Pharmacotherapy of the Failing Heart

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Acute or chronic heart failure inevitably results in acute or chronic circulatory shock. Appropriate clinical pharmacotherapy of the failing heart is aided by a concise hemodynamic analysis of its pathogenesis (1). A first step is to consider the systemic circulation as a simple circuit. The heart pumps blood into an arterial system, whose tone governs systemic vascular resistance (SVR) and determines afterload; a capillary bed that provides tissue nutrition and metabolite removal; and a venous system that governs venous return and determines preload.

Circulatory shock may be defined in simplest terms as inadequate perfusion of the vital capillary bed. It may be classified by its primary clinical manifestation as vasoconstricted shock or vasodilated shock, and analyzed hemodynamically by "Ohm's Law of the Circulation", i.e., blood pressure (BP) is the product of cardiac output (CO) and SVR:

$$BP = CO \times SVR$$

Vasoconstricted shock may be caused by cardiogenic shock or hypovolemic shock. The primary event is either pump failure or hypovolemia leading to a decrease in CO and hypotension ("low output shock"). The etiology of cardiogenic shock may be "pre-cardiac (e.g., cardiac tamponade), "intra-cardiac" (e.g., myocardial infarction) or "post-cardiac" (e.g., saddle pulmonary embolism). The consequences are identical. Profound hypotension triggers massive baroreceptor-induced sympathetic stimulation, resulting in diffuse arterial and venous constriction in an attempt to restore BP toward normal levels. At the arteriolar and venular level, there is constriction of the pre- and post-capillary sphincters that further impairs tissue perfusion.

The primary difference between cardiogenic and hypovolemic shock is the elevated and decreased central venous pressure (CVP), respectively. However, in severe hypovolemic shock, venoconstriction may be so intense as to actually elevate the CVP. Profound intravascular hypovolemia is revealed as soon as venoconstriction is reversed by the administration of sedation or anesthesia. Because the cerebral and coronary circulations are relatively devoid of α-adrenergic receptors, blood flow to the heart and brain is conserved at the expense of other vital organs, notably the kidney, gut, and lungs.

Vasodilated shock is most often associated with sepsis or the systemic inflammatory response syndrome (SIRS). The primary event is profound cutaneous vasodilation and decrease in SVR, in large part caused by diffuse macrophage activation of inducible nitric oxide synthase (iNOS) and massive release of nitric oxide. As a consequence of hypotension and baroreceptor-induced sympathetic stimulation, CO increases in an attempt to restore BP to normal levels ("high output shock"). However, the terms vasodilated shock and high output shock are, in fact, misnomers. A more accurate and descriptive term is distributive shock. Although SVR is decreased, it is not uniformly so. Many vascular beds (renal, splanchnic, and pulmonary) are severely vasoconstricted and become ischemic. Moreover, circulating depressant factors (including nitric oxide and tumor necrosis factor) cause substantial myocardial dysfunction and, when CO declines, result in decompensated shock.

Protracted shock of any etiology culminates in the accumulation of lactic acid, which dilates the more sensitive pre-capillary sphincter, allowing blood to reflow into the capillary bed but not out of it. Hydrostatic pressure builds up and increases capillary leak and interstitial edema, further impairing cellular nutrition. The blood that remains in the capillaries becomes increasingly viscous and sludges, triggering platelet activation and disseminated intravascular coagulation (DIC). Lactic acidosis and DIC are hallmarks of all forms of protracted shock. In protracted cardiogenic and hypovolemic shock, intracellular lactic acidosis results in catecholamine-resistant vasodilatory shock.

Principles of Hemodynamic Management

Natural History of the Failing Heart

The development of cardiogenic shock implies the loss of more than 40% of functioning myocardium. It may develop as a consequence of acute myocardial infarction, acute intraoperative ischemia, and reperfusion injury, especially during cardiopulmonary bypass

(CPB). Stunned myocardium refers to acute loss of function resulting from ischemia that may recover with time. Hibernating myocardium refers to chronic loss of function resulting from ischemia (usually identified by positron emission tomography [PET] scan) that may be recruitable with revascularization. End-stage heart disease resulting from ischemic, viral, or idiopathic cardiomyopathy ultimately culminates in a state of chronic cardiogenic shock with progressive multisystem organ dysfunction.

