Vasoactive Drugs

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General Considerations

Vasoactive drugs affect vasomotor tone. Depending on the direction of such effect, vasoactive drugs can be subdivided into vasoconstrictors and vasodilators. Vasodilators, in turn, can be subdivided into predominantly arterial (e.g., hydralazine, nicardipine) or venous (e.g., nitroglycerin) vasodilators. Many of them are mixed arteriovenous vasodilators (e.g., nitroprusside, α-adrenoceptor antagonists).

Mechanisms of Action. Mechanisms of action of vasoconstrictors include stimulation of peripheral α-adrenoceptors (phenylephrine) and arginine vasopressin V_{1a} receptors (vasopressin). Mechanisms of action of vasodilators include stimulation of peripheral β_2-adrenoceptors (isoproterenol), antagonism of α-adrenoceptors (phentolamine), inhibition of inward flow of calcium ions through calcium channels (nicardipine), stimulation of dopaminergic receptors (fenoldopam), nitric oxide-induced formation of cyclic guanosine monophosphate (nitroglycerin), phosphodiesterase inhibition-induced inhibition of breakdown of cyclic AMP (milrinone), and angiotensin-converting enzyme inhibition (enalaprilat).

Direct Cardiac Effects. Many vasoactive drugs directly affect cardiac performance because they act on receptors, ion channels, or enzymes that are located not only in vascular smooth muscle but also in the heart. These effects may accentuate or counteract the primary effect on vasomotor tone. Depending on whether and on which cardiac cellular structure and activity is (are) being simultaneously stimulated or inhibited, a vasoactive drug can be a pure vasoconstrictor (e.g., phenylephrine), a combined vasoconstrictor + positive inotrope (e.g., norepinephrine), a pure vasodilator (e.g., nitroprusside), a combined vasodilator + positive inotrope (e.g., isoproterenol), or a combined vasodilator + negative inotrope (e.g., nifedipine).

Indirect Cardiac Effects. Vasoactive drugs may affect cardiac performance not only directly but also indirectly. Vasodilator-induced changes in systemic vascular resistance (SVR) can elicit baroreceptor-mediated responses that may counteract the primary drug effect. For example, hypotension-induced baroreflex tachycardia may negate some of the hypotensive effect of a vasodilator. However, excessive tachycardia may accentuate the hypotensive drug effect by diminishing stroke volume (SV) because of shortening of ventricular filling time.

Vasodilator-induced decreases in cardiac preload can elicit similar baroreceptor-mediated tachycardia. The simultaneous decrease in SV as a consequence of the decrease in preload may accentuate the hypotensive drug effect. However, if the vasodilator-induced decrease in cardiac preload results in normalization of an abnormally elevated cardiac preload, cardiac performance will improve and systemic blood pressure rise.

Effect on Myocardial Perfusion. By affecting systemic blood pressure, vasoactive drugs directly affect coronary perfusion pressure. This aspect becomes particularly important in the presence of underlying coronary artery disease in which myocardial perfusion becomes increasingly perfusion pressure dependent. Potentially beneficial effects of vasodilator therapy on myocardial performance through normalization of cardiac preload and afterload may be offset by the simultaneous detrimental effect on coronary perfusion pressure.

Net Cardiovascular Effect. Depending on the mechanisms of action of the respective vasoactive drug and on underlying cardiac function, administration of a vasodilator may actually increase blood pressure by improving myocardial function, whereas inappropriate administration of a vasoconstrictor may result in a decrease in blood pressure by worsening myocardial performance.

Principles of Myocardial Function

Preload. Cardiac preload is the force (or load) that stretches ventricular myocardial fibers at end-diastole. It is an intrinsic property of the heart to increase the force of contraction in response to a lengthening of ventricular myocardial fibers at end-diastole. This preload-recruitable function leads to an increase in cardiac pump function (stroke volume) in response to an increase in end-diastolic volume (EDV).

The relationship between SV and EDV is linear not only in healthy hearts but also in the failing heart (1). However, although preload-recruitable function may

be preserved in the failing heart, it is at the expense of markedly elevated ventricular filling pressures. Ultimately, filling pressures will rise excessively without further or only slight increase in EDV and SV.

