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EDUCATIONAL OBJECTIVES

After reading this chapter, the reader should be able to:

1) Discuss the basic physiology and pharmacology of catecholamines, PDE-inhibitors and nitroderivatives

2) Make appropriate choices for administration of cardiotonic agents to critically ill patients

3) Identify anticipated physiologic and unanticipated pathophysiologic responses to a variety of cardiotonic compounds used in the ICU

INTRODUCTION

Cardiotonic drugs are those which act upon the cardiovascular system to enhance cardiac performance, increase blood pressure and cardiac output (CO) and/or improve regional blood flow and oxygen delivery. Pharmacologically, they can be divided into sympathomimetic amines, non-adrenergic inotropes, and vasodilators (Table 1). Sympathomimetic amines can be further divided into catecholamines (both natural endogenous and synthetic exogenous) and non-catechol sympathomimetics. Clinically, drugs are more simply categorized as inotropes, vasopressors or vasodilators although without question may clinically available compounds fit into more than one category
Clinical categorization of these compounds leads to groupings with relatively defined hemodynamic effects (Table 3). Inotropes by definition increase cardiac contractility and increase CO. Preload typically falls resulting in decreased ventricular filling pressures including pulmonary wedge pressure (PWP). As a consequence, symptoms of congestive failure can be improved. On the other hand, if ventricular filling pressure becomes inadequate, hypotension may result. Many inotropes also tend to decrease afterload because of mild vasodilatory properties. This supports the increase of CO but again hypotension may be a consequence. Heart rate (HR) is variably affected by these compounds. One interesting effect of inotropes (as well as vasodilators) is their tendency to increase the pulmonary shunt fraction.

Vasopressors increase preload and ventricular filling pressures including PWP. As a consequence, congestive heart failure may be aggravated. CO almost universally falls and myocardial oxygen requirements increase as afterload and MAP rise. α-adrenergic stimulation does result in mild inotropic stimulation but this is masked by the increase in afterload. A pure vasopressor will typically cause a relative bradycardia. However, if there is a major element of β₁ stimulation, tachycardia may be observed.

Vasodilators have effects opposite those of vasopressors. Venodilation results in decreased pre-load. Ventricular filling pressures including PWP may fall resulting in improvement of congestive heart failure. Arteriolar dilating effects cause decreased afterload. Mean arterial pressure (MAP) falls both due to decreased afterload and
decreased venous return due to venodilatation. CO usually increases due to decreased afterload. However, if venodilation dominates over arteriolar dilatation, a decreased CO may be observed. Like inotropes, vasodilators tend to increase pulmonary shunt fraction and can, in cases of marginal oxygenation, be associated with the development of overt hypoxemia.

\[\text{β-Adrenoreceptors, Phosphodiesterases, and Cyclic AMP}\]

Catecholamines are compounds containing a 3,4-hydroxyl β-phenylethylamine structure. They are composed of both natural endogenous (dopamine, norepinephrine, epinephrine) and synthetic exogenous (isoproterenol, dobutamine, dopexamine) sympathomimetic amines (Fig. 1) [1].

One of the primary mechanisms through which catecholamines exert their effects is through the β-receptor/adenylyl cyclase pathway [2,3]. Catecholamines and other sympathomimetics specifically bind to the target cell surface β-adrenoreceptor. Binding activates a stimulatory membrane-bound guanine nucleotide-binding (Gs) protein. There also exists an associated inhibitory G protein (Gi) which serves to modulate adrenoreceptor responsiveness. The Gs coupling protein activates stimulates an associated adenylyl cyclase which, in turn, generates cellular cyclic AMP (cAMP). This c-AMP activates a class of enzymes, the cAMP-dependent kinases, which phosphorylate intracellular contractile regulatory proteins such as the slow “L” calcium channel, phospholamban, and troponin I (Fig. 2). The net result is increased calcium influx through the slow calcium channels and increased calcium sensitivity of certain contractile regulatory cellular proteins. As long as cAMP remains elevated, intracellular calcium
remains increased and contractility is enhanced (inotropy). In addition, evidence
suggests that β-adrenergic stimulation is also associated with an enhanced relaxation
phase (lusitropy) through related mechanisms. Once the additional cAMP is
metabolized by the enzyme, phosphodiesterase III (PDE), cAMP levels fall rapidly,
phosphate is removed from regulatory proteins, calcium levels decrease, and augmented
inotropy and lusitropy return to baseline.

PDE inhibitors act to inhibit the activity of phosphodiesterase enzyme, thereby
preventing the metabolism and breakdown of cAMP [4]. The net effect is to increase the
intracellular concentration of cAMP. In many respects, PDE inhibitors mimic the effects
of β-adrenoreceptor activation. Amrinone and milrinone are the clinically available
compounds in this class. Administration of milrinone at doses which cause no change in
MAP or SVR result in a substantial increase in cardiac contractility. In addition, these
drugs relax vascular smooth muscle resulting in decreased cardiac afterload. They are
sometimes referred to as “inodilators.” In fact, some studies have suggested that CO
augmentation in clinical practice is primarily related to the drugs vasodilatory properties
[5].

