, electrical activity and myocardial contractility (Table V).[66,67] Because of this difference in selectivity, one agent may be preferred over another, depending on the condition.

TABLE V Relative cardiovascular potency *in vivo*

	Nifedipine	*Verapamil*	*Diltiazem*
Vascular			
Coronary resistance	↓↓↓↓	↓↓	↓↓
Systemic resistance	↓↓↓↓	↓↓↓	↓↓
Electrophysiologic			
Heart rate	↑↑↑	O/↓EX	O
A-H interval	O	↑↑	↑
Left ventricular			
Cardiac output	↑↑	↑/↓	↑/O
LVEDP	↓	↓/O	↓/O

↓ = decrease; ↑ = increase; O = unchanged; EX = during exercise. Modified from Pepine CJ, Conti CR: Modern Concepts of Cardiovascular Disease 1981, 50: (Reprinted with permission).

Clinical applications

VARIANT ANGINA

Various clinical studies, have demonstated that the CEBs are effective in reducing symptoms and coronary artery spasm in patients with variant angina.[58–60] Although excellent results have been obtained with nifedipine[57,59] and verapamil,[60] the former is more effective.[67] This could be anticipated in view of the more prominent coronary and peripheral vasodilatation that is produced with nifedipine.[66,67]

Since CEBs have yielded such favourable results outside of the operating room, these agents are now being administered more frequently in the intraoperative period to treat conditions refractory to standard therapy. Intraoperative myocardial ischaemia secondary to coronary artery spasm is one of these conditions which has responded well to CEBs. This may present as ST-T wave changes on ECG, dysrhythmias or AV conduction block. There are reports in the literature describing the successful treatment of cardiac ischaemia, which was refractory to intravenous nitroglycerin.[56,69–72] All of these patients were undergoing myocardial revascularization. Soon after being weaned from cardiopul-

monary bypass, they experienced sudden cardiovascular collapse. A diagnosis of myocardial ischaemia was made and nitroglycerin was administered without any response. A calcium entry blocker was then administered, which was associated with marked improvement. There also seems to be a place for CEBs in the treatment of life-threatening ventricular arrythmias. In two recent reports, verapamil was found to be successful in converting intractable ventricular arrythmias, after the standard therapeutic approach of lidocaine, procainamide, bretylium and DC cardioversion had failed.[73,74] The mechanism of action by which they suppress ventricular arrythmias is not clear. The CEBs may block slow channel currents which serve as a focus of irritability or they may decrease influx of calcium into the cell, which may contribute to reperfusion injury, predisposing the patient to ventricular irritability.[75] In addition the antiarrhythmic effect is most likely due, at least in part, to an improvement in myocardial oxygen balance, reducing ischaemia. This results from a reduction in ventricular wall tension due to peripheral vasodilation. Reversal of coronary artery spasm leading to an increased blood flow is also a factor in improvement of ventricular function.

CLASSIC ANGINA PECTORIS

The efficacy of verapamil and nifedipine in the treatment of classic variant angina has been proven.[61,76,77] In one study a significant increase in exercise threshold was found in the group treated with oral nifedipine as compared to the group receiving placebo.[62] Again, because of the more potent effect nifedipine has on vasodilatation compared to verapamil or diltiazem,[66,67] it appears that this would be the CEB of choice. The mechanism by which ischaemia is relieved is unclear. However, the beneficial results are most likely due to a decrease in MVO_2, resulting from peripheral[77] vasodilatation leading to a decrease in afterload. Improvement in myocardial oxygenation due to coronary artery dilation and increased myocardial perfusion probably plays less of a role. There is evidence that the combination of nifedipine and a beta blocker may yield the best results.[78,79] This beneficial interaction may occur because both drugs decrease MVO_2 through different mechanisms. Propranolol decreases heart rate and myocardial contractility. Nifedipine's major effect is a reduction in systemic vascular resistance, and coronary artery dilatation leading to increased myocardial perfusion playing a minor role.

BLOOD PRESSURE CONTROL

The CEBs have been used during surgery and neurolept anaesthesia to produce controlled hypotension.[80] Verapamil 0.07 $mg \cdot kg^{-1}$, given as an IV bolus was used to decrease MAP from 108 mmHg to 84 mmHg, which occurred within one minute. This was associated with a significant decrease in SVR and an increase in ventricular stroke volume and P-R interval. Changes in intracranial pressure (ICP) associated with nifedipine induced hypotension in cats have been investigated.[81] Although there was an increase in ICP in cats with decreased intracranial compliance, it was much less than that associated with SNP or NTG induced hypotension. Even though the CEBs have been shown to be effective in producing controlled hypotension, NTG and SNP may be preferable under most circumstances because of a faster onset of action and shorter half-life, affording more precise regulation of the BP.

