LEARNER OBJECTIVES:

- Update on mechanical circulatory support with the ventricular assist device: LVAD, RVAD and BiVAD.
- Update on management of elevated pulmonary vascular resistance, including inhaled nitric oxide, prostacyclin and other pharmacotherapy.
- Update on management of vasodilatory shock, including vasopressin, selective vasopressin analogs and methylene blue.
- Update on renal protection, including new biomarkers and the evidence basis for pharmacologic interventions.

THE VENTRICULAR ASSIST DEVICE (VAD)

Indications

There has been considerable progress in the utilization and effectiveness of the ventricular assist device (VAD) as a means of support for the patient with end-stage heart disease (ESHD) (Table 1). The VAD may be placed¹ as a bridge to decision, i.e. as a temporizing, life-saving intervention during a crisis to provide support until a decision can be made regarding further definitive therapy;² as a bridge to a bridge, i.e. as a short-term rescue device that is emergently placed to provide support until a longer-term, larger device can be placed;³ as a bridge to recovery, i.e. to provide life-saving support during an acute crisis, until the ventricle recovers and the patient can be weaned off the VAD;⁴ as a bridge to transplant, considering that at least 50% of patients awaiting heart transplant would die because of inability to obtain a timely organ; and⁵ as destination therapy, in patients with ESHD who are not candidates for heart transplantation.

The VAD may be placed to support the left ventricle (LV), i.e. an LVAD, right ventricle (RV), i.e. an RVAD, or both ventricles (BiVAD). However, all internal long-term devices are currently available as an LVAD only.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Correction of Structural Abnormalities

Certain structural abnormalities must be corrected at the time of VAD implantation to avoid abnormal intracardiac circuits. Tricuspid regurgitation should be repaired to enhance RV function, which is especially important in a patient receiving an LVAD only. Aortic regurgitation must be corrected to prevent blood pumped from the outflow limb of the LVAD in the ascending aorta to recirculate back into the LV. Mitral stenosis must be corrected to facilitate ventricular (and VAD) filling from the left atrium. Patent foramen ovale, atrial and ventricular septal defects must be closed to avoid the development of a left to right shunt when the left atrium and LV are decompressed by the LVAD and become low pressure chambers.

Pulmonary Vascular Resistance

It is essential to control elevated pulmonary vascular resistance (PVR) in patients receiving a VAD. With an LVAD, an elevated PVR will compromise delivery of blood from the right to the left side of the heart, diminish LVAD filling and decrease LVAD output. It may also contribute to right heart failure in the unassisted right ventricle. With an RVAD, elevated PVR may result in excessive right sided atrial pressure. An update on the management of elevated PVR is provided in the next section of this Review Course.

Management of RV Function

Maintenance of effective RV function is essential to ensuring good outcome after LVAD placement.¹ Acute right heart failure (RHF) may occur in up to 40% of patients receiving an LVAD.² It is associated with an increased rate of reoperation for bleeding, postoperative acute kidney injury (AKI), ICU length of stay (LOS) and early mortality. Successful bridge to transplantation is impaired and about a third of the patients with RHF ultimately require an RVAD.

The principles of the management of right ventricular function¹ include¹ maintenance of RV coronary perfusion pressure by keeping mean arterial pressure (MAP) > 80 mmHg using vasopressor drugs;² avoidance of RV overload by keeping central venous pressure (CVP) as close to 10 mmHg as possible;³ control of elevated PVR and avoidance of excessive afterload by use of appropriate pulmonary vasodilator therapy;⁴ enhancement of RV contractility by administration of inodilator drugs (see below).

A fifth principle specific to newer LVADs is the avoidance of excessive LV emptying. Second and third generation LVADs provide non-pulsatile flow and maintain a parallel circuit of flow out of the native aorta. Excessive pump rates may cause the LV to empty, which induces leftward septal shift and RV dyskinesis. This may be revealed on transesophageal echocardiography (TEE) by conversion of the short-axis round LV to a “D”-shape induced by the flattened or convex intraventricular septum.¹

Inodilator Therapy

Inodilator therapy is usually provided by the phosphodiesterase (PDE) III inhibitor, milrinone, with or without superadded dopamine, a direct acting beta-1 and beta-2 agonist. These agents both increase cyclic adenosine monophosphate (cAMP),
the former by decreasing its breakdown and the latter by increasing its production. Milrinone’s vasodilator effects may be limiting and invariably require concomitant vasopressors administration; dobutamine preserves blood pressure but its chronotropic and bathmotropic effects promote arrhythmias. Combining a PDE inhibitor with a beta-adrenergic agonist provides superior enhancement of RV stroke volume than either drug used alone, and allows much lower dosage of each drug, with fewer side effects.

Levosimendan, a potent inodilator not currently available in the USA, acts independently of the beta receptor or cAMP by stabilization of the troponin C-calcium complex in myofibrils, strengthening the actin-myosin cross bond. Levosimendan may have a more sustained benefit on postoperative stroke volume than milrinone and require less norepinephrine (NE) vasoconstrictor support. In patients with low EF, the combination of levosimendan with dobutamine is more effective in improving stroke volume than the combination of milrinone and dobutamine. Levosimendan undergoes biotransformation to an active metabolite that exerts potent effects for up to a week, so it is not infused for more than 24 hrs, and there may be a benefit to starting the infusion 48 hrs before surgery.