The α-Adrenoreceptor

The α1- and α2-receptors modulate peripheral vasomotor tone, myocardial contractility,
and CNS (medullary) output [6]. Postsynaptic vascular α1-adrenergic receptors mediate
vasoconstriction while presynaptic α2-adrenergic receptors modulate endogenous
neurotransmitter concentration in the synaptic cleft. The direct vasoconstrictive effects
of α-agonists appears ultimately to be mediated by augmented calcium influx into
vascular smooth muscle cells. α receptors also exist in myocardium. These receptors
are thought to mediate limited inotropic effects also through increased calcium influx. The second messenger system appears to involve phospholipase C mediated generation of diacylglycerol and inositol phosphates along with activation of protein kinase C.

Pure $\alpha$ agonists such as phenylephrine cause increases in blood pressure which are accompanied by a proportional increase in myocardial blood flow and maintenance of the endocardium-to-epicardium flow ratio. Myocardium does not appear to be at risk when phenylephrine is used to treat hypotension because intrinsic autoregulation of coronary tone overrides $\alpha$-adrenergic-induced constriction at the arteriolar level. Phenylephrine titrated to treat hypotension associated with septic shock increases oxygen delivery, oxygen consumption, urine output, and decreases blood lactate concentrations.

**Specific Vasoactive Receptor Effects**

Cardiovascular pharmacology strives to separate the receptor effects from drug effects. Receptors generally have very specific and defined effects within the target organ (cardiac cells, vascular smooth muscle, etc), while any given drug has multiple and variable effects due to stimulation of more than one type of receptor, individual variability, and pathophysiology of disease.

$\alpha_1$: Primary effect: vasoconstriction

*Peripheral vasculature:* vasoconstriction of arteries and veins

*Heart:* directly increases contractility, reflex bradycardia

*Coronaries:* mild direct coronary vasoconstriction, but net effect on coronary blood flow is a complex interaction involving afterload and diastolic coronary perfusion pressure.
α2: Primary effects: feedback and vasoconstriction

*Feedback:* acts as a feedback mediator to decrease the release of norepinephrine from nerve terminals

*Peripheral vasculature:* there are receptors in peripheral vessels which also cause vasoconstriction, but this is minor

β1: Primary effects: chronotropy and inotropy

*Peripheral vasculature:* Little to no effect, as most β1 receptors are in the heart

*Heart:* direct inotropic and chronotropic effects in atria and ventricles. Also increase conduction and automaticity of the heart (via the sinoatrial [SA] node, atrioventricular [AV] node, and the conducting fibers of the HIS-Purkinje system).

β2: Primary effects: vasodilation and bronchodilation

*Peripheral vasculature:* direct vasodilation of skin, kidneys, skeletal muscles, visceral, and pulmonary arteries

*Heart:* constitutes about 20% of endogenous contractility. The relative contribution of the β2 receptors becomes more important in cases of heart failure, (β1 system is downregulated)

*Coronaries:* direct vasodilation of coronary vessels

*Bronchi:* relaxes bronchiolar smooth muscle

*Metabolic:* Numerous metabolic stress responses (e.g., gluconeogenesis, renin secretion, insulin secretion, gluconeogenesis, glycogenolysis, intracellular K+ shift)

DA1 (dopaminergic): Primary effect: splanchnic vasodilation
Peripheral vasculature: no effect on peripheral vasculature other than vasodilator effects on splanchnic and renal vasculature: similar effects in myocardial and cerebral vasculature but autoregulation dominates

Heart: the few DA$_1$ receptors in the myocardium mediate modest increases in HR and contractility. The majority of chronotropic and inotropic activity of intravenous dopamine results from DA$_1$-induced myocardial sympathetic nerve release of norepinephrine. DA$_1$ receptors in the splanchnic and renal vasculature result in a relative redistribution of the increased total perfusion (CO) towards the renal and splanchnic vascular beds.

Coronaries: may have a small dilatory effect on coronary arteries

DA$_2$: Primary effect: feedback inhibition

Feedback: affects presynaptic receptors to decrease norepinephrine release, thereby having the indirect effect of vasodilation. These effects are most prominent at very low concentrations of dopamine and are occasionally responsible for the hypotension seen when starting dopamine. DA$_2$-receptors also modulate nausea and vomiting in awake patients and inhibit secretion of prolactin, TSH, aldosterone, and other hormones.

Each sympathomimetic has its own unique receptor affinities and, therefore, its own unique cardiovascular stimulatory profile (Table 4).

Altered β-Receptor Function

Continuous exposure to catecholamines desensitizes β-receptors (changes in receptor number and/or affinity). Examples include congestive heart failure, myocardial ischemia,
stressful surgical operations, cardiopulmonary bypass, and sepsis (Table 5) [7,8]. This neurohormonal-induced densensitization results in a reduction of $\beta_1$-receptor density but $\beta_2$-receptor density remains unchanged. The normal ratio of $\beta_1/\beta_2$ receptors (80:20) is decreased (60:40) in chronic heart failure. While $\beta_2$-receptors are quantitatively maintained, decreased function due to reversible signal transduction uncoupling at the G-protein level is apparent. Conditions associated with excess proinflammatory cytokine generation such as septic shock have also been associated with decreased $\beta$-adrenoreceptor density and uncoupling of signal transduction.

**Vasodilation and Vasodilators**

Under normal circumstances, a variety of factors including acetylcholine, bradykinin and others act on vascular endothelium to stimulate a constitutive nitric oxide synthetase (cNOS) to produce nitric oxide (NO), a free radical with a half life measured in seconds [9]. NO diffuses to adjacent smooth muscle to activate guanylate cyclase producing cyclic GMP (cGMP) from GTP. cGMP is a distal mediator of smooth muscle relaxation.

