Managing the Hemodynamically Unstable Patient

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Learning Objectives:

1. To describe the pathogenesis of acute postoperative heart failure and cardiogenic shock
2. To develop an algorithm for hemodynamic management
3. To review the role beta-adrenergic agents and phosphodiesterase inhibiting agents for inotropic support
4. To appreciate the pathogenesis and rationale for management of associated vasodilatory shock.

Introduction, and some Caveats

Postoperative heart failure may be encountered as (1) acute cardiogenic shock - a consequence of acute intraoperative ischemia, reperfusion injury and stunned myocardium; (2) as end-stage heart disease - a continuation of chronic heart failure or inability to recruit hibernating myocardium; (3) acute on chronic heart failure. Each presents its own challenges.

Cardiogenic shock implies the loss of > 40% of functioning myocardium, and may complicate acute myocardial infarction, acute intraoperative ischemia and reperfusion injury during CPB. Stunned myocardium refers to acute loss of function due to ischemia that usually recovers within a few hours or days. Hibernating myocardium refers to chronic loss of function due to ischemia (usually identified by PET scan) that may be recruitable with revascularization. End-stage heart disease due to ischemic, viral or idiopathic cardiomyopathy ultimately culminates in a state of chronic cardiogenic shock with progressive multisystem organ dysfunction.

Ischemic cardiogenic shock after CPB is a classic example of a vicious cycle. Decreased perfusion leads to cardiac injury, resulting in decreased stroke volume and hypotension. Catecholamine release (or administration) induces tachycardia that further impairs myocardial oxygen balance and exacerbates acute myocardial injury. Pharmacologic interventions may not be able to reverse this situation and intra-aortic balloon counterpulsation must be considered.

Chronic cardiomyopathy, with elevated endogenous or exogenous catecholamines, is associated with progressive beta receptor down-regulation. Normally, the ratio of inotropic response is mediated by beta-1 vs. beta-2 receptors is 80:20. In chronic cardiomyopathy, this changes to 60:40. Thus the response to beta-1 adrenergic agents (e.g. dopamine) becomes progressively impaired, while that to beta-2 agents (e.g. dobutamine) becomes progressively more important.

An Algorithmic Approach to Hemodynamic Management

Hemodynamic management of impaired cardiac output should be organized in an orderly sequence, with reassessment to response at each step. First, correct abnormalities of the milieu that may prevent any hemodynamic interventions from being effective:
these include acidosis, hyperkalemia, hypoxemia and hypercarbia. Establishment of normal rate and rhythm is an essential step in creating a stable platform on which the subsequent interventions may be applied. Inadequate preload should be augmented, excessive preload decreased. Inotropic support is then applied, with reduction of increased SVR, or augmentation of inadequate SVR.

**Inotropic Support**

*Beta Adrenergic Agonists*

Beta-adrenergic agents enhance inotropy (force of contraction), chronotropy (heart rate), dromotropy (conduction velocity) and bathmotropy (ectopic beats and rhythms). The dromotropic effect is illustrated by catecholamine-induced increase in A-V conduction and heart rate in atrial fibrillation. Any beta-adrenergic agent may induce tachycardia and tachyarrhythmias.

It is useful to classify beta-adrenergic agents according to their effect on the peripheral circulation. *Inoconstrictors* confer inotropy with alpha-adrenergic induced vasoconstriction, and *inodilators* confer inotropy with beta-2 adrenergic induced vasodilation.

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

The beta adrenergic inodilators are all synthetic derivatives of dopamine, and include dobutamine, dopexamine and isoproterenol. Dobutamine is a potent direct acting beta adrenergic agent, whose beta-2 mediated inotropic effect is particularly helpful in chronic cardiomyopathy. Its beta-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) which acts predominantly through beta-2 mediated afterload reduction, with secondary release of norepinephrine that enhances its inotropic effect. Isoproterenol is limited by its potent chronotropic effect, which precedes its inotropic effect, and its use is largely confined to pharmacologic pacing.