**FIRST GENERATION VADS: PULSATILE FLOW**

**Thoratec HeartMate XVE**

The Thoratec HeartMate I or XVE became established as the LVAD that achieved the widest use in the decade from its introduction in 1994 through about 2005. It served primarily as a bridge to transplant, but in 2001 was shown to be superior to maximal medical therapy in survival as well as quality of life in destination therapy. It has a large metallic pump placed sub-diaphragmatically but pre-peritoneally in the abdomen (LVAD pocket), with an inflow from the left ventricle (LV) and an outflow into the ascending aorta above the aortic valve. Porcine valves are placed in the inflow and outflow tubes just proximal and distal to the pump. The pump has a driveline that provides electrical power and emerges from the abdominal wall some distance from the LVAD pocket. The interior of the pump consists of a rotating flange that moves up or down (diastole) a circular cam, generating pulsatile flow out the aorta and essentially emptying the LV during each cycle.

The HeartMate XVE has a number of design benefits. It maintains pulsatile flow so the patient has a palpable pulse and blood pressure can be measured externally by a blood pressure cuff. Its physiology most closely mimics normal hemodynamics, i.e. the LV fills and empties and thereby supports right ventricular (RV) function. The entire LV stroke volume is ejected into the aorta above the valve so that aortic stenosis becomes redundant (and the valve may actually be sewn closed). The interior of the pump is lined with textured polyurethane that becomes endothelialized within a few days. This so greatly reduces contact activation of procoagulants that the risk of thrombosis is minimized and patients do not need to be fully anticoagulated with Coumadin – aspirin is sufficient – which in turn greatly decreases the risk of bleeding.

However, the HeartMate XVE has numerous limitations that have rendered it virtually obsolete today. It is extremely loud, which may disrupt sleep for the patient and their spouse. Its large size precludes placement in children or small adults. Even in larger adults, its anatomic position may compress the stomach to the extent of causing a gastric outlet syndrome and making placement of an enteral feeding tube very difficult. The new endothelial lining expresses abnormal antigens that increase the risk of antibody formation and rejection with a subsequent heart transplant. Systemic hypertension increases pressure fatigue to the LVAD and its components and shortens its expected life, which at best is no more than two years.

**The PVAD and IVAD**

The Thoratec Company also produced a first generation, pulsatile external device called the PVAD (paracorporeal VAD), which consists of a fist-sized pump that lays on the patient’s abdomen. It has the advantage of being able to provide LVAD, RVAD and BiVAD support so that it could be utilized as an in-hospital bridge to transplant or in conjunction with an internal LVAD to provide short or longer term RV support. However, the cannulas are large and the console is huge. More recently, the company has modified the pumps to allow them to be placed subcutaneously (IVAD, intracorporeal VAD) and developed a much smaller, portable console, that allows the device to be used as a bridge to transplant or destination therapy out of hospital.

**SECOND GENERATION VADS: NON-PULSATILE AXIAL (ROTARY FLOW)**

**Thoratec HeartMate® II**

The Thoratec HeartMate® II is a pencil-like pump that rotates at 8000-10000 rpm and creates axial flow within a long term internal LVAD that has a number of advantages over its predecessor. It has virtually replaced the HeartMate® XVE as a bridge to transplant or destination therapy. The profile of the HeartMate® II is less than a quarter that of the HeartMate® XVE, creating a much smaller LVAD pocket with no gastric compression, and allowing placement in small adults. It is much quieter, has far fewer moving parts, and much greater longevity. Compared to the HeartMate® XVE, the HeartMate® II provides significantly greater two year survival (58% vs. 24%) and freedom from disabling stroke or device malfunction (46% vs. 11%).

The challenge of the HeartMate® II is that its physiology is far more complex and its hemodynamic management requires considerably more attention to detail. It provides non-pulsatile flow so the patient has no palpable pulse, which precludes cuff blood pressure measurement and requires Doppler assessment.
Because drainage from the LV is continuous, excessive flow generated by high rpm in the LVAD may cause the LV chamber to collapse, especially if the inflow cannula is sucked against the LV wall (a “suction event”). This in turn displaces the intraventricular septum and may acutely compromise RV function. A similar situation may be caused by intravascular hypovolemia. The relative volume (or unloading) status of the LV is indicated on the LVAD monitor by a unit-less parameter called the pulsatility index (PI), which must be closely assessed and kept between 4.0 and 6.0.

Pump flow is calculated based on power and blood viscosity; at the extremes of flow it is subject to error and may indicate “normal” flow in low flow states such as cardiac tamponade. The nature of the device precludes polyurethane coating, so patients must be fully anticoagulated, which increases the risk of postoperative bleeding. However, thromboembolic cerebrovascular events appear to be if anything less common than with the HeartMate XVE (see above).