There are multiple uses for peripheral vasodilators in clinical practice today, including (a) control of hypertension, (b) production of controlled hypotension; (c) reduction of left ventricular afterload to improve forward stroke volume, and (d) reduction of preload on the left ventricle during periods of ischemia and/or depressed contractility. Clinically, vasodilators can be categorized as shown in Table 6. The most commonly used vasodilators in ICU practice are intravenous nitrodrilators with relatively short half-lives such as nitroprusside and nitroglycerin. These NO donors with substantially longer
half-lives than NO similarly stimulate guanylate cyclase to produce cGMP.

**Cardiotonic Agents**

**Inotropes**

**Dopamine:** Dopamine, a biochemical precursor of norepinephrine and an important CNS and peripheral neurotransmitter stimulates dopaminergic (DA$_1$ and DA$_2$) as well as β- and α-adrenergic receptors in a dose-dependent fashion (Fig. 3) [10].

In the range 2-3 $\mu$g/kg/min, dopamine is occasionally employed alone or in combination with vasopressors to maintain renal perfusion and enhance diuresis. DA$_2$ receptors are activated in the lowest dose range (0.2-0.4 $\mu$g/kg/min), while slightly higher infusion rates recruit DA$_1$ receptors (0.5-3.0 $\mu$g/kg/min). Dopamine may selectively increase renal blood flow to an extent greater than its effect on total perfusion (CO). However, this appears to have little benefit clinically. No evidence supports a “renal protective” effect in this context. In addition, DA$_1$ stimulation directly inhibits tubular solute reabsorption resulting in a natriuresis which can occasionally be useful in some scenarios. β-receptor blockade does not alter the dopaminergic responses.

During incremental increases in dopamine infusion (rate >3 $\mu$g/kg/min), progressive recruitment of β$_1$-adrenoreceptors followed by α-adrenoreceptors occurs. β-receptor stimulation results in increased inotropicity, increased HR and augmented CO. This β-receptor stimulatory response is blocked by β-blockers. The dose of dopamine required to increase blood pressure (“α-range”) in both healthy volunteers and in patients is extremely variable, but usually exceeds 6 to 10 $\mu$g/kg/min. At these infusion rates,
inotropicity and dopaminergic responses persist but may be overshadowed by 
$\alpha$-adrenergic increases in afterload. Since dopamine increases HR in addition to 
afterload (=myocardial wall stress), myocardial ischemia can be precipitated. 
Increasing infusions rates of dopamine frequently cause progressive tachycardia. In 
addition, ventricular filling pressures (CVP and PWP) may increase.

Part of the $\beta$-receptor mediated inotropic response to dopamine depends on the release 
of endogenous norepinephrine from myocardial sympathetic innervation. However, 
dopamine-stimulated release of norepinephrine from presynaptic terminals results in rapid 
downregulation of post-synaptic $\beta$-receptors and tachyphylaxis. This downregulation 
affects inotropic response more than the chronotropic effects so tachycardia persists 
even through increased contractility may not. Tachyphylaxis to the myocardial effects of 
dopamine also occur, in part, because myocardial norepinephrine stores become 
depleted. As a consequence, the inotropic effects of dopamine are attenuated in 
catecholamine-depleted states (chronic congestive heart failure).

At its higher dose range dopamine tends to aggravate the pulmonary hypertension of 
congestive heart failure like other vasopressors. Centrally, hypoxic ventilatory drive is 
decreased. Endocrine effects include decreased insulin release resulting in 
hypoglycemia on rare occasions and suppression of TSH and prolactin production 
possibly resulting in a degree of immunosuppression.

Dopamine is metabolized within minutes and steady state levels reached in 5-10
minutes. β-blockers can attenuate dopamine’s effect on contractility but not the
dopaminergic properties. Monoamine oxidase inhibitors (which have been used as
anti-depressants) can augment dopamine effects. In contrast, major tranquilizers and
tricylic antidepressant can block the α effect. The most accepted indications for the use
of dopamine are for the management of shock and, at low dose, for maintenance of renal
perfusion while on vasopressors [10,11]. It has also been used for the maintenance of
natriuresis in cirrhotics. It’s usefulness in maintaining renal perfusion following acute
tubular necrosis (ATN) and low cardiac output states is unproven.

Epinephrine: Epinephrine, the prototypical endogenous catecholamine, is also the most
potent inotrope (β > α-agonist activity) of the sympathomimetic drugs and is produced by
the adrenal gland during physiologic stress. It stimulates β₁, β₂, and α-adrenergic
receptors in a dose-dependent fashion. Epinephrine is 2-10 times more potent than
norepinephrine and 100 times more potent than isoproterenol. At low dose (5 to 20
ng/kg/min) epinephrine’s β₁ and β₂ stimulatory properties dominate. A marked increase
in cardiac contractility and CO occurs. In addition, there may be an increase in afterload
and MAP; HR may be modestly increased. In doses greater than 50 ng/kg/min, α effects
dominate with a marked increase in MAP; marked tachycardia may also occur.
Between the marked increase in blood pressure and HR, myocardial oxygen
demand/delivery ratio may be substantially worsened.