*Phosphodiesterase (PDE) Inhibitors*

PDE inhibitors have particular advantages in patients with protracted cardiac failure, who have down-regulation of beta receptors. Their action in preventing the breakdown of cyclic adenosine monophosphate (cAMP) is independent of the beta receptor. 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).

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 hrs vs 5.8 hrs). 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 loading dose, which should be administered over at least 10 min, is 50 µg/kg, and the maintenance infusion ranges from 0.375 - 0.75 µg/kg/min.

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. Compared to dobutamine, its effects are greater on the SVR but there is less tachycardia and fewer tachyarrhythmias.

There are certain limitations and caveats with the use of PDE inhibitors. Careful loading is required because acute hypotension can occur, especially in hypovolemic patients. Fluid challenges should be administered at the first signs of hypotension, and the loading infusion should be given over a longer period of time (e.g. 20-30 min) in unstable patients. Because of the large volume of distribution, the loading dose should be increased when it is given during CPB. Institution of the maintenance dose without loading achieves a clinical effect within 30 min.

Although milrinone is rapidly redistributed, unlike catecholamines it is much more slowly eliminated and depends on the kidneys for about 40% of its excretion. It accumulates with time and has a long duration of action, especially in patients with renal dysfunction, in whom the maintenance dose should be decreased. Finally, these drugs are not cheap. In the US, a 48 hour course of milrinone has an acquisition cost of about $500.

**Natriuretic Peptides**

A series of natriuretic peptides are produced in the heart and great vessels that promote the formation of cyclic GMP, which opposes the vasoconstrictor and salt-retaining effects of norepinephrine and angiotensin II, and inhibits renin, aldosterone and AVP release.

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 ARF. Unfortunately it failed to demonstrate effectiveness, possibly because of excessive hypotension induced by its vasodilator effects.

B-type natriuretic peptide (BNP) is synthesized in the ventricles and is released in response to ventricular dilation. Rapid assay of BNP is now widely used in the ED for the diagnosis of acute heart failure (BNP > 300 pg/L). The baseline level of endogenous BNP correlates with long-term risk of death, heart failure and myocardial infarction. There is increasing evidence that it is an independent predictor of cardiac outcome after cardiac and non-cardiac surgery.
C-type natriuretic peptide (CNP) is synthesized in the aorta and great vessels, and urodilatin is synthesized in the kidney and lower urinary tract.

**Nesiritide**

Nesiritide is the human recombinant formulation of BNP, and has been approved by the FDA for the parenteral treatment of patients with advanced decompensated heart failure (ADCHF). In these patients it provides preload and afterload reduction, enhances cardiac function, and also can promote a sustained diuresis with improvement in pulmonary congestion, edema and anasarca. It compares favorably with nitroglycerin, and long term mortality and health care costs are decreased compared to dobutamine infusion. It is not proarrhythmogenic and its actions are not altered by the concomitant use of beta-blockers.

The major adverse effect is dose-related hypotension, which can limit diuresis and impair renal function. Recently, there has been considerable controversy elicited by implications that nesiritide may adversely affect renal function in ADCHF. A prospective study on 489 patients with ADCHF and renal insufficiency (SCr ≥ 2 mg/dL) found that, compared with nitroglycerin, nesiritide improved preload and dyspnea while preserving renal function. However, in a small, blinded, controlled study on patients with ADCHF and worsening renal function (SCr increasing from 1.5 to 12.8 mg/dL), nesiritide infusion did not improve renal function. Finally, a retrospective meta-analysis of 5 studies including 1269 patients with ADCHF, found that nesiritide infusion, even at low doses, was associated with a significantly increased risk of worsening renal function. However there was no indifference in the need for renal replacement therapy.

**Nesiritide and Cardiac Surgery**

We examined the effects of postoperative nesiritide infusion on hemodynamic and renal function in a prospective open-label study on patients with CHF undergoing cardiac surgery, and found that it induced a significant diuresis in the first 12 hrs. Subsequently, we participated in a multicenter randomized placebo-controlled study (Natrecor Administered Peri-anesthesia in CT surgery, NAPA) examining the effects of nesiritide infusion 0.01 mcg/kg/min administered from induction of anesthesia to 24-96 hrs after surgery. Nesiritide infusion had no significant hemodynamic effect but there was a significant improvement in postoperative SCr as well as six month mortality. The mechanisms for these observed benefits has not been elucidated.