**Abiomed® Impella® 5.0**

The Abiomed® Impella® device is a short term, external device used as a bridge to decision or bridge to a bridge. It consists of a long cannula that is placed via the femoral or axillary artery through to the ascending aorta and across the aortic valve into the LV. There the rapid rotational force of the microaxial rotary pump at its tip generates forward flow up to 5 L/min. It is designed for short-term (<24 hrs) use only. It cannot be placed in the presence of aortic stenosis, and prolonged use damages red blood cells and may induce a hemolytic anemia.

**THIRD GENERATION VADS: NON-PULSATILE CENTRIFUGAL FLOW**

There is an emerging series of third-generational long term centrifugal LVADs, all of which are still investigational in the U.S. A major advance is that through magnetic or hydrodynamic levitation there is no contact between the impeller and the drive mechanism. There is almost minimal contact with the blood, and the impeller rotates centrifugally much more slowly than the rotary devices, at 2750–3000 rpm. The advantages claimed are decreased hemolysis and thrombogenesis, and greater mechanical durability.

**Terumo® DuraHeart™**

The Terumo® DuraHeart™ is a third-generation long-term LVAD in which the pump is provided by a magnetically levitated impeller with centrifugal flow. In other respects its concept is similar to the HeartMate® II, with a small intra-abdominal, preperitoneal LVAD pocket, driveline and external battery packs. The device is approved in the European Union (EU), where compared to pulsatile LVADs it demonstrates significantly improved survival (85% at 6 months, 79% at 1 year), and only a 4% replacement rate at 2 years.

**HeartWare® HVADTM**

The HeartWare® HVADTM is a miniaturized third-generation LVAD in which the inflow cannula is cored directly into the LV apex so that the entire system is intrapericardial and above the diaphragm. It has a small driveline that is exteriorized and attached to small portable battery packs. The HVADTM is already approved in the EU and is undergoing extended trials in the USA as both bridge to transplant and destination therapy.

**Levitronix® CentriMag**

The Levitronix® CentriMag device is an external, short-term device that may be utilized as an LVAD, RVAD or BiVAD. The magnetically levitated centrifugal pumps are small and may be attached to an IV pole; the cannulas are very small (7 mm), so the device can be placed quickly and easily in the OR or Cath Lab. A console provides rpm and flow rates determined by ultrasound. Since its introduction at our medical center in 2007, the CentriMag has become the predominant VAD utilized as a bridge to decision, bridge to a bridge or even short-term bridge to transplant.

The CentriMag has a further advantage in that, because its cannulas are all external, hypovolemia may be detected by a phenomenon known as “chattering”, when the cannulas start to vibrate.

The LVAD is FDA-approved for 6 hr only, and the RVAD for 30 days, but in our practice the devices have been left in place for considerably longer. Although the external nature of the device mandates constant supervision, with care, it is possible to allow patients to get out of bed, mobilize and even ambulate, but in most cases, the device is converted to a longer-term device before the patient leaves the ICU.

**MANAGEMENT OF ELEVATED PULMONARY VASCULAR RESISTANCE (PVR)**

**Principles of Management**

The pulmonary vascular resistance (PVR) is a critical determinant of RV afterload. The LV is made up of concentric muscle fibers geared toward the pressure work conferred by the systemic vascular resistance (SVR). In contrast, pressures in the RV are normally one-fifth those in the LV, and the RV fibers are arranged like those of a bellows, conducive to volume work. Acute elevation in PVR can cause the RV to rapidly decompensate, and must be treated promptly.

The first step in treating elevated PVR is to treat abnormal physiologic states that exacerbate it, notably acidosis, hypercarbia, hypoxemia and excessive catecholamine activity (induced by pain, anxiety, hypovolemia, increased work of breathing etc.). If this is not done effectively, none of the pharmacologic interventions mentioned below will be effective either.

In the LV 70–90% of coronary perfusion occurs during diastole. Because the aortic diastolic pressure (ADP) is normally greater than the RV systolic pressure, RV coronary perfusion occurs throughout the cardiac cycle. When the PVR is markedly elevated, RV coronary
perfusion depends on the gradient between the ADP and the RV end-diastolic pressure (RVEDP). This is an important limitation of pulmonary vasodilators that also cause systemic vasodilation and hypotension. Systemic blood pressure can be maintained with vasopressors such as phenylephrine and NE, but these agents may exacerbate pulmonary vasoconstriction at high doses. The co-administration of low doses (< 4 μg/hr) of arginine vasopressin (AVP) does not induce pulmonary vasoconstriction and markedly decreases NE dose requirements, which may in turn benefit PVR.

**INHALED NITRIC OXIDE (INO)**

**Mechanism of Action**

Inhaled nitric oxide (INO) mediates pulmonary vasodilation through activation of soluble guanylate cyclase (sGC), which catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), a potent vascular smooth muscle relaxant.

Once inhaled, the nitric oxide molecule is rapidly inactivated in the pulmonary circulation by binding to heme proteins (including oxyhemoglobin, oxymyoglobin, guanylate cyclase, cyclooxygenase, and cytochrome P450).

**Therapeutic Benefits**

Heme binding ensures that INO provides selective pulmonary vasodilation without any effect on the systemic circulation. The effect is dose dependent in the range of 5-40 ppm, and is proportionately greater with increasing degrees of pulmonary vasoconstriction. Elevated PVR and mean pulmonary artery pressure (MPAP) are consistently decreased, while systemic blood pressure, ADP and RV coronary perfusion remain unaffected. The decrease in RV afterload in turn may enhance RV performance, with improvement in ejection fraction (EF) and RV end-diastolic volume (RVEDV).