Non-cardiac effects of epinephrine infusion include bronchodilation through bronchial β₂
receptors; decreased renal blood flow through direct α effects and indirectly through β
stimulation of the JG apparatus resulting in renin release; and central respiratory
stimulation. Metabolically, infusion of epinephrine can increase plasma lactate, glucose
and ketones by increased gluconeogenesis and glycogenolysis, skeletal muscle insulin
resistance and decreased insulin release. In addition, serum potassium and PO₄ may
be decreased through a β₂ effect.

Epinephrine, like most catechol inotropes, may induce myocardial ischemia in patients
with coronary artery disease even at doses well within the therapeutic range. In the
absence of coronary artery disease, adverse cardiac events (arrhythmias, ST-segment
depression, chest pain) are mostly observed at infusion rates > 120 ng/kg/min. In
healthy volunteers, cardiac surgery patients, and septic patients epinephrine infusion
rates of 20-100 ng/kg/min effectively increase CO, moderately increases HR, and have an
acceptable incidence of untoward side effects. Higher doses must be used with caution.

Notable interactions include enhanced effects with reserpine, guanethidine, and
monoamine oxidase inhibitors.

The half life of infused epinephrine is approximately two minutes leading to a steady state
in six to ten minutes. Epinephrine is well absorbed through the tracheobronchial tree
and can be administered through an endotracheal tube during cardiac arrest. It is
available as a 1:10,000 dilution (0.1 mg/mL) for intravenous use during cardiac arrest and
anaphylaxis and as a 1:1,000 dilution (1mg/mL) for subcutaneous administration. As the
most potent catecholamine available, epinephrine is used in refractory shock states
including cardiogenic shock and septic shock. In addition, it is used during
cardiopulmonary resuscitation from cardiac arrest. In the latter context, the utility of high dose therapy is unproven. Subcutaneous epinephrine can also be useful during asthma exacerbation or severe anaphylaxis.

**Dobutamine:** Dobutamine, a synthetic catecholamine related to isoproterenol, exists as a racemic mixture of two stereoisomers. α-adrenergic activity resides in the levo isomer and the β-activity is expressed in the dextro isomer. Dobutamine exerts β₁, β₂ and α effects. The cardiac β₁ effect (↑ contractility) is entirely direct. Peripheral β₂ effects (vasodilation) dominates over the α effect at usual infusion rates (5-20 μg/kg/min). α stimulation limits vasodilation and tachycardia as seen with isoproterenol. At supratherapeutic infusion rates, the α-adrenoreceptor pressor effect can become more prominent. Dobutamine generally produces a dose-dependent increase in CO and a reduction in diastolic filling pressures and SVR, properties which can be very useful in the management of congestive heart failure. Compared to dopamine, dobutamine tends to increase the CO more, has little effect on MAP, and tends to decrease ventricular filling pressures [12]. Other effects of dobutamine include augmentation of pulmonary shunt fractions due to the increased CO. There are no specific effects on mesenteric, renal, cardiac, and cerebral perfusion and no specific metabolic effects.

Standard texts often recommend dobutamine as an agent to increase cardiac output without increasing HR. This opinion is based on studies of dobutamine in patients with chronic congestive heart failure, a population noted for β-receptor downregulation, myocardial catecholamine depletion and severe metabolic disturbances. Other patients
may exhibit a different hemodynamic profile in which tachycardia maybe a much more prominent feature, particularly at higher doses. An increasing incidence of arrhythmias and ischemia have been noted with escalating doses especially in those with coronary artery disease.

The half life of dobutamine is approximately 2 minutes with steady state being reached in 6 to 8 minutes. Tachyphylaxis does occur due to receptor down regulation. Because dobutamine has very limited $\alpha$-adrenergic stimulatory effects, it can be safely administered using peripheral veins.

Dobutamine is particularly useful for normotensive or minimally hypotensive congestive heart failure. In this setting, coronary flow is increased more than myocardial work. In addition, dobutamine substantially decreases ventricular filling pressures along with augmenting forward flow; pulmonary edema and other symptoms of congestive heart failure may be substantially improved. Dobutamine can also be very useful for maintaining CO during right ventricular failure due to right ventricular infarction, pericardial tamponade, cor pulmonale or restrictive cardiomyopathy. Finally, dobutamine has also seen significant use in recent years as an inotropic agent for the production of a supratherapeutic CO during septic shock. In this context, caution should be used as volume dependent hypotension may occur if ventricular filling pressures are inadequate.

**Dopexamine:** Dopexamine, a synthetic analog of dopamine, lacks any direct $\alpha$-adrenergic activity, but expresses $\beta_2, \beta_1$ and dopaminergic activity [13]. The $\beta_2:\beta_1$
receptor affinity ratio is estimated at 100:1 so that vasodilation contributes substantially to the \( \uparrow \) CO. The dopaminergic and \( \beta_2 \) arteriolar vasodilation produced by dopexamine reduces cardiac afterload while simultaneously increasing blood flow to the kidneys, intestines, liver, and spleen.

The overall effect is similar to dobutamine with the added element of specific renal and mesenteric vasodilation. Adverse effects are similar to those of dobutamine. The primary current indication is CHF. Administration is in doses of 0.5 to 6 \( \mu \text{g/kg/min} \).