When systemic hypotension is associated with such condition, a pure α-adrenoceptor agonist that constricts not only arterioles but also venules (possibly leading to a further increase in preload) may not be the drug of choice. A more rational choice of drug treatment could consist of either a venodilator alone (low-dose nitroglycerin), a combination of a venodilator + an α-adrenoceptor agonist (e.g., phenylephrine), or a substance that increases contractility and peripheral vascular resistance (e.g., low-dose norepinephrine).

Afterload. Cardiac afterload is the force that opposes myocardial fiber shortening at the onset of systole. Ventricular wall stress and arterial impedance are the major determinants of afterload. In clinical practice, SVR is usually accepted as a surrogate measure of LV afterload.

As afterload increases, the normal heart maintains pump function. This is largely a result of the preload-recruitable function. The effect of an acute increase in afterload to decrease fiber shortening is counterbalanced by a compensatory increase in end-diastolic filling (i.e., the Frank-Starling mechanism), thereby maintaining SV. Thus, the healthy heart is preload-sensitive and afterload-insensitive.

By contrast, the failing heart is considerably more sensitive to increases in afterload because it maintains pump function, in part or entirely, on the basis of preload-recruitable function. As a result, fiber shortening and pump function may decline in response to an increase in afterload (2). Overcorrection of hypotension in the presence of impaired LV function by injudicious use of a vasoconstrictor may provoke acute LV failure.

Contractility. The effect of a vasoactive drug on cardiac contractility *per se* is difficult to predict because of simultaneous changes in preload, afterload, and heart rate. In general, myocardial oxygen consumption (MVO_2) is proportional to myocardial contractility. However, contractility and MVO_2 must not necessarily change in the same direction. A major determinant of the effect on MVO_2 is the effect on heart size. When an increase in contractility restores normal heart size, wall stress and, subsequently, MVO_2 will decline. Under such conditions, the administration of a combined inotrope and vasoconstrictor (e.g., epinephrine) or a combined inotrope and vasodilator (e.g., dobutamine) may have beneficial effect on MVO_2—not despite but rather because of increasing contractility. By contrast, the same drugs administered in the presence of normal heart size and wall stress will increase MVO_2 in parallel with the increase in contractility.

Heart Rate. An increase in heart rate can be of particular detriment to myocardial performance because it simultaneously increases MVO_2 and decreases myocardial oxygen supply (MDO_2) by decreasing diastolic coronary filling time. When in the presence of clinically relevant coronary artery disease hypotension-induced baroreflex-mediated activation of the sympathetic nervous system not only increases heart but also contractility, myocardial ischemia is likely to develop quickly (3).

Principles of Coronary Physiology

The following relationships apply:

1. Myocardial oxygen delivery (MDO_2) = coronary blood flow (CBF) $\times$ arterial oxygen content (CaO_2).
2. CBF = coronary perfusion pressure (CPP) $\div$ coronary vascular resistance (CVR).
3. CPP = coronary driving pressure $-$ intramyocardial pressure. CPP is the major determinant of myocardial perfusion. For the LV endocardium where coronary flow occurs primarily during diastole, CPP can be assumed to be CPP_{LV} = diastolic systemic arterial pressure $-$ LV end-diastolic pressure.

For the right ventricular (RV) endocardium where coronary flow occurs throughout the cardiac cycle, CPP can be assumed to be CPP_{RV} = mean systemic arterial pressure $-$ mean RV pressure.

As myocardial oxygen extraction is almost maximal at rest (65%–75%), at constant CaO_2 an increase in MVO_2 can only be met by an increase in CBF. According to CBF Equation 2 above, within the autoregulatory range such increase in CBF is usually achieved by a decrease in CVR.

Normally, metabolically induced coronary vasodilatation can increase CBF fivefold. In the presence of significant coronary artery disease, however, maximal or near maximal coronary vasodilatation may already be present distal to a critical coronary stenosis, so that CVR is relatively fixed. As a result, myocardial blood flow will become increasingly perfusion pressure-dependent (Equation 2 above). Furthermore, because the compensatory mechanism of coronary vasodilatation is blunted or absent, the time available for coronary perfusion becomes increasingly important. This is particularly relevant for the LV because coronary perfusion takes place predominantly during diastole. As the duration of diastole is inversely proportional to heart rate, tachycardia will decrease myocardial blood flow at a time when the increase in heart increases MVO_2. This means that especially in the presence of coronary artery disease, the combination of systemic hypotension and tachycardia is particular detrimental and a vasodilator-induced reflex tachycardia must be avoided.