When administered after cardiopulmonary bypass (CPB), INO decreases elevated PVR and promotes RV recovery from transient ischemic injury, while maintaining LV filling by increasing pulmonary arterial blood flow. This is particularly helpful after placement of an LVAD, whose filling and ejection is very dependent on pulmonary venous return to the left atrium and LV.

**Adverse Effects**

By increasing pulmonary blood flow, INO increases LV filling. In patients with isolated LV dysfunction and poor ventricular compliance, this can result in a rapid increase in LV filling pressure, acute volume overload, ventricular failure and pulmonary edema. Acute, potentially life-threatening increases in PVR and MPAP can occur when INO is abruptly discontinued. This may be the consequence of suppression of endogenous nitric oxide formation by down-regulation or inactivation of endogenous endothelial nitric oxide synthase (eNOS). INO improves ventilation-perfusion (VA/Q) matching by vasodilating the pulmonary circulation in the best-ventilated lung zones. Rapid weaning of INO < 5 ppm is often associated with worsening VA/Q and hypoxemia. Weaning of INO should always be done with close attention to its effects on oxygenation (SpO2, PaO2), PVR (MPAP) and RV function (CVP).

**Delivery and Toxicity**

INO dosage > 80 ppm provides an increasing risk of toxicity from the pro-inflammatory effects of nitric oxide itself or its reactive products. In the presence of high oxygen levels (i.e. at high FiO2) nitric oxide forms toxic nitrogen dioxide (NO2), which reacts with water to form nitric acid (HNO3). It may also react with oxygen to form peroxynitrite (ONOO-), which rapidly decomposes to form NO2 and the very reactive hydroxyl radical (OH-).

When nitric oxide binds to hemoglobin it oxidizes ferrous (Fe2+) to ferric (Fe3+) ion, to create methemoglobin (MetHb), which is incapable of binding oxygen. The degree of methemoglobinemia is INO dose-related, more likely in premature neonates or at doses > 40 ppm, and results in cyanosis, dyspnea and abnormal pulse oximetry readings.

**Delivery Systems**

At the present time there is only one distributor of INO and INO delivery systems (INOMAX®, Ikaria®), and as a consequence, INO is extremely expensive. However, it is essential to use such an approved delivery system for safe administration of INO. The injection module is inserted between the ventilator output and the humidifier, and INO is injected proportionally to the measured ventilator flow to provide the desired dose. Gas is sampled downstream in the inspiratory circuit and analyzed electrochemically, and the display provides FIO2, INO and NO2 concentrations, with multiple alarms. The system can also be adapted to a manual bag system for transport, providing NO at 20 ppm.

**SILDENAFIL**

As specified above, the vasodilator effects of nitric oxide are mediated through activation of cGMP. Phosphodiesterase V (PDE V) converts cGMP to guanosine monophosphate (GMP) and thereby limits its duration of action. Administration of a selective PDE V inhibitor, sildenafil, enhances the duration of action of cGMP. In its own right sildenafil induces dose-dependent decreases in elevated PVR, but it also enhances the effect of INO, and attenuates acute pulmonary hypertension caused by abrupt INO withdrawal.

Sildenafil is approved as maintenance therapy in pulmonary arterial hypertension (PAH); it is dosed orally as 10-30 mg three times a day. In 2009 an intravenous (IV) preparation of sildenafil was approved which facilitates its use in the perioperative period; an IV dose of 10 mg is pharmacodynamically equivalent to an oral dose of 20 mg. Sildenafil is not available as...
an inhaled preparation, and its pulmonary effects are limited by unwanted systemic vasodilation.

**INHALED PROSTACYCLINS**

**Mechanism of Action**

Prostacyclin (PGI$_1$) is a vasodilator prostaglandin that induces smooth muscle relaxation by activating cyclic adenosine monophosphate (cAMP). There is both experimental and clinical evidence that the combination of INO (and/or sildenafil) and an inhaled prostacyclin provide greater pulmonary vasodilation than either used alone, by simultaneously activating cGMP and cAMP.$^{16,17}$ Prostacyclin impedes platelet aggregation and could promote bleeding but this concern appears to be more theoretic than real.

**Epoprostenol**

Epoprostenol (Flolan®) is a short-acting prostacyclin that is approved for continuous IV infusion for patients with PAH. However, IV infusion causes as much systemic as pulmonary vasodilation, which is poorly tolerated in the perioperative period, especially when there is concomitant vasodilatory shock. In the blood, epoprostenol undergoes rapid spontaneous hydrolysis ($t\frac{1}{2}$ 2-3 min) to 6-keto-prostaglandin Flα. Administration by inhalation provides relatively selective, short-acting and titrateable pulmonary vasodilation and improved RV function.$^{18}$ A number of US centers administer (off-label) inhaled epoprostenol via a syringe infusion pump coupled to a nebulizer, and by dilution with saline the dose is varied from 12.5 to 50 ng/kg/min.