Effect on myocardial contractility

It is clear that the CEBs have differences in potencies for affecting electrical conduction, vascular tone, and myocardial contractility.[64,66] It is therefore not surprising that nifedipine, with minimal, if any, effect on the AV node[82] is not used as an antiarrhythmic agent. Although verapamil has a greater tendency to cause myocardial depression than nifedipine,[76] when used in antiarrhythmic doses, it rarely causes clinically significant CHF.[67,78] However, the preexisting cardiovascular status of the patient is a critical factor in determining whether significant depression of ventricular function will occur. Investigators have shown that in patients with normal or only moderately impaired left ventricular function, verapamil produced minimal depression of contractility.[83] However, if left ventricular function was already impaired as indicated by a decreased ejection fraction of less than 30 per cent, or an elevated pulmonary capillary wedge pressure, verapamil exacerbated this decompensation. All three patients in this study, became dyspnoeic, which was associated with adverse haemodynamic changes. The potential for the CEBs to precipatate or exacerbate congestive heart

failure has also been observed by others. [84–86] It is clear that the net haemodynamic effects of CEB's will depend on the patient's preexisting cardiac status, sensitivity to myocardial depression, peripheral and coronary vasodilatation and reflex responses.

Phentolamine

Phentolamine was introduced into clinical practice as an antihypertensive agent. Its action is mediated through alpha adrenergic blockade. Although some investigators felt that phentolamine had some intrinsic beta agonst activity,[87] it now appears that increases in inotropy and heart rate are reflexly induced.[88]

The beneficial effects of phentolamine induced afterload reduction in patients with congestive heart failure have been demonstrated.[89] In patients with left ventricular failure secondary to ischaemic heart disease, 5 mg was administered as a bolus intravenously, and an infusion of 1–2 $mg \cdot min^{-1}$ was started until the mean arterial pressure was decreased to 95–105 mmHg. Systemic vascular resistance and left ventricular end diastolic pressure were decreased significantly while cardiac output increased significantly, and heart rate remained unchanged. Its ability to improve low cardiac output states associated with high SVR was subsequently confirmed.[89] Forearm vascular resistance and venous tone were also measured to determine its site of action. It was found that phentolamine predominantly affects systemic arterial vessels, NTG predominantly affects venous vessels and SNP's action is balanced between arterial and venous vessels.

Sodium nitroprusside and NTG have largely replaced phentolamine in clinical situations requiring vasodilators, mainly because of their easier titratability and higher potency.

Trimethaphan

Trimethaphan, a vasodilator, was introduced into clinical practice in 1953. Indications for administration include treatment of hypertension, induced hypotension and severe vasoconstriction. Investigators have demonstrated that its effects are mediated through direct vasodilatation and ganglionic blockade.[90] It has been found that coronary and renal blood flows were decreased more with trimethaphan induced hypotension than SNP-induced hypotension.

There are a number of undesirable side effects associated with trimethaphan infusion. These are due to ganglionic blockade and include bladder and intestinal atony, xerostomia and anhidrosis. Cycloplegia can also occur, which may hinder the postoperative evaluation of the neurosurgical or open heart surgery patient.

Bradycardia, secondary to inhibition of cardiac sympathetic fibres can be beneficial, through its improvement of myocardial oxygen balance. This contrasts with the reflex tachycardia which can result from most of the other vasodilators.

Tachyphylaxis is a common problem. Many techniques have been attempted to overcome this; none have been entirely successful. These include use of intermittent bolus doses of trimethaphan during infusion, increasing the rate or concentration of infusion, phenoxybenzamine, guanethidine and halothane administration.

Because of the drawbacks associated with trimethaphan usage, other vasodilators are more commonly employed.

Hydralazine

Hydralazine is a direct acting vascular smooth muscle relaxant which has a predominant effect on arterial beds, and no direct action on the heart. The vasodilatory effects are not uniform, being more pronounced in the coronary, cerebral, renal and splanchnic circulation. Athough its most frequent indication is control of hypertension, it has been used perioperatively as a vasodilator.