Treatment of Systemic Hypotension

The following relationships between arterial pressure, cardiac output (CO) and SVR exist:

Arterial pressure =
CO × SVR (→ SVR = arterial pressure ÷ CO)
↓
CO = heart rate × stroke volume (SV)
↓
SV = EDV − ESV

(where EDV = end-diastolic volume, and ESV = end-systolic volume).

It is obvious that low or high blood pressure or SVR can have numerous causes.

Systemic Hypotension and Normal Cardiac Output. The first equation implies that in the presence of hypotension, initial assessment of CO is warranted. If CO is normal, low SVR has to be the main cause of hypotension. In such case, administration of a pure vasoconstrictor (e.g., phenylephrine) is usually the preferred option.

In patients with coronary artery disease but normal LV function, a pure vasoconstrictor like phenylephrine can counteract nitroglycerin-induced venodilation to maintain coronary perfusion pressure and to prevent reflex tachycardia. By contrast, in patients with myocardial insufficiency and impaired LV function, the increase in afterload by phenylephrine may decrease stroke volume, increase EDV and LV wall stress and MVO_2, and may thus reverse the beneficial effect of nitroglycerin (4).

Systemic Hypotension and Low Cardiac Output. If CO is low and bradycardia is ruled out, then an inadequate stroke volume must be assumed and EDV must be assessed. In the presence of low LV end-diastolic dimensions or filling pressures, volume expansion may be indicated. In the presence of elevated LV end-diastolic dimensions or filling pressures, the aim must be to improve LV ejection by drug therapy. The options are an inotrope, a vasodilator, or a combination of both. Vasodilators alone are only likely to improve SV and blood pressure under very special circumstances (e.g., mitral and aortic regurgitation). Usually, however, a drug with positive inotropic effect is required. Depending on the primary hemodynamic goal, a drug with mostly inotropic effect (e.g., low-dose epinephrine), with combined inotropic and vasodilator effects (e.g., phosphodiesterase inhibitors), or with combined inotropic and vasoconstrictor effect (e.g., norepinephrine) is chosen. Particularly in cases of underlying myocardial ischemia, care must be taken to prevent increases in heart rate associated with inotropic or vasodilator therapy.

Treatment of Acute Heart Failure

Therapy for acute LV failure depends on the overall hemodynamic and clinical status and often requires administration of drugs that act at various sites. Initial treatment usually includes drugs that increase cardiac contractility (e.g., sympathomimetic inotropes) and reduce preload (e.g., furosemide, IV nitrates). The choice for the additional administration of a peripheral vasodilator or vasoconstrictor depends on the underlying blood pressure, SVR, and peripheral perfusion (Table 1).

Sympathomimetic drugs should benefit the failing heart through β_1-receptor-mediated increase in contractility, β_2-receptor-mediated decrease in afterload, and α-receptor-mediated restoration of perfusion pressure in hypotensive states. However, catecholamines must be used with extreme caution in low-output states that are caused by coronary insufficiency. β_1-receptor stimulation may cause tachycardia and arrhythmias that, in turn, may worsen myocardial ischemia. Prolonged β_1-receptor stimulation may also lead to β-receptor down-regulation with subsequently diminished inotropic response. Excessive α-receptor stimulation may result in abnormal elevation of afterload that, in turn, will worsen myocardial ischemia and performance. β_2-receptor stimulation causes hypokalemia, which increases the risk of arrhythmias. Finally, catecholamines induce myocytolysis. For all of these reasons, catecholamines should not be used for a prolonged period of time in acute heart failure.

If LV failure is accompanied by a shock-like state and a systolic blood pressure of <70 mm Hg, norepinephrine (0.5–30 $\mu g/min$) or dopamine (5–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) are drugs of choice (5). If LV failure is accompanied by a shock-like state and a systolic blood pressure of 70–100 mm Hg, dopamine (2.5–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is an option. If treatment is inadequate, norepinephrine may be added. If LV failure is not accompanied by a shock-like state and systolic blood pressure is in the range of 70–100 mm Hg, dobutamine (2.5–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) would be a rational choice (5). Finally, if LV failure is accompanied by a systolic blood pressure of >100 mm Hg, IV nitroglycerin (started at 10–20 $\mu g/min$) or nitroprusside (started at 0.1–5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) are indicated.