**Isoproterenol:** Isoproterenol is a synthetic catechol derived from epinephrine. In some ways, dobutamine and dopexamine have evolved from isoproterenol. The drug expresses \( \beta_1 \) and \( \beta_2 \) activity without \( \alpha \) activity. HR and contractility are markedly increased through \( \beta_1 \) stimulation. Decreased afterload and increased venodilation are mediated through \( \beta_2 \) activity. The dominant clinical effect is increased CO. However, in the presence of suboptimal intravascular volume, systemic venodilatation can result in decreased venous return, CO and hypotension. One of the major concerns with this drug is that myocardial oxygen demand/delivery ratio can be substantially worsened due to substantial increases in HR resulting in overt myocardial ischemia in predisposed individuals. Since \( \beta_2 \)-adrenergic receptor density is greatest in the skeletal muscle vasculature, isoproterenol tends to shunt blood to skeletal muscle and away from vital organs relative to the increase in CO. \( \beta_2 \) vasodilatory effects are also responsible impairment of pulmonary hypoxic vasoconstriction resulting in increased pulmonary shunt and decreased arterial oxygen tension in patients with parenchymal lung disease. The
drug also relaxes bronchial smooth muscles through $\beta_2$ activity.

Isoproterenol has a half life of approximately two minutes and steady state is reached in 6 to 8 minutes. The utility of isoproterenol is relatively limited. It has largely been supplanted by dobutamine because of isoproterenol’s propensity to cause marked tachycardia and myocardial ischemia. The prominent chronotropic effects remain useful as a temporizing measure for the symptomatic bradycardia especially with heart block. The same property can be useful for torsade ventricular tachycardia if overdrive pacing is unavailable. Since the drug also relaxes bronchial smooth muscle through $\beta_2$ activity, it can be nebulized as a bronchodilator (although more selective agents are now available). Like dobutamine, isoproterenol can be infused peripherally because it has no vasoconstrictive actions. The starting dose is $0.01 \mu g/kg/min$ and is titrated upward to desired effect.

**Phosphodiesterase Inhibitors:** Phosphodiesterase inhibitors such as milrinone and amrinone are related to methylxanthine such as theophylline. These compounds block phosphodiesterase activity in myocardium and vascular smooth muscle resulting in increased cAMP. Positive inotropic effects (increased myocardial contractility and CO) is coupled with a peripheral vasodilating action (decreased afterload and SVR). In fact there has been some debate as to whether the increased CO seen with phosphodiesterase inhibitors in clinical circumstances is due more to their inotropic or vasodilatory properties. As with other inotropes and vasodilators, PWP and CVP fall. If intravascular volume is adequate, MAP is unchanged; if volume contraction is present,
hypotension may ensue. Although phosphodiesterase inhibitors have no direct effect on heart rate, a modest reflex tachycardia may occur in response to arteriolar vasodilation. Despite an increase inotropy, these drugs induce no change in myocardial oxygen demand. In fact, they improve the myocardial oxygen demand/supply ratio by increasing myocardial blood flow.

Although somewhat more common with amrinone than milrinone, thrombocytopenia can occur with prolonged infusion of either phosphodiesterase inhibitors. Arrhythmias can occur rarely. The half life of amrinone is 3 to 4 hours but is prolonged to 5 to 8 hours in congestive heart failure. The half life of milrinone is 45 minutes. Both are metabolized by the liver and excreted in the urine. The primary use for these drugs is in congestive heart failure and post-op cardiac surgery. There may also be some utility for right ventricular failure and right ventricular infarction. They are often used in place of dobutamine. Since these drugs act through a different mechanism, the inotropic effects of phosphodiesterase inhibitors are at least additive to those of adrenergic compounds such as dobutamine and epinephrine. Amrinone is typically given as a loading dose of 1 to 1.5 mg/kg followed by an infusion of 5 to 15 mg/kg/min. Similarly milrinone is administered by loading 37.5 to 75 mg/kg over 10 minutes followed by an infusion of .375 to .75 mg/kg/min.

Vasopressors

Norepinephrine: Norepinephrine is a biosynthetic precursor of epinephrine. It is the
neurotransmitter of the post-ganglionic sympathetic nerve and is also released along with epinephrine by the adrenal medulla under conditions of physiologic stress. Powerful inotropic and vasoconstrictive effects are mediated through potent $\beta_1$ and $\alpha$ activity but minimal $\beta_2$ effects. At low dose, $\beta_1$ effects dominate with increased HR, contractility and CO. At high dose, $\alpha$ receptor mediated vasopressor effects become dominant; CO plateaus while MAP and SVR increase. This pressor effect limits further increases in HR.

Because of the strong pressor effect, norepinephrine can decrease CO if the myocardium is sufficiently damaged that $\beta_1$ stimulation is ineffective. Norepinephrine greatly increases myocardial work and oxygen demand and can precipitate myocardial ischemia. Pulmonary artery vasoconstriction results in pulmonary hypertension. Renal, splanchnic and peripheral perfusion are usually decreased at high dose infusion although if initial MAP is very low, the increased perfusion pressure may actually increase perfusion to vital organs. Non-cardiovascular effects are similar to those of epinephrine.

Norepinephrine acts as a respiratory stimulant through carotid and aortic arch chemoreceptors. There is decreased insulin release, insulin resistance and increases of glucose and ketone concentrations in the blood.