**Iloprost**

Iloprost is a synthetic prostacyclin analog that has a longer half-life (20-30 min) and is approved for administration by a metered dose inhaler, given at a dose of 2.5-5 mcg every 2-4 hrs. The device can easily be adapted for connection to an endotracheal or tracheostomy tube. Iloprost is approved for the treatment of PAH, but is used off label to treat acutely elevated PVR after cardiac surgery and lung transplantation.

Compared to epoprostenol, iloprost’s primary limitation is the need for repetitive inhalations every 2-4 hrs. It has slower onset and offset than INO and it is not immediately inactivated, undergoing biotransformation in the liver. Thus, there is some potential for systemic vasodilation and hypotension. The advantages of iloprost are that it is much less expensive than INO, has no toxic metabolites and there is little if any risk of rebound pulmonary hypertension. In the intraoperative and early postoperative periods, INO may be preferable because of its rapid onset and titrateability and lack of systemic hypotensive effects. However, when they are more hemodynamically stable patients can be easily transitioned to inhaled iloprost, which provides an effective means of weaning INO, avoiding rebound pulmonary hypertension, and continuing pulmonary vasodilation after tracheal extubation.

A third analog, trepostinil, has a longer duration of action than iloprost,$^{19}$ but has not been adapted for use in the perioperative period.

**Inhaled Prostacyclin vs. NO**

Inhaled PGI$_2$ was compared to inhaled nitric oxide in a prospective, randomized cross-over trial for the treatment of pulmonary hypertension following heart or lung transplantation.$^{20}$ Both agents were effective in decreasing PVR, pulmonary artery pressure and right atrial pressure, and improved cardiac index and mixed venous oxygen saturation. There were no significant differences in these parameters after cross-over to the other agent. Neither medication affected systemic blood pressure.

Given their lower cost and lack of potential toxicity, inhaled prostacyclins should be considered as primary or transitional therapy in the treatment of perioperative pulmonary hypertension.

**Inhaled Milrinone**

Milrinone is a selective PDE III inhibitor that results in the intracellular accumulation of cAMP. In myocardium this enhances inotropy, whereas in smooth muscle it promotes vasodilation (inodilation). The pulmonary vasodilator effects of milrinone are limited by systemic vasodilation, requiring the concomitant use of vasopressors such as norepinephrine and arginine vasopressin (see next section).

There are some reports of a beneficial effect of administration of inhaled milrinone by ultrasonic nebulization, resulting in much more specific pulmonary vasodilation and decrease in elevated PVR.$^{21}$ The combination of inhaled prostacyclin and inhaled milrinone appears to have an additive effect on decreasing elevated PVR, presumably through an action in stimulating cAMP formation and preventing its breakdown that is analogous to combining INO and sildenafil.$^{22}$

**VASODILATORY SHOCK AND VASOPRESSOR THERAPY**

**Vasopressin and its Analogues**

Arginine vasopressin (AVP) is a nonapeptide produced in the paraventricular and supraoptic nuclei of hypothalamus as a prohormone, cleaved to AVP and stored in secretory vesicles in the posterior pituitary.$^{23}$ AVP has a plasma half-life of 6-20 min and is rapidly metabolized by vasopressinases in the liver and kidney. Vasopressin receptors, sites of action and actions are summarized in Table 1.

Increased serum osmolality (> 1%), generates plasma AVP levels of 1-5 pg/mL that act on V$_2$ receptors, inducing an antidiuresis. Severe hypotension generates plasma AVP levels of 10-100 pg/mL that act on V$_1$ (formerly called V$_{1a}$) receptors, inducing peripheral vasoconstriction as a component of the baroreflex response. Activation of V$_3$ (V$_{1b}$) receptors induces ACTH and insulin release and may reflect the relationship
between AVP and glucocorticoid metabolism (see below). At high levels, AVP may activate purinergic (P2) receptors in the cardiac endothelium, inducing coronary vasoconstriction.23 Oxytocin is a nonapeptide that differs from AVP by only two amino acids, yet its actions are very different (uterine contraction, milk let-down) and there is little cross-reactivity.

Table 1: Receptors, Sites of Action and Actions of Endogenous Vasopressin (AVP)23

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Site of Action</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (V1a)</td>
<td>vascular smooth muscle</td>
<td>vasoconstriction</td>
</tr>
<tr>
<td>V2</td>
<td>collecting duct of nephron</td>
<td>antidiuresis</td>
</tr>
<tr>
<td>V3 (V1b)</td>
<td>anterior pituitary, pancreas</td>
<td>ACTH, insulin release</td>
</tr>
</tbody>
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**Evidence basis for use of AVP and its analogues in vasodilatory shock**

The most definitive randomized controlled study (RCT) performed on AVP thus far is the Vasopressin and Septic Shock Trial (VASST).27 It was designed to test the hypothesis that low-dose AVP infusion (0.01-0.03 u/min or 0.6-1.8 u/hr) would decrease 28-day mortality among patients with septic shock who were being treated with NE 5-15 mcg/min. In the 778 patients studied, there was no significant difference in mortality between the AVP and NE (35.4% vs. 39.3%). However, in patients with less severe septic shock (prospectively defined as requiring NE 5-14 mcg/min), there was a significant improvement in mortality with AVP over NE (26.5% vs. 35.7%, p < 0.05). It is possible that the lack of benefit in more severe septic shock (NE > 14 mcg/min) was due to an inadequate dose of AVP or late intervention.