Hydralazine 2.5–5.0 mg IV was administered to vasodilate cardiac surgical patients in the immediate postoperative phase.[91] The patients initially had a low cardiac index ($CI < 2.8\ L \cdot min^{-1} \cdot m^{-2}$), an elevated systemic vascular resistance ($SVR > 1200$ $dyne \cdot sec \cdot cm^{-5}$), and high pulmonary capillary wedge pressure (PCWP > 20 mmHg). After administration of hydralazine, there was a significant increase in CI with a significant decrease in SVR and essentially no change in blood pressure or PCWP.

Peak haemodynamic effects may not occur for 60 minutes. Intraoperatively or in the immediate postoperative period faster response is frequently desired. For this reason, other vasodilators with a

faster onset of action and which are easier to titrate are usually administered.

Miscellaneous agents

Potent inhalation agents

Isoflurane,[92] enflurane[93] and halothane[94] are inhalation anaesthetics which cause vasodilatation through their relaxant effect on smooth muscle and their depression of the central nervous system, inhibiting sympathetic activity, decreasing vascular tone. However, their potencies differ in this respect, isoflurane producing the most profound vasodilatation, enflurane being intermediate and halothane resulting in the least amount of decrease in vascular resistance. This effect is dose-related, and may be related to duration of anaesthesia in the case of halothane. It has been demonstrated that vasodilatation increases with duration of halothane administration,[95] in contrast to the vasodilatation produced by isoflurane, which is unrelated to duration of anaesthesia.[96]

Although all the potent inhalation agents produce coronary artery vasodilatation, isoflurane has a greater effect than halothane[97] or enflurane.[98] Their effects on myocardial perfusion are also not uniform. Investigators have found that while isoflurane increases myocardial perfusion, equipotent doses of halothane decreased it.[99] Results of other studies indicate that isoflurane may result in a coronary steal phenomenon in patients with atherosclerotic heart disease.[100–102] In studies done on patients with stable coronary artery disease who were undergoing major vascular procedures, coronary sinus and great cardiac vein blood flows and lactate extraction were measured, in addition to the standard haemodynamic parameters. During isoflurane administration, coronary perfusion pressure was decreased, with coronary blood flow unchanged, indicating that there was a reduction in coronary vascular resistance. However, in one study ten out of 21 patients developed EKG and metabolic alterations consistent with ischaemia. Patients who did not develop EKG changes, did not experience any metabolic changes indicative of ischaemia, i.e., a decrease in lactate extraction. These investigators concluded that isoflurane may lead to redistribution of myocardial blood flow resulting in regional ischaemia in patients with coronary artery disease. However, the decrease in coronary perfusion pressure could not be ruled out as the cause of these alterations. These findings were supported in a canine model of chronic coronary occlusion.[102] Regional myocardial perfusion was assessed by nine micron radioactive microspheres and regional contraction was measured with piezoelectric crystal sets. During isoflurane administration there was a decrease in coronary vascular resistance, with total coronary flow remaining the same as compared to control values. However, there was a redistribution of flow from the collateral dependant zone to the normal zone. In addition contractility decreased in the collateral zone, and increased in the normally perfused area. This study provides further evidence that isoflurane may cause intracoronary steal in patients with critical coronary artery stenosis.

The potent inhalation agents have been administered during cardiopulmonary bypass via a vaporizer interposed into the oxygen line to treat patients who are vasoconstricted. However, all of these agents can cause significant myocardial depression.[103–106] With the availability of vasodilators which have no direct effect on myocardial contractility, the use of potent inhalation agents has become less frequent during and post cardiopulmonary bypass, a time when contractility may already be impaired from various metabolic abnormalities. These include ischaemic arrest during aortic cross clamping, hypothermia, trauma from manual manipulation, cardioplegia solution, etc.

Chlorpromazine

Chlorpromazine is a major tranquilizer with alpha blocking action. It has been used during cardiopulmonary bypass as a vasodilator, to permit higher pump flows when vasoconstriction limits this. The haemodynamic effects of chlorpromazine induced vasodilatation have been investigated in cardiac surgical patients in the early postoperative period.[107] The cardiac index increased 26 per cent with a decrease in systemic vascular resistance of 31 per cent. However, there was an increase in heart rate of 20 per cent, which could result in an increase in myocardial oxygen consumption, offsetting its beneficial effects. Because of this, the production of sedation, which may not be desired and less control over haemodynamics than with SNP or NTG, chlorpromazine is less frequently used than in the past for its vasodilating effect.

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