Norepinephrine has a half life of approximately 2 minutes and steady state is reached in 7 to 10 minutes. It is cleared by both enzymatic degradation in the liver and kidney and by uptake degradation in neuronal and nonneuronal effort organ sites. Prazosin increases norepinephrine plasma concentrations while bretylium can produce an exaggerated cardiovascular response to the drug. Low dose dopamine has been shown to ameliorate renal vasoconstriction to norepinephrine. The usual dose range is 2 to 16 $\mu$g/min.
although doses of up to 1.5 $\mu$g/kg/min have been used. The primary indication is refractory shock, particularly septic shock. It has been found to be useful in calcium channel overdose, and other overdoses associated with vascular collapse (e.g. tricyclic antidepressants, antihypertensives). Supraventricular and venricular arrhythmias, myocardial ischemia and organ hypoperfusion may be limiting at high doses.  

**Phenylephrine:** Phenylephrine is a sympathomimetic but not a catechol. Although it is somewhat less potent than norepinephrine as a vasoconstrictor, it is characterized by essentially pure $\alpha$ activity. Phenylephrine increases SVR and MAP via arteriolar vasoconstriction. A reflex decrease in HR is typical. Venconstriction with an increase of ventricular filling pressures (including PWP) is characteristic. CO falls but coronary and cerebral blood flow may increase due to the autoregulatory abilities of those organs.

The half life of phenylephrine is approximately 2 minutes. Infusion is initiated at 0.1$\mu$g/kg/min and is titrated to effect. There is no real upper dose limit as it does not tend to cause arrhythmias. Phenylephrine is useful for pure distributive shock such as spinal or septic shock. Particular utility exists in septic shock associated with impaired ventricular filling due to severe tachcardia or tachyarrhythmias. Prior to the advent of AV nodal blocking agents such as calcium channel blockers, phenylephrine was useful for management of supraventricular tachycardias with hypotension. In such circumstances IV bolus of .1 to .5 m frequently terminated the arrhythmias. As a pure $\alpha$ agent, phenylephrine is relatively contraindicated for left ventricular failure, aortic insufficiency, mitral regurgitation and vascular disease.
**Vasodilators:** The indications for vasodilator therapy in the ICU include hypertensive crisis including hypertensive encephalopathy, hypertension related brain hemorrhage including SAH, vascular dissection, and congestive heart failure [14]. Contraindications include hypotension or shock, severe aortic stenosis, and hypertrophic cardiomyopathy (idiopathic hypertrophic subaortic stenosis). Although vasodilators can worsen the pulmonary shunt fraction, pre-existing hypoxemia with a significant shunt is only rarely a contraindication.

Adverse effects of common to all vasodilators include hypotension, hypoperfusion of areas of vascular compromise (for example, mesenteric ischemia or angina), and increased pulmonary shunt. Reflex tachycardia may also be a problem. Adverse effects associated with specific agents include thiocyanate toxicity which can be seen during the use of nitroprusside in renal failure, ethanol toxicity when ethanol-diluted nitroglycerin is infused at high doses, methemoglobinemia which can be seen rarely with all nitrodlators, renal failure following administration of angiotensin-converting enzyme inhibitors in patients with bilateral renal artery stenosis, and drug-induced lupus with hydralazine.

a) **Sodium nitroprusside:** This drug is a balanced arteriolar and venous vasodilator which directly activates vascular smooth muscle guanylate cyclase producing cGMP. It contains cyanide as part of its intrinsic structure. It’s arteriolar dilating properties lead to a decrease in vascular resistance, and MAP. HR frequently increases on a reflex basis. It’s venodilating properties results in a decrease of PWP and CVP. Arteriolar dilating properties dominate the overall hemodynamic effect with an increase in stroke volume.
and CO. It also decreases myocardial work and oxygen demand while potentially increasing coronary flow (although steal may be a problem in coronary artery disease). There is no effect on non-vascular smooth muscle at therapeutic doses.

Specific indications include normotensive or hypertensive congestive heart failure (particularly in the setting of MR, AI or VSD), hypertensive urgency or emergency, and aortic dissection (in combination with beta-blockade to blunt reflex tachycardia). For congestive heart failure with hypertension, 0.1-0.2 ug/kg/min is started and titrated upwards with similar increments every few minutes. A 20-50% decrease in PWP and increase in CO can be targeted. Failure to reach these targets with the development of hypotension suggests a suboptimal response. A dose of 1-2 ug/kg/min is usually sufficient. For hypertensive emergencies, nitroprusside is the usual drug of choice. A dose of 0.5 to 1 ug/kg/min can be initiated with a maximum recommended infusion of 10 ug/kg/min. An arterial line is preferred. Resistance is rare.

The half-life of nitroprusside is approximately 1 minute with steady state concentrations being achieved within 3-4 min. Nitroprusside is initially metabolized to cyanide and then to thiocyanate in the liver. Thiocyanate is excreted in the urine with a half-life of 4-7 days.