**Role of corticosteroids in vasodilatory shock**

An retrospective analysis of the VASST study by its authors demonstrated that the concomitant administration of corticosteroids with AVP significantly decreased mortality (35.9% vs. 44.7%, p = 0.03), and increased plasma AVP levels by one to two thirds.28 This further implicates the relationship between AVP and steroid metabolism, considering that V3 receptor activation increases ACTH release and cortisol levels. It also warrants future prospective studies.

Indeed, the role of steroids in septic shock remains in flux.29 The use of ACTH-stimulation tests to evoke adrenal hyporesponsiveness as an indication for hydrocortisone therapy has been discredited by subsequent equivocal outcomes, intra-study use of etomidate (which impairs cortisol synthesis), and the observation that these studies were based upon total rather than free cortisol levels.30 The 2008 Surviving Sepsis Campaign recommends the administration of hydrocortisone (≤ 300 mg/day) when hypotension responds poorly to adequate fluid resuscitation and vasopressors, and that it should be weaned once vasopressors are no longer required.26

**Terlipressin**

Terlipressin (tricyl-lysine vasopressin) is an AVP analogue used in Europe but not currently available in the US or Canada. It is twice as potent at the V1 receptor than AVP, but has a much more prolonged half-life (4-6 hr), which makes it more difficult to titrate.25 A small European RCT (TERLIVAP) compared continuous infusion of AVP (0.03 u/min) and terlipressin (1.3 mcg/kg/hr) with NE (15 mcg/min) as first-line therapy in septic shock in 45 patients.31 Terlipressin appeared
superior to AVP in decreasing NE requirements, with lower bilirubin levels and less rebound hypotension, but had a greater effect in lowering platelet count.

**METHYLENE BLUE**

**Actions of methylene blue**

Methylene blue appears to inhibit guanylate cyclase, the enzyme that catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which mediates the vasodilator effect of NO. It may also cause selective inhibition of iNOS.

**Evidence basis for use of methylene blue in vasodilatory shock**

Anecdotal observations of the benefits of methylene blue (MB) in severe vasodilatory shock have been made for many years. Dosing has ranged between 1-4 mg/kg given as a single dose infused over 30 min to 4 hrs. MB increases MAP and cardiac index (CI). The latter may be due to increase preload secondary to venoconstriction, or a decrease in the impact of high levels of NO, which is a myocardial depressant that impedes the inotropic effect of catecholamines. Arterial lactate decreases, but this may be in part from its effect as a reducing agent. However, PVR also increases and arterial oxygenation may decrease. Although decreases in endogenous production of NO, interleukins and tumor necrosis factor (TNF) have not been noted, urinary excretion of NO metabolites is substantially lower. Attenuation of the urinary excretion of renal tubular injury markers has also been noted.

A small dose-ranging randomized control trial (RCT) on 15 patients evaluated MB at 1mg/kg, 3mg/kg or 7mg/kg over 20 min. The authors noted a dose-dependent enhancement of hemodynamic function even at the lowest dose, but cautioned that high doses of MB may compromise splanchic perfusion. In another small RCT of 20 patients with septic shock, patients were randomized to placebo or MB 2 mg/kg, followed two hrs later by increasing infusion rates between 0.25 and 2 mg/hr over 4 hrs. The most striking finding was a 40-87% decrease in dose requirement for NE, epinephrine and dopamine.

In the largest postoperative RCT performed to date, the vasoplegic syndrome was defined as a combination of hypotension due to low SVR, low cardiac filling pressures, normal or high cardiac index, and high vasopressor requirement. Consecutive cardiac surgery patients met criteria and were randomized to MB 1.5 mg/kg or placebo. Patients who received MB had a significantly shorter duration of vasoplegia (6 vs. > 48 hrs) and lower mortality (0% vs. 21.4%).

A novel approach was taken by Ozal et al., who administered MB 2 mg/kg over 30 min or placebo one hr preoperatively to 100 patients undergoing coronary revascularization who were at high risk for vasoplegic syndrome because they were on ACE inhibitors, calcium channel blockers or heparin. Patients who received MB before surgery had a significant reduction in postoperative vasoplegia (0% vs. 26%), ICU and hospital LOS.

We have observed occasionally dramatic responses to MB 2 mg/kg administered over 30 min in severe vasoplegia. However, because of its potential to increase PVR, in our practice we restrict its use to patients who are already receiving inhaled NO.

**RENALE PROTECTION: BIOMARKERS AND PHARMACOLOGIC INTERVENTIONS**

**Biomarkers**

Ischemic acute kidney injury (AKI) progresses through several phases (prerenal, initiation, extension, maintenance and recovery). The success of any intervention to restore GFR thus depends on its timing – the earlier, the better. However, traditional renal function tests do not allow early recognition of AKI. Development of robust, easily detectable and prompt biomarkers of renal injury might allow us to assess the site, duration, etiology, prognosis and course of renal injury, and the effect of prophylactic or therapeutic interventions.