In chronic cardiomyopathy with sustained release (or administration) of catecholamines there is progressive β receptor down-regulation (2). In the normal myocardium approximately 80% of the inotropic response is mediated by β-1 receptors and 20% by β-2 receptors. In chronic cardiomyopathy the proportion mediated by β-2 receptors increases to 40%, and the response to β-1 adrenergic agents such as dopamine becomes progressively impaired, whereas that to β-2 agents such as dobutamine becomes progressively more important (3).

The Vicious Cycle of Ischemic Cardiogenic Shock

Ischemic cardiogenic shock that develops after CPB is a classic example of a vicious cycle. Decreased perfusion leads to cardiac injury, resulting in impaired compliance, decreased stroke volume, and tachycardia. Sinus tachycardia is an underestimated sign of acute myocardial injury and an important harbinger of increasing ischemia. Acute hypotension triggers a potent sympathetic response, and catecholamine release (or administration) further increases tachycardia, impairs myocardial oxygen balance, and exacerbates acute myocardial injury (1).

Once this cycle is established it cannot be broken by pharmacologic therapy, it can only be made worse. Increasing doses or potency of inotropic agents may increase contractility but further increases myocardial oxygen consumption. Adding or increasing doses of vasoconstrictors may enhance coronary perfusion pressure but at the expense of cardiac output and organ perfusion. The most effective intervention at this stage is insertion of an intra-aortic balloon pump (IABP) to provide counterpulsation, which can help to restore myocardial oxygen balance. The balloon is positioned distal to the left subclavian artery and inflated during diastole, and increases coronary perfusion pressure and myocardial oxygen supply, whereas deflation in late diastole and early systole decreases aortic pressure, afterload, and myocardial oxygen consumption. No combination of inotropic, vasodilator, or vasoconstrictor therapy can truly mimic the advantage provide by intra-aortic counterpulsation (4). On the other hand, the IABP is not a ventricular assist device; any increases in cardiac output reflect enhanced ventricular compliance and contractility as a consequence of reduction in acute ischemia.

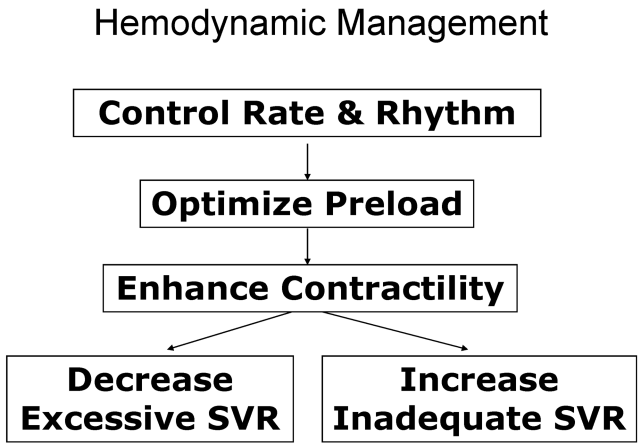

Figure 1. A systematic approach to hemodynamic management. The milieu (acid-base and electrolyte balance), rhythm and preload should be optimized prior to choosing an inotropic agent. Choice of inotropic agent may be predicated on afterload conditions, i.e., an inodilator when systemic vascular resistance (SVR) is high, an inoconstrictor when SVR is low. Alternatively, a vasodilator (e.g., sodium nitroprusside) could be titrated separately to decrease high SVR when combined with an inoconstrictor; a vasoconstrictor (norepinephrine, AVP) could be titrated separately to increase low SVR when combined with an inodilator (dobutamine, milrinone).

A Systematic Approach to Hemodynamic Management

Hemodynamic management of impaired cardiac output should be organized in an orderly sequence, with reassessment to response after each intervention (Fig. 1). Even before this is commenced, efforts should be directed at creating a stable milieu and reversing acid-base and electrolyte disorders that may themselves impair cardiac function (e.g., hypoxemia, acidosis, hyperkalemia). Establishment of near-normal rate and rhythm is an essential first step, after which the subsequent interventions may be applied. Inadequate preload should be augmented and excessive preload decreased. Inotropic support is then applied, with reduction of increased SVR, or augmentation of inadequate SVR (5).