The most common side effect is hypotension and is easily handled by dose reduction. Hypotension at low dose suggests the possibility of hypovolemia. Thiocyanate toxicity presents with tinnitus, blurred vision, confusion, psychosis, hyper-reflexia, seizures and
lactic acidosis with an anion gap. Such toxicity is limited to situations involving prolonged, high dose exposure particularly in the setting of renal failure (<3 ug/kg/min for up to 3 days is considered safe). The anion gap and thiocyanate levels should be monitored if high dose infusions continue for more than 3 days and in the setting of renal failure. Toxicity can be managed by following the anion gap, lactate and thiocyanate (<10 mg/dL is considered safe) levels. Thiosulfate, sodium nitrate and hydroxycobalmin enhance conversion of cyanide to thiocyanate and promote renal excretion. Other potential adverse effects include rebound with abrupt discontinuation, methemoglobinemia, hypothyroidism and thrombocytopenia.

b) Nitroglycerin: Like nitroprusside, nitroglycerin directly activates vascular smooth muscle guanylate cyclase producing cGMP. Unlike nitroprusside, nitroglycerin has dominantly venodilating properties (decreased PWP and CVP; no change MAP) although at high doses, arteriolar dilating properties (decreased MAP and SVR) also become clinically relevant. Because venodilating properties dominate, cardiac output falls unless filling pressure are maintained by fluid administration. Other effects include coronary artery vasodilatation (somewhat controversial as to whether this explains it anti-anginal action), mild relaxation on non-vascular smooth muscle, tachycardia or bradycardia, headache, hypotension (usually dose related), methemoglobinemia and occasionally ethanol toxicity (from high dose administration of NTG in an ethanol base).

The half-life is 2-2.5 minutes with steady state being reached in 6-10 minutes. A dosage of 0.1 ug/kg/min (10 ug/min) is typically started and titrated every 5-10 minutes to effect.
A dose of 0.3-1.0 ug/kg/min (up to 30-100 ug/min) is typically sufficient for its antianginal effects. Doses greater than 1 ug/kg/min (>100 ug/min) are associated with increased arteriolar dilation and an antihypertensive effect. Nitroglycerin is indicated unstable angina, acute or evolving myocardial infarction, hypertensive urgency/emergency in the setting of significant cardiac ischemia, and post-op cardiac surgery hypertension. It is of note that nitroglycerin is absorbed by polyvinylchloride plastics which have been occasionally used for IV tubing.
Practice Questions

1) A 65 year old male vasculopath with hypertensive crisis and moderate chronic renal failure is started on nitroprusside for hypertensive crisis with congestive heart failure. Within 36 hours (Friday afternoon), hypertension is under good control and oral medications are initiated. However, on Friday evening (while you are visiting your in-law's), hypertension and congestive heart failure recur and the intern places your patient back on nitroprusside. When you round Monday afternoon your patient has developed a marked anion gap metabolic acidosis and is no longer orient to person or place. Your intern tells you that over the weekend blood pressure has risen despite nitroprusside and lactate levels have been climbing. The cause of lactic acidosis in this patient is most likely:

a) cardiogenic shock due to myocardial infarction
b) cardiogenic shock due to increased afterload (systolic dysfunction)
c) new onset septic shock
d) arteriolar shunting caused by toxic accumulation of nitroprusside
e) impaired oxygen metabolism of cells through accumulation of nitroprusside metabolites

2) A 73 year old woman with known CAD, hypertension and a previous inferior wall MI presents with a subacute anterior MI. She has had swelling of ankles and increasing shortness of breath the last 5 days. She has been taking increasing oral doses of her husband’s supply of Lasix (last 36 hours ago). Extremities are cool and underperfused...
but the patient is alert. A pulmonary artery catheter demonstrates a PWP of 15 mm Hg and a CI of 1.8 L/min/m^2. Blood pressure is 87/55. Your response should include:

a) immediate initiation of dopamine, followed by IABP placement
b) immediate initiation of dobutamine, followed by IABP placement
c) immediate IABP placement
d) careful fluid challenge followed by more fluids, dopamine or dobutamine depending on the response
e) immediate echocardiography to rule out a mechanical lesion

3) Which of the following is true?

a) nitroglycerin has minimal arteriolar vasodilating properties at all therapeutic doses
b) dopamine’s dopaminergic activity is lost at higher dose ranges
c) dobutamine is effective in the initial resuscitation of septic shock
d) milrinone is well tolerated in volume depleted patients
e) isoproterenol has some current therapeutic utility
**Key Points**

1) While increasing CO, Inotropes also typically decrease ventricular filling pressures without substantial effects on blood pressure.

2) While increasing blood pressure, vasopressors typically decrease CO and increase ventricular filling pressures.

3) Vasodilators can have variable effects on CO depending on whether or not venodilatation is prominent but blood pressure and ventricular filling pressures uniformly fall.

4) Many cardiotonic agents can have divergent hemodynamic effects depending on the patient’s intravascular volume.

5) Many cardiotonic agents have different cardiovascular response profiles at different drug infusion rates.


### TABLE 1

**Cardiotonic Drugs**

1) **Sympathomimetic Compounds**
   
a) **Catecholamines**
   
i) *Endogenous Catecholamines*  
   Epinephrine  
   Norepinephrine  
   Dopamine

   ii) *Synthetic Catecholamine*  
   Dobutamine  
   Isoproterenol  
   Dopexamine

b) **Non-Catecholamine Sympathomimetics**

   Metaraminol  
   Methoxamine  
   Ephedrine  
   Phenylephrine

2) **Nonadrenergic Inotropes**

   Calcium  
   Cardiac glycosides (digitalis, digoxin)  
   Phosphodiesterase III inhibitors (amrinone, milrinone, enoximone)  
   Glucagon