Treatment of Acute Uncontrolled Hypertension

In general, it is advisable to lower uncontrolled hypertension more slowly than aggressively to avoid inadequate regional organ perfusion (especially of brain, heart, or kidney) and to closely monitor the overall hemodynamic effects during careful IV titration of the appropriate drugs. The choice of drug depends on the

Table 1. Pharmacological Treatment of Acute Circulatory Failure

	Mediating receptor(s)	Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Inotropic effect	HR-effect	SVR-effect	BP-effect
Dobutamine	$\beta_1 > \beta_2 > \alpha$	2–15	↑ ↑	↑	↓ HD: ↑	↑
Dopamine	DA > β > α	"renal": 2–5			0	0
		↑ inotropy: 5–10	↑ ↑	0, ↑	↓ ↓	0
		↑ SVR: 10–20			HD: ↑ ↑	HD: ↑
Norepinephrine	$\beta_1 > \alpha > \beta_2$	0.01–0.03 maximal: 0.1	↑	↑	↑ ↑	↑
Epinephrine	$\beta_1 = \beta_2 > \alpha$	0.01–0.03 maximal: 0.1–0.3	↑ ↑	↑ ↑	↓ HD: ↑	0, ↑
Isoproterenol	$\beta_1 > \beta_2$	0.01–0.1	↑ ↑ ↑	↑ ↑ ↑	↓	↑
Phenylephrine	α	0.2–0.3	0	0	↑ ↑ ↑	↑ ↑ ↑
Amrinone	PDE inhibitor	bolus: 750 (3 min) infusion: 2–10	↑	0	↓ ↓	↓
Milrinone	PDE inhibitor	bolus: 50–75 (10 min) infusion: 0.375–0.75	↑	0	↓ ↓	↓

↑ = increase; 0 = no change; HR = heart rate; SVR = systemic vascular resistance; BP = blood pressure; HD = high dose; DA = dopaminergic; PDE = phosphodiesterase.
Modified after (5).

Table 2. Treatment of Acute Uncontrolled Hypertension

Condition	Mechanism of drug action	Drug(s) of choice	Dose
Severe acute HTn + urgent need to lower BP	NO donor	Sodium nitroprusside	0.3–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$
HTn + ischemia (± ↓ LV function)	NO donor	Nitroglycerin	0.25–5 $\mu g \cdot kg^{-1} \cdot min^{-1}$
HTn + ischemia + tachycardia	β-blocker	Esmolol	50–250 $\mu g \cdot kg^{-1} \cdot min^{-1}$
	α-/β-blocker	Labetalol	2–10 mg bolus 2.5–30 $\mu g \cdot kg^{-1} \cdot min^{-1}$
HTn + poor LV function	ACE inhibitor	Enalaprilat	0.5–5 mg bolus
		Captopril SL	12.5–25 mg SL
HTn ∅ cardiac problems	Various vasodilators	Hydralazine	5–10 mg boluses
		Phentolamine	1–4 mg boluses
		Nicardipine	5–10 μg/kg bolus 1–3 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Severe or malignant HTn + ↓ renal function	Dopamine (DA_1) agonist	Fenoldopam	0.2–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$
HTn + pheochromocytoma	α-blocker or α-/β-blocker	Phentolamine	1–4 mg boluses
		Labetalol	2–10 mg bolus 2.5–30 $\mu g \cdot kg^{-1} \cdot min^{-1}$

HTn = hypertension. NO = nitric oxide.
Modified after (6).

underlying cause of the acute hypertension and possible concomitant morbidity, e.g., by poor LV function, myocardial ischemia, tachycardia, bradycardia, or poor renal function (6) (Table 2).

In hypertensive encephalopathy, drugs that cause sedation (methyldopa, reserpine) or a decrease in cerebral blood flow (diazoxide) should be avoided. Preferred drugs would be labetalol, nicardipine, or nitroprusside. In the presence of underlying LV insufficiency, negative inotropic drugs (labetalol, β-blockers) should be avoided or used only with great caution. Drugs of choice would be enalaprilat, nitroglycerin, or nitroprusside. When acute hypertension is accompanied by myocardial ischemia, drugs that may lead to increases in contractility and heart rate *via* reflex sympathetic stimulation (e.g., hydralazine) or that carry the potential for inducing coronary steal (nitroprusside) should be avoided. In such situation, drugs like nitroglycerin, esmolol, or nicardipine are preferable. Similar considerations apply in the presence of a dissecting aortic aneurysm (6).