**Serum Creatinine**

Serum creatinine (SCr) is not a marker of renal injury, but of renal function, and reflects the balance between muscle creatinine production and renal excretion. SCr is a useful marker of glomerular filtration rate (GFR) in a steady state, but it is important to appreciate that the relationship between SCr and GFR is inverse and exponential. A doubling of the serum creatinine implies a halving of the GFR. There are numerous limitations to SCr as a reflection of steady state GFR as well as of acute changes in GFR.

Many physiologic molecules (e.g. glucose, protein, ketones) or drugs (e.g. cephalosporins) interfere with the chromogenic assay for creatinine. N-acetylcysteine (NAC), an antioxidant renoprotective agent in radiocontrast nephropathy (RCN) actually decreases SCr levels.

SCr does not increase above the normal range until GFR is <50 mL/min, so any decrease in GFR above this level will still be associated with a “normal” SCr. This is pertinent in the elderly (whose normal GFR is 50-80 mL/min) and c Achycicients (who have very low creatinine generation). Creatinine is freely soluble and distributes throughout the total body water (TBW), so perioperative increases in TBW are reflected by artifically low SCr immediately after surgery.

Importantly, it may take 2 to 7 days before the SCr reaches a new steady state that reflects acute changes in GFR. This explains why intraoperative AKI is so often reflected by a postoperative SCr that does not peak until 5-7 days after surgery. Indeed, after a transient renal insult (e.g. suprarenal aortic cross-clamping) SCr may increase for a few days while GFR is actually recovering.
Cystatin C

Cystatin C is a cysteine-protease inhibitor that is released into the circulation by all nucleated cells. It is completely filtered by the glomerulus, reabsorbed and not secreted by the tubules; thus, increased serum cystatin C levels reflect decreased GFR, and increased urinary levels reflect tubular injury.\(^{47}\) Elevation of urinary cystatin C within 6 hr of cardiac surgery has been shown to have a strong correlation with AKI defined by subsequent elevation of SCr48. Unlike creatinine, cystatin C levels are not affected by muscle mass, age or gender, and there is evidence that it more accurately tracks GFR and responds more quickly.\(^{49,50}\) However, certain factors such as cigarette smoking, inflammation and immunosuppressive therapy do independently elevate cystatin C.\(^{51}\)

Classic biomarkers of tubular injury

Beta-2 microglobulin (B2M) is a small protein component of the major histocompatibility complex that is present on the surface of almost all cells.\(^{52}\) It is normally filtered by the glomerulus and then undergoes partial tubular reabsorption. The ratio of serum to urine B2M may help distinguish glomerular from tubular injury. In the former, serum B2M increases because it is not filtered. In the latter, urinary B2M increases because it is not reabsorbed.

Increased urinary concentration of the tubular enzyme, N-acetyl beta D-glucosaminidase (NAG) is an index of subclinical tubular injury.\(^{53}\) Urinary NAG levels, or the ratio of its isoenzymes, is used in the early detection of rejection after renal transplantation. However, the relationship between tubular enzymuria and clinical AKI is not known.

New biomarkers of tubular injury

Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25 kDA polypeptide expressed in proximal tubular cells. Within minutes after ischemic tubular injury NGAL expression is dramatically up-regulated - 3-4 fold within 2-3 hrs, and up to 10,000 fold by 24 hrs.\(^{54}\) NGAL is readily detected by ELISA in tiny (micromilliliter) amounts of urine almost immediately after renal injury, preceding the appearance of NAG and beta2-microglobulin.

Urinary NGAL increases significantly within 2 hr of CPB in pediatric or adult patients who subsequently go on to develop a 50% increase in postoperative SCr, whose peak is delayed until 2-5 days after surgery.\(^{55}\) However, the sensitivity and specificity in individual patients is much greater in pediatric (AUC 0.98) than adult cardiac surgery (0.74).\(^{56}\) This may be explained by pediatric patients having a single insult imposed upon previously normal renal function, whereas, adults have varying preoperative GFR and co-morbidity, with multiple disparate renal insults. Thus although urinary NGAL may represent an early, sensitive, noninvasive urinary biomarker for ischemic and nephrotoxic AKI, it is not yet useful for management decisions in an individual patient.

Interleukin-18 (IL-18) is a pro-inflammatory cytokine that is involved in ischemic AKI. After CPB, urinary IL-18 is elevated within 4-6 hrs (i.e. later than NGAL), and levels may reflect the severity and duration of ischemic AKI.\(^{57}\)

Kidney injury molecule-1 (KIM-1) is an immunoglobulin that normally resides in proximal renal tubular cells. After ischemic or nephrotoxic AKI, KIM-1 levels become dramatically elevated, perhaps because the protein plays a role in scavenging apoptotic and necrotic tubular cells.\(^{58}\) However, compared with NGAL and IL-18, the levels of KIM-1 peak considerably later, at about 12-24 hrs.

Conclusions

Despite their promise, individual biomarkers of AKI have not yet replaced traditional markers in clinical and investigational studies. There is considerable interest in the development of a panel of early markers of acute tubular injury (NGAL, IL-18, KIM-1) together with a more reliable marker of GFR (cystatin C).\(^{41}\) The hope is that these panels will be more useful for timing the initial insult and duration of AKI, and in predicting outcome (requirement for dialysis, mortality). Much work remains to be done to validate their sensitivity and specificity in large, diverse patient populations.