Inotropic Agents

Beta-Adrenergic Agonists

Beta-adrenergic agents are administered to enhance inotropy (force of contraction) but will also enhance chronotropy (heart rate), dromotropy (conduction velocity), and bathmotropy (ectopic beats and rhythms). The dromotropic effect is illustrated by the increase in

Table 1. β-Adrenergic Agents

Inoconstrictors: Inotropic action + peripheral α-1 adrenergic induced vasoconstriction					
	DA-1	DA-2	Beta-1	Beta-2	Alpha
Norepinephrine	0	0	+++	0	+++
Epinephrine	0	0	+++	++	+++
Dopamine	++	+	++	±	+++
Inodilators: Inotropic action + peripheral β-2 adrenergic induced vasodilation					
	DA-1	DA-2	Beta-1	Beta-2	Alpha
Dobutamine	0	0	+++	+++	0
Dopexamine	++	+	±	+++	0
Isoproterenol	0	0	+++	+++	0

DA = dopaminergic; Beta = β-adrenergic; Alpha = peripheral α-1 and α-2 adrenergic.

atrioventricular conduction and heart rate when catecholamines are administered to patients with atrial fibrillation. It should be expected that any β-adrenergic agent may induce tachycardia and tachyarrhythmias.

It is useful to classify β-adrenergic agents according to their effect on the peripheral circulation (Table 1). Inoconstrictors confer inotropy with α-adrenergic induced vasoconstriction, and inodilators confer inotropy with β-2 adrenergic-induced vasodilation.

Inoconstrictors include the naturally occurring catecholamines, norepinephrine, epinephrine, and dopamine. Norepinephrine is a potent, direct-acting β-1 adrenergic agent as well as an α-adrenergic vasoconstrictor. This makes it especially useful in states of vasodilated shock, where myocardial depression and profound vasodilation coexist. Because of its β-2 adrenergic action, epinephrine has a more unpredictable effect on SVR and is more prone to precipitate tachycardia and tachyarrhythmias.

The β adrenergic inodilators are all synthetic derivatives of dopamine and include dobutamine, dopexamine, and isoproterenol. Dobutamine is a potent direct-acting β adrenergic agent, whose β-2 mediated inotropic effect is particularly helpful in chronic cardiomyopathy (6). Its β-2 vasodilator effects also provide pulmonary artery vasodilation that may be helpful in weaning patients off CPB with acute right ventricular failure. Dopexamine is an investigational agent (available in Europe) that acts predominantly through β-2 mediated afterload reduction, with secondary release of norepinephrine that enhances its inotropic effect (7). Isoproterenol is limited by its potent chronotropic effect, which precedes its inotropic effect, and its use is largely confined to pharmacologic pacing.

Phosphodiesterase Inhibitors

Administration of phosphodiesterase (PDE) inhibitors has particular advantages in patients with cardiomyopathy or protracted cardiac failure, who have down-regulation of β receptors (8). Their action in preventing the breakdown of cyclic adenosine monophosphate (cAMP) is independent of the β receptor (9). In cardiac muscle the increase in cAMP promotes intracellular calcium release and muscle contraction (inotropic effect). In smooth muscle it has the opposite effect, preventing the release of calcium and promoting smooth muscle relaxation (vasodilation). The PDE inhibitors function as true inodilators and provide afterload reduction for both the left and right ventricles. They also promote diastolic relaxation (positive lusitropic effect), which enhances myocardial oxygen balance. They are less bathmotropic (arrhythmogenic) than catecholamines. Finally, and very importantly, their combination with catecholamines provides a synergistic increase in stroke volume, i.e., cAMP is increased by a combination of increased production (catecholamines) and decreased breakdown (PDE inhibition) (10).

Milrinone has largely replaced amrinone as the archetype PDE inhibitor. It is about 15 times more potent than amrinone, there is a lower risk of thrombocytopenia, and it has a shorter elimination half life (2.4 h versus 5.8 h). Unlike amrinone, milrinone does not decompose in dextrose solutions and does not need protection from the light, and it contains no bisulfite, which can induce asthma in susceptible subjects.

The hemodynamic effects of milrinone are mediated by a combination of afterload reduction and enhanced inotropy and result in about 30% increase in cardiac output (11). Compared with dobutamine, its effects are greater on the SVR but there is less tachycardia and fewer tachyarrhythmias.

The loading dose of milrinone is 50 $\mu g/kg$ and should be administered over at least 10 min, together with rapid fluid administration to compensate for the onset of systemic vasodilation. Acute hypotension is likely when patients are hypovolemic or have severely impaired ventricular function. The loading infusion should be given over a longer period of time (e.g., 20–30 min) in unstable patients. In the intensive care unit (ICU), we almost always withhold the loading dose because it has been demonstrated that institution of the maintenance dose without loading achieves a clinical effect within 30 min (12). The maintenance infusion is usually started at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, but it is initiated at lower doses when patients are very unstable.