Selected Sympathomimetics and Phosphodiesterase Inhibitors

Dopamine. Dopamine is the precursor of norepinephrine and releases it from intracardiac adrenergic nerve endings. In the periphery, dopamine stimulates

prejunctional dopaminergic DA_2-receptors, which results in inhibition of norepinephrine release and, in turn, facilitates vasodilatation. By activating specific postjunctional DA_1-receptors, low-dose dopamine may increase renal, mesenteric, coronary, and cerebral blood flow in low output states. At high doses, dopamine stimulates predominantly α-receptors resulting in increased SVR and decreased renal blood flow.

Scientific proof for a specific renal protective effect of dopamine at a "renal" dose (0.5–2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is missing. In a recent randomized study, low-dose dopamine (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) neither reversed renal failure nor improved outcome in critically ill patients (7). The increase in urine output observed after the addition of low-dose dopamine to norepinephrine in the treatment of patients with septic shock did not improve renal function and was probably related to a dopamine-induced increase in cardiac output (8). Two meta-analyses confirm the lack of beneficial effect of low-dose dopamine (9,10). In addition, low-dose dopamine depresses hypoxic (and possibly hypercapnic) ventilatory drive (11) and impairs regional ventilation/perfusion matching in the lung (12).

There is tremendous intraindividual variability as to the relative responsiveness of the various receptors to dopamine. In some individuals, the predominantly vasoconstrictive effect of dopamine will become evident at relatively low dosage. The dose should, therefore, be kept as low as possible to achieve the desired hemodynamic goal. At times, it may be preferable to use a combination of dopamine + a vasodilator or a combination of dopamine + dobutamine rather than a high-dose monotherapy with dopamine.

Mixed Inotropic-Vasodilator Drugs ("Inodilators"). The phosphodiesterase (PDE) inhibitors (milrinone, enoximone) are the prototype drugs of "inodilators." They inhibit the breakdown of cyclic AMP in cardiac and peripheral vascular smooth muscle resulting in increased cardiac contractility and arterial and venous vasodilatation. For reasons not well understood, heart rate, blood pressure and, subsequently, MVO_2 are relatively little affected. However, PDE inhibitors predispose to ventricular arrhythmias.

Vasopressin. Vasopressin, also known as antidiuretic hormone (ADH), is a nonapeptide hormone that is produced in the posterior pituitary. Arginine vasopressin (AVP) is the most active form of ADH.

Three different AVP receptor subtypes exist: the V_{1a}, V_{1b}, and V_2 receptor subtypes. V_{1a} receptors are located on vascular smooth muscle cells and cardiomyocytes. Binding of AVP to these two vasopressin receptor subtypes modulates vasomotor tone and myocardial function (13).

Two novel indications for the use of AVP have recently come to the forefront. Vasopressin may be superior to current standard of care in the treatment of vasodilatory (septic) shock and in cardiopulmonary arrest secondary to ventricular fibrillation or pulseless ventricular tachycardia (14).

Vasopressin in Septic Shock. Traditionally, support of blood pressure during sepsis is based on the administration of catecholamines (Table 3). However, patients sometimes become unresponsive to even high doses of these drugs. This may be caused by down-regulation of β-adrenoceptors (15) or by increased NO production (16). Vasopressin suppresses NO production, which may, in turn, increase the responsiveness to catecholamines and decrease NO-induced hypotension (17). Interestingly, whereas blood pressure in patients with normal hemodynamic status did not respond to the administration of 0.26 U/min of vasopressin, in shock states hypersensitivity to vasopressin combined with decreased responsiveness to catecholamines has been observed (18). It is also noteworthy that there is little physiologic reflex bradycardia in response to an increase in SVR during infusion of vasopressin (18,19).