3) **Vasodilators**
<table>
<thead>
<tr>
<th>Inotropes</th>
<th>Vasopressors</th>
<th>Vasodilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechols</td>
<td></td>
<td>Nitrodiators</td>
</tr>
<tr>
<td>dopamine</td>
<td>dopamine</td>
<td>nitroglycerin</td>
</tr>
<tr>
<td>dobutamine</td>
<td>norepinephrine</td>
<td>nitroprusside</td>
</tr>
<tr>
<td>dopexamine</td>
<td>epinephrine</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>epinephrine</td>
<td>phenylephrine</td>
<td>captopril</td>
</tr>
<tr>
<td>isoproterenol</td>
<td>ephedrine</td>
<td>enalapril</td>
</tr>
<tr>
<td>PDI’s</td>
<td>methoxamine</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>amrinone</td>
<td>metaraminol</td>
<td>Ca channel blockers</td>
</tr>
<tr>
<td>milrinone</td>
<td></td>
<td>Phentolamine</td>
</tr>
<tr>
<td>enoximone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>digoxin/digitalis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# TABLE 3

## HEMODYNAMIC RESPONSE: CATECHOLAMINES AND BIPYRIDINES

<table>
<thead>
<tr>
<th>Catecholamine</th>
<th>Renal Perfusion</th>
<th>Cardiac Output</th>
<th>Total Peripheral Resistance</th>
<th>Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoproterenol</td>
<td>↑ cardiogenic or</td>
<td>↑</td>
<td>↓</td>
<td>↑ systolic</td>
</tr>
<tr>
<td></td>
<td>septic shock</td>
<td></td>
<td></td>
<td>↓ diastolic</td>
</tr>
<tr>
<td></td>
<td>↓ normotensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0</td>
<td>↑</td>
<td>↓</td>
<td>0 or ↑ (rare ↓)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>↑</td>
<td>↓ or ↑</td>
<td>↓↑</td>
<td>0 or ↑</td>
</tr>
<tr>
<td></td>
<td>(dose dependent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eprinephrine</td>
<td>↓</td>
<td>↑</td>
<td>↓ or ↑</td>
<td>↑ systolic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ diastolic</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>↓</td>
<td>0 or ↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Bipyridines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amironone</td>
<td>0</td>
<td>↑</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Milrinone</td>
<td>0</td>
<td>↑</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>0</td>
<td>↓</td>
<td>0 or ↑</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td></td>
<td>Blood Vessels</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------</td>
<td>----------------------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Contractility (Inotropic)</strong></td>
<td><strong>SA Node Rate (Chronotropic)</strong></td>
<td><strong>Vasoconstriction</strong></td>
<td><strong>Vasodilation</strong></td>
</tr>
<tr>
<td></td>
<td>$\beta_1$</td>
<td>$\beta_1$</td>
<td>$\alpha$</td>
<td>$\beta_2$</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+++ (dose dependent)</td>
<td>0 to + (dose dependent)</td>
<td>0 to + (dose dependent)</td>
<td>+</td>
</tr>
<tr>
<td>Dopamine</td>
<td>+++ (dose dependent)</td>
<td>+ to ++ (dose dependent)</td>
<td>+ to +++ (dose dependent)</td>
<td>0 to +</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++ (dose dependent)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>0</td>
</tr>
</tbody>
</table>
# TABLE 5

## CONDITIONS THAT ALTER RECEPTOR DENSITY AND AFFECT RESPONSE TO CATECHOLAMINES

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>RECEPTOR DENSITY CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>$\uparrow \beta$ (heart)*</td>
</tr>
<tr>
<td>Sepsis</td>
<td>$\downarrow \alpha$ (liver, vasculature)</td>
</tr>
<tr>
<td>Myocardial Ischemia</td>
<td>$\downarrow \beta_1 \uparrow \alpha$ (heart)</td>
</tr>
<tr>
<td>Asthma</td>
<td>$\downarrow \beta$ (lung, leukocytes)†</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>$\downarrow \beta$ (leukocytes)</td>
</tr>
<tr>
<td>Agonist administration</td>
<td>$\downarrow \alpha_1 \beta$ (heart, platelets, leukocytes)</td>
</tr>
<tr>
<td>Antagonist administration</td>
<td>$\uparrow \alpha_1 \beta$ (heart, platelets, leukocytes)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>$\uparrow \beta$ (heart)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>$\downarrow \beta$ (heart)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>$\uparrow \beta$ (heart, leukocytes)</td>
</tr>
</tbody>
</table>

$\uparrow$ Increased $\downarrow$ Decreased

* $\beta$-Adrenergic receptors are decreased in severe heart failure
  † If on $\beta$-agonist therapy for asthma
TABLE 6  
**Vasodilators**

**Arterial Vasodilators**
Hydralazine  
Calcium-channel blockers  
Phentolamine

**Venous Vasodilators**
Nitroglycerin (especially at low doses)

**Balanced Arterial & Venous Vasodilators**
Nitroprusside  
Prazosin  
Angiotensin-converting enzyme (ACE) inhibitor
Figure 1. Core structure of sympathomimetic amines. Reproduced with permission from Chernow B, Rainey TG, Lake CR: Endogenous and exogenous catecholamines in critical care medicine. Crit Care Med 1982; 10:409-416

Core structure of sympathomimetic amines

“Catechol”

Norepinephrine

Epinephrine

Dopamine

Isoproterenol

Dobutamine
Figure 2. Mechanism of action of sympathimetic amines
Figure 3. Idealized receptor dose response to dopamine with sequential recruitment of dopaminergic, β-adrenergic, and α-adrenergic activity.