In our practice, we commonly infuse a combination of milrinone (0.25–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) plus dobutamine (2–5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for synergistic inodilator effects, especially in situations of biventricular or predominantly right ventricular failure. The combined vasodilator effect is such that the SVR (and blood pressure) requires support with norepinephrine, plus or minus AVP (Fig. 2).

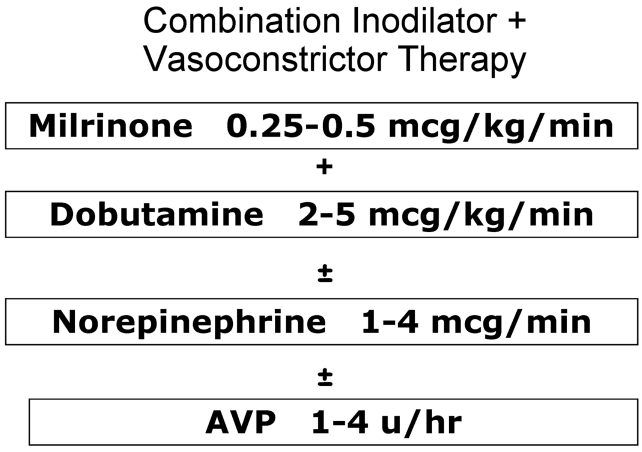

Figure 2. Combined inodilator and vasoconstrictor therapy. Milrinone may be combined with dobutamine in the dose ranges shown, to provide a synergistic inotropic effect. In consequence, lower doses of either agent are required, resulting in less vasodilation (milrinone) or tachycardia (dobutamine). The enhanced pulmonary vasodilator effects are beneficial in right heart failure, especially with coexistent pulmonary hypertension. However, their combined systemic vasodilator effects induce hypotension. Administration of norepinephrine not only counteracts hypotension by its α-adrenergic vasoconstrictor effects, but its β-agonist component acts in further synergy with milrinone's inotropic action. When heart failure is associated with catecholamine-resistant vasodilated shock, the addition of arginine vasopressin (AVP) restores responsiveness to norepinephrine and decreases its requirement. For details, see text.

Milrinone is rapidly distributed in the plasma but, unlike catecholamines, it is much more slowly eliminated and depends on the kidneys for approximately 40% of its excretion. It accumulates with time and has a long duration of action. In the ICU we usually wean the maintenance infusion over 24–48 h (e.g., from 0.5 to 0.25, then to 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$), especially in patients with renal dysfunction (13). A final note: these drugs are not cheap. In the United States, a 48-h course of milrinone has an acquisition cost of about $500.

Vasodilator Agents

Natriuretic Peptides

A series of natriuretic peptides are produced in the heart and great vessels that promote the formation of cyclic guanosine monophosphate (cGMP) (14). Their actions are to oppose the vasoconstrictor and salt-retaining effects of norepinephrine and angiotensin II and inhibit the release of renin, aldosterone, and the antidiuretic hormone, arginine vasopressin (AVP).

Atrial natriuretic peptide (ANP, now called A-type natriuretic peptide) is synthesized in specialized atrial myocytes and is released in response to atrial stretch. Based on promising preliminary animal and human investigation, a human recombinant analog of ANP, anaritide, underwent considerable study as a possible rescue agent for acute renal failure. Unfortunately it failed to demonstrate effectiveness, possibly because of excessive hypotension induced by its vasodilator effects (15).

Brain natriuretic peptide (BNP, now called B-type natriuretic peptide) is synthesized in the ventricles and is released in response to ventricular dilation. The baseline level of endogenous BNP correlates with long-term risk of death, heart failure, and myocardial infarction; plasma levels >400 pg/mL correlate very strongly with the diagnosis of acute heart failure (16).

C-type natriuretic peptide is synthesized in the aorta and great vessels.

Nesiritide

Nesiritide (human recombinant B-type natriuretic peptide, BNP) is a potent vasodilator with equivalent effects on the venous and arterial circuits. This provides a decrease in cardiac afterload and preload, which has a favorable hemodynamic effect in patients with congestive heart failure (CHF).

Short-term infusion of nesiritide in CHF decreases left and right ventricular preload and afterload, enhances cardiac index and stroke volume, and relieves pulmonary congestion and edema (17). It compares favorably with nitroglycerin, and long-term mortality and health care costs are decreased compared with dobutamine infusion. It is not pro-arrhythmogenic and its actions are not altered by the concomitant use of β blockers. In some patients nesiritide has a marked diuretic effect, with relief of anasarca, but this is not consistent, perhaps because of a concomitant decrease in blood pressure.