Vasopressin potentiates the venous vasoconstrictive properties of catecholamines (20). In experimental septic shock, blood pressure increases within 15 min in response to vasopressin infusion of 0.04 U/min (18,21). Although vasopressin constricts splanchnic and coronary vessels, a vasopressin infusion at a dose of 0.04–0.12 U/min did not decrease mesenteric blood flow (17). At an average vasopressin infusion rate of 0.43 U/min in the therapy of gastrointestinal bleeding (which is ten times the dose used in vasodilatory septic shock), coronary blood flow did not significantly decrease (22).

In experimental endotoxin-induced circulatory shock in anesthetized dogs, in contrast to norepinephrine (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), AVP (0.08 U/min) restored renal blood flow and renal oxygen delivery at comparable systemic and splanchnic hemodynamic and metabolic effects (23). In cecal perforation-induced septic shock in anesthetized sheep, low-dose vasopressin alone (0.02 U/min) or in combination with norepinephrine (at 0.01 U/min) prolonged survival time and resulted in less tissue injury compared with norepinephrine alone (24).

Taking the published data together, the most appropriate indication for vasopressin appears to be sepsis-induced persistent hypotension that is resistant to catecholamine therapy (25). Under such conditions, vasopressin seems to restore perfusion pressure and to allow reduction in conventional catecholamine dosages (26,27). At low doses (0.01–0.04 U/min), vasopressin appears to be an effective vasopressor without the risk of concomitant organ hypoperfusion. At high doses (>0.04 U/min), the increase in systemic pressure may be accompanied by potentially harmful renal, splanchnic, pulmonary, and coronary vasoconstriction (28). However, no randomized clinical trial

Table 3. Vasopressors in Septic Shock

Vasopressor	Dose	Indications
Dopamine	1–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Primary vasopressor
Norepinephrine	2–200 $\mu g/min$	When dopamine fails; not used with high SVR
Epinephrine	1–8 $\mu g/min$	Use in low output state
Phenylephrine	20–200 $\mu g/min$	When arrhythmias develop during use of other drugs
Vasopressin	0.01–0.04 U/min	Catecholamine-resistant vasodilatory (septic) shock

SVR = systemic vascular resistance.
Modified after (14).

exists that would demonstrate improved organ function or survival after administration of vasopressin in vasodilatory shock. Accordingly, the use of vasopressin in vasodilatory shock following cardiac arrest is a "class indeterminate" recommendation in the 2000 AHA guidelines for postresuscitation management. Those guidelines state "If vasodilator shock is refractory to adrenergic vasopressor agents, a continuous infusion of vasopressin may be beneficial" (29).

Vasopressin in Cardiac Arrest. In the 2000 guidelines for advanced cardiovascular life support (ACLS) of the American Heart Association (30) vasopressin was given a "class IIb" recommendation (acceptable, possibly helpful, not harmful, and supported by fair evidence) for treatment of cardiac arrest secondary to ventricular fibrillation and ventricular tachycardia. By contrast, for the same indication epinephrine was reassigned from a previous "class Iib" recommendation to "class indeterminate."

Coronary perfusion pressure (CPP) is a major predictor of successful cardiopulmonary resuscitation. In the experimental animal, compared with epinephrine, vasopressin caused larger increases in SVR, cerebral perfusion pressure, and CPP (31,32). During hypoxia and acidosis, vasopressin is a more effective vasoconstrictor than epinephrine (32). In addition, in contrast to epinephrine, vasopressin does not seem to increase MVO_2 or lactate production (33).

Despite some encouraging initial findings in clinical studies (33,34), a subsequent randomized trial failed to demonstrate superiority of vasopressin over epinephrine in in-hospital cardiac arrest (35). It remains to be shown by larger trials whether survival to discharge will truly be improved by vasopressin.

Conclusions

The ultimate *in vivo* effect of a given vasoactive drug is dependent on dosage, individual responsiveness, and underlying conditions (e.g., baseline cardiovascular function, underlying disease entity that requires treatment with vasoactive drugs). Age and chronic and acute disease states will change number, distribution, and responsiveness of receptors. Reduced β-adrenoceptor responsiveness has been demonstrated in the elderly and in the presence of circulating endotoxin and tumor necrosis factor. These are all reasons why there is no "magic bullet" for a given cardiovascular derangement, why patients respond differently to an identical pharmacological treatment, and why different patients require different pharmacological therapy for a seemingly identical cardiovascular derangement. As the individual response to vasoactive drug therapy is unpredictable, therapy must always be closely monitored.

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