**Pharmacotherapy of Vasodilatory Shock**

Vasodilatory shock describes a clinical entity characterized by severe hypotension caused by refractory vasodilation. It may accompany heart failure, especially in protracted cardiogenic shock, after prolonged CPB or ventricular assist device (VAD) insertion, or with the use of milrinone.

There are now considered to be at least three important mechanisms of vasodilatory shock: (1) opening of potassium-adenosine triphosphate (K\textsubscript{ATP}) channels; (2) acute arginine vasopressin (AVP) deficiency and (3) widespread activation of inducible nitric oxide synthase (iNOS) and massive release of nitric oxide.
**Opening of $K_{ATP}$ Channels**

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 $K_{ATP}$ 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.

**Acute AVP Deficiency**

Landry et al. serendipitously found that relatively modest dose AVP infusion (0.5 - 6 units/hr) results in remarkable improvement in blood pressure and urine flow in patients with vasodilated septic shock, allowing rapid tapering of catecholamines.

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/L 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 through 200 pg/L exerts a vasoconstrictor effect on $V_1$-receptors in vasculature and helps to restore blood pressure.

Patients in severe vasodilated septic shock have paradoxically low plasma AVP (about 3 pg/L). In animal models of hemorrhagic shock. AVP stores in the posterior pituitary become quite depleted that within an hour of the induction of profound hypotension. Thus, the response to infused AVP is in part accounted for by the restoration of plasma AVP to appropriate levels for the degree of hypotension.

In addition, AVP appears to block the $K_{ATP}$ channel, thereby restoring membrane polarity and vascular responsiveness to catecholamines and angiotensin. AVP also has a salutary effect on renal function because it preferentially constricts the efferent arteriole, thereby enhancing glomerular filtration pressure, filtration rate and urinary flow.

There are certain important caveats regarding infusion of AVP. It should not be used to “make blood pressure” in situations of low cardiac output or hypovolemia. Excessive dosing may lead to unwanted acral vasoconstriction, “blue fingers and toes” and even necrosis. High doses may also cause unwanted coronary and mesenteric vasoconstriction.

**Massive Release of Nitric Oxide**

Endogenous nitric oxide (NO) is formed by the action of nitric oxide synthase (NOS) on the amino acid arginine. Nitric oxide in turn activates soluble guanosine cyclase (sGC), which acts on guanosine triphosphate (GTP) to produce cyclic guanosine monophosphate (cGMP), which induces vasodilation. A form of constitutive NOS, endothelial NOS (eNOS) is responsible for the continuous (“tonic”) production of low levels of nitric oxide that maintain vascular patency.

Inducible NOS (iNOS) is activated by the action of cytokines on macrophages in sepsis or the systemic inflammatory response syndrome (SIRS) and produces huge amounts of nitric oxide over protracted periods of time. A similar situation is encountered after prolonged cardiogenic shock, CPB or VAD insertion. This induces
profound systemic vasodilation refractory to norepinephrine, and also inhibits beta-
adrenergic inotropy and results in myocardial depression. In animal models of sepsis, hypotension is reversed and response to catecholamines restored by NOS inhibitors. However, mortality is increased because non-selective NOS inhibitors (e.g. L-NAME, L-NMMA) also suppress eNOS, thus impairing tonic vasodilation and tissue oxygen delivery. Studies using selective iNOS inhibitors show promise in decreasing the inflammatory and vasodilator response to sepsis while maintaining tissue oxygen delivery. Methylene blue is a dye that crosses cell membranes and competes with nitric oxide for the heme moiety of soluble guanylate cyclase and inhibits the formation of cGMP. It appears to be more selective for inducible NOS and has been used with some success in vasoplegic states refractory to standard vasopressors in doses of 0.5 mg/kg over 20 minutes.

References