Acute hypotension is the most consistent side effect of nesiritide, and this may decrease renal perfusion and glomerular filtration rate (GFR) (18). It is interesting to speculate whether this could be reversed by the simultaneous administration of arginine vasopressin (AVP).

Studies are currently underway to evaluate the effects of perioperative nesiritide infusion on hemodynamic function, pulmonary vascular resistance, and renal function in patients with CHF undergoing cardiac surgery.

Vasoconstrictor Agents

Pathogenesis of Vasodilated Shock

It seems counterintuitive to use vasoconstrictor drugs for the failing heart. However, it is important to appreciate how commonly the contact activation syndrome complicates heart failure after CPB and in the postoperative period. It is characterized by an acute

inflammatory syndrome, coagulopathy, refractory vasodilation, and anasarca. Contact with an abnormal surface (e.g., CPB, ventricular assist device) activates Hageman Factor (Factor XII), which simultaneously activates the pathways of intrinsic coagulation (consumption coagulopathy), fibrinolysis (bleeding), and complement (vasodilation and capillary leak). These patients may develop catecholamine-resistant vasodilatory shock (CRVS), with persistent vasodilated hypotension despite high doses of norepinephrine or epinephrine.

Landry (19) discovered serendipitously that in patients with CRVS, a low-dose infusion of AVP (0.5–4 u/h) results in remarkable improvement in blood pressure and urine flow, allowing rapid tapering of catecholamines.

Actions of AVP in Vasodilated Shock

Restoration of Catecholamine Sensitivity. Vasoconstrictors such as norepinephrine and angiotensin stimulate G-protein coupled endothelial receptors that open cell membrane calcium channels and promote an influx of calcium. This, together with the release of calcium from intracellular stores, activates a kinase that enhances the phosphorylation of myosin and results in muscle contraction and vasoconstriction. In the presence of intracellular acidosis, lactate accumulation, and ATP depletion, membrane potassium-adenosine triphosphate (K_{ATP}) channels open and allow an efflux of potassium. This hyperpolarizes the membrane and closes the calcium channels, resulting in vasodilation that is refractory to norepinephrine. There is evidence that AVP binds to the K_{ATP} channel. In so doing, it closes it, reverses membrane hyperpolarization, reopens calcium channel AVP, and restores α-1 receptor sensitivity to norepinephrine (20).

Reversal of Acute AVP Deficiency. Normally, AVP exerts an antidiuretic effect on V_2-receptors in the distal renal tubule and collecting duct in response to tiny (1%) elevations in serum osmolality. Plasma AVP over the range of 1 through 5 pg/mL increases urine osmolality from 300 to 1200 mOsm/kg. Severe hypotension induces a baroreceptor response that releases large amounts of AVP from the posterior pituitary. Plasma AVP of 10–200 pg/mL exerts a vasoconstrictor effect on V_1-receptors in vasculature and helps to restore blood pressure. However, patients with CRVS have paradoxically low plasma AVP (approximately 3 pg/mL) (21). In animal models of hemorrhagic shock, AVP stores in the posterior pituitary become depleted within 1 h of the induction of profound hypotension (20). We have observed that infusion of AVP at doses of 2–6 u/h results in a plasma AVP of around 30–40 pg/mL, i.e., commensurate with the normal baroreceptor response to hypotension.

Use of AVP in Catecholamine-Resistant Vasodilated Shock (CRVS). Infusion of low-dose AVP (1–4 u/h) is indicated when heart failure is associated with CRVS. This is characterized by warm peripheries and hemodynamic evidence of low SVR, despite increasing doses of vasoconstrictors (e.g., norepinephrine >3 μg/min). As elucidated above, it may be associated with the contact activation syndrome, protracted cardiogenic shock with acidosis, or AVP depletion, or as a consequence of high-dose inodilator therapy (22). Unlike high-dose norepinephrine, low-dose AVP does not induce pulmonary vasoconstriction or renal afferent arteriolar constriction. Its use may therefore be favorable in patients with CRVS associated with pulmonary hypertension or oliguria.