PHARMACOLOGIC PROTECTION

Osmotic and Loop Diuretics

Mannitol (25-50 g) is routinely added to the pump prime, although there are few clinical data that define its true role in renal protection during CPB. It does not prevent subclinical renal injury (microalbuminuria, tubular enzymuria), but AKI after uncomplicated CPB in patients with previously normal renal function is rare. Mannitol increases urine flow during infra-renal cross-clamping but does not prevent intraoperative decreases in GFR Postoperative osmotic diuresis can exacerbate hypovolemia and hypokalemia; persistent isosthenuria actually is predictive of CPB-induced tubular injury.

Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) have long been used to “convert” oliguric to nonoliguric AKI. However, it is most likely that oliguric patients who respond to diuretics have a lesser renal injury than those who do not, with an intrinsically more favorable outcome. Once dialysis is required, high dose furosemide does not alter the natural history of AKI.

Dopaminergic Agonists

Dopaminergic agents (dopamine, fenoldopam) potentially confer renal protection by increasing renal blood flow (RBF), diuresis and saliuresis. By activating cyclic AMP they “turn off” the energy-dependent tubular sodium pump and thereby decrease tubular oxygen consumption; increased intratubular urine flow protects against tubular obstruction.

Low dose (1-3 µg/kg/min) dopamine, added to high dose furosemide and mannitol, can also convert oliguric to nonoliguric states if given within a few hours of injury. However there is little evidence that
“Prophylactic” low dose dopamine has any role in cardiac surgery. In part this may be because there is very wide variability in dopamine pharmacokinetics, i.e. some patients given low dose dopamine may achieve high plasma levels, i.e. in the beta- or alpha-adrenergic range. When oliguria is associated with slow heart rate and low blood pressure in a volume repleted patient, initiation of dopamine as an inotropic agent can be very helpful. However, its usefulness is limited by its propensity to induce supraventricular arrhythmias especially postoperative atrial fibrillation.

Fenoldopam is a phenol derivative of dopamine that is selective for the DA-1 receptor and lacks any beta- or alpha-adrenergic effects. There is increasing evidence that prophylactic perioperative administration at low doses (0.5-1.0 mcg/kg/min) can preserve GFR during and after CPB and decrease the requirement for postoperative dialysis.

Natriuretic Peptides
The natriuretic peptides are formed by the endogenous synthesis of chains of 22-32 amino acids. They specifically oppose the sympathoadrenal, renin-angiotensin, aldosterone, and arginine vasopressin (AVP) systems, and induce vasodilation and natriuresis via activation of cyclic GMP. A-type (atrial) natriuretic peptide (ANP) is released by atrial stretch; B-type (brain) natriuretic peptide (BNP) is released by ventricular dilation. Assay of BNP (and its precursor, N-terminal-pro-BNP) is an established diagnostic tool for acute cardiac failure. C-type natriuretic peptide (CNP, great vessels) and urodilatin (kidney) are endogenous analogs.

Human recombinant ANP (anaritide) infusion during CPB significantly decreases renin-angiotensin and aldosterone responses, and preserves GFR. Preliminary data suggested that administration in patients with severe AKI it could decrease dialysis requirement and mortality. However, mortality was increased in nonoliguric patients, perhaps because the surviving nephrons are more sensitive to hypotension induced by ANP. A subsequent trial in oliguric patients showed no difference in outcome.

Human Recombinant BNP (nesiritide) is FDA-approved for the parenteral treatment of patients with advanced decompensated CHF (ADCHF). Infusion decreases cardiac preload and afterload, promotes diuresis and relieves pulmonary edema and anasarca. Considerable controversy has been elicited by implications that nesiritide may adversely affect renal function in ADCHF. However, in a prospective, controlled study in patients undergoing coronary revascularization of mitral valve surgery with CPB, a perioperative infusion of nesiritide (0.01 mcg/kg/min) was associated with lower SCR and 6-month mortality.

N-Acetylcysteine
N-acetylcysteine (NAC) is naturally occurring glutathione precursor and free radical scavenger. It is well established in the treatment of acetaminophen toxicity, and there is considerable experimental evidence of its effectiveness in ameliorating nephrotoxic AKI. When combined with hydration, prophylactic oral NAC (600 mg PO bid x 2 days) provides significant renal protection in radiocontrast nephropathy (RCN). However, NAC may decrease creatinine production and thereby give a false impression of the extent of its benefit.

No renal benefit has been demonstrated by the perioperative infusion of NAC during cardiac surgery. NAC must pass through the liver to be converted to glutathione, so in part this may be due to inadequate knowledge regarding the appropriate parenteral dose of NAC to protect against clinical IRI.

Sodium Bicarbonate
It is well established that urinary alkalinization (pH > 6.5) protects against tubular injury in myoglobinuria (rhabdomyolysis) as well as RCN. There is no preliminary clinical evidence that urinary alkalinization might ameliorate AKI during cardiac surgery, although an accompanying editorial in the same journal urged caution in interpreting the results of this pilot study.

REFERENCES