We consider adding AVP to norepinephrine only when the dose of the latter starts to exceed 3 μg/min, and attempt to wean and discontinue AVP when norepinephrine requirements decline (i.e., "last on, first off"). Once the indications for its use are met, we prepare AVP as 1 u/mL, infused into a freely flowing central venous line. We start at 1 u/h (approximately 0.016 u/min) and, if necessary, increase AVP in increments of 1 u/h to a maximum infusion rate of 4 u/h (0.07 u/min). In life-threatening situations we will infuse AVP up to 6 u/h (0.1 u/min).

There are important caveats regarding infusion of AVP. It is contraindicated in vasoconstricted shock (i.e., low cardiac output associated with high SVR). It should not be used to "make blood pressure" in hypotensive patients unless they are demonstrated to have the criteria of CRVS. Inappropriate use or excessive dosing (>6 u/h) of AVP may lead to acral vasoconstriction, "blue fingers and toes" and even cutaneous necrosis. Higher doses may also cause coronary and mesenteric vasoconstriction.

References

1. Stafford Smith M, Kaemmer DD, Sladen RN. Low cardiac output states: drugs, intra-aortic balloon and ventricular assist devices. In: Youngberg JA, Lake CL, Roizen MF, Wilson RS, eds. Cardiac, vascular and thoracic anesthesia. New York: Churchill Livingstone, 2000:436–65.
2. Bristow MR, Ginsburg R, Minobe W. Decreased catecholamine sensitivity and B-adrenergic-receptor density in failing human hearts. N Engl J Med 1982;307:205–11.
3. Brodde OE, Schuler S, Kretsch R, et al. Regional distribution of β-adrenoceptors in the human heart: coexistence of function of β 1- and β 2-adrenoceptors in both atria and ventricles in severe congestive cardiomyopathy. J Cardiovasc Pharmacol 1986;8:1235–42.
4. Kontoyannis DA, Nanas JN, Toumanidis ST, Stamatelopoulos SF. Severe cardiogenic shock, after cardioversion, reversed by the intraaortic balloon pump. Intensive Care Med 2000;26:649.
5. Tempe DK, Virmani S. Pharmacologic support of circulation in patients undergoing cardiac surgery. J Indian Med Assoc 1999; 97:411–8.
6. Majerus TC, Dasta JF, Bauman JL, et al. Dobutamine: ten years later. Pharmacotherapy 1989;9:245–59.
7. Fitton A, Benfield P. Dopexamine hydrochloride: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in acute cardiac insufficiency. Drugs 1990;39:308–30.

8. Siostrzonek P, Koreny M, Delle-Karth G, et al. Milrinone therapy in catecholamine-dependent critically ill patients with heart failure. Acta Anaesthesiol Scand 2000;44:403–9.
9. Alousi AA, Johnson DC. Pharmacology of the bipyridines: amrinone and milrinone. Circulation 1986;73:III10–24.
10. Royster RL, Butterworth JF, Prielipp RC, et al. Combined inotropic effects of amrinone and epinephrine after cardiopulmonary bypass in humans. Anesth Analg 1993;77:662–72.
11. Shipley JB, Tolman D, Hastillo A, Hess ML. Milrinone: basic and clinical pharmacology and acute and chronic management. Am J Med Sci 1996;311:286–91.
12. Baruch L, Patacsil P, Hameed A, et al. Pharmacodynamic effects of milrinone with and without a bolus loading infusion. Am Heart J 2001;141:266–73.
13. Taniguchi T, Shibata K, Saito S, et al. Pharmacokinetics of milrinone in patients with congestive heart failure during continuous venovenous hemofiltration. Intensive Care Med 2000;26:1089–93.
14. Baughman KL. B-type natriuretic peptide: a window to the heart. N Engl J Med 2002;347:158–9.
15. Lewis J, Salem MM, Chertow GM, et al. and the Anaritide Acute Renal Failure Study Group: Atrial natriuretic factor in oliguric acute renal failure. Am J Kidney Dis 2000;36:767–74.
16. McCullough PA, Omland T, Maisel AS. B-type natriuretic peptides: a diagnostic breakthrough for clinicians. Rev Cardiovasc Med 2003;4:72–80.
17. Abraham WT, Lowes BD, Ferguson DA, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. J Card Fail 1998;4:37–44.
18. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation 2005;111:1487–91.
19. Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory septic shock. Crit Care Med 1997;25:1279–82.
20. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345:588–95.
21. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997;95:1122–5.
22. Gold J, Cullinane S, Chen J, et al. Vasopressin in the treatment of milrinone-induced hypotension in severe heart failure. Am J Cardiol 2000;85:506–8